APPENDIX A

Summary of External Peer Review and Public Comments and Disposition

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APPENDIX A. SUMMARY OF EXTERNAL PEER REVIEW AND PUBLIC COMMENTS AND DISPOSITION

EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (Reanalysis) has undergone a formal, independent, expert panel review performed by EPA's Science Advisory Board (SAB) in accordance with U.S. Environmental Protection Agency (EPA) guidance on peer review (2006c, 2000). The SAB Dioxin Review Panel held two public face-to-face meetings to deliberate on the charge questions on July 13−15, 2010 and October 27−29, 2010, as well as two public teleconferences on March 1 and 2, 2011. The SAB Dioxin Review Panel was asked to consider the accuracy, objectivity, and transparency of EPA's Reanalysis. Initially, the charge questions presented to the SAB Dioxin Review Panel were divided into six sections: *General Charge Questions, Transparency and Clarity in the Selection of Key Data Sets for Dose-Response Analysis, The Use of Toxicokinetics in the Dose-Response Modeling for Cancer and Noncancer Endpoints, Chronic Oral Reference Dose, Cancer Assessment,* and *Feasibility of Quantitative Uncertainty Analysis From NAS Evaluation of the 2003 Reassessment*. Because of EPA's decision to release the cancer assessment and quantitative uncertainty sections in a separate document, SAB and public comments related to those topics are not addressed in this appendix but will be addressed in the Reanalysis Volume 2. A summary of significant comments made by the SAB Dioxin Review Panel and EPA's responses to these comments, arranged by charge question, follow. In many cases, the comments have been synthesized and paraphrased in development of this appendix. In response to a Federal Register notice (75 FR 28610 [May 21, 2010]), EPA also received, comments from the public on the draft document. Each section provides EPA's charge question, followed by SAB comments and specific recommendations related to the charge question, and then EPA's responses to the recommendations. Major public comments that are relevant to specific sections, along with EPA responses to the comment, are provided at the end of each respective section. Section A.5 provides additional public comments that were not associated with a particular charge question, along with EPA's responses.

A.1. GENERAL CHARGE QUESTIONS

A.1.1. SAB Comments and Recommendations and EPA Responses

SAB Charge Question 1.1

*Is the draft Response to Comments clear and logical? Has EPA objectively and clearly
presented the three key NRC recommendations?*

Comment: In general, the Report was clear, logical, and responsive to many but not all of
National Academy of Sciences (NAS) recommendations; although there are opportunities for
improvement. The Panel found that EPA was effective in developing a clear, transparent, and
logical response to NAS recommendations, and that EPA has objectively and clearly presented
the three key NAS recommendations. The Executive Summary was valuable in providing a
concise and accurate summary. The Report was dense and repetitive in some places, and could
benefit from greater clarity in writing. Although the Panel found that the Report was clear in its
presentation of the key NAS recommendations, it was not complete in consideration of
two critical elements: (1) nonlinear dose response for 2,3,7,8-Tetrachlorodibenzo-p-dioxin
(TCDD) carcinogenicity and (2) uncertainty analysis.

Response: EPA is moving forward to complete the draft Reanalysis and is planning to
publish two reports (U.S. EPA's *Reanalysis of Key Issues Related to Dioxin Toxicity and
Response to NAS Comments* Volumes 1 and 2 [Reanalysis Volumes 1 and 2]) that
together will respond to the recommendations and comments on TCDD dose-response
assessment included in the NAS 2006 review. The current report, Reanalysis Volume 1,
includesthe following information and corresponds to Sections 2 through 4 of the external
review draft Reanalysis:

1. The study selection criteria used for the selection of studies for both noncancer
   and cancer TCDD dose-response analysis

2. The results of EPA's study selection process for both cancer and noncancer
   TCDD dose-response information

3. EPA's choice and use of a kinetic model to quantify appropriate dose metrics for
   both cancer and noncancer data sets

4. A noncancer oral RfD for TCDD, including justification of approaches used for
   dose-response modeling of noncancer endpoints

5. A qualitative discussion of uncertainties in the RfD and a quantitative sensitivity
   analysis of the choices made in the development of points of departure (PODs) for
   RfD derivation

Reanalysis Volume 2 will address the SAB comments related to the nonlinear
dose response for TCDD carcinogenicity and quantitative uncertainty analysis. In
Volume 2, EPA will complete the evaluation of cancer mode of action, cancer

1   dose-response modeling, including justification of the approaches used for dose-response
2   modeling of the cancer endpoints, and an associated quantitative uncertainty analysis.
3   These issues correspond to Sections 5 and 6 of the external review draft Reanalysis.
4   In addition to editing the document for greater clarity in writing, EPA has
5   restructured Section 2 of the Reanalysis, moving large portions of summary text to
6   appendices to reduce density and enhance readabilityof the document.

7   *Recommendation No. 1*: Provide greater clarity and transparency in the discussion of
8   studies that did not satisfy inclusion criteria. Given the enormity of this task, it can be done
9   generally to indicate how the issue was considered.

10   *Response:* EPA has added a new Figure 4-2 that provides an overview of the disposition
11   of all studies. For the noncancer animal studies, additional details are provided in
12   Section 2 and Appendix D; a new Table D-2 shows the excluded animal studies and
13   identifies the study inclusion criteria that were not met. For the epidemiologic studies
14   that were evaluated, EPA reviewed and clarified the reasons for study exclusion; details
15   are provided in Section 2 and Appendix C (see Tables C-2 through C-56).

16   *Recommendation No. 2*: Carefully review the document using a qualified technical editor.

17   *Response:* EPA has had the document reviewed by a qualified technical editor.

18   *Recommendation No. 3*: Include a glossary.

19   *Response:* EPA has implemented this recommendation in Section 1.5.3 on the
20   organization of the Reanalysis by referring to the IRIS online glossary available at
21   http://epa.gov/iris/help_gloss.htm. This link provides definitions of terms typically used
22   in IRIS documents, such as the Reanalysis.

23   *Recommendation No. 4*: Find additional efficiencies (e.g., greater use of appendices and
24   elimination of redundancies) to yield a more succinct and approachable document.

25   *Response:* To improve readability, EPA has eliminated redundancies among sections of
26   the document and moved the detailed epidemiologic and animal study summaries from
27   the main text in Section 2 to Appendices C and D, respectively.

28   **SAB Charge Question 1.2**

29   *Are there other critical studies that would make a significant impact on the conclusions of the*
30   *hazard characterization or dose-response assessment of the chronic noncancer and cancer*
31   *health effects of TCDD?*

32   *Comment:* The Panel did not identify any other critical studies that would impact the hazard
33   characterization or the dose-response assessment but feels that the Report should provide more
34   clarity on the exclusion of null epidemiologic studies.

35   *Recommendation No. 5:* Provide more discussion and clarity on exclusion of null
36   epidemiologic studies.

1   ***Response:*** EPA has added as discussion of this issue in Section 2.3.1 with respect to
2   epidemiologic study selection criteria.

3   **A.2. TRANSPARENCY AND CLARITY IN THE SELECTION OF KEY DATA SETS**
4   **FOR DOSE-RESPONSE ANALYSIS**

5   In general, the Panel favorably viewed EPA's efforts in developing the section of the

6   Report that presents how transparency and clarity was ensured (see Section 2) when selecting

7   key data sets. The comments and recommendations provided below will help EPA further

8   improve Section 2.

9

10 **A.2.1. SAB Comments and Recommendations and EPA Responses**

11 **SAB Charge Question 2.1**

12 *Is this section responsive to the NAS concerns about transparency and clarity in data set*
13 *selection for dose-response analysis?*

14 ***Comment****:* The Panel found that Section 2 was responsive to NAS concerns about transparency
15 and clarity. The Panel commended EPA's use of flow diagrams and Appendix B to increase
16 transparency and clarity. The Panel noted, however, that clarity could be improved by providing
17 search words used for the MedLine searches. The Panel also noted that the Report was overly
18 verbose, which was detrimental to its overall clarity.

19 ***Response:*** EPA has further employed the use of flow diagrams and tables to show the
20   disposition of studies and study/endpoint combinations in the process used to derive the
21   TCDD RfD (e.g., see Figures 2-4, 4-2, and Table D-2). EPA has added a new Appendix
22   to the Reanalysis (see Appendix J) that lists the search terms used to conduct the
23   literature search. EPA has improved the readability of the document by moving summary
24   text to appendices and eliminating redundancies in the text where feasible.

25 ***Recommendation No. 6****:* Carefully and extensively edit to revise and consolidate Section 2
26   and the Report as a whole. Restructure Section 2 to make it easier to follow a study from
27   one section of the Report to another. Then, use Section 2 as the foundation to improve
28   overall document integration.

29 ***Response:*** In response to these recommendations, EPA has conducted extensive editing
30   and revisions to provide a clear, cohesive document. To improve readability, the detailed
31   epidemiologic and animal study summaries have been moved from the main text in
32   Section 2 to Appendices C and D, respectively). The rationale for study selection and
33   tabular presentation of results remain the main focus of Section 2. Further, EPA has
34   edited or added figures and tables to document the disposition of studies throughout the
35   study selection process (see Figure 2-4 and Table D-2) and for the development of
36   candidate RfDs (see Figures 4-1, 4-2, and 4-3).

1   **SAB Charge Question 2.2**

2   *Are the epidemiology and animal bioassay study criteria/considerations scientifically justified*
3   *and clearly described?*

4   *Comment:* The Panel's discussion of Charge Question 2.2 is highly integrated with Charge
5   Question 2.3. Therefore, comments and specific recommendations that stem from these
6   two questions are presented together under Charge Question 2.3.

7   *Response:* See recommendations and responses under Question 2.3 below.

8   **SAB Charge Question 2.3**

9   *Has EPA applied the epidemiology and animal bioassay study criteria/considerations in a*
10   *scientifically sound manner? If not, please identify and provide a rationale for alternative*
11   *approaches.*

12   *Comment:* The Panel found that study criteria and considerations were scientifically justified and
13   clearly described, and that they were presented in a scientifically sound manner, but
14   improvements could be made for clarity and on the rationale for decisions to include or exclude
15   particular studies or groups of studies from the data sets. The panel also noted that the rationale
16   for distinct criteria for epidemiological and animal studies should be made stronger, and data set
17   selection for noncancer and cancer endpoints had room for further clarification and justification.

18   *Recommendation No. 7:* Better justify the rationale (including both scientific and practical
19   reasons) for using studies where exposure is primarily to TCDD (or for animal studies only
20   to TCDD) to calculate the reference dose.

21   *Response:* EPA has added extensive text to Section 2.3 that discusses the rationale for
22   focusing on TCDD studies, rather than studies on dioxin-like compounds (DLCs) or DLC
23   mixtures. In identifying studies for quantitative TCDD dose-response analysis, EPA has
24   focused on TCDD studies and has not included studies on DLCs or DLC mixtures.
25   Because the TCDD database is quite robust, inclusion of the DLC literature would likely
26   increase the uncertainty in TCDD dose response unnecessarily. In addition, using studies
27   evaluating information primarily or exclusively on TCDD, as the index chemical,
28   provides the most appropriate data for the risk assessment of dioxins and DLCs using the
29   TEF approach. EPA has included additional information to clarify that background DLC
30   exposures are evaluated in the context of the potential impact on TCDD-only
31   quantification in certain cases as an uncertainty analysis (see new Section 4.5),
32   particularly when TCDD exposures are relatively low.

33   *Recommendation No. 8:* Incorporate studies with dioxin-like chemicals into a qualitative
34   discussion of the weight-of-evidence for cancer and noncancer endpoints.

35   *Response:* In the context of qualitative assessment of the critical effects, EPA has added
36   a focused discussion of the Goodman et al. (2010) review of studies assessing DLC
37   exposure and thyroid hormone levels in children (see response to Recommendation #34).
38   The Goodman et al. (2010) review was evaluated with respect to elevated TSH levels in
39   neonates, one of the co-critical endpoints forming the basis for the RfD. EPA found no

1   DLC exposure studies that evaluated the other co-critical endpoint, decreased sperm
2   concentrations in men exposed to TCDD as boys.

3 ***Recommendation No. 9:*** Further clarify the justifications for study inclusion and exclusion
4 criteria/considerations more effectively and clearly. Specifically, remove criterion that
5 studies must explicitly state TCDD purity because it is highly unlikely that a study would
6 be conducted using impure TCDD.

7   ***Response:*** EPA has removed the criterion for stating TCDD purity from the animal study
8   selection criteria.

9 ***Recommendation No. 10:*** Revise the explanation of the in vivo mammalian bioassay
10 evaluation, indicating that the "study design is consistent with standard toxicological
11 practices" because it is too vague. If possible, provide a reference in which these practices
12 are described.

13   ***Response:*** EPA has revised the explanation of this criterion to be clear that it excludes
14   only those studies that use genetically-altered species.

15 ***Recommendation No. 11:*** Consider eliminating the use of the phrase "outside the range of
16 normal variability."

17   ***Response:*** EPA has removed this phrase from the criteria.

18 ***Recommendation No. 12:*** Provide a definition when the term "common practice" is used,
19 and if possible, cite appropriate Agency documents.

20   ***Response:*** EPA has removed the phrase "common practice" from the Reanalysis report
21   and referenced the relevant Agency guidance documents where appropriate. In addition,
22   the Agency guidance used has been highlighted in a text box in Section 2.

23 ***Recommendation No. 13:*** Provide more discussion of data set limitations relevant to study
24 inclusion/exclusion criteria.

25   ***Response:*** The epidemiology study summaries (Appendix C) have been edited with
26   respect to study evaluation, meeting the study inclusion criteria and considerations, and
27   suitability for dose-response modeling; Tables C-2 and C-3 summarize the studies,
28   identifying which criteria and considerations were met.

29 ***Recommendation No. 14:*** Better justify and explain considerations relating to selection of
30 epidemiology studies.

31   ***Response:*** The descriptions for study quality considerations and study inclusion criteria
32   have been edited for clarity. Details of the implementation of these specific
33   considerations and criteria in the study summaries and tables presented in Appendix C
34   have also been edited.

1 ***Recommendation No. 15:*** Specifically, for Consideration #2 on Page 2-6 of the report, the
2 Panel recommends the following revisions: Define and clarify the term "susceptible to
3 important biases." It is nonspecific, and the biases should be explained.

4 ***Response:*** EPA has added clarifying language to Consideration #2 in Section 2 of the
5 Reanalysis. The examination of biases included assessing the likelihood of selection
6 bias, information bias, and confounding for the individual studies. EPA has also included
7 text in the individual study summaries in Appendix C to specify possible sources of bias,
8 and to determine the potential impact of these biases on individual study results.

9 ***Recommendation No. 16:*** Clarify what is meant by "control for potential confounding
10 exposures." Does this refer to only dioxin-like exposures?

11 ***Response:*** EPA has added clarifying language to Consideration #2 to address this
12 comment, which now reads "control for or account for confounding factors." EPA has
13 also provided explanations of specific confounding factors that were identified in the
14 individual study summaries and tables in Appendix C. Assessment of the potential for
15 confounding, therefore, was not limited to dioxin-like chemicals and is specified for each
16 study summary and summary tables as appropriate.

17 ***Recommendation No. 17:*** Clarify the phrase "bias arising from study design." Does it
18 refer to selection bias, or is it used more broadly to describe how exposure and outcome are
19 measured and covariate data collected?

20 ***Response:*** EPA has clarified Consideration #2 to address this comment; the current
21 phrase "bias arising from limitations of study design" was referring to selection bias.
22 EPA has also listed the main potential sources of bias (e.g., selection bias, information
23 bias, and confounding) earlier in Consideration #2 to help clarify this.

24 ***Recommendation No. 18:*** Define "bias arising from statistical analyses." Might this refer
25 to model misspecification?

26 ***Response:*** EPA has added clarifying language to Consideration #2 to address this
27 comment; the phrase "bias arising from statistical analyses" has been reworded to read
28 "bias (e.g., selection or information bias) arising from limitations of the study design,
29 data collection, or statistical analysis." This would include model misspecification, such
30 as adjustment for the incorrect functional form of certain confounders in multivariate
31 regression modeling.

32 ***Recommendation No. 19:*** For Consideration #3 on Page 2-7 of the report, the Panel
33 recommends the following revisions: Provide more discussion and clarity on the exclusion
34 of null epidemiologic studies.

35 ***Response:*** EPA has added clarifying text under Consideration #3 to address this issue.
36 Theoretically, a NOAEL can be identified from a null study (i.e., a study reporting a
37 TCDD exposure, but no response) and used to derive an RfD. However, a "free-standing
38 NOAEL" from a study in which no adverse effects have been observed is not usually
39 chosen for RfD derivation when other available studies demonstrate LOAELs. EPA has

1 determined that the large and comprehensive database available to assess quantitative
2 TCDD dose response provides many studies that are considered stronger candidates for
3 derivation of an RfD than freestanding NOAEL studies. In Section 4 of the document,
4 null and negative studies are also considered by EPA to discuss the biological
5 significance of the critical endpoint(s) used as the basis for deriving the TCDD RfD.

6 ***Recommendation No. 20:*** In Exclusion Criterion #3 on Page 2-7, define "reported dose."

7   ***Response:*** EPA has deleted the sentence under Criterion #3 that contained this phrase as
8   it did not enhance understanding of the criterion.

9 ***Recommendation No. 21:*** Clarify the discussion in Section 2 of the consideration of
10 confounding and other potential sources of bias. Specifically, the Panel noted that the
11 differences between males and females with regard to TCDD half-life are discussed, but the
12 description of the number of males and females in each study population were often
13 missing or very difficult to determine. Also, in the occupational cohort studies, the
14 possibility of men and women performing different job tasks also increased the possibility
15 that the men and women were exposed at different levels. However, when the job
16 categories with assigned TCDD exposure levels were presented, there was often no
17 discussion of the numbers by gender in the categories. For example, the Manz et al. study
18 ([1991](#)) of the Hamburg cohort (1,583 men and 399 women) does not describe the TCDD
19 categories by gender. In addition, the validity of the TCDD exposure levels assigned to the
20 categories was examined "in a group of 48 workers who provided adipose tissue samples"
21 (page 2-41, lines 18−19). How were these workers selected? How many were approached
22 but refused to provide a sample? Assessment of selection bias in this and other similar
23 circumstances was lacking in some of the studies. This is particularly notable in the lack of
24 overall response rates reported for several of these studies. Inclusion of these factors in the
25 study review would be very helpful.

26   ***Response:*** EPA has revised the summaries of the epidemiological studies in Appendix C
27   to include clarifying text, response rates, and potential sources of bias where reported in
28   the studies.

29 ***Recommendation No. 22:*** Clarify the discussion of the consideration that "statistical
30 precision, power, and study follow-up are sufficient." These metrics can be difficult to
31 determine with the smaller sample size populations, but there are studies that can be very
32 useful even given the small samples.

33   ***Response:*** EPA has revised Consideration #5 and added clarifying text to address this
34   issue. As stated in the consideration, EPA attempted to assess the possibility of not
35   detecting an association that might be present due to limited statistical power of smaller
36   studies. In addition, EPA examined all reported effect estimates in each study
37   irrespective of statistical significance.

38 **A.2.2. Summary of Public Comments and EPA Responses**

39 ***Comment:*** Three commenters were concerned that the study inclusion criteria favored studies
40 showing positive associations between TCDD and health endpoints and that this would preclude

1   a weight-of-evidence analysis. The commenters were further concerned that the study inclusion
2   criteria in the draft Reanalysis were inconsistent with EPA's Information Quality Guidelines
3   (2002), Assessment Factors Handbook (2003), Risk Assessment Principles and Practices
4   documentation (2004), and the recommendations of the NAS committee that reviewed the 2003
5   Reassessment (NAS, 2006).

6   *Response:* The study inclusion criteria apply only to the selection of data sets for dose-
7   response modeling for the purpose of defining potential PODs and not to the elimination
8   of studies from any further consideration. The focus of this process is on first identifying
9   exposure levels associated with adverse effects, then determining an exposure level at
10   which those effects do not occur. The process does not eliminate "negative" studies for
11   other purposes, such as supporting the cancer weight-of-evidence determination or
12   assessing confidence in the endpoint(s) chosen for the POD for derivation of the RfD.
13   EPA considered all studies, negative and positive, in the qualitative assessment of the
14   RfD in Section 4 of the Reanalysis.   The study inclusion criteria are consistent with EPA
15   RfD and cancer assessment guidelines. The study selection process in this context is also
16   consistent with the NAS committee recommendation that EPA justify the selection of
17   studies for dose-response modeling. .

18   *Comment:* One commenter asked EPA to consider recent publications addressing dioxin
19   toxicology in their selection of an overall data set. They provided the following list of
20   seven publications:

21   Budinsky, R.A., J.C. Rowlands, S. Casteel et al. (2008). A pilot study of oral
22   bioavailability of dioxins and furans from contaminated soils: Impact of
23   differential hepatic enzyme activity and species differences. Chemosphere
24   70:1774–86.

25   Budinsky, R.A., C.R. Kirman, L.J. Yost, B.F. Baker, L.L. Aylward, J.M. Zabik, J.C.
26   Rowlands, T.F. Long, and T. Simon. (2009). Derivation of Soil Cleanup Levels
27   for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Toxic Equivalence (TEQD/F) in
28   Soil Through Deterministic and Probabilistic Risk Assessment of Exposure and
29   Toxicity. Presentation at Society of Toxicology Annual Meeting. March.

30   Charnley, G. and R.D. Kimbrough. (2006). Overview of exposure, toxicity and risks to
31   children from current levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin and related
32   compounds in the USA. 2005. Food and Chemical Toxicology 44:601–615.

33   Garabrant D.H., A. Franzblau, J. Lepkowski, B.W. Gillespie, P. Adriaens, A. Demond, E.
34   Hedgeman, K. Knutson, L. Zwica, K. Olson, T. Towey, Q. Chen, B. Hong, C-W.
35   Chang, S-Y. Lee, B. Ward, K. LaDronka, W. Luksemburg, and M. Maier. (2009).
36   The University of Michigan Dioxin Exposure Study: Predictors of human serum
37   dioxin concentrations in Midland and Saginaw, Michigan.

38   Hays, S.M. and L.L. Aylward. (2003). Dioxin risks in perspective: past, present, and
39   future. Regulatory Toxicology and Pharmacology 37:202–217.

40   Kimbrough R.D., C.A. Krouskas, M. Leigh Carson, T.F. Long, C. Bevan, and R.G.
41   Tardiff.(2009). Human uptake of persistent chemicals from contaminated soil:
42   PCDD/Fs and PCBs. Regulatory Toxicology and Pharmacology 2009 Dec 24;

1   [Epub ahead of print], Center for Health Risk Evaluation P.O. Box 15452

2   Washington, DC 20003, United States.

3   LaKind, J.S., S.M. Hays, L.L. Aylward, and D.Q. Naiman. (2009). Perspective on serum

4   dioxin levels in the United States: an evaluation of the NHANES data. Journal of

5   Exposure Science and Environmental Epidemiology 19:435-441.

6   *Response:* EPA has reviewed these studies and considered their applicability in

7   informing the hazard identification dose response following TCDD exposure. None of

8   these studies provide in vivo mammalian dose-response study results that would be useful

9   in quantitative dose-response analysis for derivation of an RfD or oral slope factor for

10   TCDD, nor do they inform the hazard identification. Therefore, none of these studies

11   qualifies as an appropriate study type in EPA's study selection process for quantitative

12   TCDD dose-response assessment.

13 *Comment:* One commenter felt that the development of the proposed RfD was not transparent

14 because it did not rely on toxicological assessment work completed since the

15 2003 Reassessment. Additionally, the commenter requested additional clarity and transparency

16 in the rationale for the Agency's selection of key data and more explanation of why EPA did not

17 pursue benchmark dose modeling for the two human data sets used to derive the RfD.

18   *Response:* EPA collected and evaluated studies through October 2009, including studies

19   from the 2003 Reassessment and newer studies found via literature searches and through

20   public submissions. In addition, EPA has included evaluations of several studies

21   published in 2010 and 2011. The RfD is based on two studies published in 2008.

22   EPA has, however, provided additional clarity on the study inclusion criteria with

23   revisions to the Reanalysis based on SAB and public comments.

24   EPA relied on the study authors' modeling of the epidemiologic study data, which

25   included the important covariates affecting the relationship between health outcome and

26   TCDD exposure. EPA's benchmark dose modeling software does not allow for

27   modeling of covariates.

28

29 **A.3. THE USE OF TOXICOKINETICS IN DOSE-RESPONSE MODELING FOR**

30   **CANCER AND NONCANCER ENDPOINTS**

31 **A.3.1. SAB Comments and EPA Responses**

32 **SAB Charge Question 3.1**

33 *The 2003 Reassessment utilized first-order body burden as the dose metric. In the draft*

34 *Response to Comments document, EPA used a physiologically based pharmacokinetic (PBPK)*

35 *model (Emond et al., 2006; 2005; 2004) with whole blood concentration as the dose metric*

36 *rather than first-order body burden. This PBPK model was chosen, in part, because it includes*

37 *a biological description of the dose-dependent elimination rate of TCDD. EPA made specific*

38 *modifications to the published model based on more recent data. Although lipid-adjusted serum*

39 *concentrations (LASC) for TCDD are commonly used as a dose metric in the literature, EPA*

40 *chose whole blood TCDD concentrations as the relevant dose metric because serum and serum*

41 *lipid are not true compartments in the Emond PBPK models (LASC is a side calculation*

42 *proportional to blood concentration). Reviewers were asked to comment on Questions 3.1.a–d.*

1   **SAB Charge Question 3.1.a**

2   *The justification of applying a PBPK model with whole blood TCDD concentration as a*
3   *surrogate for tissue TCDD exposure in lieu of using first-order body burden for the*
4   *dose-response assessment of TCDD.*

5   ***Comment:*** The use of whole blood concentration is a better choice than body burden, as was
6   used in the 2003 Reassessment, because it is more closely related to the biologically relevant
7   dose metric. However, the rationale for the use of blood concentration rather than lipid adjusted
8   serum concentration (LASC) should not be based on the Emond model structure. The question
9   that should be addressed is only whether blood concentrations or LASCs provide better
10   surrogates for cross-species and cross-study comparisons of free dioxin concentration in the
11   target tissues. LASC is the preferred measure for reporting dioxin biomonitoring data and is the
12   measurement reported in most of the human epidemiological studies. A metric that considers
13   blood lipid content is also more likely to reflect free dioxin concentration in the plasma and,
14   hence, free concentration in the target tissue. The EPA pointed out that the LASC was related to
15   the blood concentration by a scalar; however, EPA incorrectly concluded that the metrics are
16   equivalent and later discussed the fact that the relationship between them was subject to
17   inter-individual and inter-species variation. If the LASC were used to drive the distribution of
18   TCDD to tissues, the pharmacokinetic outcome would be different from using blood as the driver
19   because the tissue:blood ratio would differ. If the blood fat:blood and tissue:blood values were
20   accounted for in the model, the use of blood and LASC would be similar. It is not clear at this
21   point how this issue was addressed in the dose metric calculations. Consideration of this issue is
22   unlikely to drastically affect the outcome of the risk calculations, but it would be important for a
23   quantitative uncertainty analysis.

24   ***Recommendation No. 23:*** The use of the blood metric is acceptable for the PBPK model.
25   Clarify how the model deals with studies that report the concentration of dioxin in plasma,
26   serum, blood, or blood fat:blood measurements.

1 *Response:* EPA has clarified that the TCDD LASC values reported in the epidemiology studies
2 were used directly to estimate equivalent human intakes from the Emond PBPK model. EPA
3 also clarified that, for interspecies extrapolation, whole-blood concentrations were used because
4 distribution of TCDD to the liver and subsequent processing for dose-dependent elimination in
5 the liver in this model is dependent on whole-blood concentrations, not LASC. In both the
6 Emond rodent and human models, LASC values are calculated post-processing by application of
7 scalars representing the proportion of plasma and fat in the whole-blood compartment. That is,
8 translating results from the rodent model to the human model requires an estimate of the TCDD
9 concentration in the whole-blood compartment whether starting from whole-blood
10 concentrations or LASC. This approach assumes that differences in serum and serum lipid
11 fractions between rodents and humans do not result in large differences among the species in the
12 transfer of TCDD from blood to liver.

13 **SAB Charge Question 3.1.b**

14 *The scientific justification for using the Emond et al. model as opposed to other available TCDD*
15 *kinetic models.*

16 *Comment:* The Emond model provided the best available basis for the dose metric calculations
17 in the assessment; however, additional discussion of other published models and quantitative
18 evaluation of the impact of model selection on dose metric predictions should also be provided.

19 *Recommendation No. 24:* Discuss how the model was intended to be used in the
20 assessment, which would then dictate why a particular model was selected. That is, for the
21 intended purposes, was the Emond model more robust and/or simpler than other models,
22 and did it contain sufficient details for biological determinants deemed important by the
23 Agency?

24 *Response:* EPA has clarified that the Emond PBPK model was used to (1) estimate oral
25 intakes corresponding to measured LASC TCDD concentrations in human subjects and
26 (2) estimate animal blood concentrations based on measured doses in bioassays as the
27 appropriate dose metric for modeling equivalent human intakes. EPA has also clarified
28 that the Emond model was selected because of its technical sophistication for simulating
29 physiological processes associated with TCDD and because the model covered all of the
30 relevant life stages (particularly gestational and childhood exposures), which the
31 alternative model (CADM) did not. Other models were not presented because they did
32 not account for dose-dependent elimination processes, which EPA established as an *a*
33 *priori* criterion for model selection.

34 **SAB Charge Question 3.1.c**

35 *The modifications implemented by EPA to the published Emond et al. model.*

36 *Comment:* The model changes are minor, scientifically appropriate, and well supported.

37 *Response:* No response necessary.

SAB Charge Question 3.1.d

Whether EPA adequately characterized the uncertainty in the kinetic models.

Comment: The Report presents a reasonably thorough qualitative characterization of the uncertainty in the kinetic models that is sufficient to support their use in the assessment; however, a more quantitative uncertainty analysis is needed. It is critical to demonstrate the dependence of human equivalent dose (HED) and risk predictions on uncertainty and variability in the model parameters. Dose metric uncertainty needs to be determined under the same exposure conditions that dose metrics are calculated—both for the various studies that serve as the basis for the dose-response assessments and for human exposures at the corresponding HEDs and risk-specific doses.

The Hill coefficients for CYP1a1 and CYP1a2 induction used in the Emond model were 1.0 and 0.6, respectively, based on fitting of kinetic data from single doses of dioxin (Santostefano et al., 1998; Wang et al., 1997). However, Walker et al. (1999) subsequently estimated a Hill coefficient of 0.94 for both CYP1a1 and CYP1a2 induction using chronic exposures, which were more relevant to the use of the Emond model in the dioxin risk assessment. The value of 0.6 used in the Emond model was well outside the confidence interval of 0.78 to 1.14 reported by Walker et al. (1999). The use of a Hill coefficient value well below unity would lead to a nonlinear model behavior that is biologically implausible (hypersensitivity to induction at doses near zero). As a result, when the human model was used for extrapolation to lower doses (as in the calculation of risk-specific doses), the model would tend to estimate a lower exposure level for a given blood concentration. This effect could be seen in Table ES-1 of the Report, where a 5 order-of-magnitude change in risk was associated with a 6 order-of-magnitude change in risk-specific dose. That is, the model-estimated risk-specific doses in the vicinity of 10^{-6} risk were about a factor of 10 lower (more conservative) than linear extrapolation. The evidence for this parameter needs to be carefully reviewed and the reasonable range of values determined. At the least, the Emond human model calculations will need to be repeated with multiple values to characterize the resulting uncertainty in the estimates.

When this is done, the Agency should also consider increasing the fat:blood partition in the human model from 100 to 200 to be more consistent with the human data (Maruyama et al., 2002; Iida et al., 1999; Patterson et al., 1989; Schecter and Ryan, 1989; Schecter et al., 1989). The Hill coefficient is not likely to have as significant an effect on calculations with the animal models, because low-dose extrapolation was not performed in the animals, but this should also be verified by sensitivity/uncertainty analysis of the animal models. Public comments were submitted to the Panel, recommending consideration of a Hill coefficient value of 1.0 and pointing out why lower values are inappropriate (comments from Drs. Thomas Starr, July 7, 2010 and October 26, 2010 and Melvin E. Andersen, November 4, 2010).

Recommendation No. 25: Undertake additional efforts to fully characterize the uncertainty in the model, with special consideration of the Hill coefficient value.

Response: In response to this comment, EPA has conducted a sensitivity analysis by varying each parameter in the model individually to determine the effect on the average whole-blood concentrations (as the dose metric used for species extrapolations and reference dose calculations). In addition, the effect of varying the Hill parameter on the model fits to literature data was explored. In response to this comment, two sections

were added to Section 3. Section 3.3.4.2.3.5 describes the results of the sensitivity analysis preformed on the PBPK models as suggested by the reviewers, and Section 3.3.4.2.3.6 documents the impact of changing the Hill coefficient on PBPK model simulations of dioxin blood levels in humans. Included in this section is a sensitivity analysis using alternative CYP1A2 induction parameters determined from data presented in Budinsky et al. (2010). The Walker et al. (1999) CYP1A1 and CYP1A2 induction analysis, in which a value of 0.94 was found for the Hill coefficient, uses a different model structure formulation than the one in the Emond model, in which the parameters have different interpretations, such that the Hill coefficient values represent different processes and are not strictly comparable.

In regards to the recommendation that the fat:blood partition coefficient (PC_{FB}) should be increased to 200, the PC_{FB} of 100 in the Emond model is a fitted value in the original rat model (Wang et al., 1997), in which other parameters (including the value of 0.6 for the Hill coefficient; most sensitive parameter in the model) were also fitted simultaneously against animal and human data. EPA evaluated the literature cited by the SAB and has concluded that a PC_{FB} of 160 is more representative of the data presented in those papers. A value of 158 is directly estimated by Patterson et al. (1989) based on 30 individuals from Times Beach, MO. Iida et al. (1999) measured levels of 2,3,7,8-TCDD in blood and adipose tissue from eight human subjects, who varied in age (19 to 82 years) and gender (four females and four males). Using the individual measurements presented in Iida et al. (1999) and assuming relative lipid contents of 0.85 and 0.0057 in adipose tissue and blood, respectively, EPA estimated a mean and median PC_{FB} of 166 and 161, respectively. A value of 247 reported by Maruyama et al. (2002) was based on the data from Iida et al. (1999) and may have been calculated as the average of the pooled fat concentrations divided by the pooled blood concentrations instead of from the distribution of individual fat:blood ratios. Schecter and Ryan (1989) present data on a single individual who was also exposed to high levels of DLCs and PCBs in an acute event (transformer explosion). Several serum and fat measurements were taken over the next 5 years, during which the patient lost 30 pounds and took medicine to reduce serum lipids. The combination of all of these factors suggest that the internal concentrations may not have equilibrated in this time frame and introduce too much uncertainty for use of these data in estimating a PC_{FB} for TCDD. Schecter et al. (1989) report fat TCDD concentrations but not blood or serum concentrations. EPA then evaluated the impact of replacing the PC_{FB} of 100 in the Emond human PBPK model with 160 on modeled human intakes corresponding to a range of lifetime average TCDD serum concentrations in the range of interest for the RfD. The result was that the alternative value of 160 increased the intakes by less than 10% in the range of the adjusted LOAEL POD (0.02 ng/kg-day) for the RfD and only slightly more for intakes 100-fold lower. Based on this analysis, there is not sufficient justification to change the parameter value in the model at this time.

SAB Charge Question 3.2

Several of the critical studies for both noncancer and cancer dose-response assessment were conducted in mice. A mouse PBPK model was developed from an existing rat model in order to estimate TCDD concentrations in mouse tissues, including whole blood. Reviewers were asked to comment on Questions A.3.2.a–c.

1   **SAB Charge Question 3.2.a**

2   *The scientific rationale for the development of EPA's mouse model based on the published rat*
3   *model (Emond et al., 2006; 2005; 2004).*

4   *Comment*: The Panel agrees that an appropriate approach was used to develop the mouse model
5   on the basis of the published rat model and the available mouse kinetic data. It should be noted
6   that the NAS recommendation to use human data for dose metric could be accomplished because
7   dose-dependent elimination of TCDD has been described in humans, albeit in just a few cases.
8   Dose-dependent elimination has been reported repeatedly in animals, and the PBPK model
9   reflected this dose-dependence. Using CYP1A2 data from humans (caffeine metabolism) and
10 mice would offer an opportunity to validate and/or adjust the mouse model.

11   *Recommendation No. 26:* Conduct an external peer review of the mouse model because it
12   has not been published in the peer-reviewed literature.

13   *Response:* EPA has recommended that the authors submit their work for publication in
14   the peer-reviewed literature. Although EPA used revised estimates for some of the
15   published parameters, no modifications were made to the structure of the Emond model.
16   Using these revised parameters, EPA has described the evaluation of the PBPK model in
17   Section 3. An important point is that the mouse data were not used directly in estimation
18   of reference values.

19 **SAB Charge Question 3.2.b**

20 *The performance of the mouse model in reference to the available data.*

21 *Comment*: The Panel found that the mouse model performed reasonably well, apart from
22 under-prediction of urinary excretion data. The urinary excretion data can be improved by
23 taking into account the fact that urine contains metabolites only, which partition differently from
24 the parent compound. The model appeared to be adequate for use in estimating dose metrics for
25 the assessment, but with greater uncertainty than the rat and human models. This was considered
26 a reasonable approach to solve a deficiency in published PBPK models to meet the needs of this
27 assessment.
28   The Panel noted, however, that the EPA's suggestion in the RfD chapter that the
29 clustering of mouse points of departure (PODs) at the lowest doses was due to mouse model
30 failure, was inappropriate, and should be rewritten.

31   *Recommendation No. 27:* Use the mouse model and try to get the model published in the
32   peer-reviewed literature to enhance scientific credibility.

33   *Response:* EPA has revised the text describing the mouse PODs to eliminate the
34   impression that the result was due to failure of the mouse PBPK model, which was not
35   intended. See the response above (Recommendation 26) regarding the comment on the
36   publication of the mouse model.

37 **SAB Charge Question 3.2.c**

1 *Whether EPA adequately characterized the uncertainty in the mouse and rat kinetic models.*
2 *Please comment specifically on the scientific justification of the kinetic extrapolation factor from*
3 *rodents to humans.*

4 **Comment***:* EPA provided an adequate characterization of the qualitative uncertainty in the
5 mouse and rat kinetic models sufficient to justify their use, together with the human model, to
6 estimate rodent-to-human extrapolation factors. On the other hand, formal recalibration of the
7 PBPK model parameters using a Hierarchical Bayesian approach such as Markov chain Monte
8 Carlo analysis was not considered necessary or particularly useful. However, a more
9 quantitative uncertainty analysis is needed.

10 **Recommendation No. 28:** Perform a more quantitative uncertainty analysis using methods
11 suggested in response to Charge Question 6.2.[1]

12 **Response:** In response to this recommendation and other comments, EPA has conducted
13 a sensitivity analysis and added it to Section 3 (see response to Recommendation 25)
14 EPA has undertaken additional quantitative sensitivity analyses for the kinetic modeling
15 relevant to the RfD (see Section 4.5; see also responses to Recommendations 29 and 32).

16 **SAB Charge Question 3.3**

17 *Please comment on the use of the Emond et al. PBPK model to estimate human intakes based on*
18 *internal exposure measures.*

19 **Comment***:* The modified Emond model is the best available approach for estimating exposures
20 on the basis of internal exposure measurements. Nevertheless, there is considerable uncertainty
21 associated with attempting to reconstruct prior exposures in a human population (e.g., Seveso).

22 **Recommendation No. 29:** Describe the modeling of the Cheng et al. (2006), Mocarelli
23 et al. (2008), and Baccarelli et al. (2008) studies in more detail, and quantitatively evaluate
24 the impact of model parameter uncertainty and exposure uncertainty in these studies.

25 **Response:** EPA has revised the document to describe the modeling of Mocarelli et al.
26 (2008) and Baccarelli et al. (2008) in more detail. Sensitivity analyses pertaining to the
27 choice of model inputs have been performed for Mocarelli et al. (2008) and Baccarelli
28 et al. (2008) and are described in Section 4.5 of the document. Cheng et al. (2006) is a
29 cancer-modeling study and will be addressed in Volume 2 of this report.

30 **SAB Charge Question 3.4**

31 *Please comment on the sensitivity analysis of the kinetic modeling (see Section 3.3.5).*

32 **Comment***:* The Report only presented the sensitivity analysis published by Emond et al. (2006),
33 which was not entirely adequate for the purposes of this assessment. The analysis left out the

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[1] SAB comments on Sections 5 and 6 are not addressed in Volume 1 of the Reanalysis, but can be viewed at the
following URL:
http://yosemite.epa.gov/sab/sabproduct.nsf/WebReportsLastMonthBOARD/2A45B492EBAA8553852578F9003EC
BC5/$File/EPA-SAB-11-014-unsigned.pdf.

1　Hill coefficient, which was one of the most important parameters in the model for low-dose
2　extrapolation (Evans and Andersen, 2000). Moreover, model sensitivities were species, dose,
3　and dose-scenario dependent, so they need to be determined under the same exposure conditions
4　as those for which dose metrics were calculated: both for the various studies that serve as the
5　basis for the dose-response assessments and for human exposures at the corresponding HEDs
6　and risk-specific doses. This represents the most pragmatic path forward for an evaluation of
7　model sensitivity as it relates to potential environmental regulation.

8　　**Recommendation No. 30:** Provide a sensitivity analysis of the model to authenticate the
9　　model for its intended purpose.

10　　　**Response:** EPA has conducted a sensitivity analysis (see response to
11　　　Recommendation 25).

12　**SAB Charge Question 3.5**

13　*Both EPA's noncancer and cancer dose-response assessments are based on a lifetime average*
14　*daily dose. Did EPA appropriately estimate lifetime average daily dose? If not, please suggest*
15　*alternative approaches that could be readily developed based on existing data.*

16　*Comment:* The Panel agrees with the average daily dose calculation approaches, but it was not
17　clear to some Panel members how the computational estimates of internal dose for newborns
18　were carried out because a lactation model was not used. This is important because of the use of
19　TSH (thyroid stimulating hormone) in newborns as a critical effect.

20　　**Recommendation No. 31:** Explain how the early life-stage internal doses are calculated.

21　　　**Response:** EPA has clarified that the PBPK model accounts for physiological changes
22　　　including body weight and tissue volumes over different life stages, including during
23　　　gestation. The only life stage that is not accounted for is lactational exposure, but EPA
24　　　found no models pertaining to this life stage. The details of how the model estimates
25　　　tissue and blood levels of TCDD during these exposures are described in Section 3 and
26　　　by Emond et al. (2006). Internal neonatal exposures were not estimated directly because
27　　　the PODs for neonatal effects are necessarily based on maternal exposures.

28　**A.3.2. Summary of Public Comments and EPA Responses**

29　*Comment:* One commenter noted that CADM (i.e., Concentration- and Age-Dependent
30　Elimination Model) should be given more consideration as a credible alternative to the Emond
31　et al. model. When CADM and the Emond et al. model have been evaluated on the same human
32　data sets, CADM appears to provide substantially better results, and the Emond et al. model
33　appears to markedly overpredict the early serum concentration levels. Another commenter noted
34　that CADM allows estimation of the relevant risk-specific doses using the PBPK model but is
35　applied in the exposure range relevant to real-world exposures, reproduces the elimination
36　behavior of TCDD relevant to risk assessment and risk management, and takes into account
37　background body burdens of TCDD and non-TCDD contributors to TEQ and their impact on
38　TCDD elimination behavior.

1   ***Response:*** EPA used the Emond model for human toxicokinetics because the model
2   covered all of the relevant life stages (particularly gestational and childhood exposures),
3   which CADM does not, and also because of its technical sophistication for simulating
4   physiological processes associated with TCDD toxicokinetics. The Emond model also is
5   able to account for background TCDD and DLC body burdens and their impact on TCDD
6   elimination behavior; pertinent simulations and discussions on these aspects have been
7   added in the new Section 4.5. For animal bioassays, EPA undertook, and reported in the
8   document, modeling analyses that compared the predicted values from both the Emond
9   PBPK model and CADM for all administered doses. Throughout the document, separate
10   simulations for both the PBPK model and CADM were conducted for comparison to
11   experimental or literature data for animals. In Section 3, EPA presents extensive
12   comparisons of the Emond model and CADM. In Appendix E, EPA also presents whole
13   blood, fat, and liver TCDD concentrations and body burdens that were predicted by both
14   the Emond model and CADM for each key animal bioassay.

15 ***Comment:*** One commenter noted that the Hill function dependence of CYP1A2 induction on
16 AhR-bound TCDD has a nonphysical, nonsensically infinite slope at zero dose, due to the fact
17 that its exponent parameter has a numerical value smaller than 1, namely 0.6. This phenomenon
18 has no predictive value at low doses. According to the commenter, the values that are predicted
19 at low doses are simply artifactually constrained by the supralinear shape of the Hill function,
20 which is imposed by the data at far higher doses. Because no data occur in the low-dose region
21 that is well below the EC50, no counterbalancing force exists that would keep the Hill exponent
22 value at or greater than 1. This leads to artifactual and arbitrarily large increases in the oral slope
23 as the TCDD intake approaches zero.

24   ***Response:*** EPA has conducted a sensitivity analysis for the Hill coefficient (see response
25   to Recommendation 25) and has evaluated the impact of eliminating the supralinear
26   behavior on relative human intakes. Changing the Hill coefficient to 1, which results in
27   linear low-dose behavior, and optimizing to several human data sets results in somewhat
28   lower oral intakes for a range of TCDD serum concentrations in the range of interest (i.e.,
29   near the RfD and LOAEL POD). This result is well within the range of other
30   uncertainties evaluated by EPA (see Section 4.5). EPA has concluded that, given the
31   uncertainties in the value of this parameter and interdependent parameters in the model,
32   and the lack of a substantial impact on predicted intakes in the range of the POD for the
33   RfD, there is no compelling reason to change the value of the Hill coefficient or related
34   parameters. In response to this comment, two sections were added to Section 3.
35   Section 3.3.4.2.3.5 describes the results of the sensitivity analysis performed on the
36   PBPK models as suggested by the reviewers, and Section 3.3.4.2.3.6 illustrates the
37   impact of changing the Hill coefficient on PBPK model simulations of dioxin blood
38   levels using available human data.

39 ***Comment:*** Two commenters noted that EPA incorrectly assumed a partition factor of 100 for
40 TCDD in human fat compared to blood. The commenters state that available human data
41 demonstrate that the actual partition factor is between 150 and 200 (Iida et al., 1999; Patterson et
42 al., 1989).

1   ***Response:*** While EPA has not changed the value in the model, a sensitivity analysis was
2   conducted that indicated this is not a sensitive parameter in the model (see response to
3   Recommendation 25).

4   ***Comment:*** Some commenters felt that use of modeled concentrations is not acceptable for
5   deriving toxicity values when measured data are available. The commenters noted that EPA's
6   use of modeled whole-blood concentration results in underestimation of PODs, HEDs at the
7   BMDLs, and calculated reference dose.

8   ***Response:*** EPA modeled the blood concentrations for the rat exposures in NTP (2006),
9   when actual liver and fat TCDD concentrations were reported in the study. This was
10   done primarily for consistency across all rat bioassays. The whole liver concentrations
11   are not likely to be relevant because they include TCDD bound to CYP1A2, which is not
12   part of the biologically-active TCDD fraction. However, in response to this comment,
13   EPA has added a sensitivity analysis to Section 4.5 that evaluates the effect of using the
14   measured fat TCDD concentrations on modeled human intakes based on (NTP, 2006).

15   ***Comment:*** Several commenters noted that the Emond et al. (2005) PBPK model did not account
16   for the enhanced elimination rate of TCDD observed in infants and children, which would
17   substantially underestimate the daily dose rates associated with identified target body burdens,
18   and, thus, underestimate the derived RfD estimated in modeling for the Mocarelli et al. (2008)
19   data set. Commenters provided references of Clewell et al. (2004), Ott et al. (1987), Hochstein
20   et al. (2001), Kerger et al. (2006), Leung et al. (2006), and Milbrath et al. (2009) and suggested
21   that EPA address the role of differential elimination rates in children in their quantitative analysis
22   of a reference dose.

23   ***Response:*** The changes in elimination rate with age reported in Kerger et al. (2006) are
24   thought to reflect growth processes as a child ages. The Emond PBPK model accounts
25   for this phenomenon implicitly by modeling growth and age-related changes in fat
26   content and physiology explicitly. Including an explicit variable-elimination term in the
27   model would then "double count" for this effect. The TCDD half-life calculations in
28   Kerger et al. (2006) are based on blood level rather than whole-body measurements.
29   Blood levels of the chemical are influenced by the dynamic processes of storage in fat
30   deposits and elimination rates (including binding to proteins in the liver). The inclusion
31   of these physiological process and the dynamic interplay among them provide the
32   biological basis for an observed increase in elimination rate in children. At early life
33   stages, less fat volume in the body results in more TCDD available for deposit in liver.
34   More TCDD in the liver results in a higher elimination rate. Leung et al. (2006) indicated
35   that the more rapid clearance in children was due to their lower fat content, which is
36   accounted for in the model.

37   ***Comment:*** A commenter noted that non-TCDD TEQ contributes to the induction of CYP1A2,
38   which will influence the elimination rate for TCDD. Given the current background body
39   concentrations of TCDD and other TEQ contributors, the commenter felt that the appropriate
40   application of the PBPK model would be to start from current background concentrations
41   (including some accounting for non-TCDD TEQ).

1 ***Response:*** Induced levels of CYP1A2 due to dioxin are calculated using a Hill function.
2 The relative difference between induced levels of CYP1A2 and basal levels of the
3 enzyme are then used to describe the dose–dependent elimination rate for TCDD in the
4 liver. Application of the PBPK model to estimate the elimination of TCDD is based on
5 an assumption that background effects of dioxin-like chemicals and any others that may
6 influence CYP1A2 levels in the liver are implicitly included in the basal-level estimates.
7 EPA also added a simulation of total TEQ background exposure as a sensitivity analysis
8 in Section 4.5 to investigate this phenomenon and concluded that the influence of
9 background non-TCDD TEQ is small for exposures near the POD for the RfD.

10 ***Comment:*** Several commenters noted deficiencies and limitations with the PBPK model, and
11 some stated that EPA failed to adhere to its own guidance on selection and application of PBPK
12 models (i.e., U.S. EPA (2006a), *Guidelines on PBPK Model Selection in Risk Assessments*
13 report). Specifically, the PBPK model was not peer reviewed and was not validated.
14 Two commenters noted a need for an uncertainty analysis of key parameters in the model, such
15 as the Hill coefficient.

16 ***Response:*** Although EPA used revised estimates for some of the published parameters,
17 no modifications were made to the structure of the Emond model. Using these revised
18 parameters, EPA describes the evaluation of the PBPK model in Section 3. Also, see
19 the response to Recommendation 25 concerning the sensitivity analysis.
20
21 **A.4. REFERENCE DOSE**

22 **A.4.1. SAB Comments and EPA Responses**

23 **SAB Charge Question 4.1**

24 *The Mocarelli et al. (2008) and Baccarelli et al. (2008) studies were selected as co-critical*
25 *studies for the derivation of the RfD. Is the rationale for this selection scientifically justified and*
26 *clearly described? Please identify and provide the rationale for any other studies that should be*
27 *selected, including the rationale for why the study would be considered a superior candidate for*
28 *the derivation of the RfD. In addition, male reproductive effects and changes in neonatal thyroid*
29 *hormone levels, respectively, were selected as the co-critical effects for the RfD. Please*
30 *comment on whether the selection of these critical effects is scientifically justified and clearly*
31 *described. Please identify and provide the rationale for any other endpoints that should be*
32 *selected as the critical effect.*

33 ***Comment:*** The use of the Mocarelli et al. (2008) and Baccarelli et al. (2008) studies was
34 appropriate for identifying "cocritical" effects for the RfD calculation, and the rationale for
35 selecting these two studies over others was clearly described. However, the weaknesses of the
36 two studies were not always clearly delineated. For example, in the Baccarelli (2008) study,
37 there was limited discussion of how the presence of polychlorinated dibenzo-*p*-dioxins (PCDDs),
38 polychlorinated dibenzofurans (PCDFs), and coplanar polychlorinated biphenyls (PCBs) that
39 were also found in the blood might confound the interpretation of TCDD association with
40 elevated TSH levels. In addition, there was no discussion of the potential impact of residential
41 histories (e.g., individuals who may have moved in and out of Zone A after the accident). The
42 Panel believes that more discussion of the strengths and weaknesses of these two studies is
43 needed.

1   The Panel found that in isolation from each other, and lacking a description of supportive
2   animal and epidemiological studies, the studies were less useful for setting the RfD, and
3   emphasizes the need to consider supportive animal and epidemiological studies for dioxin and
4   dioxin-like compounds in order to demonstrate a consistent and integrative signal of toxicity
5   across species and endpoints for TCDD. While Figures 4.3 and 4.4 show quantitative
6   comparisons across RfDs and benchmark dose lower bounds (BMDLs) from animal and
7   epidemiological studies, the figures do not indicate which endpoints are being measured, and
8   consistency in signal is not readily apparent.
9   The Panel noted that although it has been addressed in the Report, the discussion of the
10   known human age-specific variability in endpoints such as sperm counts should be expanded,
11   though the data from Mocarelli et al. (2008) do show ranges and variance (in Figure 3 and
12   Table 2), and neonatal TSH levels.

13   ***Recommendations No. 32:*** Provide a discussion of the strengths and weaknesses of the
14   Mocarelli et al. (2008) and Baccarelli et al. (2008) studies with an indication of whether the
15   weaknesses affect determination of the RfD.

16   ***Response:*** In Appendix C, EPA presents an assessment of both the Baccarelli et al.
17   (2008) and Mocarelli et al. (2008) studies, delineating their strengths and weaknesses.
18   Additionally, in Section 4.5.1, EPA presents a quantitative sensitivity analysis that
19   highlights the uncertainty associated with deriving an RfD from the Baccarelli et al.
20   (2008) and Mocarelli et al. (2008) studies. In this analysis, EPA focused on several
21   important assumptions that were made in defining variables for modeling the exposure
22   history of the cohorts and in estimating a chronic intake leading to the observed effect;
23   the analysis presents the quantitative impact of making alternative assumptions for those
24   variables on the POD estimates. EPA also modeled the potential impact of background
25   DLC exposure on the PODs derived from both of the principal studies. EPA did not
26   discuss the potential impact of residential histories because the PODs from both studies
27   were based entirely on measured serum TCDD concentrations, irrespective of zone of
28   residence. Zonal averages were not used in any way in the derivation of the RfD.

29   With respect to age-specific variability in sperm concentrations as relates to the
30   interpretation of Mocarelli et al. (2008), EPA notes that all the men evaluated in the study
31   were between the ages of 22 and 31 at the time of semen collection and would not expect
32   any substantial age-related differences. EPA does present group sperm concentrations at
33   one standard deviation below the mean as reported by Mocarelli et al. (2008),

34   ***Recommendations No. 33:*** Label the endpoints for studies included in Figures 4.3 and 4.4.

35   ***Response:*** EPA agrees with the SAB Panel's recommendation and has modified
36   Figure 4-4 as suggested. EPA attempted to implement this recommendation in
37   Figure 4-3, but the addition of the endpoint descriptions made the figure too difficult to
38   read. Therefore, rather than modifying the figure, all endpoints used in Figure 4-3 are
39   provided in Table 4-5, along with the study information, and a footnote has been added to
40   the figure to communicate this.

Recommendations No. 34: Discuss the comprehensive database of both animal studies and human epidemiological studies, including studies with dioxin-like compounds (e.g., studies cited in Goodman et al. (2010), together to demonstrate a consistent and integrative signal of toxicity across species and endpoints for TCDD.

Response: EPA methodology does not require that a consistent and integrative signal of toxicity across species and endpoints be demonstrated for derivation of an RfD. In addition, there is no formal weight-of-evidence approach in the EPA RfD methodology. However, concordance of effects, both qualitatively and quantitatively, across endpoints and species is considered, primarily in the assessment of confidence in the RfD. In response to this recommendation and consistent with EPA methodology, EPA has modified the Reanalysis as follows.

     Section 4.3.6 has been revised to provide additional supporting information for the critical effects noted in the two co-principal studies: neonatal thyroid effects from Baccarelli et al. (2008) and sperm effects from Mocarelli et al. (2008).

     In Section 4.3.6.1, EPA has evaluated the Goodman et al. (2010) review and added a discussion of the findings. EPA concluded that, because of relatively low DLC exposures in the studied populations and different timings of measurements in the cited studies, it would be unlikely that any consistent patterns would be detected. EPA confirmed that there were no additional studies identified in this review that meet the selection criteria outlined in Section 2.

     EPA has added an analysis of the qualitative and quantitative concordance of key effects across species and studies in Appendix D and referenced in Section 4.4 as part of the discussion of qualitative uncertainty in the RfD. The analysis includes effects from all of the animal and human studies listed in Table 4-5 in six categories: male reproductive effects, female reproductive effects, developmental effects, immunotoxicity, neurotoxicity, and thyroid toxicity. Coverage of effects was expanded beyond those in Table 4-5 to include effects at doses higher than the LOAEL in each study.

SAB Charge Question 4.2

In the Seveso cohort, the pattern of exposure to TCDD is different from the average daily exposure experienced by the general population. The explosion in Seveso created a high-dose pulse of TCDD followed by low-level background dietary exposure in the exposed population. In the population, this high-dose pulse of TCDD was slowly eliminated from body tissues over time. There is uncertainty regarding the influence of the high-dose pulse exposure on the effects observed later in life.

SAB Charge Question 4.2.a

Mocarelli et al.(2008) reported male reproductive effects observed later in life for boys exposed to the high dose pulse of TCDD between the ages of 1 and 10. EPA identified a 10 year critical exposure window. In the development of the candidate RfD, EPA used an exposure averaging approach that differs from the typical approach utilized for animal bioassays. EPA determined that the relevant exposure should be calculated as the mean of the pulse exposure and the 10-year critical exposure window average. Please comment on the following:

1   **SAB Charge Question 4.2.a.i**

2   *EPA's approach for identifying the exposure window and calculating average exposure for this*
3   *study.*

4   **Comment***:* The Panel discussed extensively extrapolation issues posed by the pattern of exposure
5   from Seveso. Issues raised included the question of whether the same endpoints and/or dose
6   response would be expected from such exposure scenarios with high-dose acute exposures when
7   extrapolating to low-dose chronic exposures.

8   **Recommendation No. 35:** Provide a discussion of published examples in which dioxin
9   studies were conducted using both high-dose acute and low-dose chronic exposures in
10   animals for the same endpoint and how the outcomes compare both qualitatively and
11   quantitatively. Determine whether similar results were observed for similar endpoints.
12   Several chronic dioxin animal studies may be useful in this regard (Sand et al., 2010;
13   Yoshizawa et al., 2010; 2009).

14   **Response:** EPA is aware of only one rodent toxicology study—Kim et al. (2003)—
15   directly comparing health outcomes following the administration of either a high acute
16   TCDD dose or a low longer-term continuous TCDD dose in animals where the long-term
17   average tissue TCDD concentrations in both dose groups were comparable; the effects
18   were more severe for the acute exposure regimen.
19   Another animal study, Sand et al. (2010), used an initial-loading dose,
20   weekly-maintenance-dose protocol in which the loading dose is 10 times higher than
21   the weekly maintenance dose but did not evaluate the equivalent continuous exposure,
22   and so does not inform the issue. Both of the Yoshizawa et al (2010; 2009) studies
23   were analyses of the NTP (2006) study that is already presented in the Reanalysis, and
24   has no acute vs. continuous component. One other study, Bell et al. (2007), mentioned
25   in Recommendation 37 following, allows for acute/continuous comparison for in utero
26   and lactational exposures, addressing a very different developmental period than the one
27   in question for the Seveso cohort children (average age >6 years). This study found that
28   acute exposure had a significantly lower impact on perpetual separation in male rat pups
29   than did the equivalent continuous exposure (similar terminal TCDD body burdens), the
30   opposite of the finding of Kim et al. (2003). EPA does not consider this finding very
31   informative for the specific exposure scenario and critical exposure period relevant to
32   the RfD.

33   **Recommendation No. 36:** Discuss the life-stage-specific approach to hazard and
34   dose-response characterization for children's health risk assessment found in EPA's
35   *Framework for Assessing Health Risks of Environmental Exposures to Children* (U.S.
36   EPA, 2006b).

37   **Response:** The approach outlined in EPA's *Framework for Assessing Health Risks of*
38   *Environmental Exposures to Children* (U.S. EPA, 2006b) encourages evaluation of the
39   potential for toxicity during all developmental lifestages, based on knowledge of external
40   exposure, critical windows of development for different organ systems, MOAs, anatomy,
41   physiology, and behavior that can affect external exposure and internal dose metrics.
42   EPA has followed the framework in evaluating the available data for TCDD and in

1   developing the Reanalysis. The concepts explored in this framework are those that apply
2   to all risk assessments—namely problem formulation, analysis, and risk characterization.
3   The Reanalysis is not a risk assessment and does not contain information on problem
4   formulation or risk characterization; however, it does follow standard EPAprocedures.

5   ***Recommendation No. 37:*** Consider adding to the discussion, Bell et al. (2010), which
6   summarized and presented data on some differences between chronic versus acute exposure
7   in maternal transfer.

8   ***Response:*** EPA considered this recommendation as discussed in the response to
9   Recommendation 35. An analysis of the data has led EPA to consider the findings of
10   Bell et al. (2010) to not be informative in the context of the Seveso exposures on which
11   the RfD is based.

12 **SAB Charge Question 4.2.a.ii**

13 *Please comment on EPA's designation of a 20% decrease in sperm count (and an 11% decrease*
14 *in sperm motility) as a LOAEL for Mocarelli et al. (2008).*

15 ***Comment****: The Panel found that changes from normal sperm counts and sperm motility are of*
16 public health relevance and, therefore, of interest for determining an RfD. There is general
17 support for EPA's approach of using the WHO reference value for determining relevant TSH
18 levels, but the Panel feels that further discussion of WHO reference values for male reproductive
19 parameters should be included in the Report. Additionally, the Report should indicate that life
20 stage differences clearly exist in sperm counts in humans; cite and discuss the EPA life stage
21 document (U.S. EPA, 2006b).

22   ***Recommendation No. 38:*** Include discussion of background information regarding WHO
23   reference values for male reproductive parameters (e.g., Skakkebaek, 2010).

24   ***Response:*** EPA agrees with this recommendation and has added additional discussion of
25   WHO reference values for male reproductive parameters in Section 4.3.4.2.

26   ***Recommendation No. 39:*** Discuss standard deviations or range of changes from the
27   Mocarelli (2008) study to provide a better understanding of the potential magnitude of
28   effect.

29   ***Response:*** In Section 4.3.4.2, EPA discusses the magnitudes and standard deviations of
30   the effects reported in Mocarelli et al. (2011).

31 **SAB Charge Question 4.2.b**

32 *For Baccarelli et al. (2008), the critical exposure window occurs long after the high-dose pulse*
33 *exposure. Therefore, the variability in the exposure over the critical exposure window is likely*
34 *to be less than the variability in the Mocarelli et al. (2008) subjects. EPA concluded that the*
35 *reported maternal exposures from the regression model developed by Baccarelli et al. (2008)*
36 *provide an appropriate estimate of the relevant effective dose as opposed to extrapolating from*
37 *the measured infant TCDD concentrations to maternal exposure. Additionally, EPA selected a*
38 *LOAEL of 5 μ-units TSH per ml blood in neonates; as this was established by World Health*

*Organization (WHO) as a level above which there was concern about abnormal thyroid
development later in life. Please comment on the following:*

SAB Charge Question 4.2.b.i

*EPA's decision to use the reported maternal levels and the appropriateness of this exposure
estimate for the Baccarelli et al. (2008) study.*

Comment: The Panel supports EPA's decision to use the Baccarelli et al. (2008) estimates of the
relevant effective doses. Because the bulk of the calculations were based on zonal averages,
clarify how these measurements relate to ranges and variations in exposure in utero.

> ***Response:*** The Baccarelli et al. (2008) calculations presented in the Reanalysis are
> derived from the individual exposure measures by the study authors and are not based on
> zonal averages. EPA has clarified this for the RfD derivation in Section 4.3.

SAB Charge Question 4.2.b.ii

EPA's designation of 5 μ-units TSH per ml blood as a LOAEL for Baccarelli et al. (2008).

Comment: The change in TSH levels reported by Baccarelli et al. (2008) was of public health
relevance and, therefore, of interest for determining an RfD. Any follow-up data on thyroid
hormone levels in the population studied should be discussed in the Report, if available.

> ***Recommendation No. 40:*** Better describe the potential adverse health outcomes related to
> altered neonatal TSH levels (e.g., effects on both cognitive and motor deficits). For
> example, in addition to effects on growth, both cognitive and motor deficits have been
> found in young adults with congenital hypothyroidism (Oerbeck, 2007, 2003). The Report
> could better describe the consequences of transient hypothyroidism on reproductive
> outcomes (e.g., Anbalagan et al., 2010). Other references that relate to this question
> include Chevrier et al. (2007), Dimitropoulos et al. (2009), and Ye (2008).

> ***Response:*** EPA has added a discussion of the potential adverse health outcomes
> associated with altered neonatal TSH levels in Section 4.3.4.1. The discussion includes
> information about thyroid hormone disruption during pregnancy and the neonatal period,
> potentially leading to neurological deficiencies, particularly in the attention and memory
> domains(Oerbeck et al., 2005). It also addresses some of the uncertainties in the
> relationship between human neonatal TSH levels and measures of neurological function
> such as IQ. EPA also identified animal bioassays, reporting that perturbations in thyroid
> status can lead to altered brain development(e.g., Sharlin et al., 2010; Royland et al.,
> 2008; 2008; Ausó et al., 2004; Lavado-Autric et al., 2003). Discussion of these findings
> has been added to Section 4.3.4.1.

SAB Charge Question 4.3

*Please comment on the rationale for the selection of the uncertainty factors (UFs) for the RfD. If
changes to the selected UFs are proposed, please identify and provide a rationale.*

1   *Comment:* The Panel agrees that the appropriate UFs were included. The exclusion or inclusion
2   of the UFs in the Report is obvious, clearly discussed, and adequately rationalized. The Report
3   would be more transparent if EPA included a short discussion for the basis of the decision not to
4   include a UF for data quality.

5   *Response:* EPA has clarified its choice of UFs for the candidate RfDs in Section 4.3.5
6   and Table 4-7.

7 **SAB Charge Question 4.4**

8   *EPA did not consider biochemical endpoints (such as CYP induction, oxidative stress, etc.) as*
9   *potential critical effects for derivation of the RfD for TCDD due to the uncertainties in the*
10   *qualitative determination of adversity associated with such endpoints and quantitative*
11   *determination of appropriate response levels for these types of endpoints in relation to TCDD*
12   *exposure. Please comment on whether the decision not to consider biochemical endpoints is*
13   *scientifically justified and clearly described.*

14   *Comment:* Biochemical endpoints such as P450 activation, increased oxidative stress, etc. may
15   be acceptable endpoints to establish PODs, particularly when the quantitative relationship
16   between the biochemical endpoint and an adverse health outcome is clearly evident. However,
17   with respect to TCDD, the Panel agrees that more traditional endpoints (e.g., immune, endocrine,
18   reproductive) are more appropriate because associations of these endpoints with health outcomes
19   are well studied and provide a stronger association to an adverse outcome than biochemical
20   endpoints. However, because of the wealth of data on P450s and their importance in disease
21   development, normal development, and chemical response to exogenous agents, EPA should
22   discuss biochemical endpoints, particularly P450s, relevant to establishing and strengthening the
23   proposed reference dose.

24   *Response:* In general, there is a lack of information linking these particular endpoints to
25   downstream adverse effects for the noncancer effects observed in the available studies.
26   Some of these endpoints, such as CYP (P450) induction and oxidative stress are
27   discussed in Section 5 of the 2010 External Review Draft of the Reanalysis in the context
28   of the mode or action for carcinogenesis or are evaluated quantitatively as potential
29   cancer precursor effects. EPA intends to consider these endpoints further in Volume 2 of
30   the Reanalysis. In the context of noncancer effects, however, an expansive coverage of
31   these endpoints will not necessarily provide a better understanding of the RfD, given the
32   lack of information on the relevant modes of action. For these reasons, further analysis
33   of these data with respect to their relevance to strengthening the reference dose was not
34   conducted.

35 **SAB Charge Question 4.5**

36   *In using the animal bioassays, EPA averaged internal blood TCDD concentrations over the*
37   *entire dosing period, including 24 hours following the last exposure. Please comment on EPA's*
38   *approach for averaging exposures including intermittent and one day gestation exposure*
39   *protocols.*

1 *Comment:* For animal studies, it has been shown that for some effects, acute exposure could give
2 different results than chronic exposure. For TCDD, however, its persistence might suggest that
3 such differences would be partly negated. In Baccarelli et al. (2008), there was extensive
4 discussion regarding the use of the exposure average time for the TCDD concentrations. This is
5 of biological significance as several papers have indicated the unique aspects of high peak
6 exposure of TCDD as occurred in Seveso and in several of the animal studies. The endpoints
7 affected as a result of these peaks do not always translate to impacts from lower chronic
8 exposures. It would be helpful to discuss any available animal studies comparing high-dose
9 acute versus low-dose chronic effects on similar endpoints for dioxin or dioxin-like compounds
10 (as stated earlier in this section).

11   *Response:* See EPA's response to Recommendation 35. For the Baccarelli et al. (2008)
12   study, the exposures over the critical exposure window (gestation) were relatively
13   constant compared to the exposures experienced by the subjects studied in Mocarelli
14   et al. (2008) and other Seveso cohort studies.

SAB Charge Question 4.6

16 *Please comment on the benchmark dose (BMD) modeling conducted by EPA to analyze the*
17 *animal bioassay data and EPA's choice of points of departure (PODs) from these studies.*

18 *Comment:* The Panel agrees with the BMD modeling approaches used in this section. However,
19 the justification for EPA's conclusions that the animal data had sufficient limitations that
20 precluded their use to establish an RfD is quite diverse and poorly linked to specific studies.

21   *Recommendation No. 41:* Discuss several of the best animal studies in some detail so that
22   their limitations are more apparent.

23   *Response:* Summaries of all of the studies are presented in Appendix D, with some
24   discussion of their limitations. Strengths and limitations of all of the animal bioassays at
25   the lower end of the candidate RfD range are presented in Table 4-6. Two studies of note
26   (Bell et al., 2007; NTP, 2006) are discussed in more detail in Section 4.4. Table 4-4 and
27   Appendix G, which summarizes the BMD modeling, highlight some of the limitations of
28   the BMD modeling for each modeled data set.

29   *Recommendation No. 42:* Better cite the endpoint guidance that is present within EPA
30   documents for defending approaches used and application of BMD models for the critical
31   effects: this is especially necessary given public comments that EPA was not following its
32   own guidelines.

33   *Response:* In response to this comment, EPA has added Text Box 2-1. In this text box,
34   EPA identifies the risk assessment guidelines and guidance documents that it relied upon
35   during development of the dose-response assessment.

SAB Charge Question 4.7

37 *For the animal bioassay modeling, EPA applied the kinetic extrapolation at the level of the POD*
38 *prior to applying the uncertainty factors because EPA has less confidence in the kinetic model*
39 *output at lower doses reflective of the RfD. Please comment on whether the kinetic extrapolation*

1	*at the level of the POD prior to applying the uncertainty factors was scientifically justified and*
2	*clearly described.*

3	**Comment**: The EPA approach of applying the kinetics on the actual data present at the POD is
4	preferred in this assessment (see additional discussion in the response to Charge Question 3).

5	 **Response:** No response necessary.

6	**SAB Charge Question 4.8**

7	*Please comment as to whether EPA's qualitative discussion of uncertainty in the RfD is justified*
8	*and clearly described.*

9	**Comment**: The Panel agreed that EPA provided a clear and justified discussion of the
10	uncertainties in deriving the RfD using the Seveso cohort. The Panel agrees with EPA that the
11	major limitation of the Seveso cohort is the uncertainty arising from how well the effects
12	resulting from high-dose acute exposure translate to low-dose daily exposures. It may be useful
13	to re-review the animal studies to identify if there are any studies where dioxin or DLCs were
14	administered by acute as well as chronic (or even subchronic), and comparable endpoints were
15	examined. If so, the information can be used to help confirm or refute the accuracy of the
16	"average daily dose" adjustment. This is of particular concern in the Mocarelli study as "time
17	periods of susceptibility" appear in male reproductive development, and these periods (windows)
18	may be very short. Animal studies, particularly those involving male reproduction, may be
19	helpful.

20	 **Recommendation No. 43:** It would be useful to include a discussion of potential
21	 uncertainty in the exposure estimates from the Baccarelli study. Serum dioxin levels were
22	 only established in a subset of the cohort (approximately 51) at the time of the study while
23	 dioxin levels from the main cohort were estimated from data collected from zone of
24	 residence (A or B) at a much earlier time.

25	 **Response:** For derivation of the POD, EPA used the regression modeling in Baccarelli
26	 et al. ((2008)), which was based only on the 51 infants with maternal TCDD
27	 measurements taken between 1992 and 1998 and did not depend on prior measurements
28	 in the main cohort. All outcomes are associated with individual serum concentrations
29	 rather than zonal averages. Baccarelli et al. (2008) extrapolated the measured values to
30	 the time of conception for each of the 51 pregnancies, which occurred between 1994 and
31	 2005. In Section 4.4, EPA has clarified the uncertainties associated with deriving an RfD
32	 from both of the principal studies (Baccarelli et al., 2008; Mocarelli et al., 2008). EPA
33	 has also added Section 4.5. In this section, EPA quantifies the impact of alternative
34	 assumptions about the exposures associated in both the Baccarelli and Mocarelli studies.
35	 Also, see response to Recommendation 32.

36	 **Recommendations No. 44:** While the Panel agrees that the true dioxin-like-compound
37	 impact cannot be determined, it might be helpful to provide some general estimates of the
38	 variability that may occur at the proposed RfD.

1   ***Response:*** In response to this comment, EPA has added Section 4.5 to the document. In
2   this section, EPA quantifies the impacts of alternative assumptions about the TCDD-only
3   and DLC exposures on the PODs for both the Mocarelli (see Section 4.5.1.1) and
4   Baccarelli (see Section 4.5.1.2) studies. In Section 4.5.2, EPA has estimated alternative
5   PODs from the NTP (2006) study based on different approaches to modeling TCDD only
6   and the DLCs. Finally, in Section 4.5.3, EPA has estimated potential PODs from several
7   different endpoints identified in Seveso cohort studies (other than those used in
8   developing the RfD) and has estimated the range of potential PODs based on
9   uncertainties encountered in their analyses; these uncertainties included the impacts of
10   DLC background exposures.

A.4.2. Summary of Public Comments and EPA Responses

12 ***Comment***: Several comments addressed the fact that when determining an RfD, EPA accounted
13 for only 2,3,7,8-TCDD exposures and did not account for exposures to dioxin-like chemicals.
14 The commenters noted that in human epidemiological studies, people are exposed to all
15 dioxin-like compounds regardless of the sources of their exposures. Specifically, the
16 commenters suggested that EPA did not account for these exposures in the Seveso population
17 when evaluating dose response and, thus, underestimated the reference doses derived from
18 Mocarelli et al. (2008) and Baccarelli et al. (2008).

19   ***Response:*** EPA agrees that the human subjects studied in the epidemiological studies
20   were subject to background DLC exposures from many sources. EPA has added an
21   analysis of the impact of background DLC exposures on the RfD to the document in
22   Section 4.5. In this analysis, EPA estimates background DLC exposures for several of
23   the Seveso exposure scenarios, including those relevant to the Mocarelli et al. (2008) and
24   Baccarelli et al. (2008) POD estimates. EPA has concluded that the impact of
25   background DLC exposures is small at exposures near the LOAEL POD used for the RfD
26   but may be significant at lower exposure levels.

27 ***Comment:*** One commenter noted that EPA's qualitative discussion of uncertainty in the
28 reference dose (pp. 4-28 to 4-32) is well written and clearly described. Two commenters felt that
29 the rationale for the selection of the male reproductive effects (Mocarelli et al., 2008) and
30 changes in neonatal thyroid hormone levels (Baccarelli et al., 2008) as critical effects was clearly
31 described and scientifically justified. One commenter felt that the LOAEL selected from the
32 Mocarelli et al. (2008) study was justified. Commenters also felt that EPA's decision not to
33 consider biochemical endpoints (such as CYP induction, oxidative stress, etc.) as potential
34 critical effects for derivation of the RfD for TCDD is clearly described and scientifically
35 justified.

36   ***Response:*** No response necessary.

37 ***Comment:*** Several commenters asked EPA to further address the uncertainties associated with
38 deriving an RfD from the Baccarelli et al. (2008) and Mocarelli et al. (2008) studies. Several
39 commenters noted that EPA does not include the use of the data from these studies for dose-
40 response modeling and reference dose derivation with a discussion of the clinical significance of
41 the effects, or the levels of change that represent an adverse effect for each endpoint.

1   ***Response:*** In Section 4.4, EPA presents a discussion of the qualitative uncertainties
2   associated with the development of an RfD from these two studies. In response to this
3   and other comments, EPA has expanded the discussion to include the potential clinical
4   significance of the two effects encountered in these epidemiological studies: (1) elevated
5   TSH levels in infants and (2) decreased semen quality in men that experienced elevated
6   TCDD exposures as young boys. Further, in the sensitivity analysis added in Section 4.5,
7   EPA evaluates some quantitative uncertainties in the derivation of PODs from the
8   Baccarelli et al. (2008) and Mocarelli et al. (2008) studies.

9   ***Comment:*** Two commenters noted that the Agency substantially underestimated liver and
10   adipose tissue concentrations in the 2006 National Toxicology Program bioassay (NTP, 2006),
11   resulting in an approximate two-fold overestimate of TCDD potency. EPA ignored reported
12   TCDD concentrations in adipose and liver tissue, which should have been used as the dosimetry
13   endpoints for extrapolation to human equivalent dosages. The use of modeled data is not
14   acceptable for deriving toxicity values used in risk assessment when measured data are available;
15   unnecessary inaccuracies in the derivation of the RfDs are introduced.

16   ***Response:*** In the new sensitivity analysis presented in Section 4.5.2, EPA has estimated
17   PODs based on the TCDD adipose concentrations reported in NTP (2006). EPA does not
18   consider the whole liver concentrations to be relevant because they include TCDD bound
19   to CYP1A2, which is not part of the biologically-active TCDD fraction. Because
20   adequate human studies were available, animal studies including the above referenced
21   NTP (2006) were not used to derive the RfD.

22   ***Comment:*** One commenter noted that several studies included in the Report examined the
23   effects of TCDD exposure on serum thyroid hormone concentrations (Crofton et al., 2005; Seo et
24   al., 1995; Sewall et al., 1995), which are toxicologically irrelevant and should be excluded from
25   the analysis.

26   ***Response:*** EPA considers serum thyroid hormone levels to be toxicologically relevant, as
27   indicators of hormonal imbalance and potential thyroid toxicity. EPA does not require
28   the observation of overt clinical effects in this respect. An expanded discussion of this
29   topic has been added to Section 4 in the document.

30   ***Comment:*** A commenter suggested that many of the animal studies, particularly developmental
31   studies, used dosing regimens that cannot be properly extrapolated to chronic exposures and,
32   thus, are inappropriate for derivation of a chronic RfD. The commenter noted that the weight of
33   evidence suggests that peak, rather than average, exposure level is most relevant to assessing the
34   effect of in utero and developmental exposure to TCDD on male rat reproductive system
35   parameters.

36   ***Response:*** EPA defines the "chronic" RfD as a lifetime protection value that includes all
37   exposures and life stages, not just long-term exposure. If shorter-term exposures over a
38   particular critical window, such as in utero or early childhood, indicate greater
39   susceptibility, the short-term exposures must be considered during the development of an
40   RfD and can be the basis of an RfD.

1 *Comment:* A commenter noted that some of the health effects that are addressed in derivation of
2 an RfD are actually precancerous lesions (i.e., hypertrophy and hyperplasia), and as such, are
3 more appropriate for use in cancer risk assessment than for deriving a chronic RfD.

4   *Response:* Hypertrophy and hyperplasia are not always considered to be precancerous.
5   For the TCDD assessment, no POD is based solely on either of these effects.

6 *Comment:* One commenter noted that in developmental studies, the appropriate unit for
7 statistical analysis is the litter; many of the developmental studies considered by EPA, however,
8 incorrectly used the individual pup as the statistical unit for analysis (e.g., Shi et al., 2007; Hojo
9 et al., 2002; Markowski et al., 2001; Ohsako et al., 2001). The commenter suggested that data
10 from developmental studies that have been incorrectly evaluated using the individual pup should
11 not be used as the basis for derivation of an RfD. Alternatively, the original study data could be
12 reanalyzed using the litter as the statistical unit of analysis.

13   *Response:* EPA guidance calls for a litter-based approach for dichotomous outcomes
14   when the data are reported on that basis. All the endpoints in the studies identified by the
15   commenter were continuous measures, to which the guidance does not apply. In
16   addition, all the data were presented only by aggregated exposure groups, so that a
17   litter-based analysis was not possible even if the responses could be dichotomized.

18 *Comment:* One commenter noted that some data are derived from guinea pigs, which are known
19 to be substantially more susceptible to the effects of TCDD treatment than humans. Because of
20 the extreme sensitivity, an uncertainty factor of 3 for animal-to-human extrapolation is
21 unfounded for these studies.

22   *Response:* There are few data to evaluate the relative sensitivities of guinea pigs and
23   humans to TCDD. As shown in Table 4-5, guinea pigs are not necessarily more sensitive
24   than other species. The use of a three-fold uncertainty factor for the toxicodynamic
25   component of interspecies uncertainty (UF_A) is standard EPA practice when using
26   modeling the toxicokinetic extrapolation component (U.S. EPA, 1994).

27 *Comment:* One commenter suggested that several studies included in the analysis are limited by
28 the number of animals used (see Shi et al., 2007; Franc et al., 2001; Sewall et al., 1995) and that
29 the determination of a NOAEL and LOAEL based on the analyses as provided by the authors is
30 not appropriate for deriving a regulatory threshold value.

31   *Response:* EPA has indicated such limitations in the animal bioassay evaluations in
32   Table 4-6. While EPA considered these studies as possible POD candidates, the RfD is
33   based on human epidemiological studies, not on data derived from animal bioassays.

34 *Comment:* One commenter felt that the LOAELs in the Van Birgelen et al. (1995a; 1995b) and
35 Fattore et al. (2000) studies were incorrectly interpreted. The commenter noted that, in the Van
36 Birgelen et al. (1995a; 1995b) study, the LOAEL should be based only on changes in thymus
37 weight because other changes (i.e., liver retinoid levels) might only be adaptive responses and
38 cannot be considered toxic effects. The commenter also noted that the LOAEL for the Fattore
39 et al. (2000) study should be interpreted as a 1-µg/kg diet (2 µg/day for 13-week old female rats)
40 with a NOAEL of 0.2 µg/kg (0.3 µg/day for 13-week-old female rats) because of the

1 dose-dependent reduction in hepatic vitamin A, with significant reductions at TCDD diet
2 concentrations of 1, 2, and 20 µg/kg, but not at 0.2 µg/kg.

> ***Response:*** EPA acknowledges that there are uncertainties in the selection of specific
> effects in these studies but believes that it has appropriately interpreted these study
> endpoints in its development of candidate RfDs. EPA does not consider depletion of liver
> retinoid levels to be adaptive.

7 ***Comment:*** Several commenters noted that EPA's evaluation of noncancer risk ignored the NAS
8 peer-review conclusions that the evidence for dioxin exposure as a cause of reproductive and
9 hormonal abnormalities is not strong and that there is no convincing evidence of adverse,
10 noncancer effects as a result of dioxin exposure.

> ***Response:*** In Sections 2 and 4 of the document, EPA identifies a number of additional
> epidemiology and toxicology studies that support associations between TCDD exposures
> and noncancer effects. Several important studies in this group (e.g., Baccarelli et al.,
> 2008; Mocarelli et al., 2008; Bell et al., 2007; NTP, 2006) were published after the NAS
> report was published.

16 ***Comment:*** Some commenters suggested that there is a significant amount of uncertainty in the
17 Mocarelli et al. (2008) study, given that the reported demographics of the control population
18 were different from those of the exposure groups, and the study authors had no information on
19 TCDD levels in the control group.

> ***Response:*** The analysis in Mocarelli et al. (2008) was performed by grouped exposures
> across all subjects. The lowest exposure group, being the reference group for the
> analysis, included individuals from all exposure zones, not just the "control" population
> (the non-ABR zone) mentioned by the commenter. TCDD serum levels were measured
> in a subset of the non-ABR population as reported in Needham et al.(1997) and
> Mocarelli et al. (1991). It is not clear how many, if any, of the individual exposures in
> the lowest exposure group were assigned a generic value rather than a measured one.
> Demographic differences among the individuals across all exposure groups were
> identified and considered as covariates in the analysis by Mocarelli et al. (2008).

29 ***Comment:*** One commenter noted that neither Mocarelli et al. (2008) nor EPA has explained the
30 biological mechanism by which dioxin demonstrated negative effects on sperm concentration in
31 1- to 9-year-old boys and positive effects on sperm concentration in 10- to 17-year-old boys.
32 Commenters questioned the study's assumption of 10 as a reasonable age for puberty in boys
33 stated that 12–16 years is the average age at onset of puberty.

> ***Response:*** EPA agrees with the commenter that the mechanism of toxic action for this
> effect is not known. For the establishment of an RfD, EPA does not require the
> establishment of a mechanism of toxic action. Neither the study authors nor EPA assume
> 10 years to be the age of puberty onset; it is simply the age that the study authors used to
> divide their study population by magnitude of effect.

1   *Comment:* In the Baccarelli et al. (2008) and Mocarelli et al. (2008) studies, the populations of
2   interest were small, especially for the high-exposure group. This leads to questions about the
3   overall representativeness of the studies.

4   *Response:* Both studies refer to specific age groups, specifically infants and young
5   children; therefore, the population is not a representative sample of the general
6   population, but of a possible sensitive population. In part, because of the small sample
7   size, EPA used a factor of 3, rather than 1, for UF_H to account for the possibility that all
8   sensitive individuals might not be represented.

9   *Comment:* One commenter felt that the lack of data on maternal iodine status in the Baccarelli
10   et al. (2008) study could affect the neonatal TSH data. The authors' explanation that potential
11   iodine-related effects would affect all study groups evenly and would not impact the findings
12   was questionable.

13   *Response:* Baccarelli et al. (2008) discount iodine status in the population as a
14   confounder because exposed and referent populations all lived in a relatively small
15   geographical area. That an iodine deficiency was present in one and not the other is
16   unlikely based on iodine levels in the soil.

17   *Comment:* One commenter stated that EPA used data that were not clinically significant and did
18   not demonstrate a dose-response relationship to derive an RfD. In determining the critical effect,
19   EPA had no information to verify that the persons with the potentially low values were
20   associated with higher exposures to TCDD.

21   *Response:* EPA does not require PODs used to derive RfDs to be based on effects that
22   have demonstrable clinical significance. EPA has expanded the discussion of the
23   potential significance of elevated neonatal TSH levels in the Reanalysis.

24   *Comment:* Several comments suggested that EPA did not acknowledge and address in an
25   appropriate weight-of-evidence evaluation several other credible studies for RfD development.
26   EPA excluded credible studies showing no adverse effect from dioxin, yet failed to address the
27   significant uncertainties associated with the studies used. The commenters felt that EPA should
28   use an approach that includes results from studies that report both positive and negative findings,
29   incorporates an appropriate dose range, and evaluates a biologically plausible endpoint.

30   *Response:* In response to this comment and others, EPA has added an analysis of the
31   qualitative and quantitative concordance of specific key effects across species in
32   Section 4.4 as a supplement to the existing discussion of the critical effects.

33   *Comment:* Commenters noted that some of the animal studies used to support derivation of a
34   chronic RfD evaluate nonadverse endpoints, have not been specifically linked to adverse events,
35   were generally unsuitable, or were of questionable toxicological relevance. See Amin et al.
36   (2000), Cantoni et al. (1981), Fattore et al. (2000), Hojo et al. (2002), Hutt et al. (2008),
37   Kattainen et al. (2001), Keller et al. (2008a; 2008b; 2007), Li et al. (1997), Miettinen et al.
38   (2006), and Van Birgelen et al. (1995a; 1995b).

39   *Response:* See response to Charge Question 4.4.

1   *Comment:* A commenter noted that some of the studies cited in support of EPA's derivation of
2   an RfD report findings that conflict with findings of other studies, thus indicating that the
3   associated responses to TCDD treatment have not been well-elucidated. The commenter also
4   added that the lack of agreement among studies regarding the evaluated responses following
5   TCDD treatment suggests that these endpoints likely are not sensitive indicators of
6   TCDD-mediated effects. Thus, they should not be used to support the derivation of an RfD.
7   (SeeAmin et al., 2000; Gray et al., 1995; Bjerke and Peterson, 1994; Mably et al., 1992.)

8   *Response:* EPA's methods for developing RfDs do not require that all studies be positive
9   for a given effect and take into account conflicting information when deciding on a
10   critical effect. As mentioned previously in response to other comments, EPA has added a
11   more expansive discussion of qualitative and quantitative concordance of effects across
12   species and studies (Section 4.4).

13   *Comment:* Several commenters stated that the sperm quality endpoints used for risk assessment
14   were of questionable clinical relevance. EPA failed to present a valid analysis of variability of
15   effects in the control. The commenters felt that the critical effect should not be based on
16   "assumed" effects, but rather, on documented effects of clinical concern and that several
17   scientific and quantitative issues should be addressed regarding the underlying data used to
18   derive an RfD.

19   *Response:* EPA does not require PODs to be based on effects that have demonstrable
20   clinical significance (see response to SAB charge question 4.4). EPA has framed the
21   concern for the sperm quality endpoints in terms of shifts in the distributions of these
22   measures in the general population. Such shifts could result in decreased fertility in men
23   at the low end of these population distributions. In a new study, Mocarelli et al (2011)
24   report that elevated TCDD exposures during and after pregnancy (via breast-feeding) led
25   to similar sperm quality degradation. EPA has expanded the discussion in Section 4.3.4.2
26   regarding the significance of this endpoint.

27   *Comment:* Some commenters suggested that owing to limitations in control for confounding
28   variables, difficulty in translating exposure scenario to the general population, and relevance of
29   the main outcome measure, the results of the Baccarelli et al. (2008) study are suitable for
30   hypothesis generation but are not strong enough on their own for generation of an RfD. The
31   commenters additionally noted that neither Baccarelli et al. (2008) nor EPA presented any data
32   that shows increasing TSH levels in the population during the years when dioxin exposures were
33   high and decreasing levels in more recent years, specifically the past 20 years.

34   *Response:* Sections 4.4 and 4.5.1.2 describe and quantify the impacts of important
35   sources of uncertainty in this analysis. In response to the issue of historical infant TSH
36   levels against changing background exposures, EPA has added a discussion of the
37   Goodman et al. (2010) review of this issue in Section 4.3. EPA notes that the SAB
38   agreed withthe choice of principal studies, including Baccarelli et al. (2008).

39   *Comment:* Several commenters suggested that EPA did not sufficiently address the
40   appropriateness of using the Seveso cohort as a basis to derive an RfD, given that the exposure
41   levels of those nearest the explosion far exceeded what is observed in the general population.

1   Nevertheless, at least one reviewer felt that EPA was justified in using the exposure estimates
2   provided by the study authors to quantify exposure for the dose response.

3   *Response:* In response to this comment and similar ones, EPA has, in addition to the
4   existing discussion of the Seveso exposure scenarios in Section 4, added an analysis in
5   Section 4.5 that investigates in more detail the uncertainties in the exposure modeling.

6   *Comment:* Several commenters felt that the exposures in Seveso also included substantial
7   exposure to other confounding chemicals that contribute to the overall TEQ, which was not
8   accounted for in the analysis. They suggested that TCDD comprised only a small fraction of the
9   total TEQ.

10   *Response:* The released fluid mixture at Seveso reportedly contained TCDD, sodium
11   trichlorophenate, ethylene glycol, and sodium hydroxide (Mocarelli et al., 2000), but the
12   presence of other dioxin-like compounds was not reported. However, EPA has evaluated
13   the impact of background DLC exposures for the Seveso population. In Section 4.5.1,
14   EPA analyzes TEQ estimates based on background exposures to DLCs in the Baccarelli
15   et al. (2008) and Mocarelli et al. (2008) studies. In Section 4.5.3, EPA analyzes TEQ
16   estimates based on background DLC exposures for other studies of the Seveso cohort and
17   has concluded that background DLC exposure is relatively small compared to TCDD at
18   the LOAEL POD.

19   *Comment:* One commenter noted that, the study by Baccarelli et al. (2008) provided a clear basis
20   for estimating a NOAEL for impacts on neonatal TSH levels. The identification of this robust
21   NOAEL, with substantial support from the weight of evidence from numerous other studies,
22   provides the basis for reduced uncertainty factors in the derivation of the RfD. The commenter
23   outlined an alternative method for deriving the RfD using the principal studies that EPA selected,
24   which included differences in calculating NOAEL/LOAEL values and applied UFs in Baccarelli
25   et al. (2008).

26   *Response:* The SAB has agreed with the approach that EPA has taken to derive the RfD
27   from this study. EPA could not define a NOAEL because it is not clear what maternal
28   intake should be assigned to the group below a TSH level of 5 µU/mL. In
29   Section 4.5.1.2, EPA quantifies the impact of sources of uncertainty in a sensitivity
30   analysis that examines the key elements encountered during the derivation of an RfD
31   from Baccarelli et al. (2008), including a potential NOAEL.

32   *Comment:* One commenter noted that in the regression analysis plots from Baccarelli et al.
33   (2008) (Figure 2), which EPA cites as the basis of the RfD derivation, if a benchmark of
34   10 µU/mL had been used rather than 5 µU/mL, the corresponding POD (in terms of a maternal
35   plasma TCDD concentration) would be >1,200 ppt, as compared with 270 ppt. The resulting
36   RfD would be about 5-fold higher. If a 10 µU/mL benchmark was applied to the Baccarelli et al.
37   (2008) regression analysis, there would be little basis for comparing exposures, because no data
38   points exceeded 10 µU/mL.

39   *Response:* In Section 4.5.1.2, EPA addresses this issue in a sensitivity analysis of the
40   Baccarelli et al. (2008) study. In this section, EPA estimates PODs based on alternative

1   increases in the neonatal TSH levels reported at different TCDD levels in Baccarelli et al.
2   (2008). The highest TSH level considered for defining an alternate LOAEL was the
3   highest one used by Baccarelli et al. (2008) in their regression model. The overall infant
4   cohort included a number of TSH levels above 10 µU/mL, but no maternal TCDD
5   concentrations were available for those infants. As it is impossible to determine what the
6   regression slope would be had those data points been included, EPA did not evaluate the
7   regression model beyond the highest TSH value in the modeled data set.

8   *Comment:* Several commenters suggested changing the uncertainty factors (UFs). One
9   commenter suggested that EPA should reduce the intrahuman uncertainty factor (UF$_H$) from 3 to
10   1 as the critical effects observed in the co-principal studies were found in sensitive
11   subpopulations (children, neonates). Another commenter stated that EPA needs to address why
12   it did not include a UF to account for the unique susceptibility and vulnerability of children and
13   why it chose to use a UF of 3 (instead of 10) to account for human interindividual variability.

14   ***Response:*** For human interindividual variability (UF$_H$), EPA used a factor of 3 ($10^{0.5}$)
15   because the effects were elicited in sensitive populations. A further reduction to 1 was
16   not made because the sample sizes were relatively small, which, combined with
17   uncertainty in exposure estimation, may not fully capture the range of interindividual
18   variability. In addition, chronic effect-levels are not well defined for humans and could
19   possibly be more sensitive. EPA has added text to Table 4-7 and believes that the
20   Report adequately describes the use of UFs.
21   In the EPA's RfD methodology, there is not a separate UF to account for the unique
22   susceptibility and vulnerability of children. Such differences are accounted for as part
23   of UF$_H$.

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APPENDIX B

Dioxin Workshop Report

November 2011

NOTICE

THIS DOCUMENT IS AN AGENCY/INTERAGENCY REVIEW DRAFT. It has not been
formally released by the U.S. Environmental Protection Agency and should not at this stage be
construed to represent Agency policy. It is being circulated for comment on its technical
accuracy and policy implications.

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

Summary of U.S. EPA
Dioxin Workshop
February 18−20, 2009

Cincinnati, Ohio

DISCLAIMER

This document summarizes the discussions presented at the Dioxin Workshop in February 2009, in Cincinnati, OH, as documented by the Session Co-Chairs. This document is not all inclusive or binding. Conclusions and recommendations to the U.S. EPA may not represent full consensus. The views expressed in this document are those of the Dioxin Workshop Panelists and do not necessarily reflect the views and policies of the U.S. Environmental Protection Agency. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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DIOXIN WORKSHOP TEAM

The Dioxin Workshop Team, under the leadership of Peter W. Preuss, Director, NCEA, comprised the following members:

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INTRODUCTION

This document provides a summary of the Scientific Workshop to Inform EPA's Response to National Academy of Science Comments on the Health Effects of Dioxin in EPA's 2003 Dioxin Reassessment. The U.S. Environmental Protection Agency (U.S. EPA) and Argonne National Laboratories (ANL), through an inter-Agency agreement with the U.S. Department of Energy, convened this scientific workshop ("Dioxin Workshop") on February 18−20, 2009, in Cincinnati, Ohio. The goals of the Dioxin Workshop were to identify and address issues related to the dose-response assessment of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). This report summarizes the discussions and conclusions from this workshop. Previously, at the request of the U.S. EPA, the National Academy of Sciences (NAS) prepared a report, *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment* (NAS, 2006), which made a number of recommendations to improve the U.S. EPA's risk assessment for TCDD (U.S. EPA, 2003). The 3-day Dioxin Workshop was convened specifically to ensure that the U.S. EPA's response to the NAS recommendations focuses on the key issues and reflects the most meaningful science.

The Dioxin Workshop included seven scientific sessions:

(1) Session 1:   Quantitative Dose-Response Modeling Issues
(2) Session 2:   Immunotoxicity
(3) Session 3A: Dose-Response for Neurotoxicity and Nonreproductive Endocrine Effects
(4) Session 3B: Dose-Response for Cardiovascular Toxicity and Hepatotoxicity
(5) Session 4A: Dose-Response for Cancer
(6) Session 4B: Dose-Response for Reproductive/Developmental Toxicity
(7) Session 5:   Quantitative Uncertainty Analysis of Dose-Response

During each session, the U.S. EPA asked a panel of expert scientists to:

- identify and discuss the technical challenges involved in addressing the key NAS comments on the TCDD dose-response assessment in the U.S. EPA Reassessment (U.S. EPA, 2003);

- discuss approaches for addressing the key NAS comments; and

- identify important published, independently peer-reviewed literature, particularly studies describing epidemiologic and *in vivo* mammalian bioassays, which are expected to be most useful for informing the U.S. EPA's response.

The sessions were followed by open comment periods during which members of the audience were invited to address the Panels. At the conclusion of the open comment periods, the Panel Co-Chairs were asked to summarize and present the results of the panel discussions. The summaries could include minority opinions stated by panelists. The main points derived from the session summaries were used to prepare this document. Additionally, this document includes a list of the session panelists and their affiliations and three appendices. Appendix A presents the Dioxin Workshop Agenda. Appendix B identifies the charge questions presented to the Panel. Appendix C describes draft study selection criteria proposed by the Dioxin Workshop Team for consideration by the workshop panelists.

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SCIENTIFIC WORKSHOP TO INFORM THE TECHNICAL WORK PLAN FOR U.S. EPA'S RESPONSE TO NAS COMMENTS ON THE HEALTH EFFECTS OF DIOXIN PRESENTED IN U.S. EPA'S DIOXIN REASSESSMENT

Dioxin Workshop Co-Chairs: Peter W. Preuss and Glenn Rice

The Dioxin Workshop session summaries were prepared by the session panel Co-Chairs with input from the panelists, as requested by the U.S. EPA prior to the workshop. The Co-Chairs subsequently presented these summaries to all of the workshop participants during designated periods at the workshop. In these summaries, the U.S. EPA asked that the Co-Chairs summarize the key issues from the panel discussions. Because the sessions were not designed to achieve consensus among the panelists, the summaries do not necessarily represent consensus opinions; rather, they reflect the essence of the panel discussions. Some of the specific points may represent the views of multiple panelists, while others only the views of a single panelist. Prior to the summarizations, there were opportunities for public comments on the discussion topics. Some Co-Chairs met with their sessions' panelists after their sessions ended to develop these summaries, while others developed reports based on their personal notes. Because Session 5 was the last session of the workshop—with little time provided to develop the summary—the Co-Chairs circulated a draft for comment by the Session 5 panelists after the workshop, prior to finalizing the session summary. The U.S. EPA collected the session summaries and then prepared this document. A draft of this document was distributed to all of the session Co-Chairs to provide them with a final opportunity to comment and make revisions. Finally, it should be noted that U.S. EPA was not prescriptive to the session Co-Chairs with respect to the format of the presentation materials and provided no specific instructions, resulting in unique formats among the session summaries.

SESSION 1: QUANTITATIVE DOSE-RESPONSE MODELING ISSUES

This session discussed the general dose-response modeling issues related to TCDD. Many of these issues were highlighted by NAS (2006). There was a general introductory presentation on TCDD kinetics, including information and uncertainties pertaining to the conversion of administered doses in animals to human body burden (BB) and additivity to background issues. This presentation was followed by a Panel discussion on the state of the science regarding dioxin dose-response modeling issues.

Session 1 Panelists (Session Co-Chairs are identified by asterisk)

- Bruce Allen, Bruce Allen Consulting
- Lesa Aylward, Summit Toxicology
- Roger Cooke, Resources for the Future
- Kenny Crump, Louisiana Tech University
- Mike DeVito, U.S. EPA
- Dale Hattis, Clark University
- Rick Hertzberg, Biomath Consulting
- Rob McDowell, U.S. Department of Agriculture
- Jim Olson, State University of New York, University at Buffalo

- *Lorenz Rhomberg, Gradient
- Woody Setzer, U.S. EPA
- *Jeff Swartout, U.S. EPA

Please note that the use of the term "concluded" or "recommended" in this summary does not mean that a consensus was reached. Session Summaries were written from the material prepared by the non-EPA/ANL Co-Chair and represent a synopsis of the panel discussions.

Key Study Selection Criteria

The Panel discussed the advantages and disadvantages of using key study criteria (Appendix C). They concluded that *a priori* criteria foster transparency and consistency, and could deflect *a posteriori* criticism. However, the Panel also acknowledged that having *a priori* criteria could introduce the potential for excluding useful data. Although the key study criteria provided by the U.S. EPA listed studies using TCDD only as a criterion, the Panel posed the possibility of using closely related dioxin-like compounds (DLCs) as surrogates for TCDD. The criterion for use of data from mammalian studies only was one criterion that received generalized support due to the lack of extrapolation protocols for nonmammalian species. The Panel also discussed the specific exposure-duration criterion and asked if there should be a preference for longer-term rather than acute studies. The Panel made three suggestions to modify U.S. EPA's key study selection criteria:

(1) Define more relevant exposure-level (i.e., dose) cut points using tissue concentrations.
(2) Reword statistical criteria to include do-it-yourself analysis.
(3) Reword the response criteria to clarify "outside of normal range."

Dose Metrics

The Panel discussed the relative merits of various measures of dose for modeling TCDD dose response. One general conclusion was that tissue concentration (TC) is the preferred metric, especially lipid-adjusted TC, because this measure more closely approximates exposures close to the target tissue when compared to administered doses. However, the Panel acknowledged that these data are often unavailable. They further noted that BB, which is defined as the concentration of TCDD in the body (ng/kg body weight) (U.S. EPA, 2003), might be useful as a surrogate for TC provided the two measures were proportional.

The Panel suggested that a linear approach to BB estimation, which was utilized by U.S. EPA (2003), is too simplistic because this approach does not take into account toxicokinetic issues related to TCDD—e.g., sequestration in the liver and fat, age-dependent elimination, and changing elimination rates over time. The Panel recommended the use of kinetic/mechanistic modeling to the extent possible to quantify tissue-based metrics.

The Panel raised the issue of whether the preferred dose metric would be different for different endpoints and exposure durations. This led to the Panel's comment that the peak exposure might be a more important metric than average BB for variable exposure scenarios. Given this discussion about different exposure durations being relevant to a specific endpoint, the Panel suggested that the U.S. EPA also consider peak measures in dose-response modeling.

The last point raised in this part of the discussion centered on the possibility of dose errors in experimental studies. The Panel highlighted the need for the U.S. EPA to consider dose error (i.e., uncertainty in the x-axis of the dose-response curve) when using dose surrogates.

Dose-Response Modeling of Mammalian Bioassays

The Panel considered several issues related to dose-response modeling of mammalian bioassay data for TCDD: supralinearity and incomplete response data ("anchoring"), defining the benchmark response (BMR) level with respect to establishing the point of departure (POD), and the use of threshold modeling—as further explained below.

The Panel discussed the specific issues of supralinearity and anchoring raised by the U.S. EPA with respect to modeling noncancer endpoints. The panel recognized that, for many of the most sensitive endpoints, the response at the lowest dose is high (e.g., quantal responses above 25% and continuous endpoints differ substantially from the mean, often implying 100% incidence in the treated animals). This lack of response anchoring at the low end of the dose-response curve (near the BMR) results in the higher responses determining the shape of the curve.

The Panel asked whether new tools might be needed or whether the current tools could be applied differently. In the context of developing new tools, the Panel emphasized the need for collaboration between biologists and mathematicians. When discussing application, the Panel suggested that the problem with supralinearity might be overcome by simply dropping the requirement for using the lower bound on the Benchmark Dose. In addition, the Panel posed several more approaches for further consideration in dose-response modeling by the U.S. EPA:

(1) Combine similar data sets to fill in data gaps.
(2) Use mechanistic approaches to model the data gaps.
(3) Dichotomize continuous data.

Finally, the Panel acknowledged that, in certain situations, there simply may not be enough information to provide meaningful answers.

The Panel discussed the BMR level for establishing a POD in the context of deriving a Reference Dose (RfD). The Panel generally agreed that, while the effective dose level (ED_{01}) used in the 2003 Reassessment may be useful for comparative analysis across endpoints, the ED_{01} estimates developed for all endpoints considered in the Reassessment were not appropriate for deriving an RfD because they were not based on the effect's adversity. The panel noted that ED_{01} also is much lower than typical EPA BMR levels. The Panel recommended that the U.S. EPA work to define endpoint-specific BMRs based on the consideration of adversity. Given that the same uncertainty factor framework is applied to all PODs, the Panel emphasized the need for consistency in BMRs; numerical consistency is needed for quantal BMRs and consistency in the choice of biological relevance should be applied for continuous BMRs.

The Panel generally discouraged threshold modeling by stating that thresholds are very difficult to pin down and suggested that the lower bound may always be zero.

Dose-Response Modeling of Epidemiological Studies

The Panel noted that many studies have been published with measured concentrations of TCDD that could be used for dose reconstruction. In this discussion, the Panel acknowledged that use of these data would entail dealing with toxicity equivalence (TEQ) issues and pharmacokinetic (PK) modeling. Pertaining to the use of these data for quantitative risk assessment by the U.S. EPA, the Panel posed the question, "At what point does indirect or confounded human data supersede controlled animal bioassay data?", or alternatively, "How much human data uncertainty can we tolerate?" The Panel suggested, at the least, that the epidemiologic data could be used to "ground-truth" the animal bioassay modeling results.

Supporting Information

The Panel acknowledged that Ah receptor (AhR) binding affinities are not necessarily tied to endpoint sensitivity, but they reiterated the need to consider mechanistic modeling to aid in developing appropriate dose metrics or filling in data gaps in the existing dose-response data.

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SESSION 2: IMMUNOTOXICITY

The U.S. EPA plans to consider development of a quantitative dose-response assessment for the immunologic effects associated with TCDD exposure. Such an assessment would be based on information in U.S. EPA (2003), NAS (2006) and key studies identified in this workshop. The purpose of this session was to identify and discuss key issues pertaining to dose-response assessment for dioxin-induced immunologic effects.

Session 2 Panelists (Session Co-Chairs are identified by asterisk)

- Roger Cooke, Resources for the Future
- Rob Goble, Clark University
- *Belinda Hawkins, U.S. EPA
- Nancy Kerkvliet, Oregon State University
- Manolis Kogevinas, Centre for Research in Environmental Epidemiology
- Robert Luebke, U.S. EPA
- Paolo Mocarelli, University of Milan
- *Allen Silverstone, State University of New York, Upstate Medical University

- Courtney Sulentic, Wright State University
- Nigel Walker, National Institute of Environmental Health Sciences

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Key Study Selection Criteria

The Panel first addressed the Key Study Selection Criteria proposed by the U.S. EPA (Appendix C). The Panel raised the issue that the key study criteria do not apply to most studies designed to investigate immunotoxicity, including those used to calculate ED_{01}s (U.S. EPA, 2003). The Panel observed that most dioxin immunotoxicity studies are relatively high dose (>200 ng/kg-d) acute studies and/or use parenteral rather than oral administration.

The Panel discussed several studies often considered important for assessing the immunotoxic effects of TCDD exposure. The Oughton et al. (1995) mouse bioassay was discussed and, although the study does meet the proposed criteria, it could not be considered a key study; specifically, the Panel contended that since there were no functional alterations observed or measured in this bioassay, the changes in cellular phenotypes are only "suggestive" of immune alterations and cannot be regarded as having immunopathologic significance.

The Panel discussed two additional studies for further consideration by the U.S. EPA:

- Baccarelli et al. (2002). The Panel discussed this as a potentially key human epidemiological study that should be reviewed and considered further by the U.S. EPA. It measured the level of IgG, demonstrating a significant decline relative to dioxin body burdens.

- Smialowicz et al. (2008). The Panel noted that this study identified the antibody response to sheep red blood cells (SRBCs) as the critical effect, labeling this protocol as a functional assay. The Panel stated that if modeled, the U.S. EPA could calculate the BMR for this endpoint as 1 standard deviation from the control mean.

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SESSION 3A: DOSE-RESPONSE FOR NEUROTOXICITY AND NONREPRODUCTIVE ENDOCRINE EFFECTS

The U.S. EPA plans to consider development of a quantitative dose-response assessment for neurological and/or nonreproductive endocrine effects associated with TCDD exposure. Such an assessment would be based on information in U.S. EPA (2003), NAS (2006) and key studies identified in this workshop. The purpose of this session was to identify and discuss key issues pertaining to dose-response assessment for dioxin-induced neurological and/or nonreproductive endocrine effects.

Session 3A Panelists (Session Co-Chairs are identified by asterisk)

- *Maryka Bhattacharyya, Argonne National Laboratory
- Mike DeVito, U.S. EPA
- Mary Gilbert, U.S. EPA
- Rob Goble, Clark University
- Nancy Kerkvliet, Oregon State University
- Fumio Matsumura, University of California-Davis
- Paolo Mocarelli, University of Milan
- Chris Portier, National Institute of Environmental Health Sciences
- Lorenz Rhomberg, Gradient
- Allen Silverstone, State University of New York, Upstate Medical University
- Marie Sweeney, National Institute of Occupational Safety and Health
- *Bernie Weiss, University of Rochester

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What Are the Key Questions Regarding These Endpoints?

The Panel used the following question to initiate discussion: "*Are there identifiable indices of neurotoxicity and nonreproductive endocrine effects in animal studies and human populations?*" Under this discussion topic, the Panel discussed three endpoints: neurotoxicity (with focus on developmental exposures), thyroid dysfunction (e.g., thyroid hormone deficits), and diabetes. The Panel also addressed the relevance of windows of vulnerability to each

endpoint. The Panel acknowledged that, in some cases, the window of exposure may precede the window of expression of toxicity.

Epidemiological Study Selection

Developmental Neurotoxicity

The Panel recognized that an unusual feature for this endpoint is that there are sufficient human data for dose-response modeling (e.g., Dutch children [Huisman et al., 1995; Patandin et al., 1999] and U.S. children [Jacobson and Jacobson, 1996]) and there is an internal dose metric (serum concentrations). Additionally, the Panel discussed recent studies that address this endpoint in humans (from Japan [reference not provided] and Holland [e.g., Koopman-Esseboom et al., 1996; Vreugdenhil et al., 2002]). For continued investigation into this endpoint, the Panel raised two issues to the U.S. EPA:

- Conduct an evaluation of whether a modeled effect can be attributed to TCDD and not some other persistent organic pollutant (POP), although the Panel recognized that it is unlikely U.S. EPA will be able to distinguish among these exposures because other POPs are intrinsic confounders in the Dutch study.

- Allow animal data to inform the dose-response modeling of epidemiological data.

Thyroid Dysfunction

The Panel identified the availability of human data for this endpoint (e.g., Calvert et al., 1999; Koopman-Esseboom et al., 1994). Much of the thyroid dysfunction literature has been published since the 2003 Reassessment (e.g., Wang et al., 2005; Baccarelli et al., 2008). The Panel also noted the availability of an internal dose metric (serum concentrations). Additionally, the Panel discussed the mechanistic studies in animals that link TCDD to thyroid dysfunction. For continued investigation into this endpoint, the Panel raised three issues for the U.S. EPA to consider:

- Consider the newly available human data since the Reassessment.

- Investigate and clarify of the role of TCDD-induced thyroid dysfunction in developmental neurotoxicity.

- Evaluate and determine whether an effect can be attributed to TCDD or other contaminants.

Diabetes

The Panel discussed that data suggest that diabetes incidence in those under 55 years old may be associated with exposure to PCBs. They acknowledged that whether this is a dioxin-like compound (DLC) mediated effect or whether other POPs are responsible is still undetermined. The Panel also acknowledged that no animal model exists for the investigation of xenobiotic-induced diabetes, and that separating the injury dose level from the current body burdens would depend on good pharmacokinetics in humans. For continued investigation into this endpoint, the Panel listed two issues for the U.S. EPA to consider:

- Results from the Anniston study and the Great Lakes Fishermen study (references not provided) should be examined for dose metrics (both studies examine human PCB exposures).

- Changes of adipose tissue status need to be considered, given that dieting can cause release of lipid-soluble contaminants.

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SESSION 3B: DOSE-RESPONSE FOR CARDIOVASCULAR TOXICITY AND HEPATOTOXICITY

The U.S. EPA plans to consider development of a quantitative dose-response assessment for cardiovascular and/or hepatic effects associated with TCDD exposure. Such an assessment would be based on information in U.S. EPA (2003), NAS (2006) and key studies identified in this workshop. The purpose of this session was to identify and discuss key issues pertaining to dose-response assessment for dioxin-induced cardiovascular and/or hepatic effects.

Session 3B Panelists (Session Co-Chairs are identified by asterisk)

- Bob Budinksy, Dow Chemical
- Manolis Kogevinas, Centre for Research in Environmental Epidemiology
- Rob McDowell, U.S. Department of Agriculture
- Jim Olson, State University of New York, University at Buffalo
- Marian Pavuk, Agency for Toxic Substances and Disease Registry
- *Jeff Swartout, U.S. EPA
- *Mary Walker, University of New Mexico
- Nigel Walker, National Institute of Environmental Health Sciences

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Key Study Selection Criteria

The Panel initially focused on the draft key study selection criteria offered by the U.S. EPA (Appendix C). The panel recommended that for cardiovascular effects, which are not usually observed in rodents, the use of knockout mouse models (ApoE KO and LDLR KO) be moved to the "primary" column because only these studies establish the cardiovascular toxicity model in mice.

The panel also was concerned that the gavage procedure can increase mouse blood pressure. Consequently, the panel recommended that gavage studies not be used for the blood pressure endpoint (i.e., only dietary dosing studies should be considered).

Human Health Endpoints

In relation to the hepatic endpoint, the Panel acknowledged the large body of dose response information on hepatic effects in rodents and that enzyme (mostly CYP1A1) induction was a sensitive effect. However, the Panel cited the lack of linkage of CYP1A1 to downstream events, which complicates the toxicological interpretation of this endpoint, and concluded that

the more important liver effects in rodents are probably on the "road to cancer." The Panel noted that hepatic effects were not seen in the epidemiological studies, but acknowledged that these studies were not designed to detect them.

In relation to the cardiovascular endpoint, the Panel identified hypertension and ischemic heart disease (IHD) as two key endpoints from the epidemiological studies. The Panel recommended that the U.S. EPA perform a meta-analysis of these data. The Panel also commented that recent animal studies support the observations linking TCDD exposure to IHD and hypertension. In particular, the National Toxicology Program (NTP) study shows inflammatory and structural effects on resistant vascular arterioles (NTP, 2006). Additional evidence from the study suggests that the vascular effects may be CYP1A1-dependent. The Panel suggested that the NTP study data might be used as a surrogate for dose-response modeling of hypertension and that such an approach would be supported by data on the role of AhR in vascular function and remodeling.

POD Issues

The Panel was not supportive of 1% of maximal response (ED_{01}), which was utilized in the 2003 Reassessment. The Panel concluded that the POD should depend on the specific endpoint and recommended the following to the U.S. EPA:

- For continuous measures, base the BMR on difference from control. Consider the adversity level—at what point does the endpoint become adverse?

- For incidence data, set the BMR to a fixed-risk level.

Supporting Information

The Panel posed several suggestions to the U.S. EPA for reducing uncertainty and improving the knowledge base for TCDD toxicity.

- Use in vitro data to define uncertainties, such as the relative sensitivity between rodents and humans and around the definition of a POD.

- Consider studies on dioxin-like compounds (DLCs).

- Use PK modeling to define the dose metric for hepatic effects.

- Use body burden or serum concentrations for cardiovascular endpoints.

Finally, the Panel recommended that U.S. EPA finish the reassessment quickly and establish a definitive plan to review and incorporate new data as they become available.

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SESSION 4A: DOSE-RESPONSE FOR CANCER

The U.S. EPA plans to consider development of a quantitative dose-response assessment for cancer associated with TCDD exposure. Such an assessment would be based on information in U.S. EPA (2003), NAS (2006) and key studies identified in this workshop. The purpose of this session was to identify and discuss key issues pertaining to dose-response assessment for dioxin-induced cancer.

Session 4A Panelists (Session Co-Chairs are identified by asterisk)

- Lesa Aylward, Summit Toxicology
- Kenny Crump, Louisiana Tech University
- Dale Hattis, Clark University
- *Janet Hess-Wilson, U.S. EPA
- Karen Hogan, U.S. EPA
- Manolis Kogevinas, Centre for Research in Environmental Epidemiology
- Marian Pavuk, Agency for Toxic Substances and Disease Registry
- Chris Portier, National Institute of Environmental Health Sciences
- Lorenz Rhomberg, Gradient
- Jay Silkworth, General Electric
- *Nigel Walker, National Institute of Environmental Health Sciences

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Key Study Selection

The Panel discussed both human and rodent studies. In reviewing the epidemiological data, the Panel agreed the EPA should focus on four cohort studies (Dutch cohort, NIOSH cohort, BASF accident cohort, and Hamburg cohort) and pointed out that there are numerous updates and reevaluations of data now in the literature and others will be published soon. The Panel stated that it is appropriate for the U.S. EPA to consider the increase in total cancers for modeling human cancer data, however, Non-Hodgkin's lymphoma, and lung tumors are the main TCDD-related cancer types seen in humans exposed to TCDD. The Panel suggested the U.S. EPA focus the quantitative dose-response modeling on the human data.

In reviewing the rat data, the Panel identified four new NTP rodent cancer bioassays with liver and lungs as the main target organs. However, they suggested that dose-response modeling efforts should model "all cancers" from these NTP data sets as well and use tumor incidence—not individual rats as measures.

Key Study Selection Criteria

The Panel discussed whether data for TCDD only should be used or if PCB126 could be used to develop a dose-response curve. From this discussion, the Panel reached a general agreement that limiting the dose-response modeling and cancer assessment to TCDD only would be the best approach.

Regarding the oral dosing regimens, the Panel discussed the differences in results from different bioassays. They concluded that there were insufficient data to pick between oral feed (Kociba et al., 1978) and oral gavage (NTP, 2006) studies, but stated "If all aspects of studies were equal, an oral feed study is preferred." However, given that current data sets are not equal, they agreed that U.S. EPA should consider both feed and gavage studies.

The Panel put forth the recommendation that studies that include initiation-promotion model data and TgAC transgenic model data from oral exposure studies should be excluded from the primary category in the key study selection criteria (Appendix C lists the draft study selection criteria distributed prior to the meeting). Studies from both classifications should be moved to the second tier.

The Panel was also unsupportive of the "response magnitude outside the range of normal variability" criterion, as they did not believe it was applicable to a cancer endpoint.

Critical Endpoints to Consider

The Panel recognized that the MOA for TCDD includes cell growth/differentiation dysregulation, that different endpoints (tumor types) across species may be expected, and that there are differences in tumor sites across species. The Panel further acknowledged that there is insufficient information to determine if rodent tumor types observed are relevant to humans. Thus, the Panel suggests the following:

- U.S. EPA should consider all the observed cancer endpoints in its evaluation.

Nonlinear (aka threshold) Versus Linear Dose-Response Modeling

The Panel agreed that NTP bioassays appear to demonstrate nonlinear dose response, but they expressed concern about using animal data to infer slope and dose response for humans. The Panel pointed out that there are differences in slopes across different bioassays, and specifically, that some appear linear while others appear nonlinear. Given the observation of both nonlinear vs. linear, the Panel concluded that neither could be ruled out for extrapolation below the POD simply based on the available data. One panelist noted that U.S. EPA Cancer Guidelines (U.S. EPA, 2005) state that only if one can demonstrate that the MOA has a threshold dose-response shape, and can exclude all other potential linear MOAs, can one use a nonlinear model. Lastly, the Panel noted that there are data and rationales to support use of both linear and

nonlinear response below POD. From this discussion, the Panel raised one possibility to the U.S. EPA:

- Both linear and nonlinear model functions should be considered in the dose-response analysis.

Dose Metrics

In considering human data, the Panel expressed a preference for lipid-adjusted serum levels over body burden (BB), and they expressed concerns over the assumptions used in the back calculation of the BB in the epidemiologic cohorts. In considering the rat data, the Panel supported the use of BB—especially lipid-adjusted BB. The Panel, however, did express concern over the sequestering of TCDD in liver and then the use of liver levels in BB calculations.

Supporting Information—Biologically-Based Dose-Response (BBDR) Models and MOA

The Panel discussed BBDR. Though once considered an attractive proposition, BBDR models may mask uncertainty within the models, necessitating them to be used with greater caution. The Panel suggested two issues for the U.S. EPA to consider:

- If there is a published model, use it if it is valid—do not generate a new model.
- Focus on the actual experimental data to drive the analysis.

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SESSION 4B: DOSE-RESPONSE FOR REPRODUCTIVE/DEVELOPMENTAL TOXICITY

The U.S. EPA plans to consider development of a quantitative dose-response assessment for reproductive and developmental effects associated with TCDD exposure. Such an assessment would be based on information in U.S. EPA (2003), NAS (2006) and key studies identified in this workshop. The purpose of this session was to identify and discuss key issues pertaining to dose-response assessment for dioxin-induced reproductive and developmental effects.

Session 4B Panelists (Session Co-Chairs are identified by asterisk)

- Barbara Abbott, U.S. EPA
- Bruce Allen, Bruce Allen Consulting
- Roger Cooke, Resources for the Future
- George Daston, Procter & Gamble
- Mike DeVito, U.S. EPA
- Rob Goble, Clark University
- *Fumio Matsumura, University of California-Davis
- Paolo Mocarelli, University of Milan
- Brian Petroff, University of Kansas
- *Glenn Rice, U.S. EPA
- Marie Sweeney, National Institute of Occupational Safety and Health
- Mary Walker, University of New Mexico
- Bernie Weiss, University of Rochester

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A Major Question Posed During this Workshop Session was "Are Human Embryos and Infants Less Sensitive to Dioxin Exposures Than Some Experimental Animals?"

The Panel recognized that animal data show a wide range of species sensitivity to dioxin for a given developmental or reproductive endpoint. Presently, there are data for some endpoints that show that human sensitivity is comparable to experimental animals (e.g., semen quality), and for other endpoints the data demonstrate that humans are insensitive compared to other species (e.g., cleft palate). Lastly, the Panel recognized that there are some endpoints for which relative human sensitivity remains uncertain.

Key Study Selection

The Panel reviewed the charge questions (Appendix B), discussed them, and listed two issues for the U.S. EPA to consider:

- Concerning key study determination, use a stepwise approach that is dependent upon the information available and needed to address the question.

- Concerning the key studies informing the POD and the POD endpoint choice, use the POD to depart from what is certain and use a high-confidence study that has found effects at a low enough level at which other effects are protected.

The Panel also developed Table 1, based on the information presented in this session. Table 1 identifies specific reproductive and developmental effects of concern, listing whether an effect has been observed in test animals and epidemiologic cohorts. It also identifies the ED_{10} estimated by the U.S. EPA (2003) for health effects observed in rodent bioassays. If the U.S. EPA did not report an ED_{10} for an effect, the table identifies a study where the effect was reported and the lowest study dose where the effect was observed. Table 1 also identifies the epidemiologic cohort where the specific reproductive and developmental effects were observed.

Epidemiological Study Utility

The Panel reviewed the charge questions (Appendix B), discussed them, and made two suggestions to the U.S. EPA:

- Concerning the ability of epidemiological studies to inform critical effects, start with concordance across species (including humans) for the spectrum of effects.

- Concerning the ability of epidemiological studies to inform dose-response modeling, start with the epidemiology and then go to animal data if the dose response has not been well characterized for an endpoint of interest and compare to animal data as a reality check.

Animal Model Utility

The Panel reviewed and discussed the charge questions (Appendix B). Table 1, which identifies the effects that occur in animals and also have relevance to humans, summarizes much of this discussion. Regarding the influence of mode of action (MOA) on animal model choice, the Panel concluded that by evaluating concordance among health effects reported in epidemiologic and animal bioassay data, the U.S. EPA could identify a set of plausible reproductive and developmental effects to consider. Actual animal and human MOA information is helpful in that it creates comfort with the animal models and in defining the boundaries of possible effects.

TABLE 1

Reproductive/Developmental Effects of Concern for Human Health

Endpoint	Rodent (ED_{10} ng/kg-d)	Human	Notes
Sperm Count/Motility	Yes (6.2−28; 66−200)	Yes	ED_{10} bases Mabley et al. (1992a,b) caudal sperm count and daily sperm production range from 6.2−28; Gray et al. (1997) epididymal sperm count and total testis sperm counts range from 66−200.
Sex Ratio	No	Yes, Seveso	
Delayed Puberty Males	Yes (94)	Yu-cheng	ED_{10} basis rat male puberty delay Gray et al. (1997). Need to qualify epidemiology data because of cohort PCDD/PCDFs exposures.
Delayed Puberty in Females	Yes	No in Seveso	Gray and Ostby (2002) report delayed puberty in female offspring of pregnant rats receiving a single dose of 1 µg TCDD/kg on GD 15.
Cleft Palate	Yes (6300−6400)	No	ED_{10} basis Birnbaum et al. (1989).
Premature Senescence	Yes	No, Seveso	Franczak et al. (2006) report that rats prematurely entered reproductive senescence, after receiving cumulative TCDD doses as low as 1.7 µg TCDD/kg. They considered first occurrence of prolonged interestrous interval (>6 d) as evidence of onset of reproductive senescence.
Hormones E2	Yes	Yes, Males— Seveso	Li et al. (1995) report serum estradiol-17β (E2) concentrations induced by equine Chorionic Gonadotropin injection were significantly elevated in female rats orally administered 10 µg/kg TCDD on PND 22. While E2 decreased dramatically in control animals during the preovulatory LH surge, it did not in TCDD-treated rats.
Low Birth Weight	Yes (190)	Suggestive effect in Seveso in first 8 years after exposure	ED_{10} basis Gray et al. (1997).
Reproductive Cycling (prolongation)	Yes	Yes, Seveso Prepubertal exposure	Franczak et al. (2006) report loss of normal cyclicity in female rats at 8 months of age following a cumulative dose of 1.7 µg TCDD/kg.

Supporting Information

The Panel reviewed the charge questions (Appendix B), discussed them, and made two suggestions to the U.S. EPA:

- Concerning deviation from default approaches for noncancer endpoints, there needs to be a careful assessment of the POD and the application of uncertainty factors in light of PK/pharmacodynamics (PD), population characteristics and variability, and MOA information.

- Concerning the MOA's ability to clarify endpoint and the incorporation of a cascade of cellular event into dose-response for noncancer endpoint, any study that helps inform the dose response should be considered—including studies not specific to dioxins. Complicated mechanistic models need not be developed. Standard dose-response models can be applied. One can look at the cascade of events in a stepwise, simple way.

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U.S. EPA (U.S. Environmental Protection Agency). 2003. Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds. NAS Review Draft (EPA/600/P-00/001Cb). U.S. Environmental Protection Agency, National Center for Environmental Assessment, Washington, DC. Available at http://www.epa.gov/nceawww1/pdfs/dioxin/nas-review/.

SESSION 5: QUANTITATIVE UNCERTAINTY ANALYSIS OF DOSE-RESPONSE

This session addressed the uncertainty analysis to be considered for the dose-response assessments. The session opened with a presentation on current estimates of dioxin exposure levels. Then it focused on the factors to include in the scope of an uncertainty analysis including dioxin kinetics.

Session 5 Panelists (Session Co-Chairs are identified by asterisk)

- Bruce Allen, Bruce Allen Consulting
- Lesa Aylward, Summit Toxicology
- Roger Cooke, Resources for the Future
- Kenny Crump, Louisiana Tech University
- Mike DeVito, U.S. EPA
- Dale Hattis, Clark University
- *Rick Hertzberg, Biomath Consulting
- Nancy Kerkvliet, Oregon State University
- Leonid Kopylev, U.S. EPA
- Rob McDowell, U.S. Department of Agriculture
- Lorenz Rhomberg, Gradient
- Woody Setzer, U.S. EPA
- Marie Sweeney, National Institute of Occupational Safety and Health
- *Linda Teuschler, U.S. EPA

Please note that the use of the term "concluded" or "recommended" in this summary does not mean that a consensus was reached. Session Summaries were written from the material prepared by the non-EPA/ANL Co-Chair and represent a synopsis of the panel discussions.

The Panel summarized the NAS comments regarding uncertainty. Areas for improvement include:

- Ensure "transparency, thoroughness, and clarity in quantitative uncertainty analysis."

- Describe and define (quantitatively to the extent possible) the variability and uncertainty for key assumptions used for each key endpoint-specific risk assessment, including choices of data set, point of departure, dose-response model, and dose metric.

- Incorporate probabilistic models to represent the range of plausible values.

- Assess goodness-of-fit of dose-response models.

- Provide upper and lower bounds on central tendency estimates for all statistical estimates.

- When quantification is not possible, clearly state it, and explain what would be required to achieve quantification.

Identification of Important Uncertainties

The Panel reviewed the charge questions (Appendix B), discussed them, and listed eight issues for consideration by the U.S. EPA:

- Concerning species and strain differences in the U.S. EPA's Response to NAS, current U.S. EPA procedures do not take this into account when selecting one data set for risk assessment. Issues include "Where are humans in the distribution of potencies that can be generated? How likely is it that human response is similar to the selected data? Can we infer inter-individual variability from these differences?"

- Concerning the use of animal data for cross species extrapolation to humans (PK and PD uncertainties), issues to consider include differences in distribution and responses following bolus doses from those of subchronic and chronic protocols; uncertainty in liver doses due to sequestration; differences in receptor binding affinity among congeners; and age factors (e.g., assumption of a lifetime constant daily dose for a cancer extrapolation).

- Concerning the description of AhR response, biochemical changes occur at lower doses than toxicological changes. There should be an effort to identify the biochemical changes that would mark Ah receptor binding to inform the BMR, and, thus, prevent toxicity.

- Concerning model uncertainty, the mathematical model choice depends on endpoint. There should be an effort towards determining what is the most sensitive endpoint(s) for humans and conducting animal studies to model that endpoint(s).

- Concerning exposure and dose response in human studies, ensure enough similarity to current human exposure profiles (mixture composition) so that a dose-response assessment can be done. Incorporate new epidemiological studies. Evaluate concordance with animal data and consistency across studies. Panel-acknowledged uncertainties include exposure estimates from person to person, shape of human dose-response curve, healthy worker effect, and age dependence.

- Concerning POD determination, uncertainty factors are inherently mathematically inconsistent and that should be conveyed in the discussion of uncertainties when interpreting the POD.

- Concerning dose metric, tissue concentration is preferred. It should be evaluated against a background of variability in AhR-binding expression. There is uncertainty in what level of binding should be considered, in different cell types, tissues, life stage (development). The relationship between dose metric and causation of adverse effects should be examined.

Low-Dose Extrapolation

The Panel reviewed the charge questions and discussed them (Appendix B). The Panel concluded that curve-fitting uncertainty (for a given dataset, dose metric, and model) can be characterized and is useful, but, by itself, it is an incomplete characterization of uncertainty. The Panel acknowledged the difficulty of fully characterizing uncertainty, especially quantitatively. Some panelists argued that the problem is insurmountable and that no meaningful uncertainty analysis is likely to be performable. Other panelists contended that, the difficulties notwithstanding, "good-faith" efforts to do something practical and forthright to characterize uncertainty in low-dose extrapolation would be useful and important. The Panel clarified "good faith" as meaning a characterization that is useful and not misleading to decision makers and is inclusive of approaches that have meaningful support in the scientific community as a whole. Being in "good faith" is more important than being complete (i.e., addressing every uncertain element), especially since completeness is not a realistic goal. From this discussion, the Panel listed four issues for consideration by the U.S. EPA:

- Review alternative data sets, dose metrics, and models to see where consequential uncertainties and impacts on low-dose implications arise.

- Consider the impacts of choices among plausible alternative data sets, dose metrics, models, and other more qualitative choices—issues include how much difference the choices make and also how much relative credence should be put to each alternative as a way of gauging and describing the landscape of imperfect knowledge regarding possibilities for the true dose-response.

    - Hard to do quantitatively, since the factors are not readily expressed as statistical distributions, but can describe the rationale for believing/doubting each alternative in terms of available supporting evidence, contrary evidence, and needed assumptions.

    - Expert judgment methods may be helpful in characterizing the relative weights of scientific credibility among alternatives. The expert judgment process, when conducted systematically, can be thought of as adding data to the assessment of credibility of alternatives, rather than as just an opinion poll.

    - Information on plausibility of alternative low-dose extrapolation approaches can come from external considerations of mode of action, and not just from statistical success at fitting particular (high-dose) data sets.

- Characterizing uncertainty through a variety of approaches could be tried, and their relative merits and shortcomings discussed, as a way forward.

- Consider the sources of potential error, particularly in epidemiological data (e.g., TEF uncertainty and variation in congener mixtures) and if possible quantify their impact on the dose-response assessment.

Considerations for Conducting Uncertainty Analysis

Overall, the Panel was split on whether U.S. EPA should do quantitative uncertainty analyses. The Panel noted that if done on only some of the uncertainties, then results would be misleading and could be misused. Ultimately, the Panel listed seven issues for consideration by the U.S. EPA:

- The Panel recapped what some consider as being the first integrated risk assessment, with structured expert judgment and uncertainty analysis, i.e., the Rasmussen Report (WASH-1400; U.S. Nuclear Regulatory Commission, 1975). In their discussion of the report, the Panel noted that in addition to standard event tree/fault tree modeling, this report also tackled difficult model uncertainty issues involved in accident progression, dispersion of released pollutants in the atmosphere, environmental transport, exposure, health, and economic impacts. And though the Panel also recognized that this method was no longer state-of-the-art, the Panel contended that it represents a good example of a structured approach and methodology that could be built upon.

- The Panel also discussed TEQs used in epidemiological studies, based on intake, and recognized that the key uncertainty in what was measured was not just intake but also involved PK/PD issues. The Panel acknowledged that the TEQ system is regularly used on a concentration basis, but they expressed concern that the qualification becomes lost. TEQs ignore pharmacokinetics and the common practice of rounding to orders of magnitude introduces more error.

- Structure the risk assessment along MOA steps—identify key biochemical measures (~5−10) common across toxic endpoints and identify the degree of meaningful change in effect or effect variance. Make a table with all options for data set, model, etc.; make best estimates/choices and determine which of these choices matter the most to the answer.

- Use expert panels—expert judgment can be collected scientifically (procedures are published). But there are known biases; central tendency estimates work much better than extremes.

- Use supporting studies to fill in critical data gaps—Info filling methods do exist (e.g., PK modeling). Put short-term studies into the "supporting info" category (unless, of course, the risk assessment is for acute exposures, such as chemical spills).

- Be creative in the analysis of uncertainty. Intermediate steps between AhR binding and the end processes can be hypothesized based on data, experiences, and analogies related to other chemicals.

- The 2003 Reassessment presented potency estimates on wide variety of endpoints/models; needed to be more transparent in that discussion. Statistical graphics can be used to convey uncertainties.

Reference

U.S. Nuclear Regulatory Commission. 1975. Reactor Safety Study: An Assessment of Accident Risks in U.S. Commercial Nuclear Power Plants. WASH-1400 (NUREG-75-014). Washington, DC.

APPENDIX A: 2009 U.S. EPA DIOXIN WORKSHOP AGENDA

SCIENTIFIC WORKSHOP
TO INFORM THE TECHNICAL WORK PLAN FOR U.S. EPA'S RESPONSE TO
NAS COMMENTS ON THE HEALTH EFFECTS OF DIOXIN
PRESENTED IN U.S. EPA'S DIOXIN REASSESSMENT

Cincinnati, OH

Date: February 18−20, 2009

BACKGROUND/WORKSHOP OBJECTIVE

At the request of the U.S. Environmental Protection Agency (U.S. EPA), the National Academy of Sciences (NAS) prepared a report, *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment* (NAS, 2006), that made a number of recommendations to improve the U.S. EPA's risk assessment for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). In response, the U.S. EPA will prepare a technical report that addresses key comments on the dose-response assessment for TCDD. The U.S. EPA intends to develop its response through a transparent process that provides multiple opportunities for input.

To assist in this effort, a Workshop will be held to inform the U.S. EPA's evaluation of the NAS recommendations. The Workshop will be open to the public. At the Workshop, the U.S. EPA will solicit input from expert scientists and the public.

The goal of the Workshop is to ensure that the U.S. EPA's response to the NAS comments focuses on the key issues and reflects the most meaningful science. The three main objectives of the Workshop are to (1) identify and discuss the technical challenges involved in addressing the NAS key comments on the TCDD dose-response assessment in the U.S. EPA Reassessment (U.S. EPA, 2003), (2) discuss approaches for addressing these comments, and (3) identify key published, independently peer-reviewed literature, particularly studies describing epidemiologic and *in vivo* mammalian bioassays, which are expected to be most useful for informing the U.S. EPA response.

Workshop participants will be encouraged to think broadly about the body of scientific information that can be used to inform the U.S. EPA's response and to participate in open dialogue regarding ways in which the science can best be used to address the key dose-response issues. This Workshop is similar to scientific workshops being conducted under the new review process for the National Ambient Air Quality Standards (NAAQS)[1] that assess health-related information for criteria pollutants.

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[1] Please see http://www.epa.gov/ttn/naaqs/ for more information on the new NAAQS review process.

The Workshop discussions are expected to build upon two prior publications:

1. Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds (U.S. EPA, 2003). This external review draft provides a comprehensive reassessment of dioxin exposure and human health effects. This "dioxin reassessment" was submitted in October 2004 to the National Academy of Sciences (NAS) for review.

2. *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment* (NAS, 2006).

Workshop participants are encouraged to review both of these documents and other relevant materials (e.g., the National Toxicology Program report on TCDD [NTP, 2006]) before the meeting because they provide important insights into the key questions and challenges. There are a number of open comment periods that are intended to facilitate a broad discussion of the issues.

Scientists with significant expertise and experience relevant to the health effects of TCDD or dioxin-like compounds and associated topics will be asked to serve on "expert panels" for discussions throughout the Workshop. Workshop panelists will include a wide range of experts representing many scientific areas needed to assess TCDD dose-response (e.g., epidemiology, human and animal toxicology, nuclear receptor biology, dose-response modeling, risk assessment, and uncertainty analysis). The Workshop panelists will be asked to highlight significant and emerging research and to make recommendations to the U.S. EPA regarding the design and scope of the technical response to NAS comments on the dose-response analysis for TCDD—including, but not limited to, recommendations for evaluating associated uncertainty. Open comment periods will follow each panel discussion session. Public participation will be encouraged by way of these designated open comment periods and, also, by participation in the scientific poster session planned for the second evening (February 19).

U.S. EPA will use the input received during this Workshop as the foundation for its development of a technical work plan for responding to the NAS comments on the TCDD dose-response analysis. The work plan will outline the schedule, process, and approaches for evaluating the relevant scientific information and addressing the key issues. The work plan also will identify the key literature to be utilized in U.S. EPA's response.

As a follow-on activity to this Workshop, a panel is being established under the Federal Advisory Committee Act (FACA) to guide and review the U.S. EPA's response to NAS comments. The FACA panel will be asked to conduct a consultation with the Agency on the draft technical work plan. At the same time, the public will also have the opportunity to provide comments to the FACA panel on the work plan. The final technical work plan will guide the development of the technical report that will constitute the U.S. EPA's response to NAS comments. During the development of this response, the U.S. EPA will seek advice from the FACA panel and the public several times. Finally, the FACA panel will be asked to review the technical report in a public forum.

The preliminary Agenda presented on the following pages may be revised prior to the Workshop following review by the session Co-Chairs; the dates and general timing of the

sessions, however, will not change. A final Agenda and a set of charge questions, intended to provide general direction for the Workshop discussions, will be posted on the Workshop Internet site (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=199923) prior to the meeting.

A poster session will be held on the evening of the second day (February 19). The purpose of this poster session is to provide a forum for scientists to present recent studies relevant to TCDD dose-response assessment and to encourage open discussion about these presentations.

REFERENCES

NAS (National Academy of Sciences). 2006. Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment. National Academies Press, Washington, DC (July). Available at http://www.nap.edu/catalog.php?record_id=11688.

NTP (National Toxicology Program). 2006. Toxicology and Carcinogenesis Studies of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) (CAS No. 1746-01-6) in Female Harlan Sprague-Dawley Rats (Gavage Studies). U.S. Department of Health and Human Services. NTP TR 521. Research Triangle Park, NC (April).

U.S. EPA (U.S. Environmental Protection Agency). 2003. *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds*, NAS review draft, Volumes 1-3 (EPA/600/P-00/001Cb, Volume 1). U.S. Environmental Protection Agency, National Center for Environmental Assessment, Washington, DC (December). Available at http://www.epa.gov/nceawww1/pdfs/dioxin/nas-review/.

WORKSHOP AGENDA

Day 1

8:00–9:00   **Registration**

9:00–9:30   **Welcome/Purpose of Meeting/Document Development Process**

9:30–9:45   **Panel Comments/Questions on Charge**

9:45–2:45   **Session 1: Quantitative Dose-Response Modeling Issues (Hall of Mirrors)**

  9:45–10:10   **Background/Introductory Remarks**

  10:10–10:35   **TCDD Kinetics: Converting Administered Doses in Animals to Human Body Burdens**
                 Presenter: Michael Devito

  10:35–11:30   **Panel Discussion**

  11:30–1:00   **Lunch**

  1:00–2:00   **Panel Discussion cont.**

  2:00–2:45   **Open Comment Period**

2:45–3:05   **Break**

3:05–5:15   **Session 2: Immunotoxicity (Hall of Mirrors)**

  3:05–3:15   **Background/Introductory Remarks**

  3:15–4:45   **Panel Discussion**

  4:45–5:15   **Open Comment Period**

Day 2

8:00–8:30   **Report-Outs for Sessions 1 and 2 (Hall of Mirrors)**

8:00–8:15   **Report-Out for 1: Quantitative Dose-Response Modeling Issues**

8:15–8:30   **Report-Out for 2: Immunotoxicity**

8:30–11:30   **Sessions 3A and 3B (concurrent sessions)**

8:30–11:30   **Session 3A: Dose-Response for Neurotoxicity and Nonreproductive Endocrine Effects (Hall of Mirrors)**

8:30–8:45   **Background/Introductory Remarks**

8:45–11:00   **Panel Discussion**

11:00–11:30   **Open Comment Period**

8:30–11:30   **Session 3B: Dose-Response for Cardiovascular Toxicity and Hepatotoxicity (Rookwood Room)**

8:30–8:45   **Background/Introductory Remarks**

8:45–11:00   **Panel Discussion**

11:00–11:30   **Open Comment Period**

11:30–1:00   **Lunch**

1:00–2:00   **Report-Outs for Sessions 3A and 3B (Hall of Mirrors)**

The structure of the session report-outs will include the following:

- Summary of session presentation including minority opinion
- Public comments
- Discussion

1:00–1:15   **Report-Out for 3A: Dose-Response for Neurotoxicity and Nonreproductive Endocrine Effects**

1:15–1:30   **Open Comment Period**

1:30–1:45	**Report-Out for 3B: Dose-Response for Cardiovascular Toxicity and Hepatotoxicity**
1:45–2:00	**Open Comment Period**

2:00–5:15   **Sessions 4A and 4B (concurrent sessions)**

2:00–5:15   **Session 4A: Dose-Response for Cancer (Hall of Mirrors)**

2:00–2:15	**Background/Introductory Remarks**
2:15–4:45	**Panel Discussion**
4:45–5:15	**Open Comment Period**

2:00–5:15   **Session 4B: Dose-Response for Reproductive/Developmental Toxicity (Rookwood Room)**

2:00–2:15	**Background/Introductory Remarks**
2:15–4:45	**Panel Discussion**
4:45–5:15	**Open Comment Period**

6:45–8:15   **Poster Session (Rosewood Room)**

Day 3

8:30–9:30   **Report-Outs for Sessions 4A and 4B (Hall of Mirrors)**

8:30–8:45	**Report-Out for 4A: Dose-Response for Cancer**
8:45–9:00	**Open Comment Period**
9:00–9:15	**Report-Out for 4B: Dose-Response for Reproductive/Developmental Toxicity**
9:15–9:30	**Open Comment Period**

9:30–3:30   **<u>Session 5: Quantitative Uncertainty Analysis of Dose-Response (Hall of Mirrors)</u>**

9:30–9:40   **Background/Introductory Remarks**

9:40–10:10   **Evidence of a Decline in Background Dioxin Exposures in Americans Between the 1990s and 2000s**
Presenter: Matt Lorber

10:10–10:30   Break

10:30–11:30   **Panel Discussion**

11:30–1:00   **Lunch**

1:00–2:15   **Panel Discussion cont.**

2:15–2:30   Break

2:30–3:00   **Open Comment Period**

3:00–3:15   **Report-Out for 5: Quantitative Uncertainty Analysis of Dose-Response**

3:15–3:30   **Closing Remarks**

3:30   Adjourn

APPENDIX B: 2009 U.S. EPA DIOXIN WORKSHOP
QUESTIONS TO GUIDE PANEL DISCUSSIONS

SESSION 1

Dose Metric

Considering all of the endpoints or target tissues, and species that U.S. Environmental Protection Agency (U.S. EPA)'s dose-response modeling might evaluate, what are the best measures of dose (e.g., ingested, tissue concentrations, body burden, receptor occupancy, other surrogate) and why?

Developing Dose-Response Models from Mammalian Bioassays

How best can the point of departure (POD) be determined when the response range is incompletely characterized (i.e., high response at the lowest dose or low response at the highest dose; observed in several key 2,3,7,8-Tetrachlorodibenzo-p-Dioxin [TCDD] studies)?

If considered to be biologically plausible, how can a threshold be incorporated into a dose-response function (e.g., for TCDD cancer data)?

How can nonmonotonic responses be incorporated into the dose-response function?

Developing Dose-Response Models from Epidemiological Studies

How can the epidemiological data be utilized best to inform the TCDD exposure-response modeling? Which epidemiological studies are most relevant?

Supporting Information

For those toxicological endpoints that are Ah receptor-mediated, how would the receptor kinetics influence the shape of the dose-response curve? How would downstream cellular events affect the shape of the dose-response curve? How can this cascade of cellular events be incorporated into a quantitative model of dose-response?

SESSIONS 2, 3A, 3B, 4A, AND 4B

Key Study Selection

For this endpoint, what refinements should be made to the draft criteria for selection of key studies?

What are the specific effects of concern for human health for this endpoint?

Based on the draft criteria for the selection of key studies, what are the key studies informing the shape of the dose-response curve above the POD and the choice of the POD for this endpoint?

Epidemiological Study Utility

How and to what extent do the epidemiological data inform the choice of critical effect?

How can the epidemiological data inform the quantitative dose-response modeling?

Animal Model Utility

Are there types of effects observed in animal models that are more relevant to humans than others? To what extent does information on mode of action (MOA) influence the choice of animal model (species, strain, sex)?

Supporting Information

Are there studies that establish a sufficient justification for departure from the default procedures that address the shape of the dose-response curve below the POD under the cancer guidelines?

Are there studies that establish a sufficient justification for departing from U.S. EPA's default approaches for noncancer endpoints?

To what extent can MOA information clarify the identification of endpoints of concern and dose-response metric for this endpoint? How can the cascade of cellular events for this endpoint be incorporated into a quantitative model of dose response?

SESSION 5

For cancer and noncancer TCDD dose-response assessments, U.S. EPA is interested in developing a quantitative uncertainty analysis addressing both parameter and model uncertainty, if feasible. Uncertainties will include, among others, choice of endpoint; underlying study uncertainties; choice of dose metric; interspecies extrapolations such as kinetic uncertainties; and choice of dose-response model, including threshold models. The U.S. EPA is currently examining techniques and tools for uncertainty analysis—including Bayesian and frequentist approaches.

Identification of Important Uncertainties

What are the major uncertainties pertaining to modeling the animal data?
> Consider the dose metric (species or tissue specificity), vehicle of administration, exposure frequency, exposure duration, and POD determination (e.g., benchmark response selection or no-observed-adverse-effect level/lowest-observed-adverse-effect level identification).

What are the major uncertainties pertaining to dose-response modeling below the POD?
> Consider how receptor kinetics and downstream cellular event information might be used to bound the uncertainties associated with dose-response modeling below the POD.

What are the major uncertainties in cross-species extrapolation (e.g., half-lives, tissue distribution, and toxicodynamics)?
> Consider the primary species dosed with TCDD: mice, hamsters, rats, guinea pigs, and monkeys.

What are the major uncertainties pertaining to intrahuman variability?
> Consider what data sets would be useful to represent sensitive subpopulations.

What are other significant sources of uncertainty for the cancer and noncancer assessments?

Considerations for Conducting Uncertainty Analysis

What data sets could be used to quantify uncertainties in cancer and noncancer TCDD dose-response assessments?
> Consider dioxin-like compound dose-response data.
> Consider MOA information.

What are the appropriate techniques for the TCDD dose-response uncertainty analysis, and what are their respective strengths and weaknesses of these approaches as applied to TCDD?

APPENDIX C: 2009 U.S. EPA DIOXIN WORKSHOP DRAFT SELECTION CRITERIA TO IDENTIFY KEY *IN VIVO* MAMMALIAN STUDIES THAT INFORM DOSE-RESPONSE MODELING FOR 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD)[a]

Study Feature	Selection Rationale		
	Primary[b]	*Secondary*[c]	*Currently Excluded*
Chemical, purity, matrix/medium	TCDD-only doses included, purity specified, matrix in which TCDD is administered is identified	TCDD purity or matrix not clearly identified	Studies of dioxin-like compounds (DLCs) or mixtures
Peer review	Independently peer-reviewed, publicly available	Supplementary materials accompanying peer-reviewed publication	Not formally peer-reviewed; literature not publicly available
Study design, execution, and reporting	Clearly documented and consistent with standard toxicological principles, testing protocols, and practice (i.e., endpoint-appropriate, particularly for negative findings)	Testing protocol provides incomplete coverage of relevant endpoint-specific measures, particularly for negative findings	Studies not meeting standard principles and practices
Study subject: species, strain, and sensitivity for given endpoint; litter; life stage; gender	Mammalian species Strain and gender identified Animal age at beginning of treatment identified Litter confounders (within/between) accounted for	Mammalian species, *in vivo*, but only studying an artificially sensitive subject (e.g., knockout mouse)	Non-mammalian or not *in vivo*
Exposure route	Oral	Parenteral (e.g., intravenous, intramuscular, intraperitoneal, subcutaneous)	Inhalation, dermal, ocular
Dose level	Lowest dose ≤200 ng/kg-d for noncancer endpoints and ≤1 µg/kg-d for cancer	Lowest dose >200 ng/kg-d for noncancer endpoints, or >1.0 µg/kg-d for cancer	
Exposure frequency, duration, and timing	Dosing regimen characterized and explained		Characterization/explanation missing or cannot be determined
Controls	Appropriate and well characterized	Effect reported, but with no negative control	
Response	Effect relevant to human health Magnitude outside range of normal variability	Precursor effects, or adaptive responses potentially relevant to human health	Lethality
Statistical evaluation	Clearly described and appropriate to the endpoint and study design (e.g., per error variance, magnitude of effect)	Limited statistical context	

[a] NAS (2006) commented that the selection of data sets for quantitative dose-response modeling needed to be more transparent. These draft criteria are offered for consideration at the kickoff workshop. These criteria would be used to identify candidate studies of non-human mammals that would be used to define the point-of-departure (POD). These criteria are not designed for hazard identification or weight-of-evidence determinations. Studies addressing data other than direct TCDD dose-response in mammals (including toxicokinetic data on absorption, distribution, metabolism, or elimination; information on physiologically-based pharmacokinetic [PBPK] modeling, and mode of action data) will be evaluated separately.

[b] Presents preliminary draft criteria for evaluating a study being considered for estimating a POD in a TCDD dose-response model.

[c] Presents preliminary draft criteria that could qualify a study as primary with support from other lines of evidence (e.g., PBPK modeling), when no study for an endpoint meets the "primary" criteria.

APPENDIX C

Summaries and Evaluations of Cancer and Noncancer Epidemiological Studies for Inclusion in TCDD Dose-Response Assessment

November 2011

NOTICE

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

CONTENTS—Appendix C: Summaries and Evaluations of Cancer and Noncancer Epidemiological Studies for Inclusion in TCDD Dose-Response Assessment

LIST OF TABLES

APPENDIX C.   SUMMARIES AND EVALUATIONS OF CANCER AND NONCANCER EPIDEMIOLOGICAL STUDIES FOR INCLUSION IN TCDD DOSE-RESPONSE ASSESSMENT

C.1. EVALUATION OF EPIDEMIOLOGICAL STUDIES FOR DOSE-RESPONSE ASSESSMENT

This appendix summarizes and evaluates studies for potential use in TCDD dose-response assessment using the study evaluation considerations and inclusion criteria for epidemiologic data (see Section 2.3.1). Those studies that meet the study inclusion criteria are listed in Section 2 of this document in Tables 2-1 and 2-2, for cancer and noncancer, respectively. The following sections, C.1.1 and C.1.2, are organized by epidemiologic study population. Following a brief summary of each study population, its associated studies are then summarized chronologically, assessed for methodological considerations relative to epidemiologic cohorts and studies and evaluated for suitability for TCDD dose-response assessment.

Sections C.2 and C.3 of this appendix provide specific details of the study selection criteria results for the cancer and noncancer epidemiologic studies, respectively. This includes a table for each study with information on how each of the five considerations and three criteria were evaluated, and why each study was or was not selected by EPA for TCDD quantitative dose-response assessment.

C.1.1. Cancer

In the 2003 Reassessment, EPA selected three cohort studies from which to conduct a quantitative dose-response analysis: the National Institute for Occupational Safety and Health (NIOSH) cohort (Steenland et al., 2001b), the BASF cohort (1996b), and the Hamburg cohort (Becher et al., 1998). Although these studies were deemed suitable for a quantitative dose-response analysis, the criteria EPA used to reach this conclusion were unclear. In this section, the study selection criteria and methodological considerations presented in Section 2.3.1 are systematically applied to evaluate a number of studies to determine their suitability for inclusion in dose-response modeling. In addition to the three cohorts used in previous TCDD quantitative risk assessment, considerations are applied to other relevant TCDD epidemiological data sets that were identified through a literature review for epidemiological studies of TCDD and cancer

1   up through 2009. Study summaries and suitability for quantitative dose-response analysis

2   evaluations are discussed below.

3

4   **C.1.1.1.** *Cancer Cohorts*

5   **C.1.1.1.1.** *The NIOSH cohort*

6   In 1978, the NIOSH undertook research that identified workers employed by U.S.

7   chemical companies that made products contaminated with TCDD between 1942 and 1982.

8   TCDD was generated in the production of 2,4,5-trichlorophenol and subsequent processes. This

9   chemical was used to make 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), which was a major

10   component of the widely-used defoliant, Agent Orange. The NIOSH cohort is the largest cohort

11   of occupational workers studied to date, and has been the subject of a series of investigations

12   spanning more than two decades. It is important to note that this cohort consists mostly of male

13   workers that were chronically exposed to TCDD via daily occupational exposure, as compared to

14   an acute accidental exposure scenario seen with other cohorts. The investigations have

15   progressed from a comparison of the mortality patterns of the cohort to the U.S. general

16   population to dose-response modeling using serum-derived estimates of TCDD that have been

17   back-extrapolated several decades. Analyses of cancer data from the NIOSH cohort that are

18   addressed in this section include studies published by Fingerhut et al. (1991a), Steenland et al.

19   (2001b; 1999), Cheng et al. (2006), and Collins et al. (2009).

20

21   **C.1.1.1.1.1.** *Fingerhut et al. (1991a)*

22   **C.1.1.1.1.1.1.** Study summary

23   The investigation of Fingerhut and her colleagues published nearly two decades ago

24   attracted widespread attention (Fingerhut et al., 1991a). This retrospective study examined

25   patterns of cancer mortality for 5,172 male workers who comprised the NIOSH cohort, which

26   combined workers from the company-specific cohorts of Dow Chemical (Ott et al., 1987; Cook,

27   1981) and the Monsanto Company (Zack and Gaffey, 1983; Zack and Suskind, 1980). These

28   workers were employed at 12 plants producing chemicals contaminated with TCDD. The

29   production processes were assumed to be the same in all 12 plants. Almost all workers in the

30   cohort (97%) had production or maintenance jobs with processes involving TCDD

31   contamination. On average, workers were employed for 2.7 years in specific processes that

1   involved TCDD contamination, and overall, were employed for 12.6 years. Serum TCDD

2   samples were obtained from 253 workers (gender not specified) from two plants (selection

3   criteria and response rates not specified in the study). Due to the high correlation between the

4   logarithm of serum TCDD levels and the logarithm of years of exposure (Pearson correlation

5   coefficient=0.72), the study used duration of exposure as a surrogate for TCDD exposure. The

6   mortality follow-up began in 1940 and extended until the end of 1987. Vital status was

7   determined using records from the Social Security Administration, the Internal Revenue Service,

8   or the National Death Index. The ascertainment of vital status in the cohort was nearly complete,

9   with less than 1% of the cohort not followed up until death or the end of the study period.

10   Two-hundred two workers were excluded because plant records did not show duration of

11   exposure, and 67 women were excluded. No additional data were presented on study

12   participants to determine how representative they were of the overall study cohort. Comparisons

13   of mortality were made relative to the U.S. male general population and expressed using the

14   standardized mortality ratios (SMRs) and 95% confidence intervals (CIs). Life-table methods

15   were used to generate person-years of risk accrued by cohort members at each plant.

16   Person-years and corresponding deaths were tabulated across age, race, and year of death strata,

17   which permitted the SMRs to be adjusted for the potential confounding influence from these

18   three characteristics. No unadjusted SMRs were presented in the paper. The cross-classification

19   of person-years and deaths was also done across several exposure-related groupings, including

20   duration of employment, years since first exposure, years since last exposure, and duration of

21   exposure. Employment duration was categorized as <5, 5− <10, 10− <15, 15− <20, 20− <25,

22   25− <30, and ≥30 years. The variable "years since first exposure" (<10, 10− <20, and ≥20 years)

23   was used to evaluate associations for different latency periods. The analysis was jointly

24   stratified by duration of employment and for varying latency intervals to evaluate whether cohort

25   members with higher cumulative TCDD levels had higher cancer mortality rates than those

26   cohort members with lower cumulative levels.

27   Overall, the cohort of workers had slightly elevated cancer mortality than the general

28   population (SMR = 1.15, 95% CI = 1.02−1.30). Comparisons to the general population,

29   however, yielded no statistically significant excess for any site-specific cancer. Cancer mortality

30   was examined for the subset of workers that worked for at least one year and had a latency

31   interval of at least 20 years ($n = 1,520$). The 1-year cut-point was selected based on analyses of

1   serum levels in a subset of 253 workers which revealed that every worker employed for at least

2   one year had a lipid-adjusted serum level that exceeded the mean (7 ppt). Relative to the

3   U.S. general population, statistically significant excesses in cancer mortality were observed for

4   all cancers (SMR = 1.46, 95% CI = 1.21−1.76), cancers of the respiratory system (SMR = 1.42,

5   95% CI = 1.03−1.92), and for soft tissue sarcoma (SMR = 9.22, 95% CI = 1.90−26.95) among

6   this subset of 1,520 male workers. The elevated SMR for soft tissue sarcoma, however, was

7   based on only three cases in this subset.

8   SMRs also were generated across joint categories of duration of exposure and period of

9   latency for deaths from all cancer sites (combined), and cancer of the trachea, bronchus, and

10   lung. Increased SMRs were observed in strata defined by longer duration of exposure and

11   latency, but no statistically significant linear trends were found.

12

13   **C.1.1.1.1.1.2.**   Study evaluation

14   This cohort was the largest of four the International Agency for Research on Cancer

15   (IARC) considered in its 1997 classification of TCDD as a Group 1 human carcinogen (IARC,

16   1997). Duration of employment in processes that involved TCDD contamination was used as a

17   surrogate measure of cumulative exposure. This was based on a high correlation detected

18   between serum TCDD levels and duration of exposure. These 253 workers selected from two

19   plants each had their last exposure 15–37 years prior to evaluation. In using this exposure

20   metric, Fingerhut et al. (1991a) made the implicit assumption that concentrations of TCDD

21   exposures were equivalent at all production plants. Doses for individual cohort members were

22   not reconstructed for these analyses, although they were in subsequent analyses of this cohort.

23   Workers in this cohort were also exposed to other chemicals, which could have

24   introduced bias if these chemicals were associated with both TCDD exposure and the health

25   outcomes being examined. At one plant, workers were exposed to 4-aminobiphenyl. Previous

26   investigators also reported that workers at another plant were exposed to 2,4,5-T and

27   2,4-dichlorophenoxyacetic acid (2,4-D) (Bond et al., 1989; Bond et al., 1988; Ott et al., 1987).

28   Although this study did not examine the impact of confounding by other occupational

29   coexposures, subsequent analyses of this cohort showed that associations between cumulative

30   TCDD and all cancer mortality persisted after excluding workers exposed to pentachlorophenols

31   from the analyses (Steenland et al., 1999). Further, the removal of workers who died from

1   bladder cancer did not substantially change the dose-response relationship between TCDD and

2   cancer mortality from all other sites combined. This finding suggests that exposures to

3   4-aminobiphenyl distort the association between cancer mortality and TCDD exposure. Overall,

4   there is little evidence of confounding by these coexposures among this cohort; however,

5   exposure to other possible confounders, such as dioxin-like compounds (DLCs), was not

6   examined.

7   The study collected no information on the smoking behaviors of the workers, and

8   therefore, the SMRs do not account for possible differences in the prevalence of smoking that

9   existed between the workers and the general population. For several reasons, however, the

10   inability to take into account smoking is unlikely to have been an important source of bias. First,

11   mortality from other smoking-related causes of death such as nonmalignant respiratory disease

12   were not more common in the cohort than in the general population (SMR = 0.96,

13   95% CI = 0.54−1.58). Second, stratified analyses of workers with at least a 20-year latency

14   (assuming this subset shared similar smoking habits) revealed that excesses were apparent only

15   among those who were exposed for at least 1 year. Specifically, when compared to the general

16   population, the SMR among workers exposed for at least 1 year with a latency of 20 years was

17   1.46 (95% CI = 1.21−1.76), while those exposed for less than 1 year had an SMR of 1.02

18   (95% CI = 0.76−1.36). Third, for comparisons of cancer mortality between blue-collar workers

19   and the general population, smoking is unlikely to explain cancer excesses of greater than

20   10−20% (Siemiatycki et al., 1988). Finally, the investigators found no substantial changes in the

21   results for lung cancer when risks were adjusted for smoking histories obtained in 1987 from

22   223 workers employed at two plants. These data were used to adjust for the expected number of

23   lung cancer deaths expected in the entire cohort (Fingerhut et al., 1991a). Following this

24   adjustment, a small change was observed in the SMR for lung cancer in the overall cohort from

25   1.11 (95% CI = 0.89−1.37) to 1.05 (95% CI = 0.85−1.30). Similarly, only a slight change in the

26   SMR for lung cancer in the higher exposure subcohort was noted from an SMR of 1.39

27   (95% CI = 0.99−1.89) to 1.37 (95% CI = 0.98−1.87).

28   The use of death certificate information from the National Death Index is appropriate for

29   identifying cancer outcomes. For site-specific cancers such as soft tissue sarcoma, however, the

30   coding of the underlying cause of death is more prone to misclassification (Percy et al., 1981).

31   Indeed, a review of tissues from four men concluded to have died from soft-tissue sarcoma

1 determined that two deaths had been misclassified (Fingerhut et al., 1991a). A review of hospital

2 data revealed that two other individuals had soft tissue sarcomas that were not identified by death

3 certificate information. The use of death certificate information to derive SMRs for cancer as a

4 whole is likely not subject to significant bias; the same might not hold true, however, for some

5 site-specific cancers such as soft tissue sarcoma.

6 Using the SMR metric to compare an occupational cohort with the general population is

7 subject to what is commonly referred to as the "healthy worker effect" (Li and Sung, 1999; Choi,

8 1992). The healthy worker effect is a bias that arises because those healthy enough to be

9 employed have lower morbidity and mortality rates than the general population. The healthy

10 worker effect is likely to be larger for occupations that are more physically demanding

11 (Aittomaki et al., 2005; Checkoway et al., 1989), and the healthy worker effect is considered to

12 be of little consequence in the interpretation of cancer mortality (Monson, 1986; McMichael,

13 1976). Few cancers are associated with a prolonged period of poor health that would affect

14 employability long before death. Also recognized is that, as the employed population ages, the

15 magnitude of the healthy worker effect decreases as the absolute reduction in mortality becomes

16 relatively smaller (McMichael, 1976). The mortality follow-up of occupational cohorts

17 generally spans several decades, which should minimize the associated healthy worker effect in

18 such studies. Bias could also be introduced in that workers who are healthier might be more

19 likely to stay employed and therefore accrue higher levels of exposure. In the NIOSH cohort,

20 however, mortality was ascertained for those who could have left the workforce or retired by

21 linking subjects to the National Death Index. Although internal cohort comparisons can

22 minimize the potential for the healthy worker effect for the reasons presented above, for cancer

23 outcomes, the SMR statistic is a valuable tool for characterizing whether occupational cohort are

24 more likely to die of cancer than the general population. Moreover, stratified analyses across

25 categories of duration of exposure, or latency periods within a cohort can yield important

26 insights about which workers are at greatest risk. Perhaps most important, subsequent analyses

27 of the NIOSH cohort that presented risk estimates derived from external comparisons using the

28 SMR were remarkably consistent with rate ratios derived using an internal referent (Steenland et

29 al., 1999).

30

C.1.1.1.1.1.3. Suitability of data for TCDD dose-response modeling

This cohort meets most of the identified considerations for conducting a quantitative dose-response analysis for mortality from all cancer sites combined. The NIOSH cohort is the largest cohort of TCDD-exposed workers, exposure characterization at an individual level is possible but not available in this particular study, and the follow-up period is long enough to evaluate latent effects. Although there is no direct evidence of any important source of bias, confounding may be present due to a lack of consideration of DLCs. For the purpose of quantitative dose-response modeling, it is important to note that subsequent studies of this cohort adopted methods that greatly improved the characterization of TCDD exposure in the NIOSH cohort and increased the follow-up interval (Cheng et al., 2006; Steenland et al., 2001b). As such, for all practical purposes, due consideration for dose-response modeling should focus on the more recently developed data sets.

For quantitative dose-response modeling for individual cancer sites, the data are much more limited. A statistically significant positive association with TCDD was noted only for soft-tissue sarcoma among those with more than 1 year of exposure and 20 years of latency (SMR = 9.22, 95% CI = 1.90−26.95). However there were only three deaths from soft tissue sarcoma among this exposed component of the cohort, and four deaths in total in the overall cohort. Also, misclassification of outcome for soft-tissue sarcoma through death registries is well recognized and supported with additional review of tissue from two of the men. Specifically, tissues from the four men who died of soft-tissue sarcoma revealed that only two of these cases were coded correctly.

Although subsequent analyses of the NIOSH cohort did not show evidence of confounding by other occupational exposures, the design of this initial publication of the NIOSH cohort did not allow for examination of exposures to other possible confounders, such as DLCs. Duration of exposure was used as a surrogate for cumulative TCDD exposure; therefore, effective doses could not be estimated. Therefore, dose-response modeling was not conducted for this study.

1 **C.1.1.1.1.2.** *Steenland et al. ([1999](#))*

2 **C.1.1.1.1.2.1.** Study summary

3   A subsequent analysis of the NIOSH cohort extended the follow-up interval of Fingerhut

4 et al. ([1991a](#)) by 6 years (i.e., from 1940−1993) and improved the characterization of TCDD

5 exposure ([Steenland et al., 1999](#)). A key distinction from the work of Fingerhut et al. ([1991a](#))

6 was the exclusion of several workers that had been included in the previous mortality analyses.

7 The authors excluded 40 workers who were either female, had never worked in TCDD-exposed

8 departments, or had missing date of birth information. An additional 238 workers were excluded

9 as occupational data for characterizing duration of exposure were lacking, preventing their use in

10 a subcohort dose-response analysis. This subcohort was further reduced by excluding workers

11 from four plants ($n = 591$) because the information on the degree of TCDD contamination in

12 work histories was limited, preventing the characterization of TCDD levels by job type.

13 Thirty-eight additional workers were excluded from the eight remaining plants because TCDD

14 contamination could not be estimated. Finally, 727 workers were excluded because they had

15 been exposed to pentachlorophenol. Exposures were assigned to 3,538 (69%) male members of

16 the overall cohort, a population substantially reduced from the 5,172 on which Fingerhut et al.

17 ([1991a](#)) reported. Steenland et al. ([1999](#)) also evaluated the mortality experience of a subcohort

18 of 608 workers with chloracne who had no exposure to pentachlorophenol.

19   For each worker, a quantitative exposure score for each day of work was calculated based

20 on the concentration of TCDD (μg/g) present in process materials, the fraction of the day

21 worked, and a qualitative contact level based on estimates of the amount of TCDD exposure via

22 dermal absorption or inhalation. The authors derived a cumulative measure of TCDD exposure

23 by summing the exposure scores across the working lifetime history for each worker. The

24 authors validated this cumulative exposure metric indirectly by comparing values obtained for

25 workers with and without chloracne. Such a validation is appropriate, given that chloracne is

26 considered a clinical sign of exposure to high doses of dioxin ([Ott et al., 1993](#)). The median

27 exposure score among those with chloracne was 11,546 compared with 77 among those without

28 ([Steenland and Deddens, 2003](#)).

29   Cancer mortality was compared using two approaches. As in Fingerhut et al. ([1991a](#)),

30 external comparisons were made to the U.S. general population using the SMR statistic. The

31 authors adjusted the SMR statistics for race, age, and calendar time. They also applied life-table

1   methods to characterize risks across the subcohort of 3,538 workers with exposure data by

2   categorizing the workers into seven cumulative exposure groups. The cut-points for these

3   categories were selected so that the number of deaths in each category was nearly equal to

4   optimize study power. Life-table analyses were extended further to consider a 15-year lag

5   interval, which in a practical sense means that person-years at risk would not begin to accrue

6   until 15 years after the first exposure occurred. The person-years and deaths that occurred in the

7   first 15 years were included in the lowest exposure grouping. The Cox proportional hazards

8   model was used to characterize risk within the cohort. Cox regression was used to provide an

9   estimate of the hazard ratios and the 95% CIs for ischemic heart disease, all cancers combined,

10 lung cancer, smoking related cancers, and all other cancers. The authors also performed Cox

11 regression analyses using the seven categories of exposure, adjusting the regression coefficients

12 for both year of birth and age. The regression models were run for both unlagged and lagged

13 (15 years) cumulative exposure scores.

14   Overall, when compared with the U.S. general population, a slight excess of cancer

15 mortality (from all sites) was noted in the 5,132 cohort study population (SMR = 1.13,

16 95% CI = 1.02−1.25). This result did not substantially differ from the earlier finding that

17 Fingerhut et al. (1991a) published (SMR = 1.15, 95% CI = 1.03−1.30). Site-specific analyses

18 revealed statistically significant excesses relative to the U.S. general population for bladder

19 cancer (SMR = 1.99, 95% CI = 1.13−3.23) and for cancer of the larynx (SMR = 2.22,

20 95% CI = 1.06−4.08). In the chloracne subcohort (n = 608), SMRs of 1.25

21 (95% CI = 0.98−1.57) and 1.45 (95% CI = 0.98−2.07) were found for all cancer sites and for

22 lung cancer, respectively, relative to the general population. The authors also found statistically

23 significant excesses for connective and soft tissue sarcomas (SMR = 11.32,

24 95% CI = 2.33−33.10) and for lymphatic and hematopoietic malignancies (SMR = 3.01,

25 95% CI = 1.43−8.52).

26   External comparisons made by grouping workers into septiles of cumulative TCDD

27 exposure and generating an SMR for each septile using the U.S. population as the referent group

28 suggested a dose-response relationship. For all cancer sites combined, workers in the highest

29 exposure score category had an SMR of 1.60 (95% CI = 1.15−1.82); increases also were

30 observed in the sixth (SMR = 1.34) and fifth (SMR = 1.15) septiles. The two-sided p-value

31 associated with the test for trend for cumulative TCDD exposure was statistically significant

1   ($p = 0.02$). A similar approach for lung cancer revealed virtually the same pattern. The

2   incorporation of a 15-year latency for the analyses of all cancer deaths, in general, produced

3   slightly higher SMRs across the septiles, although a slight attenuation of effect was noted in the

4   highest septile ($SMR_{unlagged} = 1.60$ vs. $SMR_{lagged} = 1.54$). For a 15-year lag, the lung cancer

5   SMRs were mixed compared to the unlagged results with some septile exposure categories

6   increasing and others decreasing relative to the lowest exposure group.

7   For the internal cohort comparisons using Cox regression analyses, higher hazard ratios

8   were found among workers in the higher exposure categories than those in the lowest. The linear

9   test for trend, however, was not statistically significant ($p = 0.10$). The associations across the

10   septiles for the unlagged exposure for the internal cohort comparisons were not as strong as for

11   the external cohort comparisons. The opposite was true, however, for cumulative exposures

12   lagged 15 years.

13   Relative to the lowest septile, stratified analyses revealed increased hazard ratios in the

14   upper septiles of the internal cohort comparisons for both smoking- and nonsmoking-related

15   forms of cancer. The test for linear trend was statistically significant for all other cancers (after

16   smoking-related cancers were excluded). These analyses suggest that the overall cancer findings

17   were not limited to an interaction between TCDD and smoking. Additional sensitivity analyses

18   by the authors indicated the findings for smoking-related cancers were largely unaffected by the

19   exclusion of bladder cancer cases. This observation suggests that exposure to 4-aminobiphenyl,

20   which occurred at one plant and might have contributed to an increased number of bladder

21   cancers, did not substantially bias the relationship between TCDD and all cancers combined.

22   The investigators also evaluated the dose-response relationship with a Cox regression

23   model separately for each plant using internal cohort comparisons and found some heterogeneity.

24   This finding is not unexpected particularly given the relatively small number of cancer deaths at

25   each plant, and given that exposures were quite low for one plant at which no positive

26   association was found. The variability among plants was taken into account by modeling plant

27   as a random effect measure in the Cox model, which produced little change in the slope

28   coefficient ($\beta = 0.0422$ vs. $\beta = 0.0453$, respectively).

29

1   **C.1.1.1.1.2.2.** Study evaluation

2   This study represents a valuable extension from that published by Fingerhut et al.

3   (1991a). Internal comparisons were performed to help minimize potential biases associated with

4   using an external comparison group (e.g., healthy worker effect, and differences in other risk

5   factors between the cohort and the general population). That similar dose-response relationships

6   were found for internal and external comparison populations suggests that the bias due to the

7   healthy worker effect in the cohort is minimal for cancer mortality. More importantly, the

8   construction of the cumulative exposure scores provides an improved opportunity to evaluate

9   dose-response relationships compared with the length of exposure and duration of employment

10   metrics that Fingerhut et al. (1991a) used.

11   A potential limitation of the NIOSH study was the inability to account for cigarette

12   smoking. If cigarette smoking did contribute to the increased cancer mortality rates in this and

13   other cohorts, increased cancer mortality from exposure to TCDD would be expected only for

14   smoking-attributable cancers. This study found associations with TCDD for both smoking- and

15   nonsmoking-related cancers, including a stronger association for nonsmoking-related cancers.

16   Therefore, the data provide evidence that associations between TCDD and cancer mortality are

17   not likely due to cigarette smoking.

18   The findings regarding latency should be interpreted cautiously as the statistical power in

19   the study to compare differences across latency intervals was limited. Caution also should be

20   heeded, given that latency intervals can vary on an individual basis as they are often

21   dose-dependent (Guess and Hoel, 1977). The evaluation of whether TCDD acts as either an

22   initiating or promoting agent (or both) is severely constrained by the reliance on cancer mortality

23   data rather than incidence data. This constraint is due to the fact that survival time can be quite

24   lengthy and can vary substantially across individuals and by cancer subtype. For example, the

25   5-year survival among U.S. males for all cancer sites combined ranged between 45 and 60%

26   (Clegg et al., 2002). When only mortality data are available, evaluating the time between when

27   individuals are first exposed and when they are first diagnosed with cancer is nearly impossible.

28   Starr (2003) suggested that Steenland et al. (1999) focused too heavily on the exposures

29   that incorporated a 15-year period of latency and that those who experienced high exposures

30   would inappropriately contribute person-years to the lowest exposure group "irrespective of how

31   great the workers' actual cumulative exposure scores may have been." Most cancer deaths

1   would, however, typically occur many years postemployment. Given that the follow-up interval

2   of the cohort was lengthy and the average exposure duration was 2.7 years, at the time of death,

3   person-years for those with high cumulative exposures would be captured appropriately. The

4   median 5-year survival for all cancers is approximately 50% (Clegg et al., 2002), so applying a

5   minimum latency of 5 years when using cancer mortality rather than cancer incidence data is

6   needed to assure that the exposure metric captures exposures before diagnosis. Increasing this

7   latency period, for example to 10 or 15 years, would eliminate consideration of exposures that

8   occur in the period between tumor occurrence and tumor detection (diagnosis), and allows for an

9   appropriate focus on exposures that act either early or late in the pathogenic process. If the

10 association of TCDD with cancer is causal, effects might become apparent only at high

11 exposures and with adequate latency. As such, IARC has concluded that a latency interval of

12 15 years could be too short (IARC, 1997). EPA considers the Steenland et al. (1999)

13 presentation to be balanced in that they provided the range in lifetime excess risk estimated

14 across the various models used. The authors' finding that the models with a 15-year lag

15 provided a statistically significant improvement in fit based on the chi-square test statistic should

16 not be readily dismissed.

17

18 **C.1.1.1.1.2.3.**   Suitability of data for TCDD dose-response modeling

19   This study meets most of the epidemiological considerations for conducting a

20 quantitative dose-response analysis for mortality from all cancer sites combined. This study

21 excludes a large number of workers who were exposed to pentachlorophenol, thus eliminating

22 the potential for bias from this exposure. Relative to the earlier study by Fingerhut et al. (1991a),

23 improvements were made to the methodology applied to assign TCDD exposures to the workers.

24 This study, however, is superseded by Steenland et al. (2001b), who provide a more detailed

25 presentation and modeling of the NIOSH cohort data. Therefore, dose-response modeling was

26 not pursued for this study, but was for the subsequent NIOSH study by Steenland et al. (2001b).

27

28 **C.1.1.1.1.3.   _Steenland et al. (2001b)_**

29 **C.1.1.1.1.3.1.**   Study summary

30   In 2001, Steenland et al. (2001b) published a risk analysis using the NIOSH cohort that,

31 for the first time, incorporated serum measures in the derivation of TCDD exposures for

1 individual workers. The authors applied the same exclusion criteria to the entire cohort of

2 workers across the 12 plants in the Steenland et al. (1999) study, leaving 3,538 male workers for

3 which risk estimates could be calculated. Unlike previous analyses of the NIOSH cohort that

4 considered several different mortality outcomes, the analyses presented in Steenland et al.

5 (2001b) focused exclusively on mortality from all cancers sites combined. The authors observed

6 256 cancer deaths in the cohort between 1942 and the end of 1993. All risks estimated in the

7 Steenland et al. (2001b) study were based on internal cohort comparisons.

8 Characterization of TCDD exposure levels among the workers was based on serum

9 measures obtained in 1988 from 199 workers who were employed in one of the eight plants.

10 Only those workers with both TCDD serum measures and previously developed exposure scores

11 (Steenland et al., 1999) were used to estimate the relation between these different exposure

12 metrics. Based on these findings, cumulative TCDD serum levels were estimated on an

13 individual basis for all 3,538 workers following restriction to a subset of 170 workers whose

14 1988 serum measures were greater than the upper range of background levels (10 ppt) (Steenland

15 et al., 2001b).

16 The authors developed a regression model estimated the level of TCDD at the time of last

17 exposure for the 170 workers. The model was based on the estimated half-life of TCDD, the

18 known work history of each worker, a pharmacokinetic model for the storage and excretion of

19 TCDD, and exposure scores for each job held by each worker over time. The resulting equation

20 follows:

21

22 $$y_{last\ exposure} = y_{1988}\ exp(\lambda\Delta t) \qquad\qquad (Eq.\ C\text{-}1)$$

23

24 The first-order elimination rate constant (λ) was based on a half-life of 8.7 years

25 previously reported for the Ranch Hands cohort (Michalek et al., 1996). The background rate of

26 TCDD exposure was assumed to be 6.1 parts per trillion (ppt), which was based on the median

27 level in a sample of 79 unexposed workers in the NIOSH cohort (Piacitelli et al., 1992). This

28 value was subtracted when TCDD values were back-extrapolated, and then added again after the

29 back-extrapolation was completed. A background level of 5 ppt also was used in some of the

30 analyses with minimal demonstrable effects on the results. Sensitivity analyses also were

1 incorporated to consider a 7.1-year half-life estimate that had been developed for the earlier

2 Ranch Hands study (Pirkle et al., 1989).

3   After back-extrapolating to obtain TCDD serums levels at the time of last exposure, the

4 investigators estimated cumulative (or "area under the curve") TCDD serum levels for every

5 cohort member. This estimation procedure was the same method Flesch-Janys et al. (1998)

6 applied to the Hamburg cohort to derive a coefficient for relating serum levels to exposure

7 scores. The "area under the curve" approach integrates time-specific serum levels over the

8 employment histories of the individual workers. The slope coefficient was estimated using a

9 no-intercept linear regression model. This model is based on the assumption that a cumulative

10 score of zero is associated with no serum levels above background.

11   Cox regression was also used to model the continuous measures of TCDD. A variety of

12 exposure metrics were considered that took into account different lags, nonlinear relationships

13 (e.g., log-transform and cubic spline), as well as threshold and nonthreshold exposure metrics.

14 Categorical analyses were used to evaluate risks across TCDD exposure groups, while different

15 shapes of dose-response curves were evaluated through the use of lagged and unlagged

16 continuous TCDD measures. Categorical analyses of TCDD exposure were conducted using the

17 Cox regression model to derive estimates of relative risk (RR) as described by hazard ratios and

18 95% CIs. The reference group in this analysis was those workers in the lowest septile

19 cumulative exposure grouping (<335 ppt-years). The septiles were chosen based on cumulative

20 serum levels that considered no lag and also a 15-year lag.

21   The investigators also conducted dose-response analyses using the toxicity equivalence

22 (TEQ) approach. The TEQ is calculated as the sum of all exposures to dioxins and furans

23 weighted by the potency of each specific compound. In this study, TCDD was assumed to

24 account for all dioxin exposures in the workplace. For background TEQ levels, the investigators

25 used a value of 50 ppt in the dose-response modeling. This is based on the assumption that

26 TCDD accounted for 10% of the toxicity of all dioxins and furans (WHO, 1998), and is

27 equivalent to using a background level of 5 ppt/yr that was used in the derivation of cumulative

28 serum TCDD levels. A statistically significant dose-response pattern was observed for all cancer

29 mortality and TCDD exposure based on log of cumulative TEQs with a 15-year lag. A

30 comparison of the overall model chi-square values indicated that the fit of this model was not as

31 good as that for TCDD.

1   The hazard ratios among workers grouped by categories of cumulative TCDD exposure

2   (lagged 15 years) suggested a positive dose-response relationship. Steenland et al. (2001b)

3   found statistically significant excesses in the higher exposure categories compared to the lowest

4   septile. The RR was 1.82, (95% CI = 1.18−2.82) for the sixth septile (7,568−20,455 ppt-years)

5   and 1.62, (95% CI = 1.03−2.56) for the seventh septile (>20,455 ppt-years). Cox regression

6   indicated that log TCDD serum concentrations (lagged 15 years) was positively associated with

7   cancer mortality (β = 0.097, standard error (β) = 0.032, p < 0.003). A statistically significant

8   improvement in fit was observed when a 15-year lag interval was incorporated into the model

9   compared to a model with no such lag [Model χ^2 with 4 degrees of freedom (df) = 7.5]. Results

10   were similar when using a half-life of 7.1 years rather than 8.7 years. The excess lifetime risk of

11   death from cancer at age 75 for TCDD intake (per 1.0-picogram per kilogram [pg/kg] of body

12   weight (BW) per day) was about 0.05−0.9% above a background lifetime risk of cancer death of

13   12.4%. The results from the best-fitting models provide lifetime risk estimates within the ranges

14   derived using data from the Hamburg cohort (Becher et al., 1998).

15   In both categorical and continuous analyses of TCDD based on a linear model, the

16   dose-response pattern tailed off at high exposures suggesting nonlinear effects. This

17   phenomenon could be due to saturation effects (Stayner et al., 2003) or, alternatively, could have

18   resulted from increased exposure misclassification of higher exposures (Steenland et al., 2001b).

19   Specifically, some of the highest exposures might have been poorly estimated as they occurred in

20   workers exposed to short-term high exposures during the clean-up of a spill. The choice of a

21   linear model to develop data from a single time point can also result in exposure

22   misclassification in those individuals that have differences in the length of exposure (Emond et

23   al., 2005). Misclassification would be less likely at low concentrations where dose-dependent

24   elimination is minimal.

25

26   **C.1.1.1.1.3.2.**   Study evaluation

27   An important consideration in the Steenland et al. (2001b) study was the use of a small

28   subset of workers (n = 170) to infer exposures for the remainder of the cohort. Although there is

29   limited information in the study to determine how representative the 199 workers were of the

30   overall workers in that plant, the authors report that exposures from the plant in which these

31   170 subjects worked (plant 1) were in the middle of the exposure distribution of the other plants

1   (2). This subset did comprise surviving members of the cohort (in 1988), and therefore, the

2   frequency distribution of their year of birth would have differed from the rest of the cohort.

3   Furthermore, these workers were employed at a single plant that had less detailed work histories

4   than the other plants; thus, the development of the exposure scores differed between this plant

5   and the others. Also, many of the workers at this plant had the same job title and were

6   employed during the same calendar period. The use of serum data from this subset adds a level

7   of uncertainty that is not readily characterized. The study report only states that the serum levels

8   were available for these individuals, but it does not provide any indication of how or why the

9   individuals were selected for serum evaluation or if there were a number of individuals that

10 declined to give samples. Thus, it is hard to gauge how representative this population is of the

11 plant cohort. Despite these limitations, the use of these sera data to derive cumulative measures

12 for all cohort workers seems warranted given the strong correlation observed between the

13 exposure scores, and TCDD serum levels estimates at the time of last exposure (Spearman

14 $r = 0.90$).

15   The authors performed an extensive series of sensitivity analyses and considered several

16 alternative exposure metrics to the simple linear model. The lifetime excess risk above

17 background was nearly twice as high for the log cumulative serum measures with a 15-year lag

18 when compared to the piecewise linear models with no lag. An important observation was that

19 the exposure metric based on cumulative serum (lagged 15 years) did not fit the data as well as

20 the cumulative exposure score used in earlier analyses ([Steenland et al., 1999](#)). A priori, one

21 would expect that a better fit would be obtained with serum-based measures because serum

22 provides a better measure of relevant biological dose. As the authors noted, inaccuracies

23 introduced in estimating the external-based exposure scores could have contributed to a poorer

24 fit of the data. Alternatively, exposure misclassification error could be introduced if serum

25 samples based on the 170 workers were not representative of the entire cohort. Although the

26 serum-based measures did not fit the data as well as the exposures scores, the authors regarded

27 them as providing a reasonable fit based on an improvement in log likelihood of 3.99 (between

28 the log cumulative serum model and the log cumulative exposure score model). Moreover, the

29 serum-based measures enabled better characterization of risk in units (pg/kg-day) that can be

30 used in regulating exposures.

31

1 **C.1.1.1.1.3.3.** Suitability of data for TCDD dose-response modeling

2   This study meets all of the epidemiological considerations for conducting a quantitative

3 dose-response analysis for mortality from all cancer sites combined. As mentioned previously,

4 the NIOSH cohort is the largest assembled to date for which TCDD-related risks of cancer

5 mortality can be estimated. The use of serum-based measures provides an objective measure of

6 TCDD exposure. Repeated measures in other study populations have provided reasonable

7 estimates of the half-life of TCDD, which permitted exposures to be back extrapolated in this

8 cohort.

9   The authors have made extensive efforts to evaluate a wide variety of nonlinear and

10 linear models with varying lengths of latency and log transformations. The model chi-square test

11 statistics were fairly similar for the log cumulative serum (15-year lag) (Model $\chi^2_{(4df)} = 11.3$)

12 model and the piecewise linear model (no lag) (Model $\chi^2_{(5df)} = 12.5$). These models, however,

13 produced results with twofold differences in lifetime excess risks. These differences underscore

14 the importance of characterizing uncertainty in modeling approaches when conducting

15 dose-response analysis.

16   The Steenland et al. (2001b) study characterizes risk in terms of pg/kg of body weight per

17 day. Given that tolerable daily intake dioxin levels are typically expressed in pg/kg of body

18 weight (WHO, 1998), the presentation of risks using these units is an important advance from the

19 earlier analyses that used exposure scores (Steenland et al., 1999). Many of the Steenland et al.

20 (2001b) findings are consistent with earlier work from this cohort, which is not surprising given

21 that exposures scores were used to derive serum-based levels for the cohort. The findings of

22 excess lifetime risks obtained for the best- fitting model are also consistent with those derived

23 from the Hamburg cohort (Becher et al., 1998). This study meets the epidemiological

24 considerations noted previously as there is no evidence that the study is subject to bias from

25 confounding due to cigarette smoking or other occupational exposures. Given the considerable

26 efforts to measure effective dose to TCDD among the study participants, this study also meets

27 the requisite dose-response modeling criteria and will be used in quantitative dose-response

28 analyses of cancer mortality.

C.1.1.1.1.4. *Cheng et al. (2006)*

C.1.1.1.1.4.1. Study summary

Cheng et al. (2006) undertook a subsequent quantitative risk assessment of 3,538 workers in the NIOSH cohort using serum-derived estimates of TCDD. This dose-response analysis was published after the 2003 Reassessment document was released. The goal of this study was to examine the relationship between TCDD and cancer mortality (all sites combined) using a new estimate of dose that estimated TCDD as a function of both exposure intensity and age using a kinetic model. This physiologically-based pharmacokinetic model has been termed the "concentration- and age-dependent elimination model" (CADM) and was developed by Aylward et al. (2005b). This model describes the kinetics of TCDD following oral exposure to humans by accounting for key processes affecting kinetics by simulating the total concentration of TCDD based on empirical consideration of hepatic processes (see Section 3.3). An important feature of this kinetic model is that it incorporates concentration- and age-dependent elimination of TCDD from the body; consequently, the effective half-life of TCDD elimination varies based on exposure history, body burden, and age of the exposed individuals. The study was motivated by the reasoning that back-calculations of TCDD using a first-order elimination model and a constant half-life of 7−9 years underestimated exposure to TCDD among workers. This underestimate, in turn, would result in overestimates of the carcinogenic potency of TCDD.

As with the earlier Steenland et al. (2001b) analyses, the cohort follow-up period was extended from 1942 until the end of 1993 and work histories were linked to a job exposure matrix to obtain cumulative TCDD scores. Two cumulative serum lipid exposure metrics (in ppt-years) were constructed using the data obtained from the sample of 170 workers. The first replicated the metric used in a previous analysis of the cohort (Steenland et al., 2001b) and was based on a first-order elimination model with an 8.7-year half-life (Michalek et al., 1996). The second metric was based on CADM and had two first-order elimination processes (Aylward et al., 2005a). This metric assumes that the elimination of TCDD in humans occurs at a faster rate when body concentrations are high and at slower rates in older individuals (Aylward et al., 2005a; Aylward et al., 2005b). The model was optimized using individuals for which serial measures of serum TCDD were available. These measures were obtained from 39 adults with initial serum levels between 130 and 144,000 ppt (Aylward et al., 2005b). This group included 36 individuals who had been exposed in the Seveso accident and 3 exposed in Vienna, Austria.

1   In practice, for serum levels greater than 1,000 ppt, the effective half-life would be less than

2   3 years, and for serum TCDD levels less than 50 ppt, the effective half-life would be more than

3   10 years (Aylward et al., 2005b). Results from the model indicate that men eliminate TCDD

4   faster than women do as demonstrated previously by Needham et al. (1994). These age- and

5   concentration-dependent processes were assumed to operate independently on TCDD in hepatic

6   and adipose tissues, and TCDD levels in liver and adipose tissue were assumed to be a nonlinear

7   function of body concentration. Cheng et al. (2006) calibrated CADM using a dose of 156 ng

8   per unit of exposure score and assumed a background exposure rate of 0.01 ng/kg-month. The

9   average TCDD ppt-years derived from CADM with a 15-year lag was 4.5−5.2 times higher than

10   with the first-order elimination model. The two metrics, however, were highly correlated based

11   on a Pearson correlation coefficient of 0.98 ($p < 0.001$). Comparisons of fit between the CADM

12   and first-order elimination model were made using R^2 values and presented in Aylward et al.

13   (2005b).

14   Cheng et al. (2006) compared the mortality experience of NIOSH workers to the U.S.

15   general population using the SMR statistic. SMR statistics also were generated separately for

16   each of the 8 plants and for all plants combined. Cox regression models were used to analyze

17   internal cohort dose response. These models used age as the time variable, and penalized

18   smoothing spline functions of the CADM metric also were considered. The possible

19   confounding effects of other occupational exposures and other regional population differences

20   were assessed by repeating analyses after excluding one plant at a time. Lagged and unlagged

21   TCDD exposures were analyzed separately, and stratified analyses allowed risk estimates to be

22   compared between smoking- and nonsmoking-related cancers. Cheng et al. (2006) adjusted the

23   slope estimates derived from the Cox model for the potential confounding effects of race and

24   year of birth.

25   Overall, a statistically significant excess in all cancer mortality in the cohort occurred

26   relative to the general population (SMR = 1.17, 95% CI = 1.03−1.32). The plant-specific SMRs

27   ranged from 0.62−1.87, with a statistically significant excess evident only for plant 10

28   (SMR = 1.87, 95% CI = 1.35−2.52). For lung cancer mortality, the overall SMR was not

29   statistically significant (SMR = 1.11, 95% CI = 0.89−1.37). A statistically significant excess of

30   lung cancer also was found for plant 10 (SMR = 2.35, 95% CI = 1.44−3.64). The SMRs between

1   smoking- (SMR = 1.22, 95% CI = 1.01−1.45) and nonsmoking-related cancers (SMR = 1.12,

2   95% CI = 0.94−1.33) were similar.

3   For the internal cohort analyses of serum-derived measures, the authors were able to

4   replicate the one-compartmental model used previously (Steenland et al., 2001b). As had been

5   noted by Steenland et al. (2001b), an inverse-dose-response pattern was seen for individuals with

6   high exposures (above 95th percentile); this type of pattern is frequently observed in occupational

7   studies (Stayner et al., 2003). Excluding these data produced a stronger association between

8   TCDD and all-cancer mortality. In fact, only when the upper 2.5% or 5% of observations was

9   removed did a statistically significant positive association become evident with the

10 untransformed, unlagged data. Similarly, when the model incorporated a lag of 15 years, a

11 statistically significant association was noted only for the untransformed TCDD ppt-years with

12 the upper 5% of observations removed. Stratified analyses revealed little difference in the

13 association between TCDD and smoking- and nonsmoking-related cancers, and the removal of

14 one plant at a time from the analyses of TCDD ppt-years changes did not substantially change

15 the slope.

16

17 **C.1.1.1.1.4.2.**   Study evaluation

18   The authors reported that CADM provided an improved fit over the one-compartmental

19 model, but presented no evidence regarding any formal test of statistical significance. A

20 comparison of R^2 values presented in Aylward et al. (2005b), however, does reveal that the R^2

21 value increased from 0.27 (first-order compartmental model with an 8.7-year half-life) to 0.40

22 for CADM. TCDD exposures estimated using CADM were approximately fivefold higher than

23 the one-compartmental model estimates among cohort members with higher levels of exposure.

24 Differences in exposure estimates between the two metrics were less striking among individuals

25 with lower TCDD exposures. The net effect was that CADM produced a 6- to 10-fold decrease

26 in the estimated risks compared to those previously reported (Steenland et al., 2001b).

27 Nonetheless, the estimates produced by CADM span more than two orders of magnitude under

28 various assumptions. Further uncertainties arise from between-worker variability of TCDD

29 elimination rates, possible residual confounding, and the variability associated with the use of

30 data obtained from other cohorts. Nevertheless, the use of the CADM model to estimate TCDD

1 exposure is considered a significant advantage over the previous first-order body burden

2 calculations.

3

4 **C.1.1.1.1.4.3.** Suitability of data for TCDD dose-response modeling

5   The value of including the NIOSH cohort data has already been established based on

6 investigations by Steenland et al. (2001b; 1999). The decision to include data from the

7 quantitative dose-response analysis by Cheng et al. (2006) relates to the added value that the

8 CADM exposure estimates would provide. The earlier modeling work of Aylward et al. (2005b)

9 provided some support for a modest improvement of the fit of CADM over the first-order

10 compartmental model, and they also confirmed previous studies that found that TCDD

11 elimination rates varied by age and sex. Recent work by Kerger et al. (2006) also demonstrates

12 that the half-life for TCDD is shorter among Seveso children than in adults, and that body

13 burdens influence the elimination of TCDD in humans. That estimates of half-lives among men

14 have been remarkably consistent, with mean estimates ranging between 6.9 and 8.7 years

15 (Needham et al., 2005; Michalek et al., 2002; Flesch-Janys et al., 1996; Pirkle et al., 1989),

16 however, is noteworthy. Based on the underlying strengths of the NIOSH cohort data and efforts

17 by Cheng et al. (2006) to improve estimates of effective dose, these data support further

18 dose-response modeling.

19

20 **C.1.1.1.1.5.** *Collins et al. (2009)*

21 **C.1.1.1.1.5.1.** Study summary

22   In a recent study, Collins et al. (2009) investigated the relationship between serum TCDD

23 levels and mortality rates in a cohort of trichlorophenol workers (gender not specified) exposed

24 to TCDD. These workers were part of the NIOSH cohort having accounted for approximately

25 45% of the person-years in an earlier analysis (Bodner et al., 2003). The investigators completed

26 an extensive dioxin serum evaluation of workers employed by the Dow Chemical plant in

27 Midland, Michigan, that made 2,4,5-trichlorophenol (TCP) from 1942 to 1979 and 2,4,5-T from

28 1948 to 1982. Collins et al. (2007) and Aylward et al. (2007) developed historical TCDD

29 exposure estimates for all TCP and 2,4,5-T workers. This study represents the largest group of

30 workers from a single plant ever studied for the health effects of TCDD. Little information on

31 how vital status was ascertained, was provided in this paper or in the Bodner et al. (2003) report

1   of mortality in this cohort. Although the authors indicate that death certificates were obtained

2   from the states in which the employees died, it is unclear whether vital status was ascertained

3   from company records or through record linkage to the National Death Index is unclear.

4   The follow-up interval for these workers spanned the period between 1942 and 2003.

5   Thus, the study included 10 more years of follow-up than earlier investigations of the entire

6   NIOSH cohort. Serum samples were obtained from 280 former workers (selection criteria

7   including data on gender were not specified) in 2004−2005. A simple one-compartment first-

8   order pharmacokinetic model and elimination rates as estimated from the BASF cohort were

9   used (Flesch-Janys et al., 1996). The "area under the curve" approach was used to characterize

10   workers' exposures over the course of their working careers and provided a cumulative measure

11   of exposure. Analyses were performed with and without 165 of the 1,615 workers exposed to

12   pentachlorophenol to evaluate the impact of these exposures.

13   External comparisons of cancer mortality rates to the general U.S. population were made

14   using SMRs. Internal cohort comparisons of exposure-response relationships were made using

15   the Cox regression model. This model used age as the time variable, and was adjusted for year

16   of hire and birth year. Only those causes of death for which an excess was found based on the

17   external comparisons or for which previous studies had identified a positive association were

18   selected for dose-response analyses.

19   A total of 177 cancer deaths were observed in the cohort. For the external comparison

20   with the U.S. general population, overall, no statistically significant difference was observed in

21   all cancer mortality among all workers (SMR = 1.0, 95% CI = 0.8−1.1). Results obtained after

22   excluding workers exposed to pentachlorophenol were similar (SMR = 0.9, 95% CI = 0.8−1.1).

23   Excess mortality in the cohort was found for leukemia (SMR = 1.9, 95% CI = 1.0−3.2) and soft

24   tissue sarcoma (SMR = 4.1, 95% CI = 1.1−10.5). Although not statistically significant SMRs for

25   other lymphohemopoietic cancers included non-Hodgkin lymphoma (SMR = 1.3, 95% CI = 0.6,

26   2.5) and Hodgkin disease (SMR = 2.2, 95% CI = 0.2, 6.4).

27   Internal cohort comparisons using the Cox regression model were performed for all

28   cancers combined, lung cancer, prostate cancer, leukemia, non-Hodgkin lymphoma, and

29   soft-tissue sarcoma. Whether the internal comparisons excluded those workers exposed to

30   pentachlorophenol is not entirely clear from the text or accompanying table, but presumably they

31   do not. The RR was 1.002 (95% CI = 0.991−1.013) for all cancer mortality per 1 ppb-year

1   increase in cumulative TCDD exposure was not statistically significant. Except for soft tissue

2   sarcomas, no statistically significant exposure-response trends were observed for any cancer site.

3   For soft tissue sarcoma, analyses were based on only four deaths.

4

5   **C.1.1.1.1.5.2.**   Study evaluation

6   A key limitation of this study is that SMRs were not derived for different periods of

7   latency for the external comparison group analysis. The original publication on the NIOSH

8   cohort found that SMRs increased when a 20-year latency period was incorporated (Fingerhut et

9   al., 1991a), and similar patterns have been observed in other occupational cohorts (Ott and

10   Zober, 1996a; Manz et al., 1991) and among Seveso residents (Consonni et al., 2008).

11   Additionally, dose-response analyses showed marked increases in slopes with a 15-year latency

12   period (Cheng et al., 2006; Steenland and Deddens, 2003). In this context, the absence of an

13   elevated SMR for cancer mortality is consistent with previous findings of the NIOSH cohort.

14   Additional analyses published subsequently (Collins et al., 2010) found no excess cancer

15   mortality in the cohort relative to the general population when a latency period of 20 years was

16   applied (SMR = 1.0, 95% CI = 0.8−1.1).

17   Unfortunately, the Collins et al. (2009) study did not include a categorical analysis of

18   TCDD exposure and cancer mortality. This categorical analysis would have enabled an

19   evaluation of whether a nonlinear association exists between TCDD exposure and cancer risk.

20   The analyses of both Cheng et al. (2006) and Steenland et al. (2001b) suggest an attenuation of

21   effects at higher doses, and several investigations have considered log-transformed associations

22   as a means to address nonlinearity. Also, the earlier plant-specific dose-response analyses of

23   Steenland et al. (2001b) are not consistent with the findings for the Midland plant that Collins et

24   al. (2009) presented. In response to the letter by Villeneuve and Steenland (2010) that

25   highlighted the value of characterizing risk across categories of TCDD exposure, Collins et al

26   (2010) reported SMRs across three cumulative exposure levels of 0.1−374.9, 375.0−1,999.9, and

27   2,000-112,253 ppt-month categories. No excess cancer mortality, as captured by the SMR, was

28   observed in any of the three exposure categories for analyses conducted with no latency and a

29   20-year latency. Given that excesses were not noted in the NIOSH cohort until approximately

30   14,000 ppt-months, the upper exposure grouping (2,000-112,253 ppt-months) used by Collins et

31   al. (2010) may not be able to differentiate possible associations at higher exposure levels.

C.1.1.1.1.5.3. Suitability of data for dose-response modeling

The Collins et al. (2009) study used serum levels to derive TCDD exposure estimates and does not appear to be subject to important biases. The reliance on data from one plant offers some advantages over the multiplant analyses, as heterogeneity in exposure to other occupational agents would be lower. The number of individuals who provided serum samples ($n = 280$) is greater than the 170 individuals used to derive TCDD estimates for the NIOSH cohort, but there was no information presented in either study to assess how representative subjects who provided samples were of the larger cohort. The authors found a statistically significant dose-response trend for soft tissue sarcoma mortality and TCDD exposures. Therefore, this study is considered suitable for quantitative dose-response analysis.

C.1.1.1.2. *The BASF cohort*

In 1953, dioxin contamination occurred as a result of an autoclave accident during the production of trichlorophenol at the BASF plant in Ludwigshafen, Germany. A second dioxin incident occurred in 1988 that was attributed to the blending of thermoplastic polyesters with brominated flame retardants. Of the two events, the one on November 13, 1953, was associated with more severe acute health effects, including chloracne that resulted in immediate hospitalizations for seven workers. These adverse events were not linked to TCDD until 1957 when TCDD was identified as a byproduct of the production of trichlorophenol and was shown to induce chloracne (Zober et al., 1994). Zober and colleagues (1998) noted that with the 1988 accident, affected individuals did not exhibit clinical symptoms or chloracne, but rather were identified through "analytical measures." In both instances, efforts were made to limit the potential for exposure to employees.

C.1.1.1.2.1. *Thiess and Frentzel-Beyme (1977) and Thiess et al. (1982)*
C.1.1.1.2.1.1. Study summary

A study of the mortality of workers employed at the BASF plant was first presented in 1977 (Thiess and Frentzel-Beyme, 1977) with subsequent updates in both 1982 (Thiess et al., 1982), and in 1990 (Zober et al., 1990). In the first published paper (Thiess et al., 1982), 74 employees involved in the 1953 accident were traced and their death certificate information extracted. Of these, 66 suffered from chloracne or severe dermatitis. Observed deaths were

1   compared to the expected number using three external reference groups: the town of

2   Ludwigshafen ($n = 180,000$), the district of Rhine-Hessia-Palatinate ($n = 1.8$ million), and the

3   Federal Republic of Germany ($n = 60.5$ million). Another comparison group was assembled by

4   selecting age-matched employees taken from other cohorts under study. This additional

5   comparison was aimed at avoiding potential biases associated with healthy worker effect when

6   using an external referent.

7   During a follow-up interval of up to 26 years (1953−1979), 21 individuals died. Of

8   these, seven deaths were from cancer. The expected number of cancer deaths derived for the

9   three external comparison groups ranged between 4.1 and 4.2, producing an SMR of 1.7

10   (p-values ranged between 0.12 and 0.14). Excess mortality was found for stomach cancer based

11   on the external comparisons ($p < 0.05$); however, this was based on only three cases. No other

12   statistically significant excesses were found with the external comparisons made to the other

13   cohorts of workers.

14

15   **C.1.1.1.2.1.2.**   Study evaluation

16   In the Thiess et al. (1982) study, no TCDD exposures were derived for the workers, thus

17   no dose-reconstruction was performed. The findings from this study are severely limited by the

18   small size of the cohort. The 74 workers followed in this cohort represent the smallest number of

19   workers across the occupational cohorts (McBride et al., 2009a; McBride et al., 2009b; Michalek

20   and Pavuk, 2008; Steenland et al., 2001b; Becher et al., 1998; Hooiveld et al., 1998; Fingerhut et

21   al., 1991b) that have investigated TCDD exposures and cancer mortality. Mechanisms of

22   follow-up were excellent as all individuals were traced, and death certificates were obtained from

23   all deceased workers.

24   Although the study does compare the mortality experience to other occupational cohorts,

25   the paper provides insufficient information to adequately interpret these findings. For example, a

26   description of these occupations is lacking making it impossible to determine whether these

27   cohorts were exposed to other occupational carcinogens that might have confounded the

28   associations between TCDD exposure and cancer mortality.

1   **C.1.1.1.2.1.3.**   Suitability of data for TCDD dose-response modeling

2   Subsequent data assembled for the BASF cohort provide more detailed exposure

3   characterization, and also include information for 243 male workers employed at the plant. As

4   such, this study did not meet the considerations for further dose-response analysis.

5

6   **C.1.1.1.2.2.**   ***Zober et al. (1990)***

7   **C.1.1.1.2.2.1.**   Study summary

8   Zober et al. (1990) also examined the mortality patterns of those involved in the 1953

9   accident at the BASF plant. As detailed in their paper, the size of the original cohort was

10   expanded to 247 workers through efforts to locate all who were exposed in the accident or during

11   the clean-up. Three approaches were followed in assembling the cohort. Sixty-nine cohort

12   members were identified from the company physician's list of employees exposed as a result of

13   the accident (Subcohort C1). Sixty-six of these workers were included in the original study

14   population of workers Thiess et al. (1982) examined. Eighty-four other workers who were

15   potentially exposed to TCDD due to their involvement in demolitions or operations were added

16   to the cohort. This group included 43 firemen, 18 plant workers, 7 bricklayers, 5 whitewashers,

17   4 mechanics, 2 roofers, and 5 individuals in other occupations (Subcohort C2). The cohort was

18   further augmented through the Dioxin Investigation Program, which sought to locate those who

19   were involved in the 1953 accident and were still alive in 1986. Current and former workers

20   enrolled in the study were asked to identify other current or former coworkers (including

21   deceased or retired) who might have been exposed from the accident. This third component of

22   94 workers (Subcohort C3) included 27 plant workers, 16 plumbers, 10 scaffolders,

23   10 professionals, 7 mechanics, 6 transportation workers, 5 bricklayers, 5 laboratory assistant,

24   3 insulators, and 5 individuals in other occupations. A medical examination was performed for

25   those identified through the Dioxin Investigation Program, and blood measures were obtained for

26   28 of these workers.

27   External comparisons of the workers' mortality experience to the general population of

28   the Federal Republic of West Germany were made using SMRs. Person-years were tabulated

29   across strata defined by calendar period, sex, and age-group. Sixty-nine deaths including 23

30   from cancer were detected among the workers during the 34-year follow-up period (November

31   17, 1953 through December 31, 1987). Cause-specific death rates for these same strata were

1   available for the Federal Republic of West Germany. Stratified analyses were conducted to

2   examine variations in the SMRs according to years since first exposure (0−9, 10−19, and

3   ≥20 years) for each of the three subcohorts, as well as 114 workers with chloracne.

4   Although it was consistent in magnitude with findings from the NIOSH cohort, a

5   statistically significant SMR for all cancer mortality was not observed (SMR = 1.17,

6   90% CI = 0.80−1.66). The SMRs for each of the three subcohorts varied substantially. For

7   Subcohorts C1, C2, and C3, the SMRs were 1.30 (90% CI = 0.68−2.26), 1.71

8   (90% CI = 0.96−2.83), and 0.48 (90% CI = 0.13−1.23), respectively. The SMRs increased

9   dramatically when analyses were restricted to those with 20 or more years since first exposure in

10   Subcohort C1 (SMR = 1.67, 90% CI = 0.78−3.13) and Subcohort C2 (SMR = 2.38,

11   90% CI = 1.18−4.29). Meanwhile, in a subgroup analysis of those with chloracne, for the period

12   of 20 or more years after first exposure, a statistically significant excess in cancer mortality was

13   noted (SMR = 2.01; 90% CI = 1.22−3.15).

14

15   **C.1.1.1.2.2.2.**   Study evaluation

16   An important limitation of the study is the manner in which the cohort was constructed.

17   Subcohort C3 was constructed by identifying individuals who were alive in 1986. This resulted

18   in 97 active and retired employees who participated in the program, with 94 included in the

19   analysis. Although these individuals did identify other workers who might have also retired or

20   died, inevitably, some individuals who had died were not included in the cohort. This would

21   serve to underestimate the SMRs that were generated with external comparisons to the German

22   population. Indeed, cancer mortality rates in this subcohort were about half of what would have

23   been expected based on general population rates (SMR = 0.48, 90% CI = 0.13−1.23).

24   Additionally, more than half of Subcohort C2 were firemen (43 of 84), who were likely exposed

25   to other occupational carcinogens. Quantitative analyses of epidemiologic data for firefighters

26   have demonstrated increased cancer risk for several different forms of cancer (Youakim, 2006).

27   Therefore, potential confounding from other occupational exposures of the firefighters could

28   have contributed to the higher SMR in Subcohort C2 cohort and is a concern. Data on cigarette

29   smoking were not available either. No excess for nonmalignant respiratory disease was found,

30   however, suggesting this might not be an important source of bias.

31

C.1.1.1.2.2.3. Suitability of data for TCDD dose-response modeling

As with the Thiess et al. (1982) publication, individual-level estimates of workers'
exposures were not made. Lack of exposure estimates precludes a quantitative dose-response
analysis using these data. Also, the study design is not well suited to characterization of risk
using the SMR statistic. Mortality is likely under-ascertained in the large component of the
cohort that was constructed through the identification of surviving members of the cohort.

C.1.1.1.2.3. *Ott and Zober (1996a)*

C.1.1.1.2.3.1. Study summary

Ott and Zober (1996a) extended the analyses of the BASF cohort to include estimates of
individual-level measures of TCDD. The researchers also investigated associations with cancer
mortality and incidence. The cohort follow-up period of 39 years extended until December 31,
1992, adding 5 years to the previously published study (Zober et al., 1990). Ott and Zober
(1996a) identified incident cases of cancer using occupational medical records, death certificates,
doctor's letters, necropsy reports, and information from self-reported surveys sent to all
surviving cohort members. Self-reported cancer diagnoses were confirmed by contacting the
attending physician.

This study characterized exposure by two methods: (1) determining chloracne status of
the cohort members, and (2) estimating cumulative TCDD (μg/kg) levels. In 1989, serum
measures were sought for all surviving members of the 1953 accident, and serum TCDD levels
were quantified for 138 individuals. These serum levels were used to estimate cumulative
TCDD concentrations for all 254 members of the accident cohort. Ott et al. (1993) published a
description of the exposure estimation procedure, which was a regression model that accounted
for the circumstances and duration of individual exposure. The average internal half-life of
TCDD was estimated to be 5.8 years based on repeated serum sampling of 29 individuals. The
regression model allowed for this half-life to vary according to the percentage of body fat, and
yielded half-lives of 5.1 and 8.9 years among those with 20% and 30% body fat, respectively.
Previous analyses of this cohort had used a half-life of 7.0 years (Ott et al., 1993).

TCDD half-life has been reported to increase with percentage of body fat in both
laboratory mammals (Geyer et al., 1990) and humans (Zober and Papke, 1993). Ott and Zober
(1996a) contend that observed correlations with chloracne severity and cumulative estimates of

1 TCDD exposure indirectly validated this exposure metric. Specifically, the mean TCDD

2 concentration for those without chloracne was 38.4 ppt; for those with moderate and severe

3 forms of chloracne, the mean was 420.8 ppt and 1,008 ppt, respectively.

4   Unlike the NIOSH cohort, individual-level data were collected for other cancer risk

5 factors. These factors included body mass index at time of first exposure, history of

6 occupational exposure to β-naphthylamine and asbestos, and history of smoking. Smoking data

7 were available for 86% of the cohort. SMRs were based on the external referent population of

8 West Germany. For cancer incidence, Ott and Zober (1996a) generated standardized incidence

9 ratios (SIRs) using incidence rates for the state of Saarland (1970−1991) as the external referent.

10 They calculated SMRs (and SIRs) for three or four categories of cumulative TCDD levels:

11 <0.1 μg/kg, 0.1−0.99 μg/kg and ≥1 μg/kg. The Cox regression model was used to characterize

12 risk within the cohort using a continuous measure of TCDD. These analyses considered the

13 potential confounding influence of age, smoking, and body mass index using a stepwise

14 regression modeling approach. The Cox modeling employed a stratified approach using the date

15 of first exposure to minimize possible confounding between calendar period and exposure. The

16 three first exposure groups were: exposure within the first year of the accident, exposure between

17 1 year after the accident and before 1960, and exposure after 1959. The Cox regression

18 estimates were presented in terms of conditional risk ratios (i.e., hazard ratios adjusted for body

19 mass index, smoking and age).

20   Although no statistically significant excess relative to the general population was

21 detected for all cancer mortality, there was some suggestion of an exposure-response

22 relationship. In the 0.1−0.99 μg/kg, 1−1.99 μg/kg, and ≥2.00 μg/kg exposure groups, the all

23 cancer SMRs were 1.2 (95% CI = 0.5−2.3), 1.4 (95% CI = 0.6−2.7) and 2.0 (95% CI = 0.8−4.0),

24 respectively. Higher SMRs for cancer (all sites combined) were also found with an increased

25 interval since exposure first occurred. Specifically, when observed versus expected counts of

26 cancer were compared in the time interval 20 years after first exposure, the SMR in the highest

27 combined exposure group (≥1 μg/kg) was 1.97 (95% CI = 1.05−5.36). An excess in lung cancer

28 also was noted with the same lag in this exposure group (SMR = 3.06, 95% CI = 1.12−6.66).

29 For cancer incidence, a statistically significant increased SIR for lung or bronchus cancer was

30 observed in the highest combined exposure (≥1 μg/kg) category (SIR = 2.2, 95% CI = 1.0−4.3),

1   but no other statistically significant associations were detected for any other cancer site. No

2   cases of soft-tissue sarcoma were found among the cohort members in this analysis.

3   Cox regression models also were used to conduct internal cohort comparisons by

4   generating hazard ratios as measures of relative risk for TCDD exposures with adjustment for

5   smoking, age and body mass index. A statistically significant association between TCDD dose

6   (per µg/kg) and cancer mortality was detected (RR = 1.22, 95% CI = 1.00−1.50), but not for

7   cancer incidence (RR = 1.11, 95% CI = 0.91−1.35). Statistically significant findings were

8   observed for stomach cancer mortality (RR = 1.46, 95% CI = 1.13−1.89) and incidence

9   (RR = 1.39, 95% CI = 1.07−1.69).

10   The Ott and Zober (1996a) study also compared the relationship between TCDD

11   exposure categories and cancer mortality from all sites combined according to smoking status.

12   Associations were noted between increased exposure to TCDD and mortality from cancer among

13   current smokers, but not among never or former smokers.

14

15   **C.1.1.1.2.3.2.**   Study evaluation

16   The Ott and Zober (1996a) study characterizes exposure to TCDD at an individual level.

17   Therefore, unlike past studies of this cohort, these data can provide an opportunity for

18   conducting quantitative dose-response modeling. As with the more recent studies involving the

19   NIOSH cohort, serum samples were obtained from surviving cohort members and then used to

20   back-extrapolate TCDD values for all cohort members. In the BASF cohort, however, serum

21   data were available for a much higher percentage of cohort members (54%) than in the NIOSH

22   cohort (5%). An additional study strength was the collection of questionnaire data, which

23   allowed for the potential confounding influence of cigarette smoking and body mass index to be

24   taken into account.

25   The Ott and Zober (1996a) study also evaluates the relationship between TCDD and

26   cancer incidence. Most cohort studies of TCDD-exposed workers have relied solely on mortality

27   outcomes. The availability of incidence data better allows for period of latency to be described,

28   and moreover, to characterize risks associated with cancers that typically have long survival

29   periods. The authors provide few details on the expected completeness of ascertainment for

30   incident cancer cases, which makes determining any associated bias difficult. They do, however,

31   suggest that nonfatal cancers are more likely to have been missed in the earlier part of the

1 follow-up. The net result of differential case ascertainment over time makes evaluating

2 differences in risk estimates across different periods of latency impossible.

3 The small sample size of the cohort ($n = 243$ men) limited the statistical power to detect

4 small associations for some of the exposure measures. This also effectively limited the ability to

5 analyze dose-response relationships quantitatively, particularly across strata such as time since

6 exposure. For site-specific analyses, the cancer site with the most cancer deaths was the

7 respiratory system ($n = 11$). Given the evidence of an exposure-response relationship noted for

8 all cancer sites combined, quantitative dose-response analysis using these cohort data would be

9 limited to the evaluation of this endpoint.

10 The most important limitation of this study is related to the construction of the

11 third component of the cohort. As mentioned earlier, this cohort was assembled by actively

12 seeking out surviving members of the cohort in the mid-1980s. The mortality experience of this

13 cohort is much lower than that of the general population over the entire follow-up, a result that is

14 expected given that the large component of the cohort was made up of individuals known to be

15 alive as of 1986. The net result is likely an underestimate of the SMR.

16

17 **C.1.1.1.2.3.3.** Suitability of data for TCDD dose-response modeling

18 This study was included in the quantitative dose-response modeling for the

19 2003 Reassessment (U.S. EPA, 2003). The characterization of exposure data and availability of

20 other risk factor data at an individual level are appropriate for use in quantitative dose-response

21 analyses.

22

23 **C.1.1.1.3. *The Hamburg cohort***

24 The Hamburg cohort has been the subject of several cancer risk assessments. As with the

25 NIOSH and BASF cohorts, analyses have progressed from basic comparisons of mortality rates

26 to those in the general population to more sophisticated internal cohort analyses involving the

27 reconstruction of TCDD exposures using serum measures. This cohort consists of approximately

28 1,600 workers who were employed in the production of herbicides at a plant in Hamburg,

29 Germany during 1950−1984 (Becher et al., 1998; Flesch-Janys et al., 1995). The herbicides

30 produced included 2,4,5-T, β-hexachlorocyclohexane and lindane. The production of TCP and

31 2,4,5-T was halted in 1954 following a chloracne outbreak. The plant ceased operations in 1984.

1   Approximately 20 different working areas were identified, which, in turn, were grouped into five

2   main areas based on putative TCDD exposure levels. One working area was deemed to be

3   extremely contaminated, having TCDD exposures at least 20-fold higher than in other areas. In

4   this section, the studies undertaken in this cohort that have examined cancer mortality are

5   summarized.

6

7   **C.1.1.1.3.1.   _Manz et al. ([1991](#))_**

8   **C.1.1.1.3.1.1.**   Study summary

9   Manz et al. ([1991](#)) investigated patterns of mortality in the Hamburg cohort. The study

10   population consisted of 1,583 workers (1,184 men, 399 women) who were employed for at least

11   three months between 1952 and 1989. Casual workers were excluded as they lack sufficient

12   personal identifying information thereby not allowing for associations with mortality outcomes

13   to be examined. Vital status was determined using community-based registries of inhabitants

14   throughout West Germany. Cause of death until the end of 1989 was determined from medical

15   records for all cancer deaths and classified based on the ninth revision of the International

16   Classification of Diseases ([WHO, 1978](#)). Although Manz et al. ([1991](#)) present some data on

17   cancer incidence for the cohort, the data are incomplete as information was available on only

18   12 cases; 103 (93 men and 20 women) cancer deaths were observed in the cohort.

19   In this study, the authors used information on production processes to group workers into

20   categories of low, medium, or high exposure to TCDD. This information was based on TCDD

21   concentrations in precursor materials, products, waste, and soil from the plant grounds, measured

22   after the plant closed in 1984. The distribution of workers into the low, medium, and high

23   exposure groups was 186 (79 men and 107 women), 901 (636 men and 265 women), and

24   496 (469 men and 27 women), respectively. The authors examined the validity of the three

25   exposure categories using a separate group of 48 workers not selected for the cohort who

26   volunteered to provide adipose tissue samples. Selection criteria and response rate information

27   for the 48 volunteers were not provided, nor was there any indication that comparisons were

28   made between the 48 volunteers and the individuals included in the study cohort. The median

29   exposure of the 37 volunteers in the high group was 137 ng/kg and 60 ng/kg in the remaining 11.

30   Although the results indicate higher TCDD levels in the high-exposure group, combining the

31   lower two groups precludes separate validation of the two exposure groups. In addition, the

1   authors reported that some exposure misclassification was likely given that 5 of the 37 workers

2   classified in the high exposure group had adipose levels lower than background (20 ng/kg).

3   Information about chloracne in the cohort was incomplete, and, therefore, was not used as a

4   marker of TCDD exposure. Other surrogate measures of exposure were considered in this study,

5   including duration of exposure and year of first employment. For the latter measure,

6   employment that began after 1954 was assumed to result in much lower exposures given that

7   production of 2,4,5-T and TCP stopped in 1954.

8   External comparisons of cancer mortality were made by calculating SMRs using the

9   general population of West Germany as a referent. Comparisons of mortality in the cohort also

10   were made to a separate cohort of 3,417 gas supply workers to avoid bias from the healthy

11   worker effect. Vital status and cause of death in the gas supply workers were determined using

12   the same methods as in the Hamburg cohort. SMRs were calculated relative to both referent

13   populations (West Germany and gas supply workers) across low, medium, and high TCDD

14   exposure groups. The comparison of mortality to the gas supply workers, however, extended

15   only until the end of 1985, whereas, comparisons to the general population extended until 1989.

16   Stratified analyses were undertaken to calculate SMRs for each of the three exposure groups for

17   categories of duration of employment (<20 versus ≥20 years) and date of entry into the cohort

18   (≤1954 vs. >1954).

19   When compared to the general population, overall cancer mortality was elevated in male

20   cohort members (SMR = 1.24, 95% CI = 1.00−1.52) but not in females (SMR = 0.80,

21   95% CI = 0.60−1.05). A twofold increase in female breast cancer mortality was noted although

22   it did not achieve statistical significance at the alpha level of 0.05 (SMR = 2.15,

23   95% CI = 0.98−4.09). The SMR among men was further increased when analyses were

24   restricted to workers who were employed for at least 20 years (SMR = 1.87,

25   95% CI = 1.11−2.95). Analyses restricted to those in the highest exposure group produced an

26   even higher SMR for those with at least 20 years of employment (SMR = 2.54,

27   95% CI = 1.10−5.00). Statistically significant excesses in risk were detected among those who

28   first worked before 1954, but not afterward. Furthermore, a dose-response trend was observed

29   across increasing exposure categories in the subset of workers employed before 1954. The

30   SMRs using the cohort of gas supply workers as the referent group for the low, medium, and

31   high groups in this subset were 1.41 (95% CI = 0.46−3.28), 1.61 (95% CI = 1.10−2.44), and 2.77

1   (95% CI = 1.59−4.53), respectively. This finding is consistent with what was known about

2   TCDD exposures levels at the plant, namely, that TCDD concentrations were much higher

3   between 1951 and 1954, with subsequent declining levels after 1954.

4   Generally speaking, patterns of excess mortality were similar when the cohort of gas

5   workers was used as a reference group. The overall SMR for men was 1.39

6   (95% CI = 1.10−1.75); and was 1.82 (95% CI = 0.97−3.11) when analyses were restricted to

7   workers with 20 or more years of employment. A dose-response trend also was observed across

8   exposure categories when analyses were restricted to those employed for at least 20 years. In

9   particular, with these analyses, no cancer deaths were observed among those in the lowest

10 exposure group, while the SMRs in the middle and high exposure groups were 1.36

11 (95% CI = 0.50−2.96) and 3.07 (95% CI = 1.24−6.33).

12   SMRs also were generated for several site-specific cancers relative to the West German

13 general population and the gas worker cohort. No statistically significant excesses were

14 observed using the general population reference. In contrast, statistically significant excesses

15 were observed for lung cancer (SMR = 1.67, 95% CI = 1.09−2.44) and hematopoietic system

16 cancer (SMR = 2.65, 95% CI = 1.21−5.03) relative to the gas workers cohort.

17

18 **C.1.1.1.3.1.2.**   Study evaluation

19   The Manz et al. (1991) findings indicate an excess of all cancer mortality among the

20 workers with the highest exposures, particularly those who worked for at least 20 years and were

21 employed before 1954. The findings across categories of exposure within the subsets of workers

22 employed for at least 20 years and before 1954, particularly using the cohort of gas supply

23 workers, are consistent with a dose-response relationship. These elevated cancer mortality rates

24 found among those employed before 1954 occurred at a time where TCDD exposures were

25 highest. Other carcinogenic coexposures, such as benzene, asbestos, and dimethyl sulfate, could

26 have occurred among this population. Given that no substantial changes in the production

27 processes at the Hamburg plant occurred after 1954, comparable levels of these coexposures

28 would be expected before and after 1954. Exposures to these other chemicals varied across

29 different departments/groups; therefore, confounding was unlikely since a strong association

30 between concentrations of these chemicals and TCDD exposures was not evident. No

1 information, however, was presented on potential exposure to other DLCs which may confound

2 the associations that were detected.

3   Detailed information on workers' smoking behaviors was not collected. Limited

4 evidence indicated, however, that smoking prevalence between the Hamburg cohort and the gas

5 supply workers cohort was quite similar. A nonrepresentative sample of 361 workers in the

6 Hamburg cohort and the sample of 2,860 workers in the gas supply cohort found that the

7 self-reported smoking prevalence was 73 and 76% in these two cohorts, respectively. This

8 suggests that the two cohorts are comprised predominantly of smokers. The similarity in overall

9 smoking prevalence suggests that comparisons of cancer mortality between the two groups are

10 not unduly influenced by an inability to adjust for smoking.

11

12 **C.1.1.1.3.1.3.** Suitability of data for TCDD dose-response modeling

13   The data compiled for the Manz et al. (1991) study do satisfy many of the considerations

14 for conducting quantitative dose-response analysis; health outcomes appear to be ascertained in

15 an unbiased manner, and exposure was characterized on an individual-level basis. However, as

16 demonstrated in later studies, there was a large DLC component that was not quantified or

17 assessed in this study. Dose-response associations between TCDD and cancer mortality were

18 detected, with stronger associations observed with increased periods of latency and for those who

19 first worked when TCDD was at higher levels.

20   The size of the cohort, although not as large as the NIOSH cohort, does offer sufficient

21 statistical power to evaluate TCDD-related risk for all cancers combined. The data are limited,

22 however, for characterizing cancer risks among women; only 20 cancer deaths occurred in the

23 399 women included in the cohort. It is unlikely that the excess cancer risks using the external

24 reference population are due to uncontrolled effects from smoking since dose-response patterns

25 were strengthened when comparisons were made to the cohort of gas supply workers rather the

26 general population referent where smoking rates were likely lower. The inability to account for

27 other occupational exposure when TCDD exposures were much higher (pre-1955) could result in

28 confounding if these other exposures were related to TCDD and the health outcomes under

29 consideration. This data set would be suitable for quantitative dose-response modeling if the

30 exposure characterization of the cohort could be improved using biological measures of dose.

31

1 **C.1.1.1.3.2.** _Flesch-Janys et al. (1995)_

2 **C.1.1.1.3.2.1.** Study summary

3   In 1995, Flesch-Janys et al. (1995) published an analysis of the male employees from the

4 Hamburg cohort that extended the follow-up to 40 years (1952−1992). Inclusion of these three

5 additional years of follow-up resulted in a sample size of 1,189 male workers.

6   The authors estimated a quantitative exposure variable for concentrations of TCDD in

7 blood at the end of exposure (i.e., when employment in a department ended) and above German

8 median background TCDD levels. The TCDD exposure assessment defined 14 production

9 departments according to TCDD levels in various products in the plant, in waste products, and in

10 various buildings. The time (in years) each worker spent in each department then was

11 calculated. Concentrations of TCDD were determined in 190 male workers using serum

12 ($n = 142$) and adipose tissue samples ($n = 48$). Selection criteria and response rate information

13 was not provided for this subsample. The authors used a first-order kinetic model to calculate

14 TCDD levels at the end of exposure for the 190 workers with available polychlorinated

15 dibenzo-p-dioxin (PCDD) and -furan (PCDF) at various time points. Half-lives were calculated

16 from an elimination study of 48 workers from this cohort, and the median TCDD background

17 level was estimated at 3.4 ng/kg blood fat from the German population (Flesch-Janys et al.,

18 1994; Päpke et al., 1994). Using the one-compartment, first-order kinetic model, the half-life of

19 TCDD was estimated to be 6.9 years (Flesch-Janys, 1997). Increased age and higher body fat

20 percentage were associated with increased TCDD half-life, while smoking was associated with a

21 higher decay rate for most of the congeners examined (Flesch-Janys et al., 1996). Cumulative

22 TCDD exposures for all 1,189 workers were estimated by summing exposures over the time

23 spent in all production departments (expressed in terms of ng/kg of blood fat) in combination

24 with quantitative estimates based on the blood and adipose samples from the 190 workers. The

25 contribution of each working department on overall PCDD exposure was estimated using

26 ordinary least squares regression. The authors also applied a metric of total toxicity equivalence

27 (TOTTEQ) as the weighted sum of all congeners where weights were TEQs that denoted the

28 toxicity of each congener relative to TCDD.

29   Similar to previous analyses on this cohort, comparisons were made using an external

30 referent group of workers from a gas supply company (Manz et al., 1991). In contrast to

31 previous analyses where SMR statistics were generated using this "external" reference, however,

1 Flesch-Janys et al. (1995) used Cox regression. The Cox regression models treated the gas

2 worker cohort as the referent group, and six exposure groups were defined from serum-derived

3 cumulative TCDD estimates. The groups were determined by using the first four quintiles with

4 the upper two exposure categories corresponding to the ninth and tenth deciles of the cumulative

5 TCDD. Internal cohort comparisons used those workers in the lowest quintile as the referent

6 group, as opposed to the cohort of gas workers. A similar approach was used to model TEQs.

7 No known TCDD exposures occurred in the gas workers, so they were assigned exposures based

8 on the median background levels in the general population. RRs were calculated based on

9 exposure above background levels; in other words, background levels were assumed to be

10 equivalent across all workers and also for those employed by the gas supply company. The RRs

11 derived using the Cox model were adjusted for total duration of employment, age, and year when

12 employment began.

13   The Cox regression with the cohort of gas workers as the referent exposure group yielded

14 a linear dose-response relationship between cumulative TCDD exposure and cancer mortality for

15 all sites combined ($p < 0.01$). The RRs for all-cancer mortality were 1.59, 1.29, 1.66, 1.60, 1.70,

16 and 3.30. For four of the six categories (excluding the referent group), the RRs were statistically

17 significant ($p < 0.05$); in the highest TCDD exposure category (344.7−3,890.2 ng/kg) the RR

18 was 3.30 (95% CI = 2.05−5.31). Similar findings were evident with TOTTEQ. A dose-response

19 pattern for all cancer mortality ($p < 0.01$) based on the internal cohort comparisons was also

20 detected.

21   The authors performed an additional analysis to evaluate the potential confounding role

22 of dimethylsulfate. Although no direct measures of dimethylsulfate were available, the

23 investigators repeated analyses by excluding 149 workers who were employed in the department

24 where dimethylsulfate was present. A dose-response pattern persisted for TCDD and cancer

25 mortality ($p < 0.01$), and those in the highest exposure group (344.7−3,890.2 ng/kg of blood fat)

26 had a RR of 2.28 (95% CI = 1.14−4.59).

27

28 **C.1.1.1.3.2.2.** Study evaluation

29   The Flesch-Janys et al. (1995) study used serum-based measures to determine cumulative

30 exposure to TCDD at the end of employment for all cohort members. They used the standard

31 one-compartment, first-order kinetic model and samples obtained from 190 male workers. This

1   quantitative measure of exposure permits an examination of a dose-response relationship.

2   However, there is not enough information provided on the selection of these 190 workers to

3   determine how representative they were of the larger cohort.   Confounding for other

4   occupational exposures is unlikely to have biased the results. A dose-response relationship

5   persisted after excluding workers exposed to dimethylsulfate. Other potential exposures of

6   interest included benzene and isomers of hexachlorocyclohexane. Exposure to these agents,

7   however, was highest in the hexachlorocyclohexane and lindane department, where TCDD

8   exposures were lower. Confounding was unlikely due to exposure to these chemicals, since a

9   strong association between concentrations of these chemicals and TCDD exposures was not

10   evident (due to considerable variability in concentrations across different departments/groups).

11   As outlined earlier, the study findings are unlikely to be biased for cigarette smoking as the

12   prevalence of smoking in the cohort was similar to that in the comparison population. Moreover,

13   more recent analyses of serum-based TCDD exposure measures found no correlation with

14   smoking status in this cohort (Flesch-Janys et al., 1995)—a necessary condition for confounding

15   to occur.

16   The authors used an exposure metric that quantified the cumulative TCDD exposure of

17   workers at the time they were last exposed. As a result, the authors were unable to characterize

18   risks associated with this metric for different periods of latency despite a lengthy follow-up

19   period. Subsequent analyses constructed time-dependent measures of cumulative TCDD and

20   accounted for excretion of TCDD during follow-up.

21   In contrast to most risk assessments of TCDD exposure, this study modeled the

22   relationship between other DLCs and the risk of cancer mortality using the TOTTEQ metric.

23

24   **C.1.1.1.3.2.3.**   Suitability of data for TCDD dose-response modeling

25   The data used in this study satisfy most of the considerations developed for performing a

26   quantitative dose-response analysis. However, latency period was not examined in this study.

27   Dose-response analyses were, therefore, limited to a subsequent study of this cohort (Becher et

28   al., 1998), which did examine latency.

29

C.1.1.1.3.3. *Flesch-Janys et al. (1998)*

C.1.1.1.3.3.1. Study summary

Flesch-Janys et al. (1998) undertook another analysis on this cohort that incorporated additional sera data collected from 275 workers (39 females and 236 males). The follow-up period was the same as that used in the 1995 publication, with mortality follow-up extending until December 31, 1992. Analyses were based on 1,189 males who were employed for at least 3 months from January 1, 1952 onward. The authors continued this dose-response analysis to address limitations in their previous work. One limitation was that the previous method did not account for the elimination of TCDD while exposures were being accrued during follow-up. A second limitation was that the amount of time workers spent in different departments was not considered. In the 1998 study, the "area under the curve" approach was used because it accounts for variations in concentrations over time and reflects cumulative exposure to TCDD. The authors used a first-order kinetic model to link blood levels and working histories to derive department-specific dose rates for TCDD. The TCDD background level of 3.4 ng/kg blood fat for the German population was used (Päpke et al., 1994). The dose rates were applied to estimate the concentration of TCDD at every point in time for all cohort members. A cumulative measure expressed as ng/kg blood fat multiplied by years was calculated and used in the SMR analysis. SMRs were calculated using general population mortality rates for the German population between 1952 and 1992. No lag period was incorporated into the derivation of the SMRs. The SMRs were estimated for the entire cohort and for exposure groups based on quartiles obtained from the area under the curve. Linear trend tests were also performed. The overall SMR for cancer mortality in the cohort was 1.41 (95% CI = 1.17−1.68). This SMR value was higher than the SMR of 1.21 reported for this same cohort with 3 fewer years of follow-up (Manz et al., 1991). In terms of site-specific cancer mortality, excesses were found for respiratory cancer (SMR = 1.71, 95% CI = 1.24−2.29) and rectal cancer (SMR = 2.30, 95% CI = 1.05−2.47). Increased risk for lymphatic and hematopoietic cancer (SMR = 2.16, 95% CI = 1.11−3.17) were also noted largely attributable (SMR = 3.73, 95% CI = 1.20−8.71) to lymphosarcoma (i.e., non-Hodgkin lymphoma). A dose-response relationship was observed across quartiles of cumulative TCDD for all-cancer mortality ($p < 0.01$). The SMRs for these quartiles were 1.24, 1.34, 1.34, and 1.73. Dose-response relationships were not observed for lung cancer or hematopoietic cancers using this same metric. Dose-response relationships were

1 not observed with cumulative TEQ for any of the cancer sites examined (i.e., all cancers, lung

2 cancer, hematopoietic cancer).

3

4 **C.1.1.1.3.3.2.**   Study evaluation

5   The approach used in the Flesch-Janys et al. (1998) study offers a distinct advantage over

6 earlier analyses of the same cohort. The authors used sera data on 275 male and female subjects

7 to estimate department-specific dose rates, although it is unclear whether data on females were

8 used to estimate TCDD levels among the males examined in the cancer mortality analysis. Three

9 more years of follow-up were available, and the characterization of exposure using the "area

10 under the curve" better captures changes in cumulative exposure using a person-years approach

11 when compared to estimates of cumulative TCDD at the time of last exposure. As noted

12 previously, other occupational exposures or cigarette smoking are unlikely to have biased the

13 study findings. A sufficient length of follow-up had accrued, and dose-response relationships

14 were evident. DLCs were evaluated in this study. For TCDD, the mean concentration was

15 101.3 ng/kg at the time of measurement. For other higher chlorinated congeners, the

16 corresponding mean (without TCDD) was 89.3 ng/kg.

17

18
19 **C.1.1.1.3.3.3.**   Suitability of data for TCDD dose-response modeling

20   The data used in this study satisfy most of the considerations developed for performing a

21 quantitative dose-response analysis. However, latency was not examined in this study.

22 Dose-response analyses were, therefore, limited to a subsequent study of this cohort (Becher et

23 al., 1998) which did examine latency and supersedes the Flesch-Janys et al. (1998) study.

24

25 **C.1.1.1.3.4.**   *Becher et al. (1998)*

26 **C.1.1.1.3.4.1.**   Study summary

27   The Becher et al. (1998) quantitative cancer risk assessment for the Hamburg cohort was

28 highlighted in the 2003 Reassessment as being appropriate for conducting dose-response

29 analysis. The integrated TCDD concentration over time, as estimated in the Flesch-Janys et al.

30 (1998) study, was used as the exposure variable. Estimates of the half-life of TCDD based on

31 the sample of 48 individuals with repeated measures were incorporated into the model that

32 back-calculated TCDD exposures to the end of the employment (Flesch-Janys et al., 1996). This

1   method took into account the age and body fat percentage of the workers. In Becher et al.

2   ([1998](#)), the analysis used the estimate of cumulative dose (integrated dose or area under the

3   curve) as a time-dependent variable.

4   Poisson and Cox regression models were used to characterize dose-response

5   relationships. Both models were used to conduct internal comparisons where a person-years

6   offset was used, and to an external comparison where an offset of expected number of deaths

7   was used. The person-years offset was used to account for varying person-time accrued by

8   workers across exposure categories. The use of the expected number of deaths as an offset

9   allows risks to be described in relation to that expected in the general population. Within each

10 classification cell of deaths and person-years, a continuous value TCDD and TEQ levels based

11 on the geometric mean were entered into the Poisson model. For the Cox model, accumulated

12 dose was estimated based on area under the curve for TCDD, TEQ, TEQ without TCDD, and

13 β-hexachlorocyclohexane. These other coexposure metrics were adjusted for in the Cox

14 regression analyses. Other covariates considered included in the models were year of entry, year

15 of birth, and age at entry into the cohort. A background level of 3.4 ng/kg blood fat for the

16 German population was used ([Päpke et al., 1994](#)). A variety of latencies was evaluated (0, 5, 10,

17 15, and 20 years), and attributable and absolute risks were estimated. The unexposed cohort of

18 gas workers was used for most internal analyses.

19   Internal and external comparisons using the Poisson model found positive associations

20 with TCDD exposure and mortality from all cancers combined. The slope associated with the

21 continuous measure of TCDD (μg/kg blood fat × years) for the internal comparison was 0.027

22 ($p < 0.001$), which decreased to 0.0156 ($p = 0.07$) after adjusting for age and calendar period.

23 The slope for the external comparison was 0.0163 ($p = 0.055$); this estimate was not adjusted for

24 other covariates. For TEQ, the slopes based on the internal comparisons were 0.0274 ($p < 0.001$)

25 in the univariate model and 0.0107 ($p = 0.175$) in the multivariate model after adjusting for age

26 and calendar period. The external estimate of slope for TEQ was 0.0109 ($p = 0.164$). Cox

27 regression of TCDD across six exposure categories, with a lag of 0 years, found a statistically

28 significant linear trend ($p = 0.03$) and those in the upper exposure group had a RR of 2.19

29 (95% CI = 0.76−6.29). These estimates were adjusted for year of entry, age at entry, and

30 duration of employment. A similar pattern was observed with the Cox regression analysis of

TEQ; the linear test for trend, however, was not statistically significant at the alpha level of 0.05 ($p = 0.06$).

Cox regression models that included both TCDD and TEQ (excluding TCDD) were applied. In this model, the slope (β) for TCDD was 0.0089 ($p = 0.058$), while the coefficient for TEQ (excluding TCDD) was −0.024 ($p = 0.70$). This suggests that confounding by other DLCs was unlikely and the increased risk of cancer was due to TCDD exposure. For all TEQs combined, the slope was 0.0078 ($p = 0.066$).

The authors used multiple Cox models to evaluate the effect of latency. The slope estimates for both TCDD and TEQ increased dramatically with increasing latency. The slope estimates for TCDD increased from 0.0096 to 0.0160 ($p < 0.05$) when latency was increased from 0 to 20 years. Similar changes in the TEQ slopes were noted (0.0093 to 0.0157). Evaluations of dose-response curves found that the best-fitting curve was concave in shape, thereby yielding higher risk at low exposure. Differences between the fit of the class of models considered [i.e., $RR(x,\beta) = \exp(\beta \log(kx = 1))$], however, were small.

Attributable risks were generated only for TCDD, as the data suggested no effects with other TEQs. The additional lifetime risk of cancer assuming a daily intake of 1 pg TCDD/kg body weight/day was estimated to range between 0.001 and 0.01.

C.1.1.1.3.4.2. Study evaluation

The Becher et al. (1998) study represents perhaps the most detailed analyses performed on any cohort to date. The findings were robust, as similar patterns were found with and without using the gas supply worker cohort as the referent group. Exposures to other potential confounding coexposures, such as DLCs, were taken into account, and workers with exposure to other carcinogens (e.g., lindane) were excluded. Furthermore, latency was examined in this study, unlike earlier studies of this cohort. Although the TCDD exposure estimates were derived from a sample of 275 workers with repeated serum measures, the authors indicate that the production department-specific estimates were in agreement with a priori expectations based on an understanding of the chemistry and available industrial hygiene data. The authors also reported no differences in dose rate estimates related to gender or short durations of employment. Similar to other studies, the potential for exposure misclassification based on limited number of

1   biomarker samples is hard to determine without more information on the representativeness of

2   the participants who provided samples.

3

4   **C.1.1.1.3.4.3.**   Suitability of data for TCDD dose-response modeling

5   This study was included in the quantitative dose-response modeling for the

6   2003 Reassessment (U.S. EPA, 2003). The data in the Becher et al. (1998) study are suitable for

7   conducting quantitative dose-response modeling. The exposure data capture cumulative

8   exposure to TCDD as well as exposures to other DLCs. The length of the follow-up is sufficient,

9   and the study does not appear to be subject to confounding or other types of biases. Therefore,

10   this study is utilized in quantitative dose-response analysis.

11

12   **C.1.1.1.4.**   *The Seveso cohort*

13   Several studies have evaluated the morbidity and mortality effects of residents exposed to

14   TCDD following a July 10, 1976, accidental release through an exhaust pipe at a chemical plant

15   in the town of Meda near Seveso, Italy. The released fluid mixture contained 2,4,5-T, sodium

16   trichlorophenate, ethylene glycol, and sodium hydroxide. Vegetation in the area showed

17   immediate signs of damage, and in the days following the accident, residents developed nausea,

18   headaches, eye irritation, and dermal lesions, particularly children.

19   This accident transported TCDD up to 6 km from the plant. Soil samples taken near the

20   plant revealed average levels of TCDD that ranged from 15.5 $\mu g/m^2$ to 580.4 $\mu g/m^2$ in the most

21   contaminated area near the plant (referred to as Zone A) (Bertazzi et al., 2001). Zone A covered

22   87 hectares and extended 2,200 m south from the plant. Another, more distant contaminated

23   zone (Zone B) covering 270 hectares also had contaminated soil levels, but the TCDD

24   concentration range was much lower (1.7−4.3 $\mu g/m^3$). A reference zone (Zone R), which

25   surrounded the two contaminated areas, had lower TCDD soil levels (range: 0.9−1.4 $\mu g/m^3$) and

26   included approximately 30,000 residents. Following the accident, most residents in Zone A left

27   the area. Although residents in Zone B remained, they were under strict regulations to avoid

28   consuming homegrown products. In total, 736, 4,737, and 31,800 individuals lived in Zones A,

29   B, and R, respectively. Within days of the accident, 3,300 animals (mostly poultry and rabbits)

30   were found dead. Emergency slaughtering was undertaken to prevent TCDD from entering the

31   food chain, and within 2 years more than 80,000 animals had been slaughtered. Mechanisms

1   were put into place for long-term follow-up of these residents. Unlike the other occupational

2   cohort studies, the follow-up of this population allows for risks to be characterized for females.

3   The mortality studies from Seveso published to date have not incorporated serum TCDD

4   levels that were measured in individuals. Needham et al. (1997) describe the collection of serum

5   samples from a sample of the exposed population and control subjects in 1976. In 1988, human

6   exposure to TCDD was assessed by measuring small volumes of serum remaining from medical

7   examinations done in 1976. An examination of these data revealed some of the highest serum

8   TCDD levels ever reported, that the half-life of TCDD in this population was between 7 and

9   8 years, and that half-life varied between women and men. The half-life of TCDD in serum was

10   longer in women (~9 years) than in men (~7 years) (Needham et al., 1994). In this report, the

11   findings of studies that characterized cancer risks in relation to exposure to TCDD from the 1976

12   accident are highlighted. These studies include comparisons of cancer mortality rates to the

13   general population based on zone of residence at the time of accident (Consonni et al., 2008;

14   Bertazzi et al., 2001). More recent work done by Warner et al. (2002) investigated the

15   relationship between serum-based measures of TCDD and breast cancer among participants in

16   the Seveso Women's Health Study (SWHS).

17

18   **C.1.1.1.4.1.** *Bertazzi et al. (2001)*

19   **C.1.1.1.4.1.1.**   Study summary

20   Several studies have reported on the mortality experience of Seveso residents. The more

21   recent publications having a longer follow-up of the cohort are evaluated here. In 2001, the

22   findings from a 20-year mortality study of Seveso residents was published (Bertazzi et al., 2001).

23   The Bertazzi et al. (2001) study was an extension of the 10- and 15-year follow-ups for mortality

24   (Pesatori et al., 1998; Bertazzi et al., 1997; 1989) and the 10-year follow-up for cancer incidence

25   (Bertazzi et al., 1993).

26   In this cohort, TCDD exposures were assigned to the population using a three-level

27   categorical variable representative of the individual's place of residence (Zones A, B, or R) at the

28   time of the accident or when the person first became a resident of the zone, if that was after

29   1976. An external comparison to the province of Lombardy was made by generating rate ratios

30   (RR) using Poisson regression techniques. Person-years of follow-up were tabulated across

31   strata defined by age, zone of residence, duration of residence, gender, calendar time, and

1   number of years that had elapsed since the time of exposure. Mortality rates during the

2   preaccident period also were compared to evaluate potential changes in rates due to the accident

3   and to evaluate whether patterns were consistent before and after the accident.

4   No overall excess in mortality rates from all cancer sites combined was observed in

5   Zones A or B (combined) when compared to the reference population of Lombardy

6   (n = 9 million residents) (RR = 1.0, 95% CI = 0.9−1.2). Analyses of site-specific cancer

7   mortality revealed statistically significant excesses among residents in Zones A or B (combined)

8   for cancer of the rectum (RR = 1.8, 95% CI = 1.0−3.3) and lymphatic and hematopoietic

9   malignancies (RR = 1.7, 95% CI = 1.2−2.5). Lymphatic and hematopoietic malignancies were

10   elevated in women (RR = 1.8, 95% CI = 1.1−3.2) and in men (RR = 1.7, 95% CI = 1.0−2.8).

11   Analyses stratified by the number of years since first exposure (i.e., 1976) revealed

12   higher risk among men with an increased number of years elapsed. Similar to other studies, the

13   RR for all cancers (combined) was 1.3 (95% CI = 1.0−1.7) among men 15−20 years after first

14   exposure. No such increase after 15 years postexposure, however, was noted in women

15   (RR = 0.8, 95% CI = 0.6−1.2).

16

17   **C.1.1.1.4.1.2.**   Study evaluation

18   Ascertainment of mortality appears to be excellent. Vital status was established using

19   similar methods for both the exposed and reference populations. No individual data were

20   collected and, therefore, the possibility that confounding by individual characteristics such as

21   cigarette smoking cannot be entirely dismissed. Bertazzi et al. (2001) do note that the

22   sociodemographic characteristics of residents in the three zones were similar based on

23   independently conducted surveys, and no differences in chronic respiratory disease were found

24   across the different zones. If excess mortality was attributable to cigarette smoking, such

25   excesses would be expected to be evident during the entire study period. Latency analyses

26   revealed elevated risks 15−20 years postaccident. Finally, no excesses were observed for other

27   smoking-related cancers of the larynx, esophagus, pancreas, and bladder. The observed excesses

28   in all cancer mortality do not appear to be attributed to differential smoking rates between the

29   two populations.

30   To examine potential for bias due to noncomparability in the two study populations, a

31   comparison of cancer mortality rates between the Seveso regions and the reference population of

1 Lombardy was conducted. Elevated rates for brain cancer mortality were noted in Seveso

2 relative to Lombardy, but the higher rates of leukemia mortality were found in Lombardy

3 relative to Seveso. That no excess was reported for all cancer sites combined lends credence to

4 the hypothesis that the exposure to TCDD from the accident increased rates of cancer after a

5 sufficient period of latency.

6 Stratified analyses were performed across several categorical variables including gender

7 and time since exposure. The numbers of cancer site-specific deaths are quite small in many of

8 the 5-year increments since first exposure. The study, therefore, has limited statistical power to

9 detect differences in mortality rates among the comparison groups for many cancer sites.

10 Bertazzi et al. (2001) assigned exposures based on zone of residence. Soil sampling

11 within each zone revealed considerable variability in TCDD soil levels within each zone.

12 Moreover, some individuals would have left the area shortly after the accident, and determining

13 the extent to which individuals in Zone B who were subject to the recommendations near the

14 time of the accident adhered to them is difficult. As a result, exposure misclassification is

15 possible, and the use of individual measures of TCDD level in serum is preferred over zone of

16 residence for determining exposure. As noted by the authors, the study is better suited to "hazard

17 identification" than to quantitative dose-response analysis.

18

19 **C.1.1.1.4.1.3.** Suitability of data for TCDD dose-response modeling

20 Given the variability in soil TCDD levels within each zone and the lack of individual

21 level, no effective dose can be estimated for quantitative dose-response analyses. Uncertainty in

22 identifying the critical exposure window for the Seveso cohort is a key limitation. The

23 evaluation of this study indicates that this study is not suitable for quantitative dose-response

24 analysis.

25

26 **C.1.1.1.4.2.** *Warner et al. (2002)*

27 **C.1.1.1.4.2.1.** Study summary

28 To date, Warner et al. (2002) is the only published investigation of the relationship

29 between serum-based measures of TCDD and cancer in Seveso. Eligible participants from the

30 Seveso Women's Health Study (SWHS; see Section 2.4.1.2.1.4 for details) were women who, at

31 the time of the accident in 1976, were 40 years of age or younger, had lived in one of the most

1   highly contaminated zones (A or B), and had adequate sera collected soon after the explosion.

2   Enrollment in SWHS was begun in March 1996 and lasted until July 1998. Of the total

3   1,271 eligible women, 981 agreed to participate in the study. Cancer cases were identified

4   during interview and confirmed through review of medical records. Information on other risk

5   factors including reproductive history and cigarette smoking was obtained through interview.

6   Serum volumes greater than 0.5 mL collected between 1976 and 1981 were analyzed.

7   Most sera were collected in 1976/77 ($n = 899$); samples were collected in 1978−1981 for

8   54 women, and in 1996/97 for 28 women. For samples collected after 1977, serum TCDD levels

9   were back-extrapolated using a first-order kinetic model with a 9-year half-life (Pirkle et al.,

10 1989). For 96 women with undetectable values, a serum level that was equal to one-half the

11 detection level was used.

12   Analyses were based only on women who provided serum samples; no extrapolation of

13 values to a larger population was done. Risks were therefore generated using data collected at an

14 individual level. Serum TCDD was analyzed as both a continuous variable and a categorical

15 variable. The distribution of serum TCDD levels of the 15 cases of breast cancer was examined

16 in relation to the distribution of all women in the SWHS. The median exposure was slightly

17 higher among with the 15 cases of breast cancer (71.8 ppt) compared to those without (55.1 ppt),

18 and the exposure distribution among breast cancer cases appeared to be shifted to the right (i.e.,

19 the exposures were higher but followed the same distribution); however, no formal test of

20 significance was conducted.

21   Warner et al. (2002) used Cox proportional hazards models to evaluate the risk of breast

22 cancer in relation to TCDD serum levels while controlling for a number of potential risk factors.

23 In all, 21 women had been diagnosed with cancer, and of these, 15 cases were cancer of the

24 breast. The analysis revealed that for every 10-fold increase in TCDD log-serum levels (e.g.,

25 from 10 to 100 ppt) the risk of breast cancer increased by a factor of 2.1 (95% CI = 1.0−4.6).

26 Risk estimates also were generated across four categories (<20, 20.1−44, 44.1−100, >100 ppt),

27 with the lowest category used as the reference. The RRs estimated in the third and fourth highest

28 exposure categories were 4.5 (95% CI = 0.6−36.8) and 3.3 (95% CI = 0.4−28.0). Although

29 statistical significance was not achieved for either category, likely because of the small number

30 of cases, the greater than threefold risk evident in both categories is worth noting. Given that the

31 reference category had only one incident case underscores the limited inferences that can be

1   drawn from these analyses. The authors adjusted for numerous potential confounders, but

2   observed no differences between the crude and adjusted results; the authors, therefore, presented

3   unadjusted risks.

4

5   **C.1.1.1.4.2.2.**   Study evaluation

6   The findings from the Warner et al. (2002) study differ from reports in earlier studies in

7   which mortality outcomes noted the absence of an SMR association. The design of this study is

8   much stronger than earlier ones, given the improved characterization of exposure, the ability to

9   compare incidence rates within the cohort, the ability to control for potential confounding

10   variables at an individual level, and the availability of incident outcomes. The use of incident

11   cases (versus mortality data) should also help minimize potential bias due to disease survival.

12   Another important advantage was the ability to measure TCDD near the time of the accident,

13   thereby reducing the potential for exposure measurement error.

14   A potentially important limitation of the Warner et al. (2002) study was that information

15   was collected only from those who were alive as of March 1996. Therefore, TCDD and other

16   relevant risk factor data could not be collected for those who had previously died of breast

17   cancer. Thirty-three women could not participate because they were either too ill or had died.

18   Of these, three died of breast cancer. Given that there were only 15 breast cancer cases, the

19   exclusion of these 3 cases could have dramatically impacted the findings in either direction.

20   Another limitation was that, at the time of the follow-up, most women were still

21   premenopausal and therefore, most of the cohort (average age = 40.8 years) had not yet attained

22   the age of greater risk of breast cancer (average age at diagnosis among the cases in this cohort

23   was 45.2 years). Although comparable data from Italy were not found, the median age of

24   diagnosis for breast cancer among U.S. women from 2003−2007 was 61 years (Altekruse et al.,

25   2010). An ongoing follow-up of the cohort should be completed by 2010, which should allow

26   for increased number of incident breast cancers to be identified. Given that the current analyses

27   were based only on 15 incident cases, this will substantially improve the statistical power of the

28   study. A secondary benefit is that the increased follow-up will allow for an investigation of

29   possible differential effects according to the age the women were at the time of exposure.

30

1 **C.1.1.1.4.2.3.** Suitability of data for TCDD dose-response modeling

2   Several aspects of the Warner et al. (2002) study are weaknesses in the consideration of

3 this study for further dose-response modeling. Only 15 cases of breast cancer were available,

4 and no increases in risk were found with serum TCDD exposures between 20.1 and 44 ppt

5 ($n = 2$) when compared to those with <20 ppt ($n = 1$). The average age at the time of enrollment

6 was 40.8 years while the average age at diagnosis among the cases was 45.2 years. As most

7 women had not yet reached the age when breast cancer cases are typically diagnosed, additional

8 follow-up of the cohort would improve the quantitative dose-response analysis and strengthen

9 this study. A key strength of this study, however, is that Warner et al. (2002) includes an

10 investigation of the relationship between individual serum-based measures of TCDD and cancer

11 in Seveso. Despite the weaknesses, this study meets the evaluation considerations and criteria

12 for inclusion and will be analyzed for quantitative dose-response modeling.

13 **C.1.1.1.4.3.** *Pesatori et al. (2003)*

14 **C.1.1.1.4.3.1.** Study summary

15   Pesatori et al. (2003) published a review of the short- and long-term studies of morbidity

16 and mortality outcomes in the Seveso cohort in 2003. This paper presented cancer incidence

17 data from 1977 to 1991 for Seveso males and females residing in Zones A, B and R relative to an

18 external population (i.e., uncontaminated areas). Mortality data are also presented for a 20-year

19 follow-up (1976−1996) relative to the reference population. As in the original Bertazzi et al.

20 (2001) study, RRs were estimated using Poisson regression. No associations were noted for zone

21 of residence and all cancer mortality for either males or females. Although no cases were

22 reported in Zones A and B, soft tissue sarcoma incidence rates were higher among males from

23 Zone R (RR = 2.6, 95% CI = 1.1−6.3). Among males, residence in Zones A and B was

24 associated with lymphatic and hematopoietic cancer (RR = 1.9, 95% CI = 1.1−3.1). This

25 increased risk was due primarily to non-Hodgkin lymphoma, which accounted for 8 of the

26 15 incident cases (RR = 2.6, 95% CI = 1.3−5.3). Among females, increased incidence of

27 multiple myeloma (RR = 4.9, 95% CI = 1.5−16.1), cancer of the vagina (RR = 5.5,

28 95% CI = 1.3−23.8), and cancer of the biliary tract (RR = 3.0, 95% CI = 1.1−8.2) was associated

29 with residence in Zones A and B.

30

C.1.1.1.4.3.2. Study evaluation

Limitations of the Pesatori et al. (2003) study included exposure misclassification from the use of an ecological measure of exposure (i.e., region of residency at time of accident) and low statistical power for some health endpoints. For example, all of the RRs presented above for specific cancer mortality among females in the Pesatori et al. (2003) study were based on fewer than five incident cases.

C.1.1.1.4.3.3. Suitability of data for TCDD dose-response modeling

As with the studies of mortality among Seveso residents, the Pesatori et al. (2003) study does not capture TCDD exposure on an individual basis, and soil TCDD levels considerably vary within each zone. Therefore, the quality of the exposure data is inadequate for estimating the effective dose needed for quantitative dose-response analysis.

C.1.1.1.4.4. *Baccarelli et al. (2006)*

C.1.1.1.4.4.1. Study summary

Given previous findings from Seveso, Baccarelli et al. (2006) examined t(14;18) translocations in the DNA of circulating lymphocytes of 144 healthy dioxin-exposed individuals. These translocations are associated with the development of cancer, namely follicular lymphomas. The study included 144 individuals selected from a previous population of 211 healthy subjects representative of the Seveso area, and 101 who had developed chloracne. The investigators analyzed data from 72 (52 females and 20 males) high-TCDD plasma level individuals ($\geq$10 ppt) and 72 (41 females and 31 males) low-TCDD plasma levels (<10 ppt), matched for history of chloracne and smoking. A three-level categorical exposure variable was used to evaluate dose response. This variable was developed by dividing those with exposures $\geq$10 ppt into two groups: 10- <50 ppt, and 50−475.0 ppt. Trained interviewers administered a questionnaire that collected data on demographic characteristics, diet, and residential and occupational history.

The prevalence of t(14;18) was estimated as those individuals having a t(14;18) positive blood sample divided by the t(14;18) frequency (number of copies per million lymphocytes). Baccarelli et al. (2006) found that the frequency of t(14;18) was associated with plasma TCDD levels, but no association between TCDD and the prevalence of t(14;18) was detected.

C.1.1.1.4.4.2. Study evaluation

Whether the frequency of t(14;18) associated with plasma TCDD levels translates into an increased risk of lymphoma is uncertain as prospective data of TCDD on those who developed non-Hodgkin lymphoma are lacking. Moreover, the t(14;18) translocation could be an important event in the pre-B stage cell that contributes to tumorigenicity, however subsequent exposure to carcinogenic agents might be necessary for t(14;18) cells to develop into a malignancy (Höglund et al., 2004).

C.1.1.1.4.4.3. Suitability of data for TCDD dose-response modeling

Given that current TCDD plasma levels were measured for this study, it is unclear if the effects of lymphocyte translocations may be due to an initial high exposure or are a function of the cumulative exposure accrued over a longer time window. Additionally, whether the frequency of t(14;18) associated with plasma TCDD levels translates into an increased risk of lymphoma is unknown. Dose-response analysis for this outcome, therefore, was not conducted.

C.1.1.1.4.5. *Consonni et al. (2008)*

C.1.1.1.4.5.1. Study summary

Consonni et al. (2008) analyzed cancer mortality in the Seveso cohort with the addition of a 25-year follow up period. Similar analytic methods as Pesatori et al. (2003) were applied with 25 years of follow-up added to the analysis (Consonni et al., 2008). An important addition in this paper was the presentation of RRs for Zone R, which had the lowest TCDD levels. Poisson regression models were used to calculate RRs of mortality using Seregno as the reference population. Cancer deaths observed in Zones A and B were 42 and 244, respectively.

No statistically significant differences in all cancer mortality relative to the reference population were noted in any of the zones (Zone A: RR = 1.03, 95% CI = 0.76−1.39; Zone B: RR = 0.92, 95% CI = 0.81−1.05; Zone R: RR = 0.97, 95% CI = 0.92−1.02). Statistically significant excesses in mortality from non-Hodgkin lymphoma (RR = 3.35, 95% CI = 1.07−10.46) and multiple myeloma (RR = 4.34, 95% CI = 1.07−17.52) were observed in the area with the highest TCDD levels (Zone A). No other statistically significant increases in cancer mortality relative to the reference population were apparent. The absence of elevated breast cancer mortality among women in this study was noteworthy, as this finding differs from

1 the results of a study of Seveso women for which TCDD exposures were estimated using serum

2 samples (Warner et al., 2002).

3

4 **C.1.1.1.4.5.2.** Study evaluation

5   Although no individual-level data on smoking were available, the potential for

6 confounding is likely minimal. Independent smoking surveys found that smoking prevalence

7 rates in Desio, one of cities affected by the accident, were similar to those in districts just outside

8 the study area (Cesana et al., 1995). As mentioned earlier, one would expect elevated RRs over

9 the entire study period if smoking had biased the study results, and not just after 15−20 years

10 since exposure to TCDD.

11

12 **C.1.1.1.4.5.3.** Suitability of data for TCDD dose-response modeling

13   The lack of individual-level exposure data precludes quantitative dose-response modeling

14 using these data.

15

16 **C.1.1.1.5.** *Chapaevsk study*

17   Industrial contamination of dioxin in the Chapaevsk region of Russia has been the focus

18 of research on environmentally-induced cancers and other adverse health effects. The

19 Chapaevsk region is located in the Samara region of Russia and has a population of 83,000. The

20 region is home to a chemical plant that produced lindane and its derivatives between 1967 and

21 1987, which are believed to be responsible for local dioxin contamination. Soil sampling has

22 demonstrated a strong gradient of increased TCDD concentrations with decreased proximity to

23 the chemical plant (Revich et al., 2001).

24

25 **C.1.1.1.5.1.** ***Revich et al. (2001)***

26 **C.1.1.1.5.1.1.** Study summary

27   Revich et al. (2001) used a cross-sectional study to compare mortality rates of Chapaevsk

28 residents to two external populations of Russia and the region of Samara. Mortality rates for all

29 cancers combined among males in Chapaevsk were found to be 1.2 times higher when compared

30 to the Samara region as a whole and 1.3 times higher than Russia. Similar to other studies, a

31 statistically significant excess was noted in men (SMR = 1.8, 95% CI = 1.6−1.9) but not in

1 women (SMR = 0.9, 95% CI = 0.8−1.1). Among men, the excess was highest for the

2 smoking-related cancers of the lung (SMR = 3.1, 95% CI = 2.6−3.5) and larynx (SMR = 2.3,

3 95% CI = 1.2−3.8) and urinary organs (SMR = 2.6, 95% CI = 1.7−3.6). Among females, there

4 was no increased SMR for all cancer sites combined, but excesses for breast cancer (SMR = 2.1,

5 95% CI = 1.6−2.7) and cancer of the cervix (SMR = 1.5, 95% CI = 1.0−3.1) were statistically

6 significant.

7 Revich et al. (2001) also compared age-standardized cancer incidence rates in Chapaevsk

8 to those in Samara. Although statistical tests examining these differences were not reported,

9 higher incidence rates were observed for all cancers combined, cancer of the lip, cancer of the

10 oral cavity, and lung and bladder cancer among males in Chapaevsk. Considerably lower cancer

11 incidence rates also were observed for prostate cancer, cancer of the esophagus, and

12 leukemia/lymphoma among males from Chapaevsk. Among females, incidence rates were

13 higher in 1998 for all cancers in Chapaevsk when compared to Russia and the Samara region, an

14 observation that appears somewhat counter to the presented SMR of 0.9 for all cancer mortality

15 from 1995−1998. Similar to the mortality findings, rates of breast and cervical cancer incidence

16 among women in Chapaevsk were higher than in Russia. Leukemia/lymphoma rates were higher

17 among women in Chapaevsk than the reference populations of Samara and Russia. This finding

18 is contrary to the results for males where lower rates of leukemia/lymphoma were observed in

19 Chapaevsk.

20

21 **C.1.1.1.5.1.2.** Study evaluation

22 Although the Revich et al. (2001) findings suggest TCDD exposures in Chapaevsk are

23 quite high relative to other parts of the world (Akhmedkhanov et al., 2002), the evaluation of

24 health outcomes to date is based on ecological data. One limitation is that insufficient details are

25 provided by the authors to gauge the completeness and coverage of the cancer registry and

26 mortality data. Given the ecological nature of the data, the authors did not adjust for the

27 influence of other risk factors (e.g., smoking, reproductive characteristics) that could contribute

28 to increased cancer rates for lung cancer in men and breast cancer in women. In addition,

29 occupational exposures may have also contribute to these SMR and SIR differences for cancer

30 outcomes that varied considerably between men and women. .

1   Future research in Chapaevsk includes plans to conduct a breast cancer case-control

2 study. Women who were born from 1940 onward and who have been diagnosed with breast

3 cancer before the age of 55 were included in the study, although the plan to characterize TCDD

4 using serum is uncertain (Revich et al., 2005).

5

6 **C.1.1.1.5.1.3.** Suitability of data for TCDD dose-response modeling

7   This study did not meet most of the study considerations and criteria for inclusion in a

8 quantitative dose-response assessment. Given the lack of exposure data on an individual basis,

9 no effective dose can be estimated for this study population. Therefore, no dose-response

10 modeling was conducted for this study.

11

12 **C.1.1.1.6.** *The Air Force Health ("Ranch Hands" cohort) study*

13   Between 1962 and 1971, the U.S. military sprayed herbicides over Vietnam to destroy

14 crops that opposition forces depended upon, to clear vegetation from the perimeter of U.S. bases,

15 and to reduce the ability of opposition forces to hide. These herbicides were predominantly a

16 mixture of 2,4-D, 2,4,5-T, picloram, and cacodylic acid (Committee to Review the Health

17 Effects in Vietnam Veterans of Exposure to Herbicides, 2006). A main chemical sprayed was

18 Agent Orange, which was a 50% mixture of 2,4-D and 2,4,5-T. TCDD was produced as a

19 contaminant of 2,4,5-T and had levels ranging from 0.05 to 50 ppm (Committee to Review the

20 Health Effects in Vietnam Veterans of Exposure to Herbicides, 1994). A series of studies have

21 investigated cancer outcomes among Vietnam veterans. A review of military records to

22 characterize exposure to Agent Orange led Stellman and Stellman (1986) to conclude that

23 assignment of herbicide levels should not be based solely on self-reports or a crude measure such

24 as military branch or area of service within Vietnam. Investigations have been performed on the

25 Ranch Hands cohort, which consisted of those who were involved in the aerial spraying of

26 Agent Orange between 1962 and 1971. More elaborate methods were used to characterize

27 exposures among these individuals, and these studies are summarized below.

28

29 **C.1.1.1.6.1.** *Akhtar et al. (2004)*

30 **C.1.1.1.6.1.1.** Study summary

31   Akhtar et al. (2004) investigated the incidence of cancer in the Ranch Hand cohort. The

32 Ranch Hand Unit was responsible for aerial spraying of herbicides, including Agent Orange, in

1   Vietnam from 1962 to 1971. Cancer incidence in the Ranch Hand cohort was compared to a

2   cohort that included other Air Force personnel who served in Southeast Asia during the same

3   period but were not involved in the spraying of pesticides. Study participation was voluntary,

4   but there was no indication of the participation rate for either the Ranch Hand cohort or the

5   comparison group. Health outcomes were identified during the postservice period that extended

6   from the time each veteran left Southeast Asia until December 31, 1999. The Akhtar et al.

7   (2004) study took into account concerns that both the comparison and spraying cohorts had

8   increased risks of cancer, and addressed the possibility that workers with service in Vietnam or

9   Southeast Asia might have increased cancer risk. The authors addressed the latter concern by

10 adjusting risk estimates for the time spent in Southeast Asia and for the proportion of service

11 time spent in Vietnam.

12   The Ranch Hand cohort comprised 1,196 men, and the comparison cohort had

13 1,785 men. The comparison cohort was selected by matching date of birth, race, and occupation

14 (i.e., officer pilot, officer navigator, nonflying officer, enlisted flyer, or enlisted ground

15 personnel). TCDD levels were determined using serum levels collected from veterans who

16 completed a medical examination in 1987. Blood measures also were taken in 1992, 1997, and

17 2002 for subjects with no quantifiable TCDD levels in 1987, those who refused in 1987, and

18 those new to the study; however, the 2002 data were not available for the Akhtar et al (2004)

19 analyses. For those who did not have a serum measure taken in 1987, but provided one in

20 subsequent years, TCDD levels were back-extrapolated to 1987 using a first-order kinetic model

21 that assumed a half-life of 7.6 years. Those with nonquantifiable levels were assigned a value of

22 the limit of detection divided by the square root of 2. A total of 1,009 and 1,429 individuals in

23 the Ranch Hand and comparison cohorts, respectively, provided serum measures that were used

24 in the risk assessment. Veterans also were categorized according to the time their tours ended.

25 This date corresponded to changes in herbicide use. These categories were before 1962 or after

26 1972 (no herbicides were used), 1962−1965 (before Agent Orange was used), 1966−1970 (when

27 Agent Orange use was greatest), and 1971−1972 (after Agent Orange was used). Information on

28 incident cases of cancer in the cohort was determined from physical examinations and medical

29 records. Some malignancies were discovered at death and coded by using the underlying cause

30 of death as detailed on the death certificate. A total of 134 and 163 incident cases of cancer were

1   identified in the Ranch Hand and comparison cohorts, respectively. Akhtar et al. (2004) describe

2   case ascertainment verified by record review as being complete.

3   External comparisons were made based on the expected cancer experience derived from

4   U.S. national rates by using SIRs and their corresponding 95% confidence intervals. Incident

5   events and person-year contributions per group were tabulated by 5-year calendar and age

6   intervals.

7   When compared to the general population, no statistically significant excesses in all

8   cancer incidence were observed for either the Ranch Hand (SIR = 1.09, 95% CI = 0.91−1.28) or

9   the comparison cohort (SIR = 0.94, 95% CI = 0.81−1.10). Statistically significant differences

10   were found for three site-specific cancers in the Ranch Hands cohort relative to the general

11   population. Excesses were noted for malignant melanoma (SIR = 2.33, 95% CI = 1.40−3.65)

12   and prostate cancer (SIR = 1.46, 95% CI = 1.04−2.00). In contrast, a reduced SIR was found for

13   cancers of the digestive system (SIR = 0.61, 95% CI = 0.36−0.96). The excess in prostate cancer

14   was also noted in the comparison cohort (SIR = 1.62, 95% CI = 1.23−2.10) relative to the

15   general population. External comparisons were repeated by restricting the cohorts to the period

16   when Agent Orange was used (1966−1970). Again, no statistically significant excesses in all

17   cancer incidence were noted in the Ranch Hand veterans (SIR = 1.14, 95% CI = 0.95−1.37) or in

18   the comparison cohort (SIR = 0.94, 95% CI = 0.80−1.11). Statistically significant excesses

19   persisted for malignant melanoma (SIR = 2.57, 95% CI = 1.52−4.09) and prostate cancer

20   (SIR = 1.68, 95% CI = 1.19−2.33) in the Ranch Hand veterans. No other statistically significant

21   differences were found among Ranch Hands personnel.

22   For internal cohort analyses, veterans were assigned to one of four exposure categories.

23   Those in the comparison cohort were assigned to the "comparison category." Ranch Hand

24   veterans that had TCDD serum levels <10 ppt were assigned to the "background" category.

25   Those with a TCDD levels >10 ppt had their TCDD level estimated at the end of their Vietnam

26   service with a first-order kinetic model that used a half-life of 7.6 years. These

27   back-extrapolated values that were less than 118.5 ppt were assigned to a "low" exposure group,

28   while those with values above 118.5 ppt were classified as "high" exposure. Akhtar et al. (2004)

29   used Cox regression models to describe risks across the exposure groups using the comparison

30   category as the reference. Risks were adjusted for age at tour, military occupation, smoking

31   history, skin reaction to sun exposure, and eye color. Internal cohort analyses were restricted to

1   those who spent no more than 2 years in Southeast Asia and Ranch Hand workers who served

2   exclusively in Vietnam, and the comparison cohort who served exclusively outside of Vietnam.

3   Statistically significant excesses of cancer incidence (all sites combined) were observed

4   in the highest two exposure groups. A statistically significant trend ($p = 0.04$) was detected

5   based on the RRs for the background, low, and high exposure groups: 1.44

6   (95% CI = 0.82−2.53); 2.23 (95% CI = 1.24−4.00), and 2.02 (95% CI = 1.03−3.95). For

7   malignant melanoma, a statistically significant trend ($p = 0.004$) was detected, and the RRs

8   across the three increasing exposure categories were 2.99, 7.42, and 7.51, with statistically

9   significant results for the low and high exposure groups. The corresponding risk estimates for

10 prostate cancer were 1.50, 2.17, and 6.04 with statistically significant results only detected for

11 the high exposure group.

12

13 **C.1.1.1.6.1.2.** Study evaluation

14   An important strength of this study is the manner in which TCDD exposure was

15 estimated. Serum data were available for most veterans, and therefore, generalizing exposure

16 from a small sample of cohort members is not a concern as was the case with the NIOSH and

17 Hamburg cohorts. Back-extrapolating to derive past exposures was based on a methodology that

18 has been applied in many of the cohorts, thereby facilitating risk comparisons. An additional

19 strength of the study is the examination of cancer incidence as a measure of disease occurrence

20 rather than mortality. There is limited potential for gauge how representative the study

21 participants were given the lack of information provided on participation rates for either the

22 Ranch Hands or the comparison group. The analysis by Akhtar et al. (2004) was restricted to

23 individuals who spent no more than 2 years in Southeast Asia. Previous research had

24 demonstrated that increased time spent in Southeast Asia was associated with an increased risk

25 of cancer. Confounding might have been introduced given that the comparison cohort spent

26 much more time in Southeast Asia than the Ranch Hands. To illustrate, the median number of

27 days spent in Southeast Asia was 790 for comparison cohort members, and the median days for

28 the Ranch Hand cohort in the background, low, and high exposure groups were 426, 457, and

29 397, respectively. After restricting to those who spent at most 2 years, statistically significant

30 associations were observed for all cancer sites combined, prostate cancer, and malignant

31 melanoma using the internal cohort comparisons.

1   Given that 2,4,5-T and 2,4-D were used in equal concentrations in Agent Orange, there is

2   some concern regarding the ability to distinguish independent health effects for TCDD from

3   coexposures to these two herbicides. However, in a large cohort study, called the Agricultural

4   Health Study, these herbicides were 2 of 50 pesticides and herbicides evaluated in a cohort of

5   more than 55,000 (mostly male) pesticide applicators in the United States and more than

6   33,000 spouses. Although statistically significant associations were shown between prostate

7   cancer and several individual pesticides in this cohort (Alavanja et al., 2005), neither 2,4,5-T nor

8   2,4-D was associated with prostate cancer in that study (Alavanja et al., 2003); no associations

9   were found for these 2 herbicides and lung cancer either (Alavanja et al., 2004). Therefore,

10   based on these Agricultural Health Study results, the dose-response relationship detected for

11   prostate cancer in the Akhtar et al. (2004) Ranch Hands study seems unlikely to be due to 2,4-D

12   or 2,4,5-T exposures.

13

14   **C.1.1.1.6.1.3.**   Suitability of data for TCDD dose-response modeling

15   The ascertainment of incident cases and characterization of exposure to TCDD based on

16   serum measures are strong features of the cohort. Based on findings from another study

17   (Alavanja et al., 2005; 2004; 2003), confounding by 2,4-D and 2,4-T does not appear likely to be

18   responsible for the exposure-response relationships found for prostate cancer and TCDD

19   exposures. Therefore, this study was found suitable for quantitative TCDD dose-response

20   analysis.

21

22   **C.1.1.1.6.2.**   *Michalek and Pavuk (2008)*

23   **C.1.1.1.6.2.1.**   Study summary

24   Michalek and Pavuk (2008) published an updated analysis of the incidence of cancer and

25   diabetes in the cohort of Ranch Hand veterans. As with the Akhtar et al. (2004) analysis, the

26   study included a comparison cohort of other Air Force veterans who served in Southeast Asia at

27   the same time but were not involved with the spraying of herbicides. This study extended

28   previous analyses (Akhtar et al., 2004; Henriksen et al., 1997) by stratifying the results by the

29   number of days of herbicide spraying, calendar period of service, and the time spent in Southeast

30   Asia. Veterans who attended at least one of five examinations were eligible for inclusion.

31   Incident cancer cases also were identified from medical records.

1   The methods used to determine TCDD exposures were as described above in the review

2   of the Akhtar et al. (2004) study. Blood measures taken in 1992, 1997, and 2002 were all

3   included in this new analysis. The study report did not provide the number of men with

4   measurements at the different time points or the number who refused to partake at any time

5   point. TCDD dose at the end of service in Vietnam was assigned to Ranch Hands that had

6   TCDD levels above background using a first-order kinetic model and constant half-life of

7   7.6 years. Each veteran was then assigned to one of four dose categories: comparison veteran,

8   background (i.e., Ranch Hands with 1987 levels of TCDD ≤10 ppt), low (Ranch Hands with

9   1987 levels of TCDD >10−91 ppt), and high (Ranch Hands with 1987 levels of TCDD >91 ppt).

10   Serum TCDD estimates were available for 1,597 veterans (men) in the comparison cohort, and

11   986 veterans (men) in the Ranch Hand cohort. The comparison cohort was selected by matching

12   on date of birth, race, and military occupation of the Ranch Hands.

13   Michalek and Pavuk (2008) used Cox regression to characterize risks of cancer incidence

14   across the three upper exposure categories using the comparison cohort as the referent group.

15   Risk estimates were adjusted for year of birth, race, smoking, body mass index at the qualifying

16   tour, military occupation, eye color, and skin reaction to sun exposure. Tests for trend for

17   increased risk of cancer were conducted by testing the continuous covariate $\log_{10}$TCDD.

18   Without stratification, no association between the TCDD exposure categories and RR of

19   all-site cancer incidence was observed. Those in the highest exposure group had an RR of 0.9

20   (95% CI = 0.6−1.4). Stratified analyses by calendar period of service showed a more

21   pronounced risk for those who served before 1986 (when higher amounts of Agent Orange were

22   used). A statistically significant dose-response trend ($p < 0.01$) was observed for cancer risk and

23   log10TCDD exposure. The RRs for the background, low, and high groups used in these

24   comparisons were 0.7 (95% CI = 0.4−1.3) with $p = 0.26$, 1.7 (95% CI = 1.0−2.9) with $p = 0.03$,

25   and 1.5 (95% CI = 0.9−2.6) with $p = 0.14$. The strongest statistically significant increase,

26   however, was noted when analyses were restricted to those who had served before 1968, had

27   sprayed for at least 30 days before 1967, and had spent less than 2 years in Southeast Asia. A

28   RR of 1.4 (95% CI = 1.1−1.7) per log(TCDD) exposure was detected (trend test $p = 0.005$)

29   among this subgroup, while categorical exposures also suggested associations in the Low

30   (RR=1.7, 95% CI = 0.8−3.5) and High (RR=2.2, 95% CI = 1.1−4.4) groups relative to the

31   comparison group.

1

C.1.1.1.6.2.2.   Study evaluation

Michalek and Pavuk (2008) used the same study population as Akhtar et al. (2004), and so it shares the same basic strengths and limitations as noted above. The follow-up, however, extends an additional 5 years (until the end of 2004), resulting in additional cancer data for analysis and the inclusion of the serum data from 2002. Also, in this study, all analyses were further adjusted for the number of days of spraying, which had not been done before. The findings for the dose-response analyses were not as compelling as the earlier Akhtar et al. (2004) findings, which was due in part to increased cancer risks in 2005 in the comparison cohort with years spent in SEA.

C.1.1.1.6.2.3.   Suitability of data for TCDD dose-response modeling

As stated above for the Akhtar et al. (2004) study, the ascertainment of incident cases and characterization of exposure to TCDD based on serum measures are strengths of the cohort. In addition, newer data and additional statistical adjustments improved the strength of the analysis. This study, Michalek and Pavuk (2008), was suitable for quantitative dose-response analysis of TCDD.

C.1.1.1.7.   *Other studies of potential relevance to dose-response modeling*
C.1.1.1.7.1.   *Hooiveld et al. (1998)—Netherlands workers*
C.1.1.1.7.1.1.   Study summary

Hooiveld et al. (1998) reanalyzed the mortality experience of a cohort of workers employed in two chemical plants in the Netherlands using 6 additional years of follow-up from an earlier study (Bueno de Mesquita et al., 1993). The cohort consisted of those employed between 1955 and June 30, 1985, and vital status was ascertained until December 31, 1991 (i.e., 36 years of follow-up). These cohort members were involved in the synthesis and formulation of phenoxy herbicides, of which the main product was 2,4,5-trichlorophenoxyacetic acid and monochloroacetic acid. This cohort, with a shorter follow-up interval than the original study (t' Mannetje et al., 2005), was included in the IARC international cohort. The cohort consisted of 1,167 workers, of which 906 were alive at the end of the follow-up. The average length of follow-up was 22.3 years, and only 10 individuals were lost to follow-up.

1   The authors used detailed occupational histories to assign exposures. Workers were

2   classified as exposed to phenoxy herbicides or chlorophenols and contaminants if they worked in

3   selected departments (i.e., synthesis, finishing, formulation, packing, maintenance/repair,

4   laboratory, chemical effluent waste, cleaning, shipping-transport, or plant supervision); were

5   exposed to the accident in 1963; or were exposed by proximity (i.e., if they entered an exposed

6   department at least once a week). The 1963 accident was the result of an uncontrolled reaction

7   in the autoclave in which 2,4,5-trichlorophenol was synthesized; an explosion resulted, with

8   subsequent release of PCDDs that included TCDD. Based on these methods of exposure

9   assignment, 562 workers were deemed to be exposed to phenoxy herbicides or chlorophenols,

10   and 567 were unexposed. Due to limited information, exposure could not be determined for

11   27 workers.

12   TCDD exposures also were assigned using serum measured on a sample of workers who

13   were employed for at least 1 year and started working before 1975. DLCs including PCDDs

14   were also measured in the serum samples but were not analyzed for this study. Of the

15   144 subjects who were invited to provide samples, 94 agreed. TCDD levels were

16   back-extrapolated to the time of maximum exposure using a one-compartment, first-order kinetic

17   model that used a half-life estimate of 7.1 years. The mathematical model used was

18   $\ln(TCDDmax) = \ln(TCDD) + lag \times \ln(2)/7.1$. The lag was defined as the number of years since

19   last exposure for those exposed by virtue of their normal job duties. For those exposed as a

20   result of the accident in 1963, the lag was defined as the number of years since the accident

21   occurred.

22   The authors made external comparisons of cohort mortality to the Netherlands population

23   using SMRs. Poisson regression was used to perform internal cohort comparisons using

24   unexposed workers as the referent. RRs (measured using rate ratios) generated from the Poisson

25   model also were used to compare mortality based on low, medium, and high TCDD

26   serum-derived categories. The Poisson model included the following covariates as adjustment

27   factors: age, calendar period at end of follow-up, and time since first exposure.

28   When compared to the general population, workers had an excess mortality from cancer

29   (SMR = 1.5, 95% CI = 1.1−1.9), based on 51 cancer deaths. Generally, no excesses were

30   observed for site-specific cancers. The exception included eight deaths from cancers of the

31   urinary organs (SMR = 3.9, 95% CI = 1.7−7.6). Although not statistically significant, SMRs

1 comparable in magnitude to other studies were detected for non-Hodgkin lymphoma

2 (SMR = 3.8, 95% CI = 0.8−11.0) and Hodgkin disease (SMR = 3.2, 95% CI = 0.1−17.6). A

3 statistically significant excess of cancer mortality (n = 20 deaths among workers) also was

4 observed relative to the general population when analyses were restricted to those exposed from

5 the 1963 accident (SMR = 1.7, 95% CI = 1.1−2.7). Three deaths from prostate cancer were also

6 noted among these workers (SMR = 5.2, 95% CI = 1.1−15.3), but no excess was observed with

7 any other cancer site.

8   Internal cohort comparison also demonstrated an increased risk of all cancer mortality

9 among those exposed to phenoxy herbicides, chlorophenols, and contaminants relative to those

10 unexposed (RR = 4.1, 95% CI = 1.8−9.0). A statistically significant increased risk was also

11 noted for respiratory cancer mortality (RR = 7.5, 95% CI = 1.0−56.1). Analyses across

12 categories of TCDD exposure revealed excesses in cancer mortality for all cancer sites

13 combined; however, no dose-response trend was apparent.

14

15 **C.1.1.1.7.1.2.**   Study evaluation

16   Several other studies that have characterized cohorts by TCDD levels have used the area

17 under the curve approach and thus have derived an exposure metric that is time dependent.

18 Hooiveld et al. (1998) instead created an exposure metric to capture the maximum exposure

19 attained during the worker's employment. Characterizing risks using this metric assumes that

20 other TCDD exposures accrued during a workers' lifetime are not relevant predictors of cancer

21 risk.

22

23 **C.1.1.1.7.1.3.**   Suitability of data for TCDD dose-response modeling

24   One study limitation is that, although DLCs were measured in the serum samples,

25 mortality associations were reported for TCDD only. There is some utility in examining

26 dose-response analyses using the alternative exposure metrics that were constructed for this

27 cohort. However, the small number of identified cancer deaths, exposure assessment limitations

28 (based on a nonrepresentative sample, and maximum exposure level) and concern over potential

29 confounding by coexposures preclude using these data for a dose-response analysis.

30

1 **C.1.1.1.7.2.** *t' Mannetje et al. (2005)—New Zealand herbicide sprayers*

2 **C.1.1.1.7.2.1.** Study summary

3   t'Mannetje et al. (2005) described the mortality experience of a cohort of New Zealand

4 workers who were employed in a plant located in New Plymouth. The plant produced phenoxy

5 herbicides and pentachlorophenol between 1950 and the mid-1980s. This study population also

6 was included in the international cohort of producers and sprayers of herbicides that was

7 analyzed by IARC (Kogevinas et al., 1997; Saracci et al., 1991). In this 2005 study, analyses

8 were restricted to those who had worked at least 1 month; clerical, kitchen, and field research

9 staff were excluded. The authors followed up 1,025 herbicide producers and 703 sprayers from

10 1969 and 1973, respectively, until the end of 2000.

11   The cohort consisted of two components: those involved with the production of

12 herbicides and those who were sprayers. For the herbicide producers, exposures were

13 determined by consulting occupational history records; no direct measures of exposure were

14 available. Each department of employment was assigned to one of 21 codes as in the IARC

15 international cohort (Saracci et al., 1991). Industrial hygienists and factory personnel with

16 knowledge of potential exposures in this workforce classified each job according to potential to

17 be exposed to TCDD, other chlorinated dioxins, and phenoxy herbicides. Exposure was defined

18 as a dichotomous variable (i.e., exposed and unexposed). Among producers, 813 (713 men and

19 100 women) were classified as exposed, with the remaining 212 (gender not specified)

20 considered unexposed.

21   The "sprayer" component of the cohort includes those who were registered in the national

22 registry of applicators at any time from January 1973 until the end of 1984. For the sprayers,

23 detailed occupational information was lacking. Exposure was, therefore, based on an exposure

24 history questionnaire completed in a previous study of congenital malformations (Smith et al.,

25 1982). This questionnaire, administered to 548 applicators in 1980 and 232 applicators in 1982,

26 achieved a high response rate (89%). Participants were asked to provide information about

27 2,4,5-T-containing product use on an annual basis from 1969 up to the year the survey was

28 completed. As the use of 2,4,5-T ceased in the mid-1980s, data on occupational exposure to

29 TCDD among these workers are fairly complete. Virtually all sprayers (699 [697 men and

30 2 women] of 703) were deemed to have been exposed to TCDD, higher chlorinated dioxins, or

31 phenoxy herbicides.

1   Deaths among workers were identified through record linkage to death registrations in the

2   New Zealand Health Information Service. Electoral rolls, drivers' licenses, and social security

3   records also were consulted to confirm identified deaths. External comparisons of mortality

4   were made to the New Zealand population using the SMR statistic. The mortality follow-up for

5   the producers began on January 1, 1969 and extended until December 31, 2000. For the

6   sprayers, the follow-up period extended from January 1, 1973 until December 31, 2000. A total

7   of 43 cancer deaths occurred in the producer group and 35 cancer deaths occurred in the sprayer

8   group in the cohort. Stratified analyses by duration of employment and department were

9   conducted. The departments examined for producers included synthesis, formulation and lab,

10   maintenance and waste, packing and transport, other, and unexposed. SMRs were generated

11   using the New Zealand population as an external referent. A linear test for trend was applied to

12   evaluate dose-response trends according to categories of duration of employment. Stratified

13   analyses also were also done for sprayers who started working before 1973, as TCDD levels in

14   2,4,5-T produced at the New Zealand plant dropped dramatically after 1973. Although an SMR

15   was presented for female producers, given that only one cancer death was observed, this study

16   can provide no insight on differential risks between the sexes.

17   Among TCDD-exposed producers, for all cancers combined, no statistically significant

18   excess in mortality was found when compared to the general population (SMR = 1.24,

19   95% CI = 0.90−1.67). No dose-response trend in the SMRs for all cancers was observed with

20   duration of employment ($p = 0.44$). No statistically significant elevated SMR was observed in

21   any of the duration of employment categories for any of the six specific departments examined.

22   A statistically significant positive linear trend, however, was noted among synthesis workers

23   ($p = 0.04$). There was some suggestion of reduced mortality in the upper exposure levels for

24   workers in the formulation and lab departments. For sprayers, the SMR for all cancer sites

25   combined was not elevated relative to the New Zealand general population (SMR = 0.82,

26   95% CI = 0.57−1.14), nor was a dose-response pattern observed with increasing duration of

27   employment ($p = 0.86$). Additionally, no statistically significant excess in cancer mortality for

28   all sites combined was evident in workers who were first employed either before 1973

29   (SMR = 0.75, 95% CI = 0.50−1.07) or from 1973 onwards (SMR = 1.81, 95% CI = 0.59−4.22).

30   For site-specific cancer mortality, an excess of multiple myeloma was observed among

31   production workers relative to the general population (SMR = 5.51, 95% CI = 1.14−16.1). This

1   SMR was based on three deaths. No statistically significant excess (or deficit) of mortality was

2   found for any other cancer site examined in either the sprayers or the producers.

3

4   **C.1.1.1.7.2.2.** Study evaluation

5   The physical activity demands of spraying contribute to a healthy worker effect that

6   manifests itself in a lower SMR based for both external comparisons to the general population as

7   a referent, and that generated relative to the producers in the cohort. The lack of individual-level

8   TCDD data resulted in the analyses being based upon job title and duration of employment.

9   Thus, intra-cohort comparisons were precluded due to a lack of an unexposed group (e.g. the

10   sprayers), limited exposure contrasts and the small number of cancer deaths.

11   The dose-response pattern with duration of employment coupled with the observation

12   that higher levels of exposure to TCDD occurred among workers in the synthesis department is

13   an important finding. These workers were, however, also exposed to several other contaminants

14   that include processing chemicals, technical products, intermediates, and byproducts (Kauppinen

15   et al., 1993). These included phenoxy herbicides and DLCs such as chlorinated dioxins. Since

16   the dichotomous exposure measure was based on exposure to TCDD, chlorinated dioxins and

17   phenoxy herbicides, the associated dose-response analyses presented in this study should be

18   interpreted cautiously in light of the inability to either characterize or control for these potential

19   confounders. As such, these coexposures might have contributed to the dose-response pattern

20   observed with increased duration of employment in the synthesis workers.

21

22   **C.1.1.1.7.2.3.** Suitability of data for TCDD dose-response modeling

23   Although the study authors completed a subsequent analysis of this cohort using

24   serum-derived TCDD (McBride et al., 2009b), the lack of individual-level TCDD exposures

25   precludes dose-response modeling.

26

27   **C.1.1.1.7.3.** *McBride et al. (2009b)—New Zealand herbicide sprayers*

28   **C.1.1.1.7.3.1.** Study summary

29   McBride et al. (2009b) recently published the mortality experience of the New Zealand

30   cohort in relation to serum estimates of TCDD levels. This study included 1,599 workers who

31   were employed between 1969 and November 1, 1989, which was the date that 2,4,5-T was last

1   used. The study report does not specify how many of the individuals were men or women, but

2   using the percentage that were men lost to follow-up (73% of 1,261 were men) and not lost to

3   follow-up (76% of 338 were men) would indicate 1,001 men and 598 women were included in

4   the original cohort. As in their study published earlier in the same year (McBride et al., 2009a),

5   the follow-up period extended from the first day of employment until December 31, 2004. Vital

6   status was ascertained through record linkage to the New Zealand Health Information Service

7   Mortality Collection and the Registrar General's Index to Deaths for deaths up to 1990.

8   All current and former workers who lived within 75 km of the plant were invited to

9   provide serum samples. A total of 346 of the eligible workers (68%, gender not specified)

10   provided samples, which represented 22% of the overall study population (346/1,599). Based on

11   the serum measures, 70% (241/346) had been exposed to TCDD. This percentage is similar to

12   the estimated 71% of workers who were deemed to have been exposed based on a review of

13   occupational records. The mean serum TCDD value was 9.9 ppt. The highest exposures were

14   observed for those employed in the trichlorophenol operation (23.4 ppt). Values among

15   unexposed workers averaged 4.9 ppt, which is close to the background level of 3.9 ppt among

16   individuals of similar age in the New Zealand general population (Bates et al., 2004). Details on

17   smoking histories of individuals were also collected for the 346 individuals who provided serum,

18   allowing for an examination of the potential confounding influence that smoking might have on

19   derived risk estimates for TCDD.

20   Cumulative exposure to TCDD, as a time-dependent metric, was estimated for each

21   worker. A detailed description of the methods used to derive TCDD exposure was described in

22   Aylward et al. (2009). The qualitative TCDD scores available for those with serum measures

23   were used to estimate the cumulative exposures based on a half-life of 7 years. A

24   time-dependent estimate of TCDD exposure was derived and the area under the curve was used

25   to estimate cumulative workplace TCDD exposures above background levels. Model

26   performance appeared modest as the model explained only 30% of the variance (adjusted R^2)

27   when these TCDD exposure estimates were compared with actual serum levels (Aylward et al.,

28   2009).

29   As with previous analyses of the cohort (McBride et al., 2009a; t' Mannetje et al., 2005),

30   external comparisons to the New Zealand general population were made using the SMR. The

31   SMR also was used to compare mortality across four exposure groups relative to the general

1   population, as defined by the serum TCDD estimates: 0−68.3, 68.4−475.0, 475.1−2085.7, and

2   ≥2085.8 ppt-month. The proportional hazards model also was used to conduct internal cohort

3   comparisons across these same four exposure groups. In these analyses, age was used as the

4   time variable, and the covariates of date of hire, sex, and birth year were included in the

5   proportional hazards model. The cut-points for these four exposure categories were chosen so

6   that approximately equal numbers of deaths were included in each category.

7   Consistent with earlier SMR analyses of the same cohort, no increased cancer mortality

8   was observed among "ever" exposed workers when compared to the general population

9   (SMR = 1.1, 95% CI = 0.9−1.4). No statistically significant excess was noted for any of the

10   site-specific cancers, although there was some suggestion of increased risk of soft tissue sarcoma

11   (SMR = 3.4, 95% CI = 0.1–19.5), multiple myeloma (SMR = 2.2, 95% CI = 0.2−8.1),

12   non-Hodgkin lymphoma (SMR = 1.6, 95% CI = 0.3–4.7), and cancer of the rectum (SMR = 2.0,

13   95% CI = 0.7−4.4). No statistically significant increase in cancer mortality (all sites combined)

14   was found in any of the four exposure categories as measured by the SMR statistic, nor was a

15   dose-response trend noted with increasing exposure categories. No dose-response trends (based

16   on SMR analyses) were noted for five site-specific cancers examined (i.e., digestive organs,

17   bronchus, trachea and lung, soft tissue sarcomas, lymphatic and hematopoietic tissue, and

18   non-Hodgkin lymphoma), although SMRs for three of the four exposure categories exceeded 2.0

19   for non-Hodgkin lymphoma.

20   In contrast to the external cohort comparisons, the RRs generated with the proportional

21   hazards model supported a dose-response trend, as rate ratios increased across increasing TCDD

22   exposure categories. The RRs and 95% confidence intervals for all cancer mortality relative to

23   the lowest of the four groups were 1.05 (95% CI = 0.48−2.26), 1.38 (95% CI = 0.64−2.97) and

24   1.58 (95% CI = 0.71−3.52). Neither the linear ($p = 0.29$) or quadratic ($p = 0.82$) test for trend,

25   however, was statistically significant. An increased risk of lung cancer mortality was observed

26   in the highest TCDD exposure category relative to the lowest although the precision of this risk

27   estimates was poor and was not statistically significant (RR = 5.75, 95% CI = 0.76−42.24). The

28   test for trend for lung cancer also was not statistically significant.

29   A smoking survey was administered to a sample of surviving workers of this cohort, and

30   smoking prevalence was found to be slightly higher among those with higher cumulative

31   exposure (61%) compared to lower exposures (51−56%). These minor differences in smoking

1   prevalence were unlikely to explain the five-fold increase in risk of lung cancer found in the

2   highest exposure category. Although the smoking data assessment was a strength of the study, it

3   was limited to only sample of workers and was not available for those who died of lung cancer,

4   or other causes of death.

5

6   **C.1.1.1.7.3.2.**   Study evaluation

7   Given high rates of emigration, loss to follow-up (21%) was a potential concern in this

8   study. If comparable emigration rates did occur among the general population then the SMRs

9   would be underestimated. It is unclear to what extent emigration occurred among the general

10   population and whether emigration in both the worker and general populations was dependent on

11   health status. If emigration rates were comparable among these two populations, the associated

12   bias from the under-ascertainment of mortality in the lost to follow-up group would likely

13   attenuate a positive association between TCDD and cancer mortality. Among the worker

14   population, there was not much evidence of differential loss to follow-up with respect to

15   exposure as average exposures were lower (3.2 ppt) among those loss to follow up compared to

16   those with complete follow-up (5.7 ppt). Previous studies among this population also found

17   slightly higher loss to follow-up rates among the unexposed (23%) compared to the exposed

18   (17%) workers (t' Mannetje et al., 2005).

19   McBride et al. (2009b) did not present results using a continuous measure of TCDD

20   exposure (lagged or unlagged) as was done in most other occupational cohorts. Additionally, the

21   modeling did not consider the use of different periods of latency.

22

23   **C.1.1.1.7.3.3.**   Suitability of data for TCDD dose-response modeling

24   There was limited evidence of dose-response relationships between TCDD exposure and

25   the cancer outcomes that were examined. There is also no evidence that the authors considered

26   exposure metrics that are consistent with environmental cancer-causing agents such as exposure

27   modeling that takes latency into account. Given that past occupational cohort studies of

28   TCDD-exposed workers have consistently demonstrated stronger association with lag interval of

29   15 years, such an approach should be applied to this cohort. This precludes this study from

30   consideration for quantitative dose-response modeling.

31

1 **C.1.1.1.7.4. _McBride et al. ([2009a](#))—New Zealand herbicide sprayers_**

2 **C.1.1.1.7.4.1.** Study summary

3   McBride et al. ([2009a](#)) published an updated analysis of the mortality of the New Zealand

4 cohort. The follow-up period was from January 1, 1969 to December 31, 2004 extending the

5 previous study by an additional 4 years. In contrast to the previous study where the cohort

6 comprised individuals employed for at least 1 month prior to 1982 (or 1984) ([t' Mannetje et al.,](#)

7 [2005](#)), the cohort in this study consisted of all those who worked at least one day between

8 January 1, 1969 and October 1, 2003. This resulted in a cohort of 1,754 workers, of which

9 247 died in the follow-up interval. Twenty-two percent of the cohort members were lost to

10 follow-up, which could be a source of selection bias if loss to follow-up was related to both the

11 exposure metrics and the health outcome of interest. Previous data from this cohort ([t' Mannetje](#)

12 [et al., 2005](#)), however, showed fairly comparable loss to follow-up among the unexposed (23%)

13 and the exposed populations (17%).

14   Comparisons to the New Zealand general population were made using the SMR statistic.

15 Stratified analyses were conducted by duration of employment (<3 months, ≥3 months), sex,

16 latency (<15 years, ≥15 years), and period of hire (<1976, ≥1976). The authors defined latency

17 as the period between the day last worked and the earliest of date of death, date of emigration or

18 loss to follow-up, or December 31, 2004.

19   The overall SMR for mortality from all cancer sites combined relative to the New

20 Zealand population was 1.01 (95% CI = 0.85−1.10). Although not statistically significant, there

21 was suggestion of an increased risk of rectal cancer (SMR = 2.03, 95% CI = 0.88–4.01). SMRs

22 for lymphatic and hematopoietic cancers (overall SMR = 1.21, 95% CI = 0.52–2.39) included

23 3.12 (95% CI = 0.08−17.37) for Hodgkin disease, 1.59 (95% CI = 0.43–4.07) for non-Hodgkin

24 lymphoma, and 1.66 (95% CI = 0.20–5.99) for multiple myeloma. No statistically significant

25 excess of cancer mortality was noted among workers employed for <3 months (SMR = 1.19,

26 95% CI = 0.65−2.00), or for ≥3 months (SMR = 0.98, 95% CI = 0.75−1.26). A statistically

27 significant excess of digestive cancers was found for those who worked fewer than 3 months

28 relative to the New Zealand population (SMR = 2.52, 95% CI = 1.15−4.78). No excesses were

29 observed for any site-specific cancers when analyses were restricted to those who worked for 3

30 or more months. No statistically significant elevated SMRs were found for all cancers

31 (combined) either for a latency period of fewer than 15 years (SMR = 1.14, 95% CI = 0.72−1.71)

1   or a latency period of ≥15 years (SMR = 0.96, 95% CI = 0.72−1.26). Similarly, no statistically

2   significant excess in cancer mortality was observed for all cancer sites combined, or any

3   site-specific cancer when analyses were stratified by date of hire (<1976, ≥1976) or by sex. The

4   SMR among women who were employed at the site was 0.68 (95% CI = 0.45−1.00).

5

6   **C.1.1.1.7.4.2.**   Study evaluation

7   High rates of emigration in New Zealand (9% among workers in the cohort) contributed

8   to a fairly high loss to follow-up (22% among workers) during the study period. The loss to

9   follow-up would reduce the overall mortality estimates among the workers, which could

10   underestimate the SMRs if loss to follow-up (and health status) was not comparable in the

11   general population. For example, it is unclear if workers and the general population who

12   emigrated were less healthy than those who did not. Previous data from the cohort suggests that

13   loss to follow-up rates were slightly higher among those with lower exposures (McBride et al.,

14   2009b; t' Mannetje et al., 2005).

15

16   **C.1.1.1.7.4.3.**   Suitability of data for TCDD dose-response modeling

17   This study extended the mortality follow-up of an earlier study and included stratified

18   analyses to investigate effect modification by period of latency, sex, and date of hire. A key

19   limitation was the lack of direct measures of exposure for study participants which precluded

20   estimating effective dose needed for dose-response modeling. As such, this study did not meet

21   the considerations and criteria for inclusion in quantitative dose-response analysis.

22

23   **C.1.1.2.** *Key Characteristics of Epidemiologic Cancer Studies*

24   Table C-1 summarizes the key characteristics of the available epidemiologic studies of

25   TCDD exposure and cancer. It compares the length of follow-up, latency period used, half-life

26   for TCDD used, and the fraction of TEQs accounted for by TCDD (when applicable) for each

27   study.

28

C.1.1.3. *Feasibility of TCDD Cancer Dose-Response Modeling—Summary Discussion by Cohort*

C.1.1.3.1. *Using the NIOSH cohort in dose-response modeling*

It is important to evaluate the NIOSH cohort with respect to its suitability to conduct dose-response modeling of TCDD and cancer. This cohort is the largest assembled to date, direct measures of TCDD based on serum sampling are available, and the lengthy follow-up interval allows for latent effects to be taken into account. Further, although this cohort consists mostly of male workers, these workers were occupationally exposed to TCDD daily, as compared to the acute accidental exposures of other occupational cohorts. Although the most recent analyses of a subset of the NIOSH cohort showed no association between serum TCDD levels and cancer mortality, the exposure category cutpoints did not allow for examination of health effects above levels for which associations had been observed in the larger NIOSH cohort (Collins et al., 2010; 2009)).

Most published studies of the NIOSH cohort did not evaluate exposures to DLCs. An exception is the analysis by Steenland et al. (2001b). Although Steenland et al. (2001b) did not incorporate individual-level data on DLCs, based on their previous work (Piacitelli et al., 1992) they assumed that TEQ occupational exposures occurred as a result of TCDD alone in this population. TCDD exposures provided a better fit to the data than the TEQ-based metric, and 15-year latencies improved the fit for both metrics (relative to unlagged exposures). The lifetime risk estimates for an increase in 10 TEQs (pg/kg of body weight/day/sex) ranged from 0.05−0.18%. The value added for this measure is the incorporation of the contribution of other DLCs to the background rates.

Blue collar workers, such as those in the NIOSH cohort, typically have higher rates of smoking than the general population (Lee et al., 2007; Bang and Kim, 2001). This potential source of confounding would be expected to produce a higher SMR for lung cancer mortality, and could contribute to the excess noted in the cohort with longer lag intervals. This bias, however, likely is not large as no statistically significant excess of nonmalignant respiratory mortality was found in these workers. Any associated bias from smoking would be expected to be smaller for comparisons conducted within the cohort, as fellow workers would be expected to be more homogeneous with respect to their risk factor profile than with an external general population referent group. Stratified analyses using both internal and external comparison groups also did not identify important differences in associations with TCDD exposure between

1 smoking and nonsmoking cancers. Thus, fatal cancer risk estimates reported for workers in the

2 NIOSH cohort appear to provide a reasonable estimate of the carcinogenic potency of TCDD.

3 Although the Steenland et al. (2001b) study did not directly account for the possible

4 confounding effects of other occupational exposure, the authors did address this source of

5 potential bias. No known occupational exposures to carcinogens occurred, with the exception of

6 4-aminobiphenyl, which occurred at only one plant. Two deaths from mesothelioma also

7 occurred in the cohort, so some exposure to asbestos was possible (Fingerhut et al., 1991a). The

8 statistical analyses suggested that the inability to control for other occupational exposures would

9 not have unduly affected risk estimates generated from internal cohort comparisons. For

10 instance, the removal of one plant at a time from the analysis did not materially change

11 dose-response estimates generated from the Cox model (Cheng et al., 2006). Moreover, adding a

12 variable to represent each plant in the Cox regression had little impact on the risk estimates.

13 Given that other occupational exposures varied by plant, a change in risk estimates would be

14 expected if such exposures were strong confounders.

15 The Cheng et al. (2006) analysis provides important information about the impact of

16 applying kinetic models to the data. The CADM TCDD kinetic model resulted in dramatic

17 decreases in the TCDD cancer mortality risk estimates when compared to the one-stage

18 compartmental model that had been applied. Although Cheng et al. (2006) suggested that the

19 CADM model provides a better fit to the data than the typically used simple one-compartmental

20 model, statistical comparisons of model fit were not reported. Therefore, there is value in

21 presenting the range in risk estimates across different models when characterizing dose-response

22 relationships.

23 Finally, the half-life of TCDD is generally recognized to vary according to body fat

24 percentage, and this information was not available for the NIOSH workers. The inability to

25 account for between-worker variability in body fat would introduce exposure measurement error.

26 That body fat percentage would not be expected to correlate with cumulative exposure to TCDD

27 exposure, however, would limit the potential for misclassification bias. The effect of any

28 nondifferential exposure measurement error likely would serve to attenuate the risk estimates of

29 the study.

30

1 **C.1.1.3.2.** *Using the BASF cohort in dose-response modeling*

2   The availability of blood lipid data for TCDD allows for characterization of cumulative

3 TCDD exposures in the BASF cohort. TCDD blood lipid data were collected for 90% of the

4 surviving members of the cohort (138 of 154) and these serum measures were used to generate

5 TCDD exposure estimates for all 254 cohort members. Therefore, the potential for

6 misclassification error from extrapolating these exposures to the entire cohort is less likely than

7 for the NIOSH cohort where sera data were available for only a small fraction of workers. These

8 BASF serum data were, however, collected long after the accident (36 years) and had to be

9 back-extrapolated to derive the initial exposures.

10   The data on this cohort included several risk factors such as cigarette smoking and body

11 mass index. One advantage is that cumulative TCDD levels by body mass index can be

12 estimated on an individual-level basis. As expected, the derived cumulative measures appear to

13 correlate well with severity scores of chloracne. The finding that more pronounced risks were

14 found 15−20 years after first exposure are also consistent with findings from several other

15 cohorts (Bertazzi et al., 2001; Fingerhut et al., 1991b; Manz et al., 1991).

16   A key limitation of the BASF cohort is its relatively small sample size ($n = 243$), which

17 limits the ability to evaluate dose-response relationships for site-specific cancers. Also, the

18 quality of the ascertainment of cancer incidence cannot be readily evaluated as the geographic

19 area of the cohort is not covered by a tumor registry. Ott and Zober (1996a) state that nonfatal

20 cancers could have been more likely to be missed in early years, which could partially contribute

21 to the higher standardized incidence ratio found for cancer with longer latencies. Commenting

22 on risk differences derived from incident and decedent cancer outcomes is difficult. Among

23 those comprising the cohort, the ascertainment of incident outcomes was recognized to be less

24 complete in early years. Although the ascertainment of mortality outcomes was generally

25 regarded to be good among the 243 workers, some workers who died or moved likely were

26 missed when the cohort was constructed. These deaths would have been more likely to have

27 occurred several years before the second component of the cohort was assembled.

28   The use of the SMR statistic for this study population is associated with important

29 sources of uncertainties. Deaths were surely missed, particularly for the third component of the

30 cohort that accounts for approximately 38% (94/247) of the entire cohort; this factor would serve

31 to underestimate the overall SMR. As mentioned before, this component of the cohort was

1 assembled through the recruitment of workers known to be alive in 1986. Despite this limitation,

2 the characterization of exposure data and availability of other risk factor data at an individual

3 level allow the development of quantitative dose-response analyses.

4

5 **C.1.1.3.3.** *Using the Hamburg cohort in dose-response modeling*

6 The Hamburg cohort lacked data on cigarette smoking, and, therefore, effect estimates

7 could not be adjusted for this covariate. Additional analyses that excluded lung cancers resulted

8 in an even stronger dose-response relationship between all cancer mortality and TCDD. Serum

9 levels of TCDD also were also not associated with smoking status in a subgroup of these workers

10 (Flesch-Janys et al., 1995) suggesting that smoking unlikely confounds the association between

11 all cancer mortality and TCDD.

12 An important limitation of the cohort is the reliance on blood and tissue measurements of

13 190 workers that likely represent a highly selective component of the cohort. This subset of

14 workers was identified at the end of the observation period, and therefore, excludes workers who

15 died or could not be traced. There are uncertainties in deriving department- and period-specific

16 estimates for a period that extends over three decades using this number of workers.

17 Additionally, the criteria applied to the reference population could have introduced some bias.

18 Workers were included only in the reference group if they had been employed for at least

19 10 years in a gas supply industry. The criteria were much different for the workers who were

20 exposed to TCDD (only 3 months of employment). As a result, the reference group likely would

21 be more susceptible to the healthy worker effect. Internal cohort comparisons, which should be

22 void of such bias, however, generally produced results similar to those based on the external

23 comparison population. In summary, the Becher et al. (1998) study meets the criteria and

24 additional epidemiological considerations which allowed for development of quantitative

25 dose-response analyses.

26

27 **C.1.1.3.4.** *Using the Seveso cohort in dose-response modeling*

28 Unlike many of the occupational cohorts that were examined, data from the Seveso

29 cohort are representative of a residential population whose primary exposure was from a single

30 TCDD release. A notable exception is the BASF cohort where workers were exposed principally

1 through two accidents that occurred in the plant. The Seveso data, therefore, might permit

2 cancer dose-response investigations in women and children.

3   Uncertainty in identifying the critical exposure window for most of the outcomes related

4 to the Seveso cohort is a key limitation. An important feature of the Seveso cohort, however, is

5 that TCDD levels were much lower among those in the highest exposure zones in Seveso

6 (medians range from 56−136 ng/kg) (Eskenazi et al., 2004) than those in the occupational

7 cohorts who had TCDD exposures that were sometimes more than 1,000 ng/kg. Given these

8 dramatic exposure differences in exposures, the standardized mortality ratios (after incorporating

9 a 15−20 year latency period) for all cancer sites combined are remarkably similar between the

10 Seveso and the occupational cohort analyses. Perhaps more importantly, the data from Seveso

11 might be more relevant for extrapolating to lower levels, given that exposures to TCDD are

12 two orders of magnitude higher than background levels (Smith and Lopipero, 2001), and lower

13 than many of the exposures observed in the other occupationally exposed cohorts.

14   The Warner et al. (2002) study found a positive association between serum levels of

15 TCDD and breast cancer. As noted previously, ascertainment of incident cases for all cancers

16 would allow for a dose-response relationship to be evaluated. Moreover, future breast cancer

17 analyses in this cohort that would increase sample size should strengthen the quantitative

18 dose-response analyses of this specific cancer site. The strengths of the Warner et al. (2002)

19 study outlined earlier suggest that this study should be considered for cancer dose-response

20 modeling.

21   Earlier Seveso studies likely are unsuitable for conducting quantitative risk assessment.

22 These previous studies used an indirect measure of TCDD exposure, namely, zone of residence.

23 Soil concentrations of TCDD varied widely in these three zones (Zone A: 15.5−580.4 ppt;

24 Zone B: 1.7−4.3 ppt; and Zone R: 0.9−1.4 ppt), which could have resulted in considerable

25 exposure misclassification. The Warner et al. (2002) study greatly improved the characterization

26 of TCDD exposure using serum measures, and also allowed for control of salient risk factors that

27 may have resulted in bias due to confounding.

28   At this time it is unclear whether any study has examined the relationship between cancer

29 and serum estimates of TCDD among Seveso males exposed from the 1976 accident.

30

1 **C.1.1.3.5.** *Using the Chapaevsk related data in dose-response modeling*

2   Currently, individual-level exposure data are lacking for residents of this area and there is

3 no established cohort for which cancer outcomes can be ascertained. These limitations,

4 therefore, preclude the inclusion of Chapaevsk data in a quantitative dose-response analysis.

5

6 **C.1.1.3.6.** *Using the Ranch Hands cohort in dose-response modeling*

7   Study strengths of the Ranch Hand cohort includes a relatively large cohort with

8 individual-level serum measurements taken over time in 1987, 1992, 1997, and 2002. In

9 addition, TCDD levels for later years were back-extrapolated to 1987 using a first-order kinetic

10 model that assumed a half-life of 7.6 years. Although the isolation of TCDD effects from those

11 of other agents found in Agent Orange raised some concerns about confounding, results from a

12 large agricultural cohort found no association between 2,4-D or 2,5-T and prostate cancer or lung

13 cancer (Alavanja et al., 2005; 2004; 2003). It was determined that dose-response analyses would

14 be conducted on this population using both the (Michalek and Pavuk, 2008)) and Akhtar et al.

15 (2004) studies.

16

17 **C.1.1.4.** *Discussion of General Issues Related to Dose-Response Modeling*

18 **C.1.1.4.1.** *Ascertainment of exposures*

19   Several series of epidemiological data have used serum measures to estimate TCDD

20 exposures. Serum data offer a distinct advantage in that they provide an objective means to

21 characterize TCDD exposure at the individual level. The serum measures in the occupational

22 cohorts, however, are limited in two important ways. First, these samples are generally collected

23 from small subsets of the larger cohorts; therefore, using these measures to extrapolate to the

24 remainder of the cohort could introduce bias due to exposure misclassification. The

25 second limitation is related to estimating the half-life of TCDD. As noted previously, exposures

26 to TCDD were back-extrapolated several decades from the date that serum samples were

27 collected among surviving members of several cohorts. This approach was used in the NIOSH,

28 Ranch Hands, BASF, New Zealand, and Hamburg cohorts. The reported half-life of TCDD

29 among these populations was reported between 7.1 to 9.0 years and the half-life has been shown

30 to vary with several individual characteristics including age, body fat composition, and smoking.

31 The derivation of half-lives from a sample of workers, and application of these estimates to

1 retrospectively characterize exposure can introduce uncertainty into the lifetime exposure

2 estimates. It is important to note, however, that sensitivity analyses results in several studies

3 have been fairly consistent when evaluating the impact of half-life of TCDD (Steenland et al.,

4 2001b; Flesch-Janys et al., 1995). In addition, the reliance on surviving cohort members for

5 serum samples can introduce bias as it assumes their distribution of TCDD exposures was the

6 same among those who died.

7   A unique advantage of the Seveso study is that serum measures were taken shortly after

8 the accident, and therefore characterization of TCDD exposure in this population does not

9 depend on assumptions needed to back-extrapolate exposures several decades.

10

11 **C.1.1.4.2.** *Latency intervals*

12   Many of the epidemiological studies indicate stronger associations between TCDD and

13 cancer outcomes once a latency period has been considered. Generally, risks are higher when a

14 latency period of 15−20 years is included. As noted previously, this observation is consistent

15 with many other environmental carcinogens such as radon, radiation, and cigarette smoking.

16 That recent exposures do not contribute to increased cancer risk provides some support that the

17 initiation and promotion phases might occur many years before death making recent exposures

18 irrelevant for these analyses. The ability to discriminate between models of varying latency,

19 however, was not possible in many studies. The application of biologically-based modeling

20 could provide additional important insights on which phase(s) of carcinogenesis TCDD exerts an

21 influence. Such modeling, however, would necessitate having data on an individual-level basis.

22 Ideally, this modeling would use cancer incident rather than mortality outcomes given that the

23 median survival time exceeds 5 years for many cancer sites.

24

25 **C.1.1.4.3.** *Use of the SMR metric*

26   The occupational cohorts and the studies in Seveso and Chapaevsk have relied on the

27 SMR to make inferences regarding the effects of TCDD on mortality. When compared to the

28 general population, the healthy worker effect may result in a downward bias in the SMR. This

29 often can manifest as SMRs less than 1 for several causes of mortality. The effect of this bias is,

30 however, generally smaller for cancer outcomes. Cancer outcomes, whether incidence or death,

31 typically occur later in life and do not generally affect an individual's ability to work at earlier

32 ages.

1	There are several approaches that can be taken to minimize potential biases introduced by

2	the healthy worker effect, which would account for workers being healthier than the general

3	population. Comparisons of mortality (or cancer incidence) can be made to other cohorts of

4	similar workers. If done properly, this can allow for some control of characteristics such as

5	sociodemographic characteristics and smoking as the two populations can be matched by these

6	factors. However, it may be the case that other working populations are exposed to other

7	harmful exposures, thereby making it difficult to estimate risk associated with a specific agent

8	(such as TCDD) in the cohort of interest. A second and preferred approach to control for the

9	healthy worker effect, should it prove feasible, is to conduct comparisons of health outcomes in

10	relation to exposure within the cohort. These comparisons are less likely to be influenced by

11	other potential confounding variables such as smoking, socioeconomic status, and other

12	occupational exposures that are generally more homogeneous within the cohort relative to

13	external populations. Moreover, the mechanisms used to identify health outcomes and follow

14	individuals over time are generally applied in the same manner to all cohort members. Taken

15	together, where different comparisons have been made to generate risk estimates, those that have

16	been conducted using internal cohort comparisons are preferable.

17	In addition to potential bias from the healthy worker effect, the comparison of SMRs

18	between studies is not always straightforward and is not recommended by some (Myers and

19	Thompson, 1998; Rothman, 1986). The SMR is the ratio of the observed number of deaths to

20	the expected number of deaths and is often referred to as the method of indirect standardization.

21	The expected number of deaths is estimated by multiplying the number of person-years tabulated

22	across individuals in the cohort, stratified by age, by rates from a reference population that are

23	available for the same strata. Therefore, each population cohort will have an estimated number

24	of cases derived using a different underlying age structure. As outlined by Rothman (1986), the

25	mortality rates might not be directly comparable to each other, although the impact of such bias

26	will be much less if the age-distribution of the cohorts is similar. While it might be reasoned that

27	the TCDD exposed workers would have similar age distributions this is in fact not the case

28	(Becher et al., 1998; Ott et al., 1993; Thiess et al., 1982). This may be due to exposure occurring

29	both chronically, as well as from acute exposures due to accidental releases that happened at

30	various times at different plants. This is evident with the Hamburg and the BASF cohorts, as

31	most individuals comprising the BASF cohort were employed at the time of the accident

1   (1953/1954), while most of the Hamburg cohort (852/1048) was employed after 1954; the

2   follow-up of these cohorts ended at approximately the same time.

3   The method of direct standardization allows for a more meaningful comparison of

4   mortality rates to be made between cohorts. With this approach, weights (usually based on age

5   and sex) are drawn from a standard population and are, in turn, applied to disease rates for the

6   same strata observed in the cohort of interest. A comparison of weighted rates between different

7   cohorts would then be based on the same population standard.

8   Despite these limitations in comparing SMRs between studies, Armstrong (1995) argues

9   that the comparisons are valid if the underlying stratum specific rates in each exposure grouping

10   are in constant proportion to external rates. Comparisons of the SMRs between studies will be

11   biased only if there is an interaction between age and TCDD (i.e., the RR of disease due to

12   exposure differs by age). For cancer outcomes, the finding that associations become stronger

13   after a period of latency is incorporated into the analyses suggests that this assumption does not

14   hold true. That is, risk estimates would be lower among young workers. Similarly, for

15   noncancer outcomes, some of the data from the Seveso cohort suggests differential effects

16   according to the age at exposure.

17   The use of the SMR might also be biased in that workers exposed to TCDD could be

18   subject to more intensive follow-up than the general population, and as a result, differential

19   coding biases with cause of death might occur. Moreover, some cohorts (e.g., the BASF cohort)

20   have been assembled, in part, by actively seeking out survivors exposed to accidental releases of

21   dioxins. As such, they would not include persons who have died or who were lost to follow-up.

22   This would result in underascertainment of deaths and SMRs developed from these data. The

23   use of an internal cohort comparison offers distinct advantages to overcome potential sources of

24   selection bias. Given these uncertainties about the comparability across the different studies,

25   conducting a meta-analysis of cancer outcomes for TCDD using the SMR statistic is not

26   warranted for this analysis.

27

28   **C.1.1.4.4.   *All cancers versus site-specific***

29   An important consideration for quantitative dose-response modeling is the application of

30   models for all cancers combined, or for site-specific cancers. Consistency is often lacking for

31   site-specific cancers, which might be due in large part to the relatively small number of cases

1 identified for site-specific cancers in the cohorts. Although the risk estimates produced for all

2 cancer sites have important limitations and uncertainties, the data are far more consistent in

3 terms of the magnitude of an association and latency intervals. The IARC evaluation has put

4 forth the possibility of a pleuripotential mode of action between TCDD and the occurrence of

5 cancer. Despite the criticism of this assertion by some (Cole et al., 2003), the general

6 consistency of an increased risk for all-cancer mortality across the occupational cohorts when

7 latency intervals have been incorporated, provides adequate justification for dose-response

8 quantification of all cancer sites combined.

9

10 **C.1.1.4.5.   *Summary of epidemiologic cancer study evaluations for dose-response modeling***

11 All epidemiologic cancer studies summarized above were evaluated for suitability of

12 quantitative dose-response assessment using the TCDD-specific considerations and study

13 inclusion criteria. The results of this evaluation are summarized in a matrix style array (see

14 Table C-2). Table 2-1 in Section 2 of this document summarizes the key epidemiologic cancer

15 studies suitable for further TCDD dose-response analyses.

16

17 **C.1.2. Noncancer**

18 In this section, the available epidemiological data that could be used in a dose-response

19 analysis for noncancer endpoints are evaluated. Because many of the key studies also evaluated

20 cancer outcomes, the noncancer studies are presented in the same order as in Section 2.4.1.1.

21 Generally, the strengths and limitations of the cancer studies also apply to the noncancer

22 outcomes. In this section, key features of these studies that have direct relevance to modeling of

23 noncancer outcomes in particular are highlighted. To reduce redundancy, a detailed overview of

24 many of these cohorts and studies are not provided here. Instead, the reader should refer to

25 Section 2.4.1.1.1.

26

1 **C.1.2.1.** *Noncancer Cohorts*

2 **C.1.2.1.1.** *The NIOSH cohort*

3 **C.1.2.1.1.1.** *Steenland et al. (1999)*

4 **C.1.2.1.1.1.1.** Study summary

5   The 1999 published report of NIOSH workers exposed to TCDD also conducted external

6 cohort comparisons to the U.S. general population using SMRs for mortality outcomes other than

7 cancer (Steenland et al., 1999). Analyses are based on 3,538 male workers employed at 8 plants

8 from 1942 to 1984. Four of the 12 plants originally analyzed were excluded due to lack of

9 records on the degree of TCDD contamination in the work processes or information was lacking

10 for work histories needed to estimate TCDD exposure. Workers were excluded if they were

11 female ($n = 40$) or were lacking data to evaluate exposure ($n = 238$). SMRs were based on a

12 mortality follow-up that was extended until the end of 1993. Cox regression analyses were used

13 to compare mortality risk in relation to TCDD exposure within the cohort.

14

15 **C.1.2.1.1.1.2.** Study evaluation

16   Overall, no statistically significant differences in all-cause mortality (SMR = 1.03,

17 95% CI = 0.97−1.08) were observed. Mortality from ischemic heart disease (SMR = 1.09,

18 95% CI = 1.00−1.20) and accidents (SMR = 1.25, 95% CI = 1.03−1.50) was slightly elevated.

19 Based on the external comparison population, the dose-response relationship for ischemic heart

20 disease observed with the SMRs calculated across TCDD exposure septiles was not statistically

21 significant ($p = 0.14$). Overall, no excess risk was observed for diabetes, cerebrovascular

22 disease, or nonmalignant respiratory disease using the external population comparisons. Internal

23 cohort comparisons using the Cox regression model were performed using 0 and 15-year lag

24 intervals. A dose-response trend was observed for the derived ratios across the unlagged

25 cumulative TCDD exposure septiles for ischemic heart disease ($p = 0.05$) and diabetes

26 ($p = 0.02$). For ischemic heart disease mortality, those in the upper two septiles had rate ratios of

27 1.57 (95% CI = 0.96−2.56) and 1.75 (95% CI = 1.07−2.87), respectively, relative to those in the

28 lowest septile. In contrast, an inverse dose-response relationship was observed for diabetes

29 mortality. The inverse association found for diabetes is inconsistent with the positive association

30 reported in the Ranch Hands study (Michalek and Pavuk, 2008). However, previous reports

31 have questioned the use of death certificates as the means to ascertain diabetes as these deaths

1 may be under-reported especially among those with diabetes who die from cancer (McEwen et

2 al., 2006).

3

4 **C.1.2.1.1.1.3.**   Suitability of data for TCDD dose-response modeling

5   There was no evidence of a dose-response relationship between TCDD exposure and

6 ischemic heart disease mortality in this study or other cohorts. The inverse association with

7 diabetes also precludes dose-response analysis for this outcome. As all outcomes were based on

8 mortality, dose-response modeling was not conducted for this study.

9

10 **C.1.2.1.1.2.**   ***Collins et al. (2009)***

11 **C.1.2.1.1.2.1.**   Study summary

12   Collins et al. (2009) described the mortality experience of Dow employees who worked

13 in Midland, Michigan. This plant produced 2,4,5-trichlorophenol between 1942 and 1979, and

14 2,4,5-T between 1948 and 1982. The cohort consisted of 1,615 workers (number of each gender

15 not specified) exposed to TCDD from as early as 1942; the follow-up of the cohort extended

16 until 2003.

17   TCDD exposures were derived using serum samples obtained from 280 surviving

18 individuals (gender and selection criteria not reported). A simple one-compartment, first-order

19 pharmacokinetic model was used to estimate time-dependent TCDD measures. The area under

20 the curve approach was then applied to estimate cumulative TCDD exposure above background.

21 A half-life of 7.2 years for TCDD based on earlier work was incorporated into the exposure

22 estimation (Flesch-Janys et al., 1996).

23   Collins et al. (2009) made an external comparison of the mortality rates of the cohort to

24 the U.S. general population using the SMR. Noncancer causes of death included all causes,

25 diabetes, cerebrovascular disease, nonmalignant respiratory disease, cirrhosis of the liver, and

26 accidents. Overall, no statistically significant difference in all-cause mortality of these workers

27 was detected when compared to the general population (SMR = 0.9, 95% CI = 0.9−1.0). Except

28 for cirrhosis of the liver (SMR = 0.4, 95% CI = 0.1−0.8), no differences were found for any of

29 the noncancer causes of death relative to the general population.

30   Internal cohort analyses based on cumulative measures of TCDD were conducted for

31 mortality from diabetes, ischemic heart disease, and nonmalignant respiratory disease using the

1   Cox regression model. These models adjusted for possible confounders such as year of hire and

2   birth year. No statistically significant associations were found between the continuous measure

3   of TCDD exposure and these causes of death.

4

5   **C.1.2.1.1.2.2.**   Study evaluation

6   Given that the external comparisons may result in bias from the healthy worker effect,

7   results from the internal cohort comparisons using the Cox regression model are preferred.

8   These analyses were performed for diabetes, ischemic heart disease, and nonmalignant

9   respiratory disease. TCDD levels for these workers were estimated using a simple

10   one-compartment pharmacokinetic model (Aylward et al., 2007). Because participation rates

11   and selection criteria for the 280 individuals providing samples were not reported, it is not

12   possible to determine how representative these individuals are of the larger cohort. The hazard

13   ratios generated from the Cox regression model were not statistically significant for any of the

14   three noncancer outcomes modeled.

15

16   **C.1.2.1.1.2.3.**   Suitability of data for TCDD dose-response modeling

17   No increased risks were observed for any of the noncancer outcomes reported in Collins

18   et al. (2009). As all outcomes were based on mortality, dose-response modeling was not

19   conducted for this study.

20

21   **C.1.2.1.2.   *The BASF cohort***

22   **C.1.2.1.2.1.   _Ott and Zober_**

23   **C.1.2.1.2.1.1.**   Study summary

24   In 1996, Ott and Zober (1996a) published a report on the mortality experience of the

25   cohort of 243 BASF male workers who were accidentally exposed to 2,3,7,8-TCDD in 1954 or

26   in the clean up that followed. The mortality follow-up of this cohort extended until the end of

27   1992. External comparisons of mortality were made with the German population. Internal

28   cohort comparisons were also made by estimating cumulative TCDD for the cohort using serum

29   measures that were obtained from 138 workers. Ott et al. (1993) provided a detailed account of

30   the methodology to estimate TCDD. The 138 workers were selected based on a set of criteria of

31   duration of exposure (relative to the timing of the accident). There was no indication of the

1   participation rate among these workers, although some employee subgroups were over- and

2   under-represented. Briefly, a cumulative measure of TCDD expressed in µg/kg was derived, by

3   first estimating the half-life of TCDD using individuals who had repeated serum measures; the

4   half-life was estimated to be 5.8 years. Individual-level data on body fat were used to account

5   for the influence of body fat on decay rates. Half-life estimates of TCDD varied (range:

6   5.1−8.9 years) and were dependent on body fat composition (20% and 30%, respectively). This

7   approach differed from previous analysis of this cohort that used a constant 7-year half-life (Ott

8   et al., 1993). TCDD levels at the time of serum sampling were then estimated as the product of

9   TCDD concentration in blood lipid and the total lipid weight for each worker. Nonlinear models

10   then were applied to estimate the contribution of duration of exposure to TCDD dose

11   extrapolated to the time of exposure.

12   External comparisons to the German population using the SMR statistic also were

13   examined across dose categories. The noncancer causes of death examined by Ott and Zober

14   (1996a) included all-cause mortality, diseases of the circulatory system, ischemic heart disease,

15   diseases of the digestive system, external causes, suicide, and residual causes of death. Overall,

16   no statistically significant differences in the SMR with the general population for all-causes of

17   death (SMR = 0.9, 95% CI = 0.7−1.1), nor any other causes of death examined were found.

18   Ott and Zober (1996a) performed internal cohort comparisons using Cox regression.

19   These analyses found no dose-response patterns when cause-specific mortality was examined

20   across increasing cumulative TCDD exposure categories. Although an inverse association for

21   diseases of the respiratory system (SMR = 0.1, 95% CI = 0.0−0.8) was detected, it was based

22   only on 1 reported death. Many comparisons were limited by small sample sizes as only

23   92 deaths occurred in the cohort, and of these, 31 were from cancer. Also, the third component

24   of the cohort was identified primarily from former employees who were alive in 1986. As a

25   result, the SMR based on the general population was likely underestimated by the exclusion of

26   deceased workers.

27

28   **C.1.2.1.2.1.2.** Study evaluation

29   As noted previously, caution should be exercised in the interpretation of SMR for

30   noncancer outcomes as they could be influenced by the healthy worker effect. Although the

31   mechanism of identifying vital status appears to be excellent and unbiased, SMRs might be

1 underestimated due to the manner in which the cohort was constructed. Specifically, a large

2 component of the cohort was assembled by actively seeking out former workers known to be

3 alive in 1986.

4

5 **C.1.2.1.2.1.3.** Suitability of data for TCDD dose-response modeling

6 No dose-response patterns were observed between TCDD and the noncancer outcomes in

7 the Ott and Zober (1996a) study. Therefore, dose-response modeling was not conducted.

8

9 **C.1.2.1.3.   *The Hamburg cohort***

10 **C.1.2.1.3.1.   *Flesch-Janys et al. (1995)***

11 **C.1.2.1.3.1.1.** Study summary

12 Flesch-Janys et al. (1995) reported on the mortality experience of a cohort of individuals

13 employed by an herbicide-producing plant in Hamburg, Germany, covering the period 1952 to

14 1992. As described in more detail in Section 2.4.1.1.1.3, the authors developed a cumulative

15 measure of TCDD using serum measures from 190 workers. Selection criteria and response

16 rates for this subsample were not specified. This study also examined the relationship between

17 total TEQ and mortality. In the study population, the mean TEQ without TCDD was 155 ng/kg,

18 and for the mean TEQ including TCDD was 296.5 ng/kg.

19 Risks relative to the unexposed referent group of gas workers were estimated using Cox

20 regression across six exposed TCDD groups (i.e., the first four quintiles, and the ninth and

21 tenth deciles). A linear dose-response relationship was found with all causes of mortality and

22 cardiovascular mortality ($p < 0.01$). The RR for all cardiovascular deaths in the upper exposure

23 category was 1.96 (95% CI = 1.15−3.34), although there was no evidence of a linear

24 dose-response trend ($p = 0.27$). The dose-response relationship was strongest for ischemic heart

25 disease, with a RR of 2.48 (95% CI = 1.32−4.66) in the highest exposure group. A

26 dose-response relationship was also observed across TEQ groupings for all cause mortality,

27 cardiovascular disease mortality, and ischemic heart disease mortality. The authors did not

28 perform joint modeling of TEQ (without TCDD) and TCDD, so determining the extent that

29 DLCs contributed to an increased risk of mortality is not possible.

30

C.1.2.1.3.1.2.   Study evaluation

The Flesch-Janys et al. ([1995](#)) study lacks information on other potential risk factors for cardiovascular disease, which could result in confounding if those risk factors are also related to TCDD exposure. Dose-response patterns were strong, however, and persisted across numerous TCDD (and TEQ) exposure categories based on the use of an external reference group (i.e., gas workers) or based on the internal comparison. The findings based on the internal comparison are noteworthy in that these groups should be more homogenous with respect to confounding factors. As noted previously, the poor correlation between TCDD and smoking among workers and similar smoking prevalence estimates between the workers and the external gas company workers suggest that smoking was not likely a confounder of the TCDD and cardiovascular disease relationship. No other evaluation of noncancer mortality outcomes has been undertaken in this cohort since 1995.

A strength of the Flesch-Janys et al. ([1995](#)) study was that it included the collection of blood serum which provided an objective measure of TCDD exposure. Blood serum data, however, were obtained only for 16% of the cohort. However, the selection criteria and participation rate for individuals providing blood serum is not provided to evaluate how representative these individuals are of the larger cohort. The assumption of the first-order kinetic elimination model is critical, given that measures were taken at the end of follow-up. The model also assumed the half-life of TCDD was 6.9 years. If the kinetics are not first-order, or if the half-life estimate is inaccurate, estimates of TCDD levels during exposure would be biased, particularly for workers having longer periods between exposure and PCDD and PCDF assays. Sensitivity analyses completed by the authors suggest that such bias is not likely to present because the results were unaffected when different model assumptions regarding kinetic and half-lives were examined. The lack of an impact on RR estimates with varying half-life estimates was similar to findings by Steenland et al. ([2001b](#)).

C.1.2.1.3.1.3.   Suitability of data for TCDD dose-response modeling

Despite the aforementioned study strengths, the study focused on fatal outcomes such as all cause mortality, cardiovascular disease mortality, and ischemic heart disease mortality. As all outcomes were based on mortality, dose-response modeling was not conducted for this study.

1 **C.1.2.1.4.** *The Seveso Women's Health Study (SWHS)*

2   Eskenazi et al. (2000) presented an overview of the SWHS. The SWHS is the first

3 comprehensive epidemiologic study of the reproductive health of a female population exposed to

4 TCDD. The primary objective of the SWHS is to investigate the relationship of TCDD and

5 several reproductive endpoints, including endometriosis, menstrual cycle characteristics, birth

6 outcomes, infertility, and age at menopause. A second phase of follow-up that focuses on

7 osteoporosis, thyroid hormone, breast cancer, diabetes, and metabolic syndrome is not yet

8 completed.

9   Women were eligible for participation in the SWHS if they resided in Zones A and B (the

10 most contaminated areas) at the time of the explosion, were 40 years of age or younger at the

11 time of the explosion in 1976, and samples of their blood were collected and stored between

12 1976 and 1980. The enrollment of women in the SWHS began in March 1996 and continued

13 until July 1998. Of the 1,271 eligible women, 17 could not be found, 21 had died, and 12 were

14 too ill to participate. Of the 96% remaining women, 80% ($n = 981$) participated in the study.

15 Participation in the SWHS included a blood draw and an interview by a trained nurse who was

16 blind to subjects' TCDD level and zones of residence at the time of the accident. The interview

17 included detailed information on potential confounders including occupational, medical, and

18 reproductive, and pregnancy history. Women who were premenopausal were also asked to

19 undergo a vaginal ultrasound and pelvic exam and to complete a daily diary on menstruation.

20   Depending on the health outcome under study, TCDD exposures were characterized for

21 the women at different times. For example, TCDD exposure levels were estimated at the time of

22 the accident for some studies and at the time of conception for others. The SWHS study

23 population has been used to investigate associations between maternal TCDD levels and the

24 following health outcomes: menstrual cycle characteristics (Eskenazi et al., 2002b);

25 endometriosis (Eskenazi et al., 2002a); birth outcomes (Eskenazi et al., 2003); age at menarche

26 (Warner et al., 2004); age at menopause (Eskenazi et al., 2005); uterine leiomyomas (Eskenazi et

27 al., 2007); and ovarian function (Warner et al., 2007). An evaluation of the studies in

28 chronological order is presented in this section.

29

C.1.2.1.4.1. *Eskenazi et al. (2002b)—Menstrual cycle characteristics*

C.1.2.1.4.1.1. Study summary

Eskenazi et al. (2002b) evaluated serum TCDD exposures in relation to several menstrual cycle characteristics in the SWHS. A total of 981 women who were 40 years of age or younger at the time of the accident comprised the SWHS. The following exclusion criteria was applied 44 years of age or older, women with surgical or natural menopause, those with Turner's syndrome, and those who in the past year had been pregnant, breastfed, or used an intrauterine device or oral contraceptives.

A trained interviewer collected data on menstrual cycle characteristics using a questionnaire. Women were asked to indicate how long their menstrual cycles were, whether the cycles were regular (e.g., irregular cycle defined as length varied by more than 4 days), how many days the menstrual flow lasted, and whether this flow was "scanty, moderate, or heavy." Information was also collected on obstetric and gynecological conditions. TCDD exposures were derived from serum samples collected in 1976−1985. The authors selected the earliest available serum sample, and back-extrapolated to 1976 values using either the Filser model (Kreuzer et al., 1997) for women aged 16 years or younger in 1976 ($n = 20$) or the first-order kinetic model ($n = 6$) (Pirkle et al., 1989).

Serum TCDD levels were transformed using the $\log_{10}$ scale, and the relationships between these levels and length of menstrual cycle and days of menstrual flow were examined using linear regression. The authors applied logistic regression to characterize the risk between $\log_{10}$TCDD and heaviness of flow or regularity of cycle. In these analyses, moderate or heavy flow and regular cycle were used as the reference categories. Stratified analysis was performed by menarcheal status at the time of the accident.

Overall, the association with TCDD exposure (per 10-fold increase) and length of menstrual cycle was not statistically significant for premenarcheal ($\beta = 0.93$, 95% CI = −0.01, 1.86) women or postmenarcheal women ($\beta = −0.03$, 95% CI = −0.61, 0.54). The corresponding estimates found for days of menstrual flow were $\beta = 0.18$ (95% CI = −0.15, 0.51) and $\beta = 0.16$ (95% CI = −0.18, 0.50), respectively. Reduced flow was not associated with TCDD when compared to moderate or heavy flow (odds ratio [OR] = 0.84, 95% CI = 0.44, 1.61); effect modification by menarcheal status, however, was evident ($p = 0.03$). Specifically, women exposed to TCDD who were premenarcheal had lower odds of reduced flow, while those

1   exposed to TCDD who were postmenarcheal did not. Finally, statistically significant ORs were

2   found between serum TCDD levels (per 10-fold increase) and having an irregular cycle

3   (OR = 0.46, 95% CI = 0.23, 0.95). This inverse association was evident in both premenarcheal

4   (OR = 0.50, 95% CI = 0.18, 1.38) and postmenarcheal women (OR = 0.41, 95% CI = 0.15, 1.16).

5

6   **C.1.2.1.4.1.2.**   Study evaluation

7   Overall, the Eskenazi et al. (2002b) study reported some associations between TCDD and

8   menstrual cycle characteristics among women exposed before menarche. Exposures to TCDD

9   were well characterized using serum samples available on an individual-level basis, and the

10   design allowed for the influence of other risk factors to be controlled. Analysis of TCDD levels

11   and the length of menstrual cycle in premenarcheal women produced associations that were

12   largely not statistically significant at the alpha level of 0.05, but may have some biological

13   relevance. However, it is unclear whether the endpoints that were measured constitute adverse

14   health outcomes as they are not definitive markers of ovarian dysfunction. Another source of

15   uncertainty is measurement error due to the subjective nature of menstrual flow reporting. Any

16   resulting misclassification of the outcome would be expected to be nondifferential, as the

17   measurement error is unlikely to be dependent on TCDD exposure.

18

19   **C.1.2.1.4.1.3.**   Suitability of data for TCDD dose-response modeling

20   Rigon et al. (2010) reported the median age at menarche to be 12.4 in Italian females,

21   which would establish a critical window of susceptibility between birth and about 13 years of

22   age. The determination of a LOAEL is difficult, as there is no independent measure of an

23   adversity threshold to establish the toxicological significance of a given increase in menstrual

24   cycle length. The study authors did not present data for unexposed premenarcheal girls (in

25   1976), so an appropriate reference population is not available. However, an approximate

26   LOAEL can be estimated from Figure 1 in Eskenazi et al. (2002b), noting that both the length of

27   the menstrual cycle and its variance increases above TCDD concentrations of about 1,000 ppt.

28   This study is suitable for further consideration for quantitative dose-response modeling.

29

C.1.2.1.4.2. *Eskenazi et al. (2002a)—endometriosis*

C.1.2.1.4.2.1. Study summary

The SWHS provided the opportunity to investigate the association between serum TCDD levels and endometriosis (Eskenazi et al., 2002a). The rationale the authors provided for undertaking this study was the experimental animal studies that suggested an association, the high prevalence of endometriosis among infertile women where breast milk concentrations of dioxin are high, and the unknown etiology of endometriosis. The study consisted of 601 women who were younger than 30 years at the time of the Seveso accident. Stored sera that had been collected between 1976 and 1980 were available for these women.

The researchers classified women as having endometriosis based on laparoscopy, symptom report, gynecologic examinations, and vaginal ultrasound. Endometriosis cases were identified by a positive ultrasound or if a woman had endometriosis noted on a laparoscopy or laparotomy. A woman was classified as nondiseased if she had surgery without a finding of endometriosis or if she had a negative ultrasound, exam, and symptom history. Given that laparoscopy could not be performed on women unless clinically indicated, there was less certainty regarding endometriosis diagnoses among those without an ultrasound or prior laparoscopy. These remaining women without clinical confirmation were classified as "uncertain" based solely on positive symptom history. ,

TCDD was measured in sera in 1976 for 93% of the women. Values for women whose serum TCDD levels were collected after 1977 and had values exceeding 10 ppt were back-extrapolated to 1976 using either the Filser model (<16 years of age) (Kreuzer et al., 1997) or a first-order kinetic model (≥16 years) (Pirkle et al., 1989). These estimates of TCDD were then modeled as both continuous (on a log scale) and categorical (≤20, 20.1−100, and >100 ppt) exposures.

Polytomous logistic regression was applied to generate RRs for internal cohort comparisons. In relation to women in the lowest exposure category, the RR for endometriosis among women in the middle and upper categories was 1.2 (90% CI = 0.3−4.5) and 2.1 (90% CI = 0.5−8.0), respectively. The trend tests were not statistically significant for either the categorical ($p = 0.25$) or the continuous measures of TCDD ($p = 0.84$).

C.1.2.1.4.2.2.   Study evaluation

Based on the results of a validation study they conducted in a clinical population, the study authors found that symptom history was not predictive of disease, but that ultrasound had excellent specificity and sensitivity for ovarian endometriosis. Thus, there was some potential for disease misclassification among the uncertain group who were classified solely on symptom history. Although this disease misclassificationis could have resulted in missed cases of endometriosis, it is unlikely to have biased the study findings.   Bias is unlikely to result from differential (by exposure status) symptom reporting for the following reasons: the study interviewers and respondents were unaware of study hypotheses, the interviewers, respondents and investigators who made the diagnoses did not know the TCDD levels, and the CDC laboratory had no information about disease. Younger women were likely to be under-represented as those who had never been sexually active could not be examined due to cultural reasons; thus residual confounding by age is a possibility despite statistical adjustment in the regression models. Other DLCs (PCDD, PCDFs, or polychlorinated biphenyls [PCBs]) were not considered because of small serum volumes, but any potential TEQ exposures occurring in the population were thought to be mostly attributable to TCDD in the exposed women. Although individual-level serum samples were available, a biologically-relevant critical exposure window for this effect cannot be established.

C.1.2.1.4.2.3.   Suitability of data for TCDD dose-response modeling

There were no statistically significant dose-response patterns observed with either log-transformed TCDD exposures or across TCDD exposure categories, and the elevated risks among those with higher exposures had very wide confidence intervals (that included unity). In addition, because of the lack of definitive measures of endometriosis and the inability to define a critical exposure window, quantitative dose-response analysis was not conducted for this outcome.

C.1.2.1.4.3.   *Eskenazi et al. (2003)—birth outcomes*

C.1.2.1.4.3.1.   Study summary

Eskenazi et al. (2003) examined the relationship between serum TCDD levels and birth outcomes. Analyses were based on 745 of the 981 women from the SWHS who agreed to

1   participate (80% of the cohort) and reported having been pregnant ($n = 1{,}822$). Many of these

2   pregnancies (888 pregnancies among 510 women) occurred after the accident in 1976. Analysis

3   of spontaneous abortions was restricted to 769 pregnancies among 476 women that did not end

4   in abortion or in ectopic or molar pregnancy. Congenital anomalies were evaluated for the

5   672 pregnancies that did not end in spontaneous abortion. For the birth outcomes of fetal growth

6   and gestational age, analysis was performed using 608 singleton births from women without

7   hypertensive pregnancy disorders or diabetes.

8   TCDD exposures were based on serum measures, most of which were taken shortly after

9   the accident. Serum was collected in 1976−1977 for 413 women, between 1978 and 1981 for

10   12 women, and in 1996 for 19 women whose samples were not viable. For samples collected

11   between 1976 and 1981, the first serum sample collected was used. TCDD exposures based on

12   serum samples collected after 1977 onward were back-extrapolated to 1976 using the Filser

13   toxicokinetic model (Kreuzer et al., 1997).

14   Statistical analyses were performed on all pregnancies that ended between 1976 and the

15   time of interview. The authors also restricted the analysis to those pregnancies occurring within

16   the first 8 years (1976–1984) or roughly the first TCDD half-life after the explosion (Pirkle et al.,

17   1989), since the expectation was that exposure body burden would be greatest during this period.

18   A continuous measure of $\log_{10}$TCDD (base 10 scale) was used to investigate associations with

19   adverse birth outcomes. Logistic regression was used to characterize the relationship between

20   TCDD exposure spontaneous abortions, small for gestational age, and preterm birth (<37 weeks

21   gestation). Linear regression was used to describe the relationship between TCDD and birth

22   weight (in grams) and gestational age (in weeks) estimates.

23   The risk estimates were adjusted for various characteristics that included sex of infant,

24   history of low birth weight child, maternal height, maternal body mass index, maternal

25   education, maternal smoking during pregnancy, and parity. No associations were detected

26   between TCDD serum levels and spontaneous abortion for pregnancies between 1976 and 1998

27   (OR = 0.8, 95% CI = 0.6−1.2), or those between 1976 and 1984 (OR = 1.0, 95% CI = 0.6−1.6).

28   No statistically significant associations (ORs ranged from 1.2−1.8) were found between

29   $\log_{10}$ TCDD levels and preterm delivery or small for gestational age. The authors also saw no

30   association between TCDD exposure and mean birth weight among the entire population.

31   Although it was not statistically significant, the mean birth weight for pregnancies restricted to

1   between 1976 and 1984 decreased by 92 grams (β = −92, 95% CI = −204 to 19) for every

2   10-fold increase in TCDD serum level.

3

4   **C.1.2.1.4.3.2.**   Study evaluation

5   This study was well-designed with individual-level exposure data, although there is some

6   uncertainty in extrapolating limited serum data to such narrow critical windows of exposure

7   especially among women who were pregnant many years after the explosion in 1976. While the

8   study lacked exposure data for the fathers, the authors indicated that only a small proportion

9   were believed to have high exposures to TCDD. A key limitation of the study was a reliance on

10   self-reported measures of pregnancy history subject to maternal recall error. For example, birth

11   weight was often reported only to the nearest 100 grams. This measurement error could lead to

12   some misclassification of the birth outcomes. The observation that a large proportion of Seveso

13   women had a voluntary abortion because of fears of possible birth defects due to exposures from

14   the accident suggest that awareness bias is also possible as a result of differential reporting of

15   birth outcomes according to exposure status. Statistically significant associations were not

16   evident, although the mean birth-weight findings among those assumed to have the highest

17   TCDD body burden (exposed during first 8 years (1976–1984)) may have some toxicological

18   significance. As the study authors point out, those who were potentially the most vulnerable at

19   the time of the accident (the youngest) had not yet completed their childbearing years. Thus,

20   further follow-up of this cohort should help elucidate whether subjects with higher TCDD

21   exposures had an increased risk of adverse birth outcomes.

22

23   **C.1.2.1.4.3.3.**   Suitability of data for TCDD dose-response modeling

24   No statistically significant associations were found in the study; in addition, possible

25   awareness bias could have influenced the self-reported measures of birth outcomes. The authors

26   did not report TCDD levels at the time of pregnancy and EPA cannot extrapolate serum

27   concentrations measured in 1976 to the times of the pregnancies in these women based on the

28   information reported in the study. Therefore, quantitative dose-response modeling was not

29   conducted for this study.

30

1 **C.1.2.1.4.4.** *Warner et al. (2004)—age at menarche*

2 **C.1.2.1.4.4.1.** Study summary

3   Warner et al. (2004) examined the relationship between TCDD and age at menarche in

4 the SWHS cohort. As described earlier in this report, the SWHS comprised 981 participants.

5 This study was restricted only to those who were premenarcheal at the time of the accident

6 ($n = 282$). The proportional hazards model was used to examine the relationship between TCDD

7 exposures and age at menarche. Age at menarche was determined by questionnaire administered

8 by a trained interviewer. Covariates examined as potential confounders included height, weight,

9 body mass index, athletic training at the time of interview, smoking, and alcohol consumption.

10   TCDD exposures were determined using serum samples collected from 257 (91%) of

11 these women between 1976 and 1977. For the remaining women, TCDD levels were quantified

12 from measures collected between 1978 and 1981 ($n = 23$, 8%) and in 1996 ($n = 2$, 1% collected

13 due to inadequate volume of older samples). TCDD levels determined after 1977 were back-

14 extrapolated to the time of the explosion in 1976. TCDD was modeled as both a continuous

15 variable (log_{10}TCDD) and a categorical variable based on quartile values ($\leq$55.9, 56−140.2,

16 140.3–300, >300 ppt). The lowest group was further subdivided into those with levels $\leq$20, and

17 >20 ppt; this cut-point represented background levels found in a sample of women living in an

18 unexposed area.

19   No association (hazard ratio [HR] = 0.95, 95% CI = 0.83−1.09) was detected between

20 age at menarche and a 10-fold increase in serum TCDD concentrations (from 10 ppt to 100 ppt).

21 Analyses restricted to those who were younger than 8 in 1976 produced similar results

22 (HR = 1.08, 95% CI = 0.89−1.30). No dose-response trend was observed with categorical

23 measures of TCDD among all women, as well as those under the age of 8. A 10-fold increase in

24 serum TCDD concentrations were later reported to be associated with an earlier age of menarche

25 (HR = 1.20, 95% CI = 0.98−1.60, p for trend = 0.07) when analyses were restricted to 84 women

26 under the age of 5 at the time of the accident (Warner and Eskenazi, 2005).

27

28 **C.1.2.1.4.4.2.** Study evaluation

29   An important strength of the Warner et al. (2004) study is the ability to characterize

30 TCDD exposures using serum samples that were collected shortly after the accident occurred.

31 The outcome of interest, age at menarche, was determined by asking women "At what age did

1   you get your first menstrual period?" Previous work suggests that self-reported measures of age

2   at menarche decades later have modest agreement with responses provided during adolescence

3   with recall varying by education and by history of an adverse birth outcome (Cooper et al.,

4   2005). Although it seems unlikely, information bias could be introduced in the Seveso study if

5   recall of age of menarche varied according to exposure levels. The results from the analysis in

6   the original paper (Warner et al., 2004) were largely null there was some suggestion of an

7   association between elevated TCDD levels and earlier age of menarche in the follow-on

8   communication (Warner and Eskenazi, 2005). These more recent findings lend some support to

9   the suggestion of Wolff et al. (2005) that the first 5 years of life may be the most relevant

10   exposure period for determination of an effect on age at menarche. However, the actual change

11   in the age at menarche relative to TCDD serum concentrations was not reported and cannot be

12   established from the information presented by the study authors.

13   **C.1.2.1.4.4.3.**   Suitability of data for TCDD dose-response modeling

14   No major biases were evident, but some sources of uncertainty remain which complicate

15   interpretation of the study results and potential application to dose-response modeling. The

16   study also showed limited evidence of an association between age at menarche and TCDD

17   exposure and little evidence of a dose-response relationship. It remains unclear to what extent

18   age at menarche represents an adverse health effect. Thus, EPA cannot assess the biological

19   significance of this finding and cannot establish a LOAEL for this effect. Therefore, quantitative

20   dose-response assessment was not conducted for this study, but it was included in the RfD

21   uncertainty analysis presented in Section 4.5.3.

22

23   **C.1.2.1.4.5.** *Eskenazi et al. (2005)—Age at menopause*

24   **C.1.2.1.4.5.1.**   Study summary

25   Eskenazi et al. (2005) evaluated the relationship between the age at onset of menopause

26   and serum levels of TCDD among women in the SWHS. Of the 981 (80% of women contacted)

27   women who agreed to participate in SWHS, this analysis was restricted to those who had not

28   reached natural menopause before the time of the accident and who were at least 35 years of age

29   at the time of the interview. The recruitment and interview of women occurred approximately 20

30   to 22 years after the accident (March 1996−July 1998).

1   The population was divided into quintiles of serum TCDD levels for the categorical

2   analysis. For most women ($n = 564$), TCDD levels were estimated from samples provided in

3   1976−1977. For the remaining women included in these analyses, TCDD levels were estimated

4   from samples collected between 1978 and 1982 ($n = 28$) and between 1996 and 1997 ($n = 24$;

5   collected due to insufficient volume of earlier sample). As noted previously, exposure levels for

6   women with post-1977 detectable levels of TCDD were back-extrapolated to 1976 using either

7   the first-order kinetic model (Pirkle et al., 1989) (>16 years at time of accident) or the Filser

8   model (<16 years at time of accident) (Kreuzer et al., 1997). Women were classified as

9   premenopausal if they were still menstruating or if they had amenorrhea as a result of pregnancy

10   or lactation (at the time of interview) with an indication of subsequent menstruation based on

11   maintained diaries or further examination. Subjects for which amenorrhea had persisted for at

12   least 1 year with no apparent medical explanation were classified into a natural menopause

13   category. The category, surgical menopause, pertained to women with a medically confirmed

14   hysterectomy or an oophorectomy. Finally, impending menopause was defined for subjects in

15   which menstruation had been absent for 2 months, but who provided evidence of subsequent

16   menstruation, or had a secretory endometrial lining, or indicated less predictable cycles in the

17   previous 2−5 years. If participants' menopausal status could not be determined, they were

18   grouped into the "other" category. This category included those for whom status could not be

19   determined due to current use of oral contraceptives, hormone replacement therapy, or previous

20   cancer chemotherapy.

21   Statistical analysis was based on both a continuous measure of log-transformed TCDD

22   exposures and categories based on quintiles (<20.4 ppt; 20.4−34.2 ppt; 34.3−54.1 ppt;

23   54.2−118.0 ppt; >118.0 ppt). The Cox model was used to generate hazard ratios as estimates of

24   relative risks and their 95% confidence intervals examining natural menopause as the outcome.

25   Several covariates previously identified as associated with menopausal status in the literature

26   were considered as potential confounders. These covariates included body mass index, physical

27   activity, premenopausal smoking, education, marital status, history of heart disease and other

28   medical conditions, and other reproductive characteristics.

29   A statistically significant association with onset of menopause was not detected

30   (RR = 1.02, 95% CI = 0.8−1.3) based on the logTCDD continuous measure. The RRs were

31   found to increase across the second through fourth quintiles (RRs = 1.1, 1.4, and 1.6,

1   respectively) of serum TCDD categories in relation to those in the lowest category, but not in the

2   upper quintile (RR = 1.0, 95% CI = 0.6−1.8). A statistically significant trend was detected

3   across the first four quartiles ($p = 0.04$) but not across all five quintiles ($p = 0.44$). However,

4   when the 24 women who had back-extrapolated TCDD levels from 1996 were excluded, the

5   hazard ratios were slightly larger in magnitude. Compared with women in the lowest quintile,

6   HRs for risk of earlier menopause were 1.2 ($p = 0.5$) for quintile 2, 1.6 ($p = 0.08$) for quintile 3,

7   1.7 ($p = 0.05$) for quintile 4, and 1.2 ($p = 0.5$) for quintile 5, with a statistically significant trend

8   ($p = 0.02$) across the first four quintiles. Eskenazi et al. (2005) suggested that the stronger results

9   following exclusion of 1996 measures may have been due to reduced exposure measurement

10   error and less exposure misclassification.

11

12   **C.1.2.1.4.5.2.**   Study evaluation

13   The categorical exposure results from this study support a nonmonotonic

14   dose-related-association for earlier menopause with increased serum TCDD levels up to

15   approximately 118-ppt TCDD serum. Eskenazi et al. (2005) speculated that the inverse "U"

16   shape of the dose-response relationship is explained by the mimicking of hormones at lower

17   doses of a chemical, while at higher levels the toxic effect of a chemical does not have the

18   capacity to either inhibit or stimulate hormonal effects. Similar dose-response relationships have

19   been observed for TCDD for other endpoints in other studies for both humans and rodents (e.g.,

20   Mocarelli et al., 2008; NTP, 2006; Steenland et al., 2001a), although none with such a

21   pronounced drop in response at higher exposures. Overall, the findings suggest the possibility of

22   a nonlinear dose-response relationship for age of onset of menopause with TCDD, with increased

23   risks in the 4th quintile and perhaps the 3rd quintile. However, the actual change in the age at

24   menopause relative to TCDD serum concentrations was not reported and cannot be established

25   from the information presented by the study authors. The biological significance of these

26   findings is unclear. A biologically-relevant critical exposure window for this effect cannot be

27   established.

28   A study limitation is the potential for residual confounding due to adjustment based on

29   current smoking status and not at the time of onset of menopause. It is unclear to what extent

30   smoking status may differ between these two time periods and whether smoking is related to

31   TCDD exposures in this cohort.

1

C.1.2.1.4.5.3.   Suitability of data for TCDD dose-response modeling

3   Because the critical window of exposure that would cause an effect on age at menopause
is not apparent and EPA could not determine with confidence the biological significance of this
result for the establishment of a LOAEL, a quantitative dose-response assessment was not
conducted for this study in the context of the RfD derivation. However, this study is included in
the RfD uncertainty analysis presented in Section 4.5.3.

8

C.1.2.1.4.6.   *Warner et al. (2007)—Ovarian function*

C.1.2.1.4.6.1.   Study summary

11   Warner et al. (2007) investigated the association between serum TCDD levels and
ovarian function in subjects in the SWHS who were younger than 40 in 1976 and for whom sera
collected after the accident had been stored. These women were recruited from March 1996 until
July 1998. Ovarian function analysis was limited to 363 women between 20 and 40 years of age
and who were not using oral contraceptives. Of these, 310 underwent transvaginal ultrasound
and were included in the functional ovarian cyst analysis. Ninety-six women were in the
preovulatory stage of their menstrual cycles and were included in the follicle analysis. For the
hormone analysis, 126 women who were in the last 2 weeks of their cycle were included.

19   The authors used logistic regression to examine the relationship between TCDD and the
prevalence of ovarian follicles greater than 10 mm. Linear regression models were used to
examine the continuous outcomes: number of ovarian follicles >10 mm and diameter of
dominant ovarian follicle. Covariates considered for inclusion in the model were age at
ultrasound, age at accident, age at menarche, marital status, parity, gravidity, lactation history,
current body mass index, age at last birth, and smoking history. For the serum hormone
analyses, estradiol and progesterone were measured in blood at the time of interview. Ovulation
status was defined as a dichotomous variable (yes/no) based on a serum progesterone cut-point
value of 3 ng/mL.

28   The adjusted ORs across categories of TCDD exhibited no dose-response trend for the
presence of follicles in relation to TCDD in the follicular phase; also, no statistically significant
differences were noted in any of the upper exposure categories relative to those in the lowest.
The adjusted OR for the continuous measure of $\log_{10}$TCDD was 0.99 (95% CI = 0.4−2.2). A

1   similar nonstatistically significant finding was found for $\log_{10}$TCDD in relation to ovulation in

2   both the luteal (OR = 0.99, 95% CI = 0.5−1.9) and mid-luteal phases (OR = 1.03,

3   95% CI = 0.4−2.7). Progesterone and estradiol also were not related to serum TCDD levels for

4   either the luteal or mid-luteal phases ($p = 0.51$ and $p = 0.47$).

5

6   **C.1.2.1.4.6.2.** Study evaluation

7   The investigators found no relationship between serum TCDD levels and serum

8   progesterone and estradiol levels among women who were in the luteal phase at the time of

9   blood draw. No association with number of ovarian follicles detected from ultrasound.

10   Although no association was found, the authors suggested that the lack of significant results

11   could be because the women in SWHS were all exposed postnatally and the relevant and critical

12   time period for an effect might be in utero.

13

14   **C.1.2.1.4.6.3.** Suitability of data for TCDD dose-response modeling

15   Because of the lack of a defined critical exposure window and absence of associations

16   between TCDD and adverse health effects in this study, quantitative dose-response assessment

17   was not conducted for this study; however, this study is included in the RfD uncertainty analysis

18   presented in Section 4.5.3.

19

20   **C.1.2.1.4.7.** *Eskenazi et al. (2007)—Uterine leiomyoma*

21   **C.1.2.1.4.7.1.** Study summary

22   Associations between TCDD exposures and uterine leiomyomata (i.e., fibroids), which

23   are benign estrogen-dependent tumors, were examined among 956 women in the SWHS

24   (Eskenazi et al., 2007). The sample population was based on the original 981 SWHS participants

25   excluding 25 women diagnosed with fibroids before the date of the accident (July 10, 1976).

26   Women who previously had fibroids were identified both through the administered questionnaire

27   and the review of medical records. Transvaginal ultrasounds were performed for 634 women to

28   determine if they had fibroids at the time of follow-up. Women who had a fibroid diagnosis in

29   their medical records dated after the accident did not need to have an ultrasound. Similar to other

30   SWHS studies, exposure to TCDD was estimated using serum collected from women shortly

1 after the time of the accident, between 1978 and 1981 and in 1996. TCDD levels were

2 back-extrapolated to 1976 levels.

3 The study authors performed statistical analyses using two definitions of fibroids as

4 outcome measures. The first was fibroids detected before the study, and the second was fibroids

5 detected via ultrasound. A proportional odds method Dunson and Baird (2001) developed was

6 used to model the cumulative odds of onset of fibroids. This method combines historical and

7 current information of diagnoses of fibroids. Continuous and categorical measures of TCDD

8 were modeled. Regression models were adjusted for known or suspected risk factors of fibroids

9 including: parity, family history of fibroids, age at menarche, body mass index, smoking, alcohol

10 use, and education.

11 Categorical measures of TCDD showed an inverse dose-response relationship with the

12 onset of fibroids. Relative to those with TCDD levels less than 20 ppt, those having TCDD

13 exposures between 20.1 and 75.0 ppt and greater than 75.0 ppt (at time of measurement) had

14 hazard ratios of 0.58 (95% CI = 0.41−0.81), and 0.62 (95% CI = 0.44−0.89), respectively. The

15 hazard ratio was 0.83 (95% CI = 0.65−1.07) for a continuous measure of $\log_{10}$TCDD. . The

16 study authors concluded that TCDD may have antiestrogenic effects in the uterine myometrium,

17 in contrast to the suggestion of estrogenic effects previously found in the breast (Warner et al.,

18 2002).

19

20 **C.1.2.1.4.7.2.**   Study evaluation

21 The strengths of the Eskenazi et al. (2007) study included the longitudinal design,

22 individual-level serum measures (most taken within 2 years of the accident), and the ability to

23 include outcomes among those who did not take an ultrasound by using an adapted statistical

24 approach. An important limitation was that the differences in risk by the stage of development

25 could not be assessed as all women were exposed postnatally, and only 4 cases were observed

26 among those who were premenarcheal at the time of exposure. The authors found a statistically-

27 significant reduction in risk for uterine fibroids in SWHS women having TCDD exposures

28 between 20.1 and 75.0 ppt and greater than 75.0 ppt. A biologically-relevant critical exposure

29 window for this effect cannot be established.

30

C.1.2.1.4.7.3. Suitability of data for TCDD dose-response modeling

Although this association is suggestive of anti-estrogenic activity, EPA was unable to establish the biological significance of the findings at any particular exposure level for establishing a LOAEL. Because a LOAEL could not be established for anti-estrogenic activity (Eskenazi et al., 2007), quantitative dose-response modeling was not conducted.

C.1.2.1.5. *Other Seveso noncancer studies*

C.1.2.1.5.1. *Bertazzi et al. (1989); Consonni et al. (2008)—Mortality outcomes*

C.1.2.1.5.1.1. Study summary

Several studies have evaluated the mortality of Seveso residents exposed to TCDD following the 1976 accident. The earlier section of this report described the designs of these studies and discussed their findings as they relate to cancer mortality. In this section, some of the findings for other causes of death are described. A key feature of these studies is that patterns of mortality among Seveso residents were investigated according to their zone of residence at the time of explosion relative to general population rates.

A 10-year mortality follow-up of residents of Seveso was published in 1989 (Bertazzi et al., 1989). Poisson regression was used to derive RRs for those who had lived in Zone A at the time of explosion using a referent group consisting of inhabitants who had lived in the uncontaminated study area. Between 1976 and 1986, no statistically significant difference was observed in all-cause mortality relative to the general population among those who lived in the most highly exposed area (Zone A) at the time of the accident. This finding was evident in both males (RR = 0.86, 95% CI = 0.5−1.4) and females (RR = 1.14, 95% CI = 0.6−2.1). A statistically significant excess in circulatory disease mortality was found among males relative to those in the referent population (RR = 1.75, 95% CI = 1.0−3.2); this increased risk was more pronounced when the follow-up period was restricted to the first 5 years after the accident (1976−1981) (RR = 2.04, 95% CI = 1.04−4.2). Between 1982 and 1986, the RR decreased substantially and was not statistically significant (RR = 1.19, 95% CI = 0.4−3.5). Among females, a risk similar in magnitude was detected for circulatory disease mortality although it was not statistically significant (RR = 1.89, 95% CI = 0.8−4.2). Contrary to the calendar period-specific findings for males, the excess of circulatory mortality among females occurred between 1982 and 1986 (RR = 2.91, 95% CI = 1.1−7.8) and not between 1976 and 1981

(RR = 1.12, 95% CI = 0.3−4.5). The number of deaths in this cohort with the 10 years of follow-up was relatively small; in Zone A, 16 deaths were observed among males and 11 among females.

The most recently published account of the mortality experience of Seveso residents provides further information on follow-up of these residents until the end of 2001 (25 years after the accident) (Consonni et al., 2008). Three exposure groups were considered: Zone A (very high contamination), Zone B (high contamination), and Zone R (low contamination). The reference population consisted of those residents who lived in unaffected surrounding areas, as well as residents of five nearby towns. The authors used Poisson regression to compare mortality rates for each zone relative to the reference population.

For all causes of death, no excess was found in Zone A, B, or R relative to the reference population. Statistically significant excesses were noted for those who lived in Zone A relative to the reference population for chronic rheumatic heart disease (RR = 5.74, 95% CI = 1.83−17.99) and chronic obstructive pulmonary disease (RR = 2.53, 95% CI = 1.20−5.32). These risks, however, were based on only 3 and 7 deaths, respectively. For those in Zone A, no statistically significant excesses in mortality were noted for diabetes, accidents, digestive diseases, ischemic heart disease, or stroke. Among Zone A residents, stratified analysis by time since accident showed increased rates of circulatory disease 5−9 years since the accident (RR = 1.84, 95% CI = 1.09−3.12). Increased mortality from diabetes relative to the reference population was noted among females who lived in Zone B (RR = 1.78, 95% CI = 1.14−2.77).

C.1.2.1.5.1.2. Study evaluation

The ascertainment of mortality in this cohort appears to be nearly complete. Misclassification of some health outcomes, such as diabetes, may occur due to the use of death certificate data.

The characterization of exposure is based on zone of residence. Soil sampling indicated considerable variability in TCDD soil levels, and therefore, the generation of risks based on zone of residence likely does not accurately reflect individual exposure. Exposure misclassification might also occur because residency in the areas does not necessarily reflect whether the individual would have been present in the area at the time the accident occurred. Any exposure

1   misclassification would likely be nondifferential which would tend to bias the risk estimates

2   towards the null.

3   Although some excess of circulatory disease mortality was found, the finding was not

4   consistent between men and women. Moreover, excess circulatory disease mortality was more

5   pronounced among men within the first 5 years of exposure, while, for women, the excess was

6   more pronounced in years 5−10. Numerous other risk factors for circulatory disease were not

7   controlled for in these analyses and may be confounders if related to TCDD exposure. Taken

8   together, the possibility that TCDD increased circulatory disease mortality based on these data is

9   tenuous at best.

10

11 **C.1.2.1.5.1.3.** Suitability of data for TCDD dose-response modeling

12   There is considerable uncertainty in these data due to the potential for outcome and

13 exposure misclassification. The lack of the individual-level TCDD levels and the examination

14 only of fatal outcomes reported in this study are not a suitable basis for development of an RfD.

15 For these reasons, dose-response analysis for this outcome is not conducted.

16 **C.1.2.1.5.2. _Mocarelli et al. (2000; 1996)—Sex ratio_**

17 **C.1.2.1.5.2.1.** Study summary

18   A letter to the editor was the first report of a possible change in the sex ratio from dioxin

19 among Seveso residents following the July 10, 1976 accident (Mocarelli et al., 1996). The

20 authors reported that 65% ($n = 48$) of the 74 total births that had occurred from April 1977 to

21 December 1984 were females. This male to female ratio of 26:48 (35%) is significantly different

22 from the worldwide birth ratio of 106 males:100 females (51%) (James, 1995). Between 1985

23 and 1994, the Seveso male to female ratio leveled out at 60:64 (48%). The authors suggested

24 that the finding supported the hypothesis that dioxin might alter the sex ratio through several

25 possible mechanistic pathways.

26   Mocarelli et al. (2000) later reported on an investigation of serum-based TCDD measures

27 in parents and the sex ratio of offspring. In this study, serum samples were collected from

28 mothers and fathers who lived in nearby areas at the time of the explosion, were between the

29 ages of 3 and 45 at the time of the explosion, and produced offspring between April 1, 1977 and

30 December 31, 1996. The study population included 452 families and 674 offspring, and serum

31 measures were available for 296 mothers and 239 fathers. An estimate of TCDD at the time of

1   conception was also examined in relation to male to female birth ratios. TCDD exposure

2   estimates between the years of 1976 and 1996 were estimated using Filser's model (Kreuzer et

3   al., 1997).

4   Mocarelli et al. (2000) used chi-square test statistics to compare observed sex ratio to an

5   expected value of 0.51 in this Seveso population. Concentrations of TCDD were modeled as

6   categorical variables in several ways. First, a dichotomous variable was used whereby

7   unexposed parents were defined as those who lived outside Zones A, B, and R or had a serum

8   TCDD concentration of less than 15 ppt; parents with exposures of 15 ppt or higher were

9   considered exposed. Second, a trichotomous exposure variable was created that consisted of

10   parents who (1) lived outside Zones A, B, and R or had serum concentrations of less than 15 ppt,

11   (2) had serum concentrations of 15−80 ppt, and (3) had serum concentrations that exceeded

12   80 ppt. These cut-points were chosen as they represented tertiles based on the distribution of

13   TCDD among parents. Analyses were conducted separately for paternal and maternal TCDD

14   levels.

15   The overall proportion of 0.49 male births (based on male to female ratio of 328:346) was

16   not significantly different from the expected proportion of 0.51 ($p > 0.05$). Statistically

17   significant differences were found, however, if both parents had TCDD levels >15 ppt (sex

18   ratio = 0.44) or just the father had serum TCDD levels >15 ppt (sex ratio = 0.44). No

19   statistically significant differences were found when the fathers had TCDD levels less than

20   15 ppt, irrespective of the maternal levels. A dose-response pattern in the sex ratio was found

21   across the paternal exposure categories. That is, the sex ratio decreased with increased paternal

22   TCDD levels (linear test for trend, $p = 0.008$). In the unexposed group, the sex ratio (male to

23   female) was 0.56 (95% CI = 0.49−0.61), while in the highest exposure group

24   (281.0−26,400.0 ppt) the corresponding sex ratio was 0.38 (95% CI = 0.28−0.49).

25   Stratified analyses by age at paternal exposure revealed that the sex ratio was altered to a

26   greater degree among fathers who were younger than 19 at the time of the explosion. The male

27   to female ratio among the unexposed fathers was 0.56 (95% CI = 0.50−0.62), while it was 0.38

28   (95% CI = 0.30−0.47) for those younger than 19 when exposed and 0.47 (95% CI = 0.41−0.53)

29   for those exposed after 19. Regardless of the age at the time of exposure, however, fathers who

30   were exposed had a statistically significantly different birth ratio (they were more likely to father

31   girls) than those who were unexposed ($p < 0.05$).

1   Separate analysis of birth ratios based on paternal TCDD exposure estimated at the time

2   of conception did not show the same dose-response pattern but did show strong evidence of

3   consistently decreased male births relative to females. More specifically, the male to female

4   birth ratios among the four successive quartiles (first through fourth) were 0.41, 0.33, 0.33,

5   and 0.46.

6

7   **C.1.2.1.5.2.2.**   Study evaluation

8   Mocarelli et al. (2000) based the characterization of TCDD exposure on serum samples,

9   which is an objective method for characterizing dose. Unlike for the occupational cohorts, serum

10   measures for this study were taken close to the time of the accident, and therefore,

11   back-extrapolation of TCDD exposures is unnecessary. Maternal TCDD levels at the time of

12   conception did not demonstrate a dose-response relationship, but paternal exposures resulted in

13   consistently reduced male to female birth ratios (range: 0.33−0.46). Paternal exposures received

14   before the age of 19 at the time of the explosion were more strongly associated with a reduced

15   male to female ratio than those received after the age of 19.

16   The methods used to identify births appear to be appropriate. Even if some births were

17   missed, there is no reason to believe that ascertainment would be related to TCDD exposure and

18   the sex of the baby. Therefore, no bias is suspected due to incomplete birth ascertainment. The

19   authors report that the findings did not differ when age at conception was dichotomized ($\leq$ or

20   >35 years). They also state that age at conception was, on average, similar across calendar years.

21   However, some uncertainty remains as to what degree this influenced the sex ratio given that the

22   lowest mean age of conception periods (1973-1976 and 1977−1984) also corresponded with the

23   lowest reported male:female ratios.

24

25   **C.1.2.1.5.2.3.**   Suitability of data for TCDD dose-response modeling

26   TCDD exposures were well-characterized, and internal cohort analyses demonstrate an

27   association between paternal TCDD levels and birth ratio, particularly when exposure occurred

28   before 19 years of age. Although the data are suggestive of an effect earlier in life, perhaps even

29   pre-pubertal, the biologically-relevant critical exposure window of susceptibility cannot be

30   defined with any confidence for this endpoint.   Quantitative dose-response assessment was not

1 conducted for Mocarelli et al. ([2000](#)) in the context of the RfD derivation. However, this study is

2 included in the RfD uncertainty analysis presented in Section 4.5.3.

3

4 **C.1.2.1.5.3. *Baccarelli et al. ([2004](#); [2002](#))—Immunologic effects***

5 **C.1.2.1.5.3.1.** Study summary

6   The relationship between TCDD and immunological effects was evaluated in a sample of

7 Seveso residents ([Baccarelli et al., 2004](#); [Baccarelli et al., 2002](#)). Both studies were based on

8 findings from 62 individuals who were randomly selected during December 1992 and March

9 1994 from Zones A and B. An additional randomly selected 59 subjects were chosen from the

10 surrounding noncontaminated areas during the same time period. Residency was based on where

11 subjects lived at the time of the accident (July 10, 1976) ([Landi et al., 1998](#)). Frequency

12 matching ensured that the two groups of subjects were similar with respect to age, sex, and

13 cigarette smoking status.

14   TCDD levels were determined by mass spectrometric analysis of plasma samples.

15 TCDD levels at the time of sampling were obtained, and estimates of levels at the time of the

16 accident also were estimated by assuming an 8.2-year half-life ([Landi et al., 1998](#)). Exposure to

17 other DLCs for both the TCDD contaminated and noncontaminated areas were reported to be at

18 background levels. The plasma was also used to characterize levels of the immunoglobulins (Ig)

19 IgG and IgM and the complement components C3 and C4. One subject was excluded due to lack

20 of an immunological evaluation. Analyses are, therefore, based on 58 subjects in the

21 noncontaminated areas and 62 individuals from the contaminated areas.

22   Nonparametric tests were applied to test for differences between the two groups.

23 Multiple regression also was used to describe the relationship between the variables. Adjustment

24 was made for several potentially confounding variables that were collected via questionnaire.

25   An inverse association was noted with TCDD levels and plasma IgG levels; this result

26 remained statistically significant after adjusting for other potential confounding variables in the

27 regression models. Specifically, the regression coefficient and *p*-value for the unadjusted

28 ($\beta=-0.35$; $p = 0.0002$) and adjusted model were noted to be similar. In the 2004 analysis, the

29 authors present IgG, IgM, IgA, C3, and C4 median and interquartile values across TCDD

30 exposure quintiles. Decreased levels of IgG were observed in the highest exposure groups.

31 Specifically, the median values across the five quintiles (for lowest to highest) were 1,526;

1   1,422; 1,363; 1,302; and 1,163. The Kruskal-Wallis test for differences across the TCDD

2   categories was statistically significant ($p = 0.002$), which is consistent with the findings for the

3   continuous measures of TCDD. This finding persisted after excluding those subjects with

4   inflammatory diseases and those who used antibiotics or nonsteroidal anti-inflammatory drugs.

5   For the other plasma measures, no dose-response relationship was apparent based on median

6   values for IgM, IgA, C3, or C4 across TCDD quintiles. The authors highlight the need for

7   additional research, particularly given the excess of lymphatic tumors noted in the area.

8

9

10 **C.1.2.1.5.3.2.**   Study evaluation

11 Both TCDD exposure and health outcome measures are relatively well characterized.

12 TCDD exposures, however, are based on concurrent serum measures and are far-removed from

13 the initial peak-exposure event. Therefore, back-extrapolation to earlier time periods of exposure

14 would be highly uncertain. EPA cannot determine with confidence whether the health outcome

15 is a result of current exposure or longer-term continuous exposure to elevated TCDD levels.

16 Furthermore, EPA cannot determine what effect the much higher initial peak exposure might

17 have had on the outcome observed 17 years later. A dose-response relationship between TCDD

18 and IgG was evident in the unadjusted model, but no details are provided on any changes that

19 may be present when other covariates were added to the model.

20 Interpreting the inverse association between TCDD exposure and IgG in terms of clinical

21 significance is not possible. The 24% reduction in IgG at the highest exposures cannot be linked

22 to any adverse health outcome without more specific testing. The IgG values reported are much

23 higher than those associated with antibody immunodeficiency disorders, as discussed by

24 Baccarelli et al. (2002). The biologically-relevant critical window of TCDD exposure associated

25 with possible IgG impacts is uncertain, because it is unclear whether the current serum TCDD

26 levels or the higher prior TCDD serum levels are associated with these impacts.

27

28 **C.1.2.1.5.3.3.**   Suitability of data for TCDD dose-response modeling

29 Although the data support an inverse dose-response relationship between IgG and TCDD,

30 the biological significance of the findings are too uncertain to define a LOAEL or a NOAEL.

31 Further the critical window of exposure that would cause an effect on IgG levels is not known

1   and thus does not allow for estimation of the effective TCDD exposure. For these reasons, these

2   data were not suitable for quantitative dose-response modeling.

3

4   **C.1.2.1.5.4.   _Landi et al. (2003)—Gene expression_**

5   **C.1.2.1.5.4.1.**   Study summary

6   The impact of TCDD on the aryl hydrocarbon receptor (AhR) was evaluated by Landi

7   et al. (2003) in a population-based study of Seveso residents. AhR, a mechanistically based

8   biomarker of dioxin response, must be present for manifestation of most of the toxic effects of

9   TCDD, including tumor promotion and immunological and reproductive system effects (Puga et

10 al., 2000; Safe, 1986). AhR activates the transcription of several metabolizing enzymes in

11 addition to certain genes (Whitlock, 1999). The primary objective of the study was to determine

12 whether plasma levels of TCDD and TEQ are associated with the AhR-dependent pathway in

13 lymphocytes among Seveso residents. The genes involved in the pathway that were examined

14 included: AhR, aryl hydrocarbon receptor nuclear translocator, CYPA1A1 and CYP1B1

15 transcripts, and CYP1A1-associated 7-ethoxyresorufin O-deethylase (EROD).

16   Study recruitment occurred from December 1992 to March 1994. A total of 62 subjects

17 were randomly chosen from the highest exposed zones in Seveso (Zones A and B), while

18 59 were chosen from the noncontaminated area (non-ABR). Those chosen from the

19 noncontaminated zone were matched by age, sex, and smoking. Assignment of zones was based

20 on place of residence where subjects lived at the time of the accident in 1976. Subjects provided

21 data via questionnaire on a variety of sociodemographic and behavioral risk factors, including

22 cigarette smoking. Multivariate models were adjusted for a variety of confounders including:

23 age, gender, date of assay, actin expression, postculture viability, experimental group, and cell

24 growth.

25   TCDD levels were determined using high-resolution gas chromatography, and 21 other

26 dioxins, or DLCs, were measured to examine TEQ. Eleven measurements taken on the

27 121 subjects were deemed inadequate and excluded, but no further information was provided on

28 these exclusions. Nine subjects from Zone B and fourteen subjects from Zone ABR had TCDD

29 levels below detection, and were assigned a value equal to the lipid-adjusted detection limit

30 divided by the square root of 2. The toxic equivalent for the mixture of DLCs (i.e., TEQ) was

1 calculated by summing the products of the concentration of each congener by its specific toxic

2 equivalency factor.

3   The subjects provided between 5 and 50 mL of whole blood, which was centrifuged to

4 separate mononuclear cells. The cells were frozen and later thawed. Cells were cultured,

5 removed from the culture medium, and resuspended in a stimulation medium, 14 mL of which

6 was used for RNA analysis. Reverse transcription-PCR was conducted and EROD was assayed.

7 Differences in gene expression and EROD activity observed for various cell culture conditions

8 were compared using paired t-tests. The unpaired Student's t-test was applied to test for

9 differences between groups, while a Bonferroni factor was used to account for multiple

10 comparisons. Data for continuous variables were log-transformed.

11   TCDD accounted for 26% of the TEQ among the study subjects, but varied by zone (35%

12 in zone A and 18% in zone non-ABR). After adjusting for confounding, AhR was inversely

13 related to plasma TCDD levels in uncultured cells ($p < 0.03$) and in mitogen-stimulated cells

14 ($p < 0.05$). EROD was lower in cells cultured from subjects with higher plasma TCDD and TEQ

15 levels, and the corresponding continuous measure of EROD was statistically significant

16 ($p < 0.05$). No statistically significant associations with TCDD or TEQ were found with ARNT

17 or CYP1B1 in uncultured cell medium, nor with CYP1A1 or CYP1B1 in mitogen-stimulated

18 cells. In general, females had lower AhR transcripts and higher levels of dioxin.

19   Collectively, the findings suggest that TCDD exposure might reduce AhR expression in

20 unstimulated cells. Therefore, TCDD could exert an influence on the AhR pathway regulation.

21

22 **C.1.2.1.5.4.2.** Study evaluation

23   The study used biologically-based measures of both TCDD exposures and biomarkers or

24 AhR. Subjects were randomly selected from the larger cohort; some individuals with severe

25 medical illnesses were excluded ([Landi et al., 1998](#)). Although few details are provided on the

26 number of subjects excluded for these reasons, given the objective nature of the biomarker

27 outcomes that were evaluated, such exclusions are unlikely to be an important source of bias.

28 The exclusion rates were also reported to be low and comparable across the zones (five subjects

29 from the noncontaminated zone non-ABR and four subjects from zone B).

30   A strength of the study was the examination of other DLCs via the TEQ analysis. A

31 limitation of the study included the relatively small number of subjects which resulted in the

1   grouping of several covariates, including TCDD exposures, into a small number of categories.

2   As such, slope coefficients derived from modeling continuous measures were emphasized in the

3   data presentation. Another key limitation of the study is the uncertainty of how effects on AhR

4   translate into subsequent development of cancer and other chronic health effects.

5

6   **C.1.2.1.5.4.3.**   Suitability of data for TCDD dose-response modeling

7   It is unclear how associations between AhR biomarkers and TCDD levels translate into

8   an increased risk of adverse health effects. Dose-response analysis for this outcome, therefore,

9   was not conducted.

10

11   **C.1.2.1.5.5.   *Alaluusua et al. (2004)—Developmental dental defects***

12   **C.1.2.1.5.5.1.**   Study summary

13   Alaluusua et al. (2004) examined the relationship between TCDD and dental defects,

14   dental caries, and periodontal disease among Seveso residents who were children at the time of

15   the accident. Subjects were randomly selected from those individuals who had previously

16   provided serum samples in 1976, which was shortly after the accident. A total of 65 subjects

17   who were less than 9.5 years of age at the time of the accident, and who lived in Zones A, B, or

18   R were invited to participate. Recruitment was initiated 25 years after the time of the Seveso

19   accident. An additional 130 subjects from the surrounding area (outside Zones A, B, or R or

20   "non-ABR zone") having the same age restriction were recruited. Subjects were frequency

21   matched by age, sex, and education. Questionnaires were administered to these individuals to

22   collect detailed information on dental and medical histories, education, and smoking behaviors.

23   Ten subjects who had completed at least high school were randomly excluded from the non-ABR

24   zone to create groups with similar educational profiles. Participation rates for the ABR and

25   non-ABR zones were 74% and 58%, respectively.

26   One dentist who was blind to the patients' TCDD exposure levels assessed dental

27   aberrations. Dental caries were assessed using recommendations of the World Health

28   Organization. Periodontal status was described following a detailed evaluation of the surfaces of

29   the teeth. A radiographic examination was done to identify missing teeth, alveolar bone loss,

30   deformities in the roots, and jaw cysts.

1   Comparisons of the presence of dental enamel defects according to exposure status were

2   made using logistic regression. Chi-square test statistics were applied to compare the

3   distributions in the prevalence of dental defects across several categorical covariates (i.e.,

4   education, age, and serum TCDD level). For those who were younger than 5 at the time of the

5   accident, dental defects were more prevalent among patients in zone ABR (42%) than those in

6   the non-ABR zone (26%) ($p = 0.14$). Zone ABR is characterized by higher levels of soil TCDD

7   levels relative to non-ABR. Serum levels permitted an improved characterization of risk as they

8   were available at an individual level, rather than using a zone of residence. The continuous

9   measure of serum TCDD was associated with developmental dental defects ($p = 0.007$) and

10   hypodontia ($p = 0.05$). The authors classified less-exposed individuals in the non-ABR zones as

11   the reference population and also examined exposure tertiles for the ABR residents. The

12   prevalence of dental effects for the reference group was 26% (10/39). The prevalence of dental

13   effects in the 1st, 2nd and 3rd tertile exposure groups was 10% (1/10), 45% (5/11) and 60% (9/15),

14   respectively. A total of 12.5% of the zone ABR subjects had missing permanent teeth (lateral

15   incisors and second premolars) compared with 4.6% of the zone non-ABR residents. For zone

16   ABR subjects, missing teeth were more frequent with higher serum TCDD levels.

17

18   **C.1.2.1.5.5.2.** Study evaluation

19   TCDD exposures were characterized using serum measures for those who resided in

20   zone ABR in 1976 (within a year of the accident). Alaluusua et al. ([2004](#)), however, provide few

21   details about the sampling frame used to identify these participants. Despite this, it is important

22   to note that a dose-response pattern was observed between TCDD exposure and presence of

23   developmental dental defects in the ABR population alone ($p = 0.016$). This finding is based on

24   27 subjects with developmental dental defects. This positive association provides support for a

25   quantitative dose-response modeling of developmental dental defects. The numbers of such

26   subjects are small, however, with one, five, and nine subjects having defects in the exposure

27   tertiles ; the concentration ranges in the 1st, 2nd and 3rd tertiles were 31−226, 238−592, and

28   700−26,000 ng/kg TCDD, respectively.

29

C.1.2.1.5.5.3. Suitability of data for TCDD dose-response modeling

The considerations for conducting a dose-response analysis have been satisfied with the study population. A critical window of exposure can be defined for the subjects with individual-level serum samples. The enamel defects combined with the prevalence of missing permanent teeth in the higher-exposed subjects allows for a LOAEL to be established for the 2nd tertile exposure range. A NOAEL is evident for the 1st tertile and a NOAEL and LOAEL could be established. Dose-response analyses were conducted for this outcome.

C.1.2.1.5.6. *Baccarelli et al. (2005)—Chloracne*

C.1.2.1.5.6.1. Study summary

Baccarelli et al. (2005) published findings from a case-control study of 110 chloracne cases and 211 controls. The authors collected information on pigment characteristics and an extensive list of diseases. This study was performed to yield information about the health status of chloracne cases, TCDD-chloracne exposure response, and factors that could modify TCDD toxicity. TCDD was measured from plasma from subjects recruited during 1993 to 1998. Following adjustment for confounding, TCDD was associated with chloracne (OR = 3.7, 95% CI = 1.5−8.8), and the risk of chloracne was considerably higher in subjects younger than 8 at the time of the accidents (OR = 7.4, 95% CI = 1.8−30.3). Among individuals with lighter hair, the association between TCDD and chloracne was stronger than among those with darker hair.

C.1.2.1.5.6.2. Study evaluation

Statistical power was limited in this study especially to assess potential interactions. Study strengths included unique distribution of age and sex of chloracne cases, characterization of individual-level TCDD exposures using sera samples, and the availability of both clinical and epidemiological data. Although a dose-response relationship was observed, chloracne is a rare health outcome likely only to occur among those highly exposed.

C.1.2.1.5.6.3. Suitability of data for TCDD dose-response modeling

Given the very high TCDD levels needed to cause chloracne (Ott et al., 1993), this health endpoint would not be considered as the basis for the RfD. Therefore, dose-response analyses for the Baccarelli et al. (2005) study were not conducted.

1

C.1.2.1.5.7. _Baccarelli et al. (2008)—Neonatal thyroid hormone levels_

C.1.2.1.5.7.1.   Study summary

   Baccarelli et al. (2008) investigated the relationship between thyroid function and TCDD among offspring of women who were of reproductive age at the time of the 1976 accident. This health endpoint is relevant because thyroid function is important for energy metabolism and nutrients and for stimulating growth and development of tissues. Neonatal thyroid function at birth is evaluated through blood thyroid-stimulating hormone (b-TSH).

   The study population was drawn from 1,772 women who were identified as having lived in the highly contaminated areas (Zones A or B) at the time of the accident or between July 10, 1976 and December 31, 1947; were of fertile age (born after 1947); and were alive as of January 1, 1994. A random sample of 1,772 unexposed women who lived in the reference area was selected using frequency matching by year of birth to the exposed women, and residency in the reference area at the time of the accident. The reference area represents the noncontaminated areas that surround the three zones of decreasing exposure (Zones A, B and R). In total, 55,576 women had lived in the reference area. Population registry offices ($n = 472$) were contacted to detect children born to these women. Records could be traced for virtually all subjects (1761/1772 exposed; 1762/1772 unexposed). Children born outside the Lombardy area were excluded as b-TSH could not be obtained for them. This accounted for 156 of the 1,170 children identified. The analyses were based on the remaining 56, 425, and 533 singletons born between January 1, 1994, and June 30, 2005 in Zone A, B, and from the reference area, respectively.

   Thyroid function is tested in all newborns by b-TSH measures in the region of Lombardy where Seveso is located. These measures are obtained from blood samples taken 72 hours after birth using a standardized protocol. The b-TSH levels were log transformed to approximate a normal distribution. Linear regression analysis was used to conduct test for trends in mean b-TSH levels across different covariates. Logistic regression was used to assess associations between elevated b-TSH levels defined by the cutpoint of 5 μU/mL and residence in particular zones of contamination. The 5 μU/mL cutpoint for TSH measurements in neonates was recommended by WHO (1994) for use in neonatal population surveillance programs. Although WHO established the standard for increased neonatal TSH in the context of iodine deficiency

1   disease, the toxicological implications are the same for TCDD exposure and include increased

2   metabolism and clearance of T4. Generalized estimating equations were used to adjust the

3   standard errors of the ORs for correlation between siblings.

4   The mean levels of b-TSH were positively associated with average soil TCDD

5   concentrations in the three areas (Zone A: 1.66 µU/mL; Zone B: 1.35 µU/mL; and Zone R:

6   0.98 µU/mL) ($p < 0.001$). Plasma TCDD levels also were shown to be much higher in a group of

7   51 newborns that had b-TSH levels >5 µU/mL. Compared to the reference population, adjusted

8   ORs were elevated for Zone B (OR = 1.90, 95% CI = 0.94−3.86) and Zone A (OR = 6.63,

9   95% CI = 2.36−18.6). These ORs were adjusted for gender, birth weight, birth order, maternal

10   age at delivery, hospital, and type of delivery. The adjusted ORs however differed only slightly

11   from those that were unadjusted (Zone B OR = 1.79, 95% CI = 0.92−3.50; Zone A OR = 6.60,

12   95% CI = 2.45−17.8). Of the risk factors considered, only gender and birth weight were

13   identified as independent predictors of neonatal b-TSH levels.

14   The paper also included an analysis of children born to 109 women who were part of the

15   Seveso Chloracne Study (Baccarelli et al., 2005). A total of 51 children were born to 38 of these

16   women, of these 12 lived in Zone A, 10 in Zone B, 20 in Zone R, and 9 from the reference

17   population. Several congeners including TCDD were measured in maternal plasma collected

18   from December 1992 to September 1998.. TCDD levels were extrapolated to the date of

19   delivery using a first-order pharmacokinetic model (Michalek et al., 1996). The elimination rate

20   used was 9.8 years based on the mean half-life estimate from a previous study of women in the

21   Seveso region (Michalek et al., 2002). TEQs were calculated for a mixture of DLCs by

22   multiplying the concentration of each congener by its toxicity equivalence factor. The maternal

23   average TEQ was 44.8 ppt (range: 11.6−330.4) among 51 mothers. The measurement of

24   noncoplanar PCBs occurred only later in the study (1996) and, therefore, total mean TEQs (i.e.,

25   including the sum of PCDDs, PCDFs, coplanar PCBs, and noncoplanar PCBs) are available only

26   on a subset ($n = 37$) of the population. DLCs were examined as earlier studies suggested

27   associations between the sum of PCBs, or individual congeners having decreased thyroxine

28   (Sandau et al., 2002; Longnecker et al., 2000), and increased TSH (Alvarez-Pedrerol et al., 2008;

29   Chevrier et al., 2007). The following confounders were examined by the authors in the plasma

30   dioxin models: maternal body mass index, smoking habits, alcohol consumption, and neonatal

31   age in hours at the time of the b-TSH measurement.

1   The authors used a linear regression model to examine the association between maternal

2   TCDD levels and b-TSH. The standardized regression coefficient obtained from this model was

3   0.47 ($p < 0.001$). For the evaluation of TEQs, a similar association was noted for PCDDs,

4   PCDFs, and coplanar PCBs ($n = 51$, $\beta = 0.45$, $p = 0.005$) but not with noncoplanar PCBs ($n = 37$,

5    $\beta = 0.16$, $p = 0.45$). Statistically significant associations between b-TSH with plasma TCDD,

6   PCDDs, PCDFs, and coplanar PCBs, but not with noncoplanar PCBs, were found based on

7   multivariate regression models adjusted for gender, birth weight, birth order, maternal age at

8   delivery, hospital, and type of delivery. No association was detected for the sum of all total

9   TEQs from the measured compounds ($n = 37$, $\beta = 0.31$, $p = 0.14$).

10

11   **C.1.2.1.5.7.2.**   Study evaluation

12   The Baccarelli et al. (2008) study satisfies the epidemiological considerations and criteria

13   for determining whether dose-response modeling should be pursued. The outcome is well

14   defined, and a dose-response pattern was observed. The study also contained a substudy that

15   characterized TCDD and exposures to other DLCs and used serum measures for a sample of

16   mothers. Results were consistent among the zone of residence analysis and the substudy based

17   on plasma measures.

18

19   **C.1.2.1.5.7.3.**   Suitability of data for TCDD dose-response modeling

20   Given the potential for exposure misclassification due to variability in TCDD soil levels

21   within each zone, modeling should rely on individual-level TCDD exposures derived from the

22   plasma sampling substudy. The study data provide an opportunity for quantitative dose-response

23   analyses as the critical exposure window of 9 months can be used for exposure assessment

24   purposes.

25

26   **C.1.2.1.5.8.**   _Mocarelli et al. (2008)—Sperm effects_

27   **C.1.2.1.5.8.1.**   Study summary

28   Mocarelli et al. (2008) examined the relationship between TCDD and endocrine

29   disruption and semen quality in a cohort of Seveso men. Study participants included 397 of the

30   eligible 417 males (<26 years old in 1976) from Zone A and nearby contaminated areas who had

31   serum TCDD levels measured in 1976. Frozen serum samples collected from 1976 to 1977 were

1   used to derive TCCD exposures. In addition, 372 healthy blood donors not living in the

2   TCCD-contaminated area were invited to participate. The researchers collected a health

3   questionnaire and semen samples from participants. Analyses were based on 257 individuals in

4   the exposed group and 372 in the comparison group. Of the 257 exposed men, 135 (53%)

5   without disease agreed to participate, while 184 of the 372 (49%) recruited men in the

6   comparison group participated. Semen samples were collected postmasturbatory at home.

7   Ejaculate volume, sperm motility, and sperm concentration were measured on these samples.

8   Fasting blood samples also were collected from the subjects for reproductive hormone analyses,

9   including 17β-estradiol (E_2), follicle stimulating hormone (FSH), inhibin B, luteinizing hormone

10   (LH), and testosterone.

11   The researchers estimated serum concentrations of TCDD from samples provided in

12   1976−1977, and also in 1997−1998 for individuals whose earlier samples had TCDD values that

13   exceeded 15 ppt. Serum concentrations for the comparison group were assumed to be less than

14   15 ppt in 1976 and 1977 and <6 ppt in 1998/2002 on the basis of serum results for residents in

15   uncontaminated areas. The exposed and comparison groups were divided into three groups

16   based on their age in 1976: 1−9, 10−17, and 18−26 years. Mocarelli et al. (2008) applied a

17   general linear model to the sperm and hormone data and included exposure status, age, smoking

18   status, body mass index, and occupational exposures as covariates. The study authors addressed

19   the potential for confounding factors.

20   Men exposed between the ages of 1 and 9 had reduced semen quality 22 years later.

21   Reduced sperm quality included decreases in sperm count ($p = 0.025$), progressive sperm

22   motility ($p = 0.001$), and total number of motile sperm ($p = 0.01$) relative to the comparison

23   group. The opposite pattern was observed for several indices of semen quality among those aged

24   10−17 at the time of the accident; this included a statistically significant increase in sperm count

25   ($p = 0.042$). The clinical significance of this increase is unknown. For the hormone analyses,

26   those in the exposed group had lower serum E_2 levels, and higher follicle stimulating hormone

27   concentrations. Neither testosterone levels nor inhibin B concentrations were associated with

28   TCDD exposure.

29

C.1.2.1.5.8.2. Study evaluation

The findings of the Mocarelli et al. (2008) study support the hypothesis that exposure to TCDD in infancy/prepuberty reduces sperm quality. The changes in serum E2 and FSH concentrations are of unknown clinical significance, and it is unclear whether they represent adverse health endpoints. Although most semen analysis studies have low compliance rates in general population samples (20−40%) (Muller et al., 2004; Jørgensen et al., 2001), the compliance rate in this study was much higher (60%). Given that the compliance rates were similar between the exposed and comparison groups and the strong differences detected across the two age groups, selection bias appears unlikely in this study.

C.1.2.1.5.8.3. Suitability of data for TCDD dose-response modeling

The health outcomes are well defined in the Mocarelli et al. (2008) study, and exposures are well characterized using serum data. Because the men exposed to elevated TCDD levels between the ages of 1 and 9 had reduced semen quality 22 years later, it is difficult to identify the relevant time interval over which TCDD dose should be considered. Specifically, it is difficult to discern whether this effect is a consequence of the initial high exposure between 1 and 9 years of age or a function of the cumulative exposure for this entire exposure window beginning at the early age. However, the differences between these two dose estimates (the initial high exposure versus the cumulative exposure for the 9 year window) are minimal (i.e., within an order of magnitude). Despite the uncertainty in estimating the critical window of exposure, dose-response analysis for this outcome was conducted.

C.1.2.1.6. *The Chapaevsk study*

C.1.2.1.6.1. *Revich et al. (2001)—mortality and reproductive health*

C.1.2.1.6.1.1. Study summary

Revich et al. (2001) describe a series of investigations that have evaluated adverse health outcomes among residents of Chapaevsk where ecological measures of TCDD have been noted to be higher than expected. In the earlier cancer section of this report, the cross-sectional comparisons of mortality that the authors carried out between Chapaevsk residents and a general population reference were described. Although the general focus of this paper is on cancer, the authors examined other adverse health outcomes.

1   For all-cause mortality, rates were found to be higher in Chapaevsk relative to the Samara

2   region and other nearby towns. The magnitude of this increase, however, was not quantified in

3   the review by Revich et al. (2001) Cardiovascular mortality accounted for nearly two-thirds of

4   women's deaths and almost half of those among men. The rates of cardiovascular mortality

5   among Chapaevsk men have been reported to be 1.14 times higher than those in Russia.

6   Revich et al. (2001) also reported on the occurrence of adverse reproductive events.

7   Although the authors indicated that official medical information was used to make comparisons

8   between regions, no details were provided about data quality, completeness, or surveillance

9   differences across areas. The presented rates for reproductive health outcomes should be

10   interpreted cautiously. A higher rate of spontaneous abortions (24.4 per 100 pregnancies

11   finished by delivery) was found in Chapaevsk women relative to rates that ranged between 10.6

12   and 15.2 found in five other areas. The frequency of preeclampsia also was found to be higher in

13   Chapaevsk women (44.1/100) relative to other towns, as was the proportion of low birth-weight

14   babies and preterm births. The percentage of newborns with low birth weight was slightly larger

15   in Chapaevsk (7.1%) when compared to other towns in Samara (5.1−6.2%); observed

16   differences, however, were not statistically significant. The authors also reported on the sex ratio

17   of newborns born between 1983 and 1997. These ratios (boys:girls) were highly variable and

18   ranged between 0.79 and 1.29. Given the annual variability of this ratio on a year-to-year basis,

19   it is unclear if this is largely due to natural fluctuations and to what extent this may result from

20   prior TCDD (or other contaminants) exposure TCDD and other contaminants.

21

22   **C.1.2.1.6.1.2.**   Study evaluation

23   The review by Revich et al. (2001) highlights analyses that have been undertaken using

24   largely cross-sectional data. Although soil sampling measures appear to demonstrate decreasing

25   levels of TCDD in the soil with increasing distance from the plant, at this time, no

26   individual-level TCDD exposure data are available. Increased rates of mortality relative to the

27   Samara region in Russia were observed among Chapaevsk men for all cancer sites combined;

28   this excess risk however, was not observed among women. Although the authors provide

29   compelling evidence of increased adverse events among residents of Chapaevsk, the study lacks

30   a discussion about the validity of comparing health data across regions, and suffers from inherent

1 limitations from ecological studies such as exposure misclassification and potential for

2 confounding.

3

4 **C.1.2.1.6.1.3.** Suitability of data for TCDD dose-response modeling

5   Insufficient details are provided by the authors to gauge the completeness and coverage

6 of the cancer registry and mortality data. Health outcomes were studied on the basis of

7 information in the official medical statistics. As with the cancer outcomes presented in this

8 study, the data for noncancer outcomes are limited by the absence of TCDD levels on an

9 individual-level basis and information on other potential confounding variables that could have

10 biased the results. The cross-sectional nature of the data that were presented does not provide

11 the necessary level of detail needed to estimate effective dose given the lack of individual-level

12 exposure data. Therefore, a quantitative dose-response analysis was not conducted.

13

14 **C.1.2.1.7.** *The Air Force Health ("Ranch Hands" cohort) study*

15 **C.1.2.1.7.1.** **Henriksen et al., (*1997*)**

16 **C.1.2.1.7.1.1.** Study summary

17   Henriksen et al. (1997) investigated the relationship between TCDD exposure and

18 diabetes among participants of the Air Force Health Study (AFHS). This study included

19 veterans of Operation Ranch Hand who served in Southeast Asia between 1962 and 1971 and

20 were exposed to high levels of dioxin from the spraying of Agent Orange during flight

21 operations and the maintenance of aircraft and herbicide spray equipment. In addition, it

22 included a comparison group of other Air Force veterans who also served in Southeast Asia

23 during the same period, but were not actively involved in the spraying of herbicides. This

24 comparison group was selected by matching to the Ranch Hands on the basis of age, race, and

25 military occupation. Data from physical examinations in 1982, 1985, 1987, and 1992 were used

26 for the study. The cohort initially consisted of 1,108 Ranch Hands and 1,494 veterans in the

27 control cohort.

28   Incident diabetes from the end of the tour of duty through June 1995 was identified based

29 responses provided from questionnaires administered from at least one of the four examinations,

30 followed by verification of medical records and laboratory results. Study subjects were

31 classified as diabetics if they had a verified history of diabetes mellitus by medical diagnosis or if

1   they exhibited a 2-hour postprandial glucose laboratory value of ≥200 mg/dL. A total of

2   315 incident cases of diabetes were identified; of these, 169 occurred in the comparison cohort.

3   The authors also examined associations between TCDD and the following health outcomes:

4   severity of diabetes, time to onset of diabetes, and glucose abnormalities. Diabetes severity was

5   determined based on a review of the medical records, and questionnaire responses and classified

6   as insulin therapy, oral medication, diet only, or no control. Fasting glucose and 2-hour

7   postprandial glucose were used to identify glucose abnormalities. The 100-gm glucose load for

8   the postprandial assay was not given to known diabetics. The outcome time-to-onset of diabetes

9   was defined as the number of years between the end of the last tour of duty in Southeast Asia,

10   and initial diagnosis of diabetes. For those without diabetes, the time to onset of diabetes was

11   the number of years since the end of tour of duty and the last physical examination; this time-to

12   onset value was right-censored.

13   Serum dioxin levels were first estimated using high resolution gas chromatography/high

14   resolution mass spectrometry using samples collected in the 1987 interview. Those whose

15   dioxin levels were not quantifiable in 1987 and those who refused or were new to the study were

16   asked to provide serum in 1992 to measure dioxin. Dioxin levels were then estimated for the

17   Ranch Hands at the end of the tour of duty by assuming a constant half-life of 8.7 years. The

18   Ranch Hands were classified on the basis of this TCDD exposure estimate into one of three

19   groups (Background, Low, or High). The study excluded those with a history of diabetes before

20   service in Southeast Asia, those with no measure of dioxin, and those in the comparison group

21   with a dioxin level that exceeded 10 ppt which was regarded as the threshold level for

22   background exposure. The analyses of diabetes mellitus and TCDD exposure were based on

23   2,265 veterans (989 Ranch Hands, 1276 Comparison veterans).

24   The relative risk (and confidence intervals) of diabetes was estimated using the ratio of

25   the prevalence of diabetes in Ranch Hands veterans relative to the comparison group using the

26   method of Rothman (1986). The risk of diabetes was associated with TCDD exposure, and

27   Ranch Hands in the highest exposure group had a relative risk of 1.5 (95% CI = 1.2, 2.0) relative

28   to those in the comparison cohort. A subsequent analysis of this cohort further adjusted for the

29   effects of triglycerides, which slightly attenuated this risk estimate (RR = 1.4, 95% CI = 1.1−1.8)

30   (Michalek et al., 1998). The severity of diabetes was associated with dioxin exposure. For

31   example, among those who required insulin therapy for the management of their diabetes, the

1   relative risk was among those in the High dioxin exposure group relative to those in the lowest

2   2.4 (95% CI=0.9 – 6.4). Time to onset of diabetes was found to be inversely related to exposure

3   to dioxin, and this association persisted across veterans stratified by body fat percentage. Serum

4   insulin abnormalities, as determined by the 2-hour postprandial glucose measure, were positively

5   associated with dioxin exposure in nondiabetics. Specifically, among Ranch Hands in the High

6   dioxin exposure category, the prevalence of those with abnormal insulin values was 8.4%

7   compared to 2.5% among those in the comparison cohort (RR=3.4, 95% CI=1.9 – 6.1).

8

9   **C.1.2.1.7.1.2.** Study evaluation

10   A strength of this study is its relatively large sample size of 2,265 veterans, and identified

11   cases of diabetes ($n = 315$). Moreover, there is a large range in exposure to TCDD across the

12   study population (i.e., the comparison cohort as well as veterans of the Operation Ranch Hands).

13   The study was able to achieve a high level of participation, and lengthy follow-up interval with

14   data from four physical examinations. As documented by Michalek et al (2001c), few veterans

15   were lost to attrition over the four physical examinations.

16   The methods used to identify newly diagnosed cases of diabetes following the tour of

17   duty were valid, and the study evaluated several different measures associated with diabetes.

18   The associations observed between these different health measures (i.e., diabetic status, time to

19   onset of diabetes, severity of diabetes, and insulin abnormalities) were consistent, and therefore,

20   strengthen the argument that exposure to TCDD may contribute to the development of insulin

21   resistance and diabetes.

22   The use of serum measures to estimate TCDD exposure was also a strength of the study.

23   The authors estimated dioxin levels in veterans at the end of their tour of duty using a constant

24   half-life of 8.7 years, and conducted additional sensitivity analyses across strata of subjects

25   grouped by body fat percentages. These results produced similar associations.

26   Unlike the subsequently published study by Longnecker and Michalek (2000) which is an

27   essentially cross-sectional analysis of the comparison cohort, the analysis presented in this study

28   is longitudinal. The dramatically higher exposure to TCDD among the Ranch Hand component

29   of the cohort during their tour of duty allows for diabetes prevalence, severity, time to onset, as

30   well as glucose abnormalities among nondiabetics to be compared across groups that differed by

31   TCDD exposure before these health outcomes were determined.

1   An important limitation of the study was raised by Slade ([1998](#)) who noted that
2   interactions between plasma lipid fractions, dioxin, and diabetes could produce a spurious
3   association between dioxin and diabetes. In her letter, she noted that hyperinsulinemia, insulin
4   resistance, impaired glucose tolerance and diabetes are all associated with lipid abnormalities,
5   and the corresponding change in lipid fractions may elevate dioxin levels. As exposure to TCDD
6   was estimated in 1987, and in some cases 1992, it is possible that these lipid abnormalities may
7   have distorted the back-extrapolation of TCDD exposure estimates at the end of the tour of duty
8   in Vietnam. The authors were not able to directly evaluate the magnitude of this source of
9   measurement error because no lipid samples were stored for this cohort that would allow for
10   dioxin to be measured. Subsequent analysis to respond to these comments found little change in
11   the risk estimates for diabetes after adjusting for triglycerides ([Michalek et al., 1998](#)). However,
12   dioxins have also been shown to affect triglyceride levels in both animals and in humans, and
13   therefore the influence of triglycerides may be responsible for a noncausal association between
14   dioxin and the health outcomes in this study.

15

16   **C.1.2.1.7.1.3.**   Suitability of data for TCDD dose-response modeling

17   The use of the individual-level TCDD serum measures and the identification of diabetes
18   through medical records and objectively-based serum tests are strengths. TCDD levels were
19   estimated based on samples collected in 1987, and in some cases 1992; the study authors note
20   that these samples were collected 20 to 30 years after the TCDD exposures. If there are
21   diabetogenic effects of TCDD, it is unclear whether TCDD-mediated diabetes onset might be a
22   consequence of an elevated TCDD exposure event over a relatively short period of exposure
23   (during service) or chronic TCDD exposure over a longer window of time. Estimation of peak
24   exposures 20 years earlier is highly uncertain. Also, the longer potential exposure window
25   occurred during a time period of decreasing exposure to TCDD and DLCs ([Lorber and Phillips,](#)
26   [2002](#)) further impeding the ability to estimate effective exposures. The uncertainty in identifying
27   a critical period of exposure precluded the estimation of an effective TCDD exposure.
28   Therefore, a quantitative dose-response analysis was not conducted for this study.

29

1 **C.1.2.1.7.2.** *__Longnecker and Michalek (2000)__*

2 **C.1.2.1.7.2.1.** Study summary

3   Longnecker and Michalek (2000) evaluated the relationship between serum levels of

4 TCDD and the incidence of diabetes and levels of serum glucose and insulin among veterans in

5 the AFHS. However, unlike the earlier work on diabetes by Henriksen et al. (1997), and

6 Michalek et al. (2003), this study did not include those in operation Ranch Hand that were more

7 highly exposed to TCDD from the spraying of Agent Orange. Instead, this study was restricted

8 to the comparison group of male veterans in the AFHS who were never in contact with

9 dioxin-contaminated herbicides, and whose serum TCDD levels were thought to fall within the

10 same range as the background levels found in the United States. These veterans included air and

11 ground personnel who participated in aircraft missions in Southeast Asia between August 1961

12 and May 1972. The manner in which this cohort of nonsprayers was assembled was originally

13 described by Wolfe et al. (1990). A total of 1,667 comparison group veterans (i.e., non Ranch

14 hands) were invited to participate in AFHS examinations in 1982. Subsequent examinations

15 were also conducted in 1985, 1987, and 1992. Participation rates were high (>70%) among this

16 comparison group of veterans, with 1,197 subjects available for analyses.

17   Incident diabetes following each veteran's tour of duty was the primary health outcome

18 under study. This outcome was defined by either (i) self-reported physician diagnosis of

19 diabetes at any of the examinations (1982, 1987, and 1992) with subsequent verification of

20 medical records through June 1995, or (ii) by a postchallenge glucose test using 100 g of glucose

21 (positive status $\geq$200 mg/dL) in 1992. All incident cases of diabetes were type II. Levels of

22 serum and insulin were also measured using fasting, and 2-hour postchallenge tests in

23 nondiabetics.

24   Serum dioxin levels were estimated using high resolution gas chromatography/high

25 resolution mass spectrometry using samples collected in the 1987 interview. For a small number

26 of veterans ($n = 21$) dioxin levels were estimated using serum collected in 1997. For the

27 108 subjects with TCDD levels below the level of detection (1.25 ng/kg lipid), they were

28 assigned a TCDD level of 0.625 mg/kg. Those with serum TCDD levels above 10 ng/kg were

29 excluded as were those who lacked complete data for the covariates of interest. The covariates

30 that were examined as potential confounders included age, dioxin, body mass index, waist size,

1   and family history of diabetes, postchallenge glucose, and triglycerides. Analyses were based on

2   the remaining 1,197 veterans, and among these 169 incident cases of diabetes were identified.

3   Logistic regression was used to estimate the odds ratios and 95% confidence intervals of

4   diabetes across quartiles of serum TCDD levels, as well as in relation to a linear increase in

5   4.0 ng/kg of TCDD. The natural logarithm of serum-insulin levels was modeled again TCDD

6   levels using linear regression. Results were adjusted for year of birth, race, military occupation,

7   body mass index at 1992, body mass index at time of TCDD measurement and waist size in

8   1992. Ordinary least squares regression was used to evaluate associations between serum

9   glucose or insulin measures and quartiles of TCDD exposure. Adjustment was made for the

10   same covariates used in the logistic regression analysis.

11   The adjusted odds ratio for diabetes increased with higher serum TCDD levels.

12   Specifically, an increase of 4.0 ng/kg of serum TCDD yielded an adjusted odds ratio of 1.55

13   (95% CI = 1.09−2.20). After further adjustment for serum triglyceride levels, the corresponding

14   odds ratio remained positive but was attenuated (OR = 1.37, 95% CI = 0.96−1. 97). Associations

15   were also observed between serum TCCD and serum glucose (and insulin) levels, although some

16   of these were not statistically significant following adjustment for confounding. This implies

17   that TCDD may contribute to increased insulin resistance and increased glucose levels among

18   those not satisfying the formal criteria for the diagnosis of diabetes. The addition of serum

19   triglycerides to this model weakened these associations. The findings for both the outcomes of

20   diabetes and serum glucose were essentially unchanged after excluding subjects whose serum

21   TCDD was measured after 1987.

22

23   **C.1.2.1.7.2.2.**   Study evaluation

24   A strength of this study is the relatively large sample size ($n = 1197$) and corresponding

25   number of incident cases of diabetes ($n = 169$). However, while exposure levels are well

26   characterized using serum-based measure of TCDD, the primary limitation of this study is that

27   the analysis is essentially cross-sectional. The measurement of serum levels of TCDD occurred

28   following onset of diabetes for many of the veterans. On the other hand, associations between

29   dioxin exposure and diabetes during the most recent follow-up interval were dependent on serum

30   based TCDD exposures taken much earlier in 1987. In short, the findings did not account for the

31   timing of the exposure in relation to when diabetes was diagnosed. Therefore, the associations

1 may be noncausal. As noted by the authors, the onset of diabetes may have affected dioxin

2 levels via the increased solubility of dioxides within increased serum triglycerides. Diabetes is

3 recognized to increase triglyceride levels, and adjustment for triglycerides attenuated the findings

4 in this study. Unlike the earlier study by Henriksen et al. (1997), this study excluded the Ranch

5 Hand workers that had considerably higher exposures. The much smaller range in exposures

6 along with the potential for serum triglycerides to affect dioxin levels implies that there is a

7 greater potential for exposure misclassification across the groups used in this study than those

8 used by Henriksen et al (1997).

9   The ascertainment of incident diabetes relied on either a self-reported measure with

10 confirmation through medical records, or a postglucose challenge serum test. These are valid

11 methods to identify cases of diabetes mellitus. The possibility existed that those with lower

12 dioxin levels may have been less likely to participate in the follow-up examination, thereby,

13 leading to an under-ascertainment of diabetes among those with lower dioxin level. However,

14 given a positive association was noted based on 1992 examination alone, and that participation

15 rates among those with 1987 dioxin less than the median was 91%, this potential source of bias

16 would likely be modest.

17

18 **C.1.2.1.7.2.3.**   Suitability of data for TCDD dose-response modeling

19   The use of the individual-level TCDD serum measures and the identification of diabetes

20 through medical records and objective serum tests are strengths of this study, however, the

21 potential noncausal role of serum triglycerides cannot be dismissed. Additionally, there is

22 uncertainty in determining the critical window of exposure. This was essentially a

23 cross-sectional analysis of diabetes in relation to a single point-in-time measure of TCDD

24 background exposure level that may have occurred over an approximate 20-year interval.

25 Considering the uncertainty in estimating the biologically relevant exposure window and the

26 uncertainty in estimating peak exposures 20 years prior to measurement, a quantitative

27 dose-response analysis was not conducted.

28
29 **C.1.2.1.7.3.** _**Michalek et al. (2001a)**_

30 **C.1.2.1.7.3.1.**   Study summary

31   Michalek et al. (2001a) examined the relationship between TCDD exposure and

32 hematopoietic effects among veterans in the Air Force Health Study. A description of the overall

1   study design has been described earlier, and can be found in the paper by Wolfe et al (1990).

2   This study included both veterans in the Ranch Hand unit, as well as those in a comparison

3   cohort who were not involved in the spraying of herbicides.

4   The study used data collected from medical examinations and self-reported

5   questionnaires completed in 1982, 1985, 1987, and 1992. TCDD levels were estimated using

6   serum collected in 1987, with some additional samples taken in 1992 for those who lacked

7   TCDD measurements. In total, TCDD was assayed for 2,198 veterans. TCDD levels below the

8   limit of detection were assigned a value of 0 ppt. The study excluded veterans with no TCDD

9   measure, those with TCDD levels above the level of detection but below the level of

10   quantification, and comparison subjects whose TCDD levels exceeded 10 ppt serum lipid

11   (threshold for background exposure). A first order kinetics model with a constant half-life of

12   8.7 years was used to estimate the initial TCDD dose at the end of the veterans' tours of duty in

13   Southeast Asia. Veterans were classified into four dioxin exposure groups: comparison cohort,

14   Ranch Hand—Background (<10 ppt), Ranch Hand—Low (10− ≤94 ppt), and Ranch

15   Hand―High (>94 ppt).

16   At each of the four physical examinations, the following hematological characteristics

17   were measured: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, white

18   blood cell count, platelet count and erythrocyte sedimentation rate. Veterans who participated in

19   at least one examination, and who had a TCDD measurement were included unless they had a

20   fever (body temperature greater than 100°F) or they tested positive for human immunodeficiency

21   virus.

22   Michalek et al. (2001a) applied a linear regression model (adjusted for other covariates)

23   to calculate estimated mean differences in the various hematological measures among the

24   comparison group and the three other exposure groups. An adjusted test for trend was also

25   applied to the restricted group of Ranch Hand veterans. Logistic regression was used to estimate

26   the adjusted odds ratio for abnormally high or low hematological characteristics across TCDD

27   exposure categories. The measures of association were adjusted for the percentage of body fat,

28   year of birth, race, military occupation, and life-time smoking patterns. A secondary analysis of

29   mean corpuscular volume adjusted for current alcohol consumption was undertaken.

30   There were no statistically significant differences in the mean values for red blood cell

31   counts, hematocrit, and white blood cell counts across the TCDD exposure categories in any of

1   the four examination periods. For three of the four examination periods, there was no

2   association observed between TCDD and hemoglobin. Relative to the comparison group, the

3   mean corpuscular volumes were elevated among those in the highest exposure category in all

4   examination periods, while platelet counts were higher in three of the four periods. Overall,

5   corpuscular volumes were about 1% higher among the most highly exposed Ranch Hands

6   compared to the comparison cohort, while the corresponding increase was 4% with platelet

7   counts.

8   Logistic regression analysis of abnormal red blood cell counts across TCDD exposure

9   categories was hampered by small sample sizes. Typically, there were fewer than 4 abnormalities

10 in each of the four examination periods. In contrast, there was some evidence for abnormally

11 high platelet counts, abnormally high mean corpuscular volume, and abnormally high hematocrit

12 in the highest Ranch Hand exposure group in some, but not all examination periods.

13   Michalek et al. (2001a) suggested that the increased corpuscular volumes may be

14 explained by the noncausal effects of TCDD on serum triglycerides. Other possible explanations

15 are also available for these associations, such as increased gamma-glutamyl transferase.

16

17 **C.1.2.1.7.3.2.**   Study evaluation

18   Strengths of the study included an assessment of dioxin at an individual-level using

19 serum based measures, a lengthy follow-up period that extended 30 years postservice, multiple

20 physical examination, and the use of valid methods of hematological function. There are some

21 uncertainties in the estimation of TCDD exposure given serum was drawn decades after the

22 exposure period. Exposure misclassification may have been introduced from measurement error

23 in exposure estimates due to variations in metabolism, use of an assumed half-life of TCDD, and

24 calculations based on first-order decay. The authors note considerable uncertainty in the

25 classification of the Background Ranch Hand veteran group as it comprised a mixture of exposed

26 and unexposed individuals. However, it is hard to gauge whether any exposure misclassification

27 would be differential by the health endpoints that were examined.

28   For the most part, there were no associations between hematological measures and

29 TCDD exposure. As noted by the authors, the associations between TCDD and mean

30 corpuscular volume may not be causally related. It may be a spurious association due to the

31 influence of TCDD on triglycerides levels which in turn affect corpuscular volume, or be due to

1   an increased prevalence of liver impairment previously noted in the cohort (Grubbs et al., 1995).

2   The positive association between TCDD and platelet count cannot be attributed directly to

3   TCDD given that many health conditions, which were not controlled for in the analysis, may

4   have influenced platelet levels. Furthermore, the relationships identified are not supported by

5   other animal or epidemiological literature, making interpretation of the associations difficult.

6

7   **C.1.2.1.7.3.3.**   Suitability of data for TCDD dose-response modeling

8   There was no consistent association between TCDD serum levels and the hematological

9   measures of red and white blood cell counts, hemoglobin, hematocrit, and erythroctyes. While

10   corpuscular volume and platelet counts were both positively associated with TCDD levels at

11   multiple examinations, evaluations of the data did not determine whether increases in these

12   measures were due to TCDD exposure during the Vietnam War. These increases may be due to

13   noncausal associations from increased levels of triglycerides, or increased prevalence of mild

14   liver abnormalities among those with higher exposures (Grubbs et al., 1995), or the presence of

15   other comorbid health conditions that were not controlled for in the analysis. The findings of

16   associations that were small in magnitude between hematological function and TCDD likely

17   have little clinical relevance, but could provide some insight on biological mechanism of disease

18   from exposure to dioxin.

19   This study analyzes the potential for associations between point-in-time measures of

20   TCDD serum levels and changes in hematological measures that may have occurred at any time

21   over approximately a 30-year interval, which precludes estimation of an effective TCDD

22   exposure over time. EPA is uncertain whether TCDD-mediated changes in hematological

23   measures are the consequence of an elevated TCDD exposure event over a relatively short period

24   of exposure (during service) or chronic TCDD exposure over a longer window of time due to

25   slow TCDD elimination rates. Also, the long potential exposure window occurred during a time

26   period of decreasing background exposure to TCDD and DLCs (Lorber and Phillips, 2002) likely

27   decreasing the accuracy of the estimated exposure levels. Given the uncertainty in defining the

28   critical window of exposure and the inability to estimate an effective TCDD exposure over time,

29   quantitative dose-response analysis was not conducted for this study.

30

1   **C.1.2.1.7.4.** *__Michalek et al. (2001b) hepatic health outcomes__*

2   **C.1.2.1.7.4.1.**   Study summary

3   Michalek et al. (2001b) investigated the association between TCDD and the prevalence

4   of liver disease, and other indices of hepatic function in the Air Force Health Study. The study

5   population included both Ranch Hands, as well as a comparison group of veterans. A detailed

6   description of the study design and methods is provided in earlier sections, as well as the paper

7   by Wolfe et al. (1990).

8   This study relied on data collected at physical examinations conducted in 1982, 1985,

9   1987, and 1992. TCDD levels were estimated using serum collected in 1987, with some

10   additional samples taken in 1992 for those who lacked TCDD measurements. In total, TCDD

11   was assayed for 2,198 veterans. TCDD levels below the limit of detection were assigned a value

12   of 0 ppt. The study excluded veterans with no TCDD measure, those with TCDD levels above

13   the level of detection but below the level of quantification, and comparison subjects whose

14   TCDD levels exceeded 10 ppt serum lipid (threshold for background exposure). A first order

15   kinetics model with a constant half-life of 8.7 years was used to estimate the initial TCDD dose

16   at the end of the veterans' tours of duty in Southeast Asia. Veterans were classified into four

17   dioxin exposure groups: (i) Comparison cohort, (ii) Ranch Hand—Background (<10 ppt),

18   (iii) Ranch Hand—Low (10− ≤94 ppt), and (iv) Ranch Hand—High (>94 ppt).

19   At each examination, participants were asked whether (1) a physician had informed them

20   that they had an enlarged liver, cirrhosis, or other liver condition (2) a physician had determined

21   presence or absence of hepatomegaly by palpitation, or (3) the presence or absence of liver

22   function test abnormalities through laboratory examination. All self-reported cases of liver

23   disease were confirmed through verification of medical records through 1993. In 1992, several

24   indices of liver function were measured using serum. These include: alanine aminotransferase,

25   aspartate aminotransferase, γ-glutamyltransferase, lactic dehydrogenase, alkaline phosphatase,

26   and total bilirubin

27   Michalek et al. (2001b)conducted statistical analysis for the measures of liver function

28   collected during the 1992 examination, since they state that "the liver function test results for

29   1992 were not consistently different from those of previous examination." Mean values of liver

30   function were compared across the four categories of exposure using a linear model with a

31   log-transformation of liver function measures to enhance normality. An adjusted test for trend

1   was also applied to the restricted cohort of Ranch Hands veterans. All analysis was adjusted for

2   the history of liver disease, percentage of body fat, year of birth, race, military occupation,

3   lifetime industrial chemical exposure, lifetime degreasing chemical exposure, as well as life-time

4   smoking and alcohol consumption. Enlisted Ranch Hands who had served in the ground crew

5   were analyzed separately because this subgroup was found to have the highest TCDD exposure.

6   The numbers of veterans included in the analysis of liver function tests across Comparison,

7   Background, Low and High TCDD exposure groups were 1195, 398, 262, and 264, respectively.

8   Logistic regression was used to evaluate the association between TCDD exposure and the

9   prevalence of liver diseases. These analyses were done among those who volunteered for at least

10 one examination, with valid dioxin measures, and excluded those with a history of liver disease

11 before their service in Southeast Asia. The numbers of veterans included in the analysis of liver

12 disease prevalence across Comparison, Background, Low and High TCDD exposure groups was

13 1,266; 420; 284; and 283, respectively.

14   There was no association between TCDD exposure and hepatomegaly, or nonalcoholic

15 chronic liver disease (p-value linear test for trend=0.6). TCDD exposure was found to be

16 associated with other liver disorders. Compared to non-Ranch Hand veterans, the adjusted odds

17 ratio in the "high" exposure group was 1.6 (95% CI = 1.2−2.1). Laboratory measures associated

18 with these disorders were also found to be increased. An increased level(s) of transaminase or

19 lactate dehydrogenase was found in veterans in the "high" exposure group (OR = 2.7,

20 95% CI = 1.4−5.1), and a dose-response trend was noted across exposure categories ($p = 0.03$).

21 Additionally, an increased odds ratio for nonspecific liver abnormalities was found in the same

22 "high" exposure group (OR = 1.4, 95% CI = 1.0−2.0), while no association was noted for

23 hepatomegaly. There were no statistically significant dose-response trends between TCDD and

24 any of the mean hepatic measures (AST, ALT, GGT, LDH, Alkaline phosphatase, or total

25 bilirubin) based on the 1992 serum data, although p-values for tests of trends for alkaline

26 phosphatase and γ-glutamyltransferase (GGT) were 0.06. Statistically significant increases

27 ($p < 0.05$) in mean GGT levels were noted among those in the highest TCDD exposure group

28 relative to the comparison cohort. No consistent patterns were detected when results were

29 stratified by drinking history or current alcohol use, but GGT levels tended to increase across

30 current drinking levels,

31

C.1.2.1.7.4.2. Study evaluation

Strengths of this study include the high rate of participation, low attrition rate, appropriately matched comparison group, and the decade long follow-up period. Within some of the exposure categories, relatively few cohort members were diagnosed with several of the liver conditions following their tours of duty. For example, there were only 10 veterans in the high exposure group diagnosed with hepatomegaly, and only 5 diagnosed with nonalcoholic liver disease and cirrhosis. As such, the statistical power to detect some associations that may be present was limited.

C.1.2.1.7.4.3. Suitability of data for TCDD dose-response modeling

The results do not unequivocally support a relationship between liver damage and TCDD exposure. Confounding and reverse causality cannot be eliminated as possible explanations of the study results, and the clinical significance of the results (which were small in magnitude) is unclear. Additionally, there is uncertainty in determining the critical window of exposure. This study analyzes the potential for associations between point-in-time measures of TCDD serum levels and possible changes in hepatic measures that may have occurred at any time over approximately a 30-year interval. Thus, it is unclear whether the differences in serum enzyme levels and liver function measures potentially affected by TCDD exposures are the consequence of an elevated TCDD exposure event over a relatively short period of exposure (during service) or chronic TCDD exposure over a longer window of time due to slow TCDD elimination rates. Also, the long potential exposure window occurred during a time period of decreasing background exposure to TCDD and DLCs (Lorber and Phillips, 2002) further impeding the ability to estimate dose accurate. Considering the uncertainty in estimating the biologically relevant exposure window and the uncertainty in estimating peak exposures 20 years prior to measurement, a quantitative dose-response analysis was not conducted.

C.1.2.1.7.5. *Michalek et al. (2001c)—peripheral neuropathy*

C.1.2.1.7.5.1. Study summary

Michalek et al. (2001c) studied the relationship between TCDD exposure and peripheral neuropathy among veterans in the Air Force Health Study. The study included the Ranch Hands who were involved in the spraying of herbicides in Southeast Asia, as well as a comparison

1   cohort of veterans. The study population and design has been described earlier in this section,

2   and is detailed in the publication by Wolfe et al. (1990).

3   This study relied on data collected at physical examinations conducted in 1982, 1985,

4   1987, 1992 and 1997. TCDD levels were estimated using serum collected in 1987, with some

5   additional samples taken in 1992 for those who lacked measures. In total, TCDD was assayed

6   for 2,198 veterans. TCDD levels below the limit of detection were assigned a value of 0 ppt.

7   The study excluded veterans with no TCDD measure, those with TCDD levels above the level of

8   detection but below the level of quantification, and comparison subjects whose TCDD levels

9   exceeded 10 ppt serum lipid (i.e., the threshold for background exposure). A first-order kinetics

10 model with a constant half-life of 8.7 years was used to estimate the TCDD levels at the end of

11 the veterans' tours of duty in Southeast Asia. Veterans were classified into four dioxin exposure

12 groups: (i) Comparison cohort, (ii) Ranch Hand—Background (<10 ppt), (iii) Ranch

13 Hand—Low (10− ≤94 ppt), and (iv) Ranch Hand—High (>94 ppt).

14   Blinded neurological examinations were conducted on volunteers at each of the five

15 examinations by staff who were blinded to the veterans' exposure levels.   These neurological

16 examination included evaluations of cranial nerves, muscle strength in both lower and upper

17 limbs, sensory perception of pain, light touch, vibration, proprioception, activity of deep tendon

18 reflexes, stance, gait, hand and foot coordination, and tremor. Velocities of nerve conduction

19 were conducted in 1982, while vibrotactile thresholds of the left and right toes were measured in

20 1992 and 1997. The study excluded veterans with a history of neurological disorders prior to

21 their service in Southeast Asia. The analysis also excluded veterans with disorders that could

22 interfere with peripheral nerve assessments. These conditions included: quadriplegia, injuries or

23 amputations, and alcohol-related disorders. Diabetes status was also determined as described by

24 Longnecker and Michalek (2000). Michalek et al. (2001c) analyzed data using main effects

25 logistic and linear regression models. An adjusted test for trend was also applied. All measures

26 of association were adjusted for body mass index, year of birth, height, and alcohol consumption.

27 As in the Michalek et al. (2001b) study, enlisted Ranch Hands who had served in the ground

28 crew were analyzed separately. Diabetics and nondiabetics were also analyzed separately.

29 Furthermore, the data was analyzed in two rounds, with the second round excluding veterans

30 with neurologic conditions with known causes unrelated to dioxin exposure, which could impact

31 the neurological findings.

1   No association was observed between TCDD and nerve conduction velocities in 1982,

2   and there were no statistically significant associations found for 'any symmetrical peripheral

3   abnormalities' in 4 of the 5 examinations. However, based on the 1997 examination, those in the

4   highest exposure category had an increased risk of any symmetrical peripheral abnormality

5   (OR = 1.8, 95% CI = 1.2−2.7). These associations were stronger for 'probable' symmetrical

6   peripheral neuropathy than they were for those designated as possible. There was no evidence of

7   effect measure modification by diabetes status for TCDD associations with probable peripheral

8   neuropathy in the 1997. An interaction was found between diabetes status and current dioxin

9   exposure for diagnosed neuropathy in 1997. Additional restrictions excluding veterans with

10   diseases, disorders or other exposures that may have produced neuropathic symptoms resulted in

11   groups that were too small to further analyze.

12

13   **C.1.2.1.7.5.2.**   Study evaluation

14   The strengths of this study are the same as described for the Michalek et al. (2001a;

15   2001b) studies. Uncertainty in the critical window of exposure, as well as uncertainty in

16   exposure classification present in the Michalek et al. (2001b), are also weaknesses of this study.

17   The Michalek et al. (2001c) study attempts to characterize risks of neuropathy while accounting

18   for the possible modifying influence of diabetes. While the associations are strong, they are

19   limited by the relatively small number of cases in the "high" exposure group. Moreover,

20   associations were for the most part, confined to only one of the five examination intervals. A

21   large number of comparisons were conducted in this study using multiple measures of

22   neuropathy that were assessed at up to 5 examination periods. As a result, the multiple

23   comparisons performed increase the chance of detecting a false-positive association due to the

24   number of statistical hypothesis tests performed.

25

26   **C.1.2.1.7.5.3.**   Suitability of data for TCDD dose-response modeling

27   The dose-response relationship between TCDD exposure and peripheral neuropathy is

28   strong, and supported by several important strengths. However, associations were not consistent

29   across the different examinations, and further work is needed to evaluate the relationship

30   between diabetes and peripheral neuropathy in this cohort. Some comparisons are limited by a

31   small number of outcomes particularly in the highest exposure group. Additionally, there is

1 uncertainty in the critical window of exposure. This study analyzes the potential for associations

2 between peripheral neuropathy and point-in-time measures of TCDD serum levels that may have

3 occurred at any time over approximately a 30-year interval, making it difficult to calculate a

4 TCDD effective dose over time. Thus, it is unclear whether the peripheral neuropathies are the

5 consequence of an elevated TCDD exposure event over a relatively short period of exposure

6 (during service) or chronic TCDD exposure over a longer window of time due to slow TCDD

7 elimination rates. Also, the long potential exposure window occurred during a time period of

8 decreasing background exposure to TCDD and DLCs (Lorber and Phillips, 2002) further

9 impeding the ability to estimate dose accurately. For these reasons, a quantitative dose-response

10 analysis was not conducted for this study..

11

12 **C.1.2.1.7.6. *Pavuk et al. (2003) thyroid health endpoints***

13 **C.1.2.1.7.6.1.** Study summary

14 Pavuk et al. (2003) published an analysis that examined the effects of TCDD exposure on

15 thyroid function among veterans enrolled in the AFHS. A summary of the design of the AFHS

16 study and methods have been already described in this section, and are provided in greater detail

17 in the paper by Wolfe et al. (1990). This current study included both those involved with

18 Operation Ranch Hand, as well as a comparison cohort of other veterans who served in Southeast

19 Asia but who were not involved with spraying of herbicides. The objective of this study was to

20 examine associations between TCDD levels estimated in 1987 and several measures of thyroid

21 function, as well the incidence of six different thyroid diseases following the completion of the

22 veterans' tours of duty.

23 The study used data collected from medical examinations and self-reported

24 questionnaires completed in 1982, 1985, 1987, 1992, and 1997. TCDD levels were estimated

25 using serum collected in 1987, with some additional samples taken in 1992 and 1997 for those

26 who lacked measures. For those with serum measures taken in 1992 or 1997, a first order

27 kinetics model with a constant half-life of 8.7 years was used to extrapolate values to 1987.

28 Veterans were classified into four dioxin exposure groups: comparison cohort, Ranch Hand—

29 Background (<10 ppt), Ranch Hand—Low (10− ≤94 ppt), and Ranch Hand—High (>94 ppt).

30 Thyroid diseases that occurred following the veterans' tours of duty were identified

31 through self-report of physician diagnosis at any of the five physical examinations and verified

32 from medical records. The following conditions were considered: unspecified goiter, nontoxic

1 nodular goiter, thyrotoxicosis, acquired hypothyroidism, thyroiditis, and other disorders of the

2 thyroid. Congenital hypothyroidism was not examined as this condition would have prevented

3 individuals from entering the military. Serum samples were used to obtain measures of thyroid

4 function. Thyroxine (T4) and thyroid stimulating hormone (TSH) were estimated at each of the

5 five examinations, while triiodothyronine percent (T3%) was determined in 1982, 1985, and

6 1987. The free thyroxine index (FTI) was only estimated in 1982. Veterans who participated in

7 at least one examination, and who had a TCDD measurement were included unless they were

8 being treated with thyroid medication, had a previous thryroidectomy or irradiation, or were

9 diagnosed with a thyroid disease before their service had ended.

10   For each physical examination, cross-sectional analysis was performed to compare the

11 mean levels of TSH, T4, T3%, and FTI across the four TCDD exposure categories. A repeated

12 measures linear model was used to compare mean TSH, T4, and T3% values across exposure

13 categories using data from all five examinations combined. This model took into account the

14 repeated nature of the data by using an autoregressive order one covariance structure. Logistic

15 regression was used to estimate the OR of thyroid diseases across TCDD exposure categories, as

16 well as abnormally high TSH levels across the five examinations. These models were adjusted

17 for confounding by age, race, and military occupation.

18   No association was found between TCDD and any of the six thyroid diseases that were

19 examined. In four of the five examinations, higher TSH values were observed in the higher

20 TCDD exposure categories. A dose-response relationship was observed in the longitudinal

21 analyses of these data ($p = 0.002$). The ORs of an abnormally high TSH among the high

22 exposure Ranch Hand group ranged from 1.4 to 1.9 relative to the comparison group, but was not

23 statistically significant in any of the five examinations ($p > 0.05$). No significant associations

24 were reported with either the cross-sectional or longitudinal analyses of the total T4 levels

25 (mean), T3% uptake, or FTI.

26

27 **C.1.2.1.7.6.2.** Study evaluation

28   The overall size of the cohort was relatively large as analyses were based on 1,009 Ranch

29 Hands, and 1,429 comparison veterans. However, there were relatively few thyroid disorders

30 identified among these veterans following their tour of duty. Specifically, there were only

1   188 such veterans, and therefore, analyses of the relationship between these six different

2   disorders and the four categories of TCDD exposure was limited by statistical power.

3   Strengths of this study include the estimation of TCDD levels using serum, and the

4   consideration of several different outcome measures of thyroid disorders from questionnaire

5   data, as well as serum TSH, T3% uptake, T4, and FTI measurements. Thyroid function was

6   assessed multiple times using serum-based measures that are valid and widely used. While the

7   authors did not take into account the timing of disease onset for the thyroid conditions examined,

8   the serum-based measures of TCDD in 1987 allowed for veterans to be classified according to

9   exposure status prior to onset of disease. In particular, these exposure levels among the Ranch

10   Hands could be attributed to exposure received during their tours in Southeast Asia, and only

11   thyroid conditions that occurred following the tour of duty were considered.

12   There was no association found between serum-based measures of TCDD and any of the

13   six thyroid conditions examined (unspecified goiter, nodular goiter, hyperthyroidism, thyroiditis,

14   or other thyroid disease). The only thyroid measure that was associated with TCDD levels was

15   TSH. Higher levels of TSH were observed among those in the higher exposure categories, and a

16   dose-response relationship was observed when data across all examinations were modeled.

17   However, those in the highest exposure group did not have a statistically significant increased

18   risk of abnormal TSH levels irrespective of when the examination date. Taken together, the

19   findings suggest that TCDD may increase TSH levels which are a marker for an underactive

20   thyroid. Lower TSH levels over the long term may increase the risk of hypothyroidism, or

21   indicate thyroid hormone resistance. However, the clinical implications are unclear in light of

22   the absence of an association between TCDD and any of the six thyroid conditions that were

23   examined. As noted by the authors, this cohort may not yet be old enough to determine whether

24   TCDD exposure increases the risk of developing thyroid disease.

25

26   **C.1.2.1.7.6.3.**   Suitability of data for TCDD dose-response modeling

27   There was no association between TCDD exposure and any of the six thyroid diseases

28   that were examined. Further, there was no association between cross sectional or longitudinal

29   analyses of TCDD and T4, T3% uptake, or FTI. While a dose-response trend was observed with

30   TCDD and TSH levels, evidence of a statistically significant increase in abnormally high TSH

31   levels was not observed among veterans in the highest exposure group. Additionally, there is

1 uncertainty in the critical window of exposure. This study examined associations between

2 thyroid conditions and measures of thyroid disorders with point-in-time measures of TCDD

3 serum levels that may have occurred at any time over approximately a 30-year interval. As a

4 whole, these analyses do not support an association between TCDD exposure and comprised

5 thyroid function, and therefore, a quantitative dose-response analysis was not conducted for this

6 study.

7

8 **C.1.2.1.7.7. *Michalek and Pavuk (2008)—diabetes***

9 **C.1.2.1.7.7.1.** Study summary

10 Michalek and Pavuk (2008) examined both the incidence of cancer and the prevalence of

11 diabetes in the cohort of Ranch Hand workers exposed to TCDD. As noted previously, these

12 veterans were responsible for aerial spraying of Agent Orange in Vietnam between 1962 and

13 1971. Exposure to TCDD was estimated using serum collected from (1) participants in 1987 or

14 (2) participants in 1992, 1997, and 2002 for those who had no quantifiable TCDD result in 1987,

15 those who refused in 1987, and those subjects who were new to the study. Exposure to TCDD

16 was estimated using a first-order pharmacokinetic model with a half-life of 7.6 years and

17 provided an estimate of TCDD at the end of the tour of duty in Vietnam. Veterans were grouped

18 into four categories: comparison, background, low, and high. Diabetes was identified from

19 diagnoses during the post-Vietnam era from medical records. Overall, no differences were

20 shown in the RR of diabetes between the Ranch Hand unit and the reference group (RR = 1.21,

21 $p = 0.16$). Stratified analyses by days of spraying (<90 days, ≥90 days), however, revealed a

22 significant increase in risk of diabetes (RR = 1.32, $p = 0.04$) among those who sprayed for at

23 least 90 days. A dose-response relationship was also evident when $\log_{10}$TCDD was modeled in

24 the combined cohort. Also, stratification by calendar period showed a dose-response relationship

25 for those whose last year of service was during or before 1969.

26

27 **C.1.2.1.7.7.2.** Study evaluation

28 The Michalek and Pavuk (2008) study provides an opportunity to characterize risks of

29 diabetes as the study is not subject to some of the potential bias of case ascertainment based on

30 death certificates (D'Amico et al., 1999). The quality of the TCDD exposure estimates is good,

31 given that serum data were available at an individual-level basis for all Ranch Hand and

32 comparison veterans used in the cohort. However, there is significant uncertainty in the

1 biologically-relevant critical window of exposure. Also, the long lag between initial exposure

2 and sera measurements limits the estimation of peak exposures 20 years earlier.

3

4 **C.1.2.1.7.7.3.**   Suitability of data for TCDD dose-response modeling

5   The reported dose-response relationship between TCDD and diabetes in the Michalek

6 and Pavuk (2008) study is supported by study strengths, including the use of the individual-level

7 TCDD serum measures and the identification of diabetes through medical records. However, it

8 is unclear whether the diabetes cases are the consequence of an elevated TCDD exposure event

9 over a relatively short period of exposure (during service) or chronic TCDD exposure over a

10 longer window of time due to slow TCDD elimination rates. In addition, the long potential

11 exposure window occurred during a time period of decreasing background exposure to TCDD

12 and DLCs (Lorber and Phillips, 2002) further impedes the ability to estimate dose accurately.

13 For these reasons, a quantitative dose-response analysis was not conducted for this study.

14

15 **C.1.2.1.8.**   *Other noncancer studies of TCDD*

16 **C.1.2.1.8.1.**   *Ryan et al. (2002)—sex ratio*

17 **C.1.2.1.8.1.1.**   Study summary

18   Ryan et al. (2002) conducted an investigation on the sex ratio in offspring of pesticide

19 workers who were involved with the production of trichlorophenol and the herbicide 2,4,5-T in

20 Ufa, Bashkortostan, Russia. Ufa was the site of a state agrochemical plant that has been in

21 operation since the 1940s. Between 1961 and 1988, the plant employed more than 600 workers,

22 most in their early 20s. Females, however, accounted for about 15% of the workforce that

23 produced 2,4,5-T and 30% for 2,4,5-trichlorophenol.

24   Serum samples previously taken in 1992 among 60 men, women, and children from the

25 factory and city of Ufa showed TCDD exposures that were approximately 30 times higher than

26 background levels (Ryan and Schecter, 2000). Blood data were subsequently measured on a

27 sample of 20 workers between 1997 and 2000, and on 23 2,4,5-trichlorophenol workers between

28 1997 and 2001. In all, 84 individuals (67 men and 19 women) who provided blood samples

29 formed the basis of the analysis in this study. Of these, 55 (43 men and 12 women) were

30 exposed to 2,4,5-T and 29 (22 men and 7 women) were exposed to 2,4,5-trichlorophenol. There

31 is no indication on how the individuals that were asked to provide and those who did provide

1   serum samples were selected. Ryan et al. (2002) reviewed company records for these workers to

2   determine the number, sex, and date of birth of any children; birth data were available for

3   198 workers (150 men and 48 women). Awareness of the study led other workers who had not

4   provided serum to provide information on births that occurred 9 months after the time of first

5   employment in the factory.

6   The authors calculated descriptive statistics for the 198 workers and compared them to

7   values for the city of Ufa between 1959 and 1996. Tests of statistical significance were made

8   using the z-test, and the chi-square test. The observed proportion of male births (0.40) among

9   the factory workers was much lower than that for the city of Ufa (0.51) ($p < 0.001$). Stratified

10   analyses revealed that this lower ratio was observed only among those paternally exposed to

11   TCDD. Specifically, the proportion of male births among exposed fathers was 0.38 and among

12   exposed mothers was 0.51. This pattern was observed in both the workers exposed to 2,4,5-T

13   (proportion of male births = 0.40) and 2,4,5-trichlorophenol (proportion of male births = 0.35).

14

15   **C.1.2.1.8.1.2.**   Study evaluation

16   The Ryan et al. (2002) findings are consistent with earlier work completed for Seveso

17   residents (Mocarelli et al., 2000). Although individual-level serum measures were available for

18   84 individuals, exposure-response relationships with birth ratios were not performed on these

19   data. This approach would have been preferred and consistent with that which Mocarelli et al.

20   (2000) used. All comparisons were made using an external comparison group, namely the sex

21   ratio observed in Ufa between 1959 and 1996.

22   Although serum measures were used to describe TCDD exposure for a sample of the

23   workers (selection criteria for these workers was not provided), individual-level dose estimates

24   were not calculated for the study population. Specifically, exposures were characterized many

25   years after exposure, and no attempt was made to back-extrapolate to the time of conception.

26   The two groups of workers in the study also reportedly had high exposure levels of

27   1,2,3,7,8-pentachlorodibenzo-*p*-dioxin. So, the group level exposure classification (by plant) did

28   not allow consideration of potential confounding due to other DLCs. Another limitation of the

29   study is that the study population is likely nonrepresentative of all workers employed at the plant.

30   Participants included only those willing to provide serum samples and those who volunteered to

1   participate in the study after learning about it in a public forum. If participation was dependent

2   on TCDD exposures and the reproductive health of these subjects, then bias may have occurred.

3

4   **C.1.2.1.8.1.3.**   Suitability of data for TCDD dose-response modeling

5   The findings are notable in their consistency with those found in Seveso residents by

6   Mocarelli et al. (2000). For the Ryan et al. (2002) study, serum data were quantified at an

7   individual-level basis. Risk estimates, however, were not derived in relation to these exposures

8   but instead in two separate subgroups (2,4,5-T and 2,4,5-trichlorophenol workers). Because of

9   this important limitation and the uncertainty in the biologically-relevant critical window of

10   exposure, a quantitative dose-response analysis was not conducted for this study.

11

12   **C.1.2.1.8.2.**   *__Kang et al.(2001)—long-term health effects__*

13   **C.1.2.1.8.2.1.**   Study summary

14   Kang et al. (2001) investigated the relationship between self-reported health measures

15   and serum-based measures of TCDD in a group of 1,499 Vietnam veterans and a control group

16   of 1,428 non-Vietnam veterans. The study subjects were identified from (1) reports of Army

17   Chemical Corps detachments in Vietnam between 1966 and 1971, (2) personnel records of

18   individuals involved in chemical operations who were on active duty between 1971 and 1974,

19   and (3) class rosters of personnel who were trained at Fort McClellan in Alabama between 1965

20   and 1973. The comparison group was selected so that branch of service, time period, and

21   military occupation were similar to those of the subjects with the exception that they did not

22   serve in Vietnam. Although 2,872 Vietnam veterans and 2,732 non-Vietnam veterans were

23   identified as potential subjects, those who were deceased as of December 1998 and those who

24   had previously participated in a pilot study were excluded. The study targeted 2,247 Vietnam

25   and 2,242 non-Vietnam veterans.

26   Exposure to TCDD was characterized for subsets of the study population that provided

27   blood samples, specifically 795 of 1,085 (73%) Vietnam veterans and 102 of 157 (65%)

28   non-Vietnam veterans. Details on these individuals selected for participation in the serum dioxin

29   study were not presented. The authors did state, however, that due to economic constraints, only

30   897 serum samples could be analyzed. Blood specimens were collected in 1999–2000 at

1   individuals' homes. TCDD concentrations were analyzed by laboratory staff blind to the group

2   status (i.e., Vietnam or non-Vietnam) of the study subjects.

3   Prevalent health outcomes were ascertained by self-reported information on selected

4   conditions diagnosed by a medical doctor. The following conditions were included: diabetes,

5   hepatitis (all types combined), heart disease, all cancer, nonmalignant chronic respiratory

6   diseases, and hypertension. Health-related quality of life was evaluated using the SF-36 survey

7   instrument ([Ware et al., 1993](#)).

8   Eligible veterans whose current residences (4,119 total) could be identified were

9   contacted for study participation. Survey participation rates were 73% for Vietnam veterans,

10 yielding data for 1,499 individuals, and 69% for non-Vietnam veterans, yielding data for

11 1,428 non-Vietnam veterans. The survey data showed that, relative to non-Vietnam veterans,

12 Vietnam veterans were more likely to be regular smokers and to be obese. They also were more

13 likely to be enlisted personnel, and a much higher proportion was 51 years of age or older (83%

14 vs. 58%). After adjusting for age, race, smoking status, rank, and body mass index, the

15 prevalence of self-reported health conditions was found to be statistically significantly higher in

16 the Vietnam group. The adjusted ORs were as follows: diabetes, OR = 1.16 (95% CI = 0.91,

17 1.49); hepatitis, OR = 1.85 (95% CI = 1.30, 2.64); heart condition, OR = 1.09 (95% CI = 0.87,

18 1.38); all cancer, OR = 1.46 (95% CI = 1.02, 2.10); nonmalignant respiratory condition,

19 OR = 1.41 (95% CI = 1.13, 1.76); and hypertension, OR = 1.06 (95% CI = 0.89, 1.27).

20   For those with Vietnam service, the mean serum TCDD concentrations were higher

21 among those who reported spraying herbicides (4.3 ppt) than those who did not (2.7 ppt)

22 ($p < 0.001$). The investigators did not back-extrapolate serum levels to the time when

23 individuals last sprayed. The adjusted ORs (adjusted for age, cigarette smoking, body mass

24 index, rank, and race) for most chronic health conditions examined revealed increased

25 prevalence among Vietnam sprayers relative to non-Vietnam sprayers. These ORs included:

26 diabetes, OR = 1.49 (95% CI = 1.10, 2.02); hepatitis, OR = 1.40 (95% CI = 0.92, 2.12); heart

27 condition, OR = 1.41 (95% CI = 1.06, 1.89); all cancer, OR = 1.36 (95% CI = 0.91, 2.04);

28 nonmalignant respiratory condition, OR = 1.57 (95% CI = 1.20, 2.07); and hypertension,

29 OR = 1.26 (95% CI = 1.00, 1.58).

30   The investigators also examined the possibility of over-reporting of chronic health

31 conditions by comparing the prevalence of self-reported conditions among 357 Vietnam sprayers

1   who mean serum TCDD levels of 2.5 ppt compared to those who had levels less than 2.5 ppt.

2   Prevalence of diabetes, heart condition, and hypertension, was higher among those with mean

3   serum TCDD levels of 2.5 ppt, although no levels of statistical significance were reported. Data

4   for cancer were not presented.

5

6   **C.1.2.1.8.2.2.**   Study evaluation

7   Data were collected from only half of the individuals in the study target population, so

8   there is some potential for selection bias in this study. First, the study excluded those who had

9   died before 1999, excluding potentially important TCDD-related adverse health effects that

10   could result in death more than two decades after veterans had been actively spraying. Survey

11   participation rates were 73% for Vietnam veterans and 69% for non-Vietnam veterans. If those

12   in poorer health were less inclined to participate, the prevalence of the selected chronic health

13   conditions would be understated. Selection bias due to study participation could also be possible

14   if, for example, those in poorer health also had higher (or lower) exposures than those not

15   participating in the study. The lack of direct evidence of differential participation and reports of

16   comparable prevalence rates of hypertension and diabetes to other general populations suggests

17   that selection bias may be minimal.

18   Because the data collected are cross-sectional, they are not well suited for evaluating the

19   relationship between the timing of exposure and the onset of disease. Whether any of the data

20   could help identify when the chronic health conditions were diagnosed is unclear. Given the

21   long period covered by the study, many of the self-reported health conditions likely were

22   diagnosed some time ago, perhaps closer to the time of potential TCDD exposure. Such detail is

23   needed to characterize health risks associated with specific TCDD levels, particularly given that

24   TCDD levels have been demonstrated to decrease from time of last exposure.

25   An important strength of the study is the availability of blood sera for a subset of the

26   study population, which allows for individual-level estimates of TCDD exposure. Serum TCDD

27   levels were available for only 897 subjects, however, which limits the ability to examine the

28   relationship between measures of TCDD and prevalence of health outcomes without restricting

29   the sample size or extrapolating exposure levels to the whole study population. For example,

30   among sprayers with available TCDD exposure data only 60 cases of diabetes and 69 cases of

31   heart disease were examined relative to exposure. Also, the small number of cancers precluded a

1   site-specific cancer analysis. Moreover, whether these TCDD levels are representative of the

2   larger eligible population is difficult to gauge, given that deceased veterans and those whose

3   current residences could not be determined were excluded.

4   The study relied on self-reported measures of disease prevalence. The ascertainment of

5   chronic health conditions using self-reported data can be fraught with difficulties. For example,

6   the sensitivity of self-reported data when compared to medical diagnosis has been shown to be

7   poor for conditions such as diabetes and hypertension (Okura et al., 2004). As Kang et al. (2006)

8   state, prevalence studies are not be well suited to examine rare diseases with short survival times

9   such as cancer. In addition, self-report of physician-diagnosed cancers by study subjects often

10   lacks the sensitivity needed in most epidemiological studies as they can be influenced by a

11   variety of factors including age and education (Navarro et al., 2006).

12   The potential for biases in the reporting of health outcomes between the sprayers and the

13   non-Vietnam veterans (i.e., differential by TCDD exposure status) is plausible, given the public

14   attention that spraying of Agent Orange has received. Although the authors examined whether

15   over-reporting was related to outcome prevalence among herbicide sprayers (prior to collection

16   and determination of actual TCDD serum levels), the possibility exists that these subjects

17   reporting could be influenced by their perceived level of exposure from herbicide spraying. The

18   authors also examined the potential for misreported diabetes by conducting a medical records

19   review of 362 veterans. Seventy-nine percent of the self-reported diabetes cases were confirmed

20   with medical records. The documentation rate was also comparable between the Vietnam

21   veterans and the non-Vietnam veterans suggesting that differential reporting was not an issue for

22   this health outcome.

23   Because the Vietnam veterans group comprised professional sprayers, it is not

24   unreasonable to assume that they would have been exposed to other potentially harmful agents

25   either during their service in Vietnam, or from the end of their service to when they provided

26   data in 1999–2000. This study did not control for other, potentially relevant occupational

27   exposures.

28

29   **C.1.2.1.8.2.3.** Suitability of data for TCDD dose-response modeling

30   Although the study demonstrates increased prevalence of several chronic health

31   conditions, these findings should be interpreted with caution due to the potential for selection

1   and recall biases. Because of the lack of demonstrated dose-response relationships with cancer

2   or other outcomes and uncertainty in the biologically-relevant critical exposure window, a

3   quantitative dose-response analysis was not conducted for this study.

4

5   **C.1.2.1.8.3. *McBride et al. (2009a) —noncancer mortality***

6   **C.1.2.1.8.3.1.** Study summary

7   The McBride et al. (2009a) mortality study of New Zealand workers employed as

8   producer or sprayers with potential exposure to TCDD was described earlier in this report.

9   These individuals were employed at a plant that manufactured 2,4,-dichlorophenoxyacetic acid,

10 and later 2,4,5-T and 4-chloro-2-methyphenoxyacetic acid. In 1987, the plant closed and 2,4,5-T

11 production ceased in 1988.

12   The cohort consisted of 1,754 individuals who were employed for at least one day at the

13 New Plymouth site between January 1, 1969, and October 1, 2003. Vital status was determined

14 until the end of 2004, and 247 deaths occurred during this time period. Comparisons of mortality

15 were made to the New Zealand general population. Exposure was characterized by duration of

16 employment. Person-years of follow-up were tabulated across strata defined by age, calendar

17 period, duration of employment, sex, latency, and period of hire. Analyses were stratified to

18 compare risks by duration of employment (<3 or ≥3 months), latency (<15 or ≥15 years), and

19 period of hire (<1976 or ≥1976).

20   Overall, no statistically significant differences in all-cause mortality relative to the

21 general population were found among those who worked for at least 3 months (SMR = 0.92,

22 95% CI = 0.80−1.06) or for less than 3 months (SMR = 1.23, 95% CI = 0.91−1.62). No

23 statistically significant excesses were found for mortality from diabetes, cerebrovascular disease,

24 heart disease, or accidents. The incorporation of a latency period of 15 years revealed no

25 statistically significant excesses for these same causes of death. Similarly, no excesses for any

26 cause of death were noted among those who were hired either before or after 1976.

27   In subsequent analyses of the same cohort that used estimated TCDD levels from serum

28 samples, McBride et al. (2009b) found no excesses for all-cause mortality or mortality from

29 diabetes or heart disease.

30

1 **C.1.2.1.8.3.2.** Study evaluation

2   For the McBride et al. (2009a) study, the size of the cohort is large enough to characterize

3 mortality risks relative to the general population for most common causes of deaths. An

4 important limitation of this study is the loss to follow-up of a substantial percentage of workers

5 (22%). This would have impacted statistical power by reducing the number of deaths among the

6 workers. If this incomplete ascertainment of mortality outcomes did not occur in a similar

7 fashion with the general population then the results may also be biased.

8   For noncancer causes of death, the use of the SMR statistic is more likely to be

9 influenced by the healthy-worker effect. Therefore, the findings obtained for these outcomes

10 should be interpreted with caution. Subsequent analyses published by the same authors

11 (McBride et al., 2009a) provide improved characterization of TCDD exposure using serum

12 samples.

13

14 **C.1.2.1.8.3.3.** Suitability of data for dose-response analysis

15   Overall, no associations were evident between surrogate measures of TCDD (duration of

16 employment, year of hire) and noncancer mortality outcomes. As all outcomes were based on

17 mortality, dose-response modeling was not conducted for this study.

18

19 **C.1.2.1.8.4.** *McBride et al. (2009b)—noncancer mortality*

20 **C.1.2.1.8.4.1.** Study summary

21   McBride et al. (2009b) further analyzed the cohort of New Zealand workers to include

22 estimates of TCDD exposure based on serum samples. Current and former employees who were

23 still alive and living within 75 km of the site were asked to provide serum samples. Samples

24 were collected from 346 workers representing 22% (346/1599) of the entire study population.

25 These serum measures were used to estimate cumulative TCDD levels for all workers. The

26 exposure assessment approach by Flesch-Janys et al. (1996) was used to estimate time-dependent

27 exposures based on area under the curve models. This was based on a one-compartment

28 first-order kinetic model with a half-life of 7.2 years.

29   Comparisons of mortality were made to the general population using the SMR. The Cox

30 proportional hazards model was used to conduct an internal cohort analysis across

31 four categories of cumulative TCDD levels for diabetes and ischemic heart disease mortality.

1   The RRs generated from these models were adjusted for sex, hire year, and birth year. No

2   diabetes deaths were observed among women, and therefore, analysis of this outcome was

3   limited to men.

4   Relative to the general population, no difference in the all-cause mortality experience was

5   observed in exposed cohort members (SMR = 1.0, 95% CI = 0.9−1.2). Similarly, no excess in

6   these workers was observed for heart disease (SMR = 1.1, 95% CI = 0.9−1.5); cerebrovascular

7   disease (SMR = 1.1, 95% CI = 0.6−1.9); diabetes (SMR = 0.7, 95% CI = 0.2−2.2); or

8   nonmalignant respiratory disease (SMR = 0.8, 95% CI = 0.4−1.4). For the internal cohort

9   analysis, the RR associated with cumulative categorical TCDD measure was 1.0 for both

10   diabetes and ischemic heart disease.

11

12   **C.1.2.1.8.4.2.**   Study evaluation

13   The McBride et al. (2009b) study extends their earlier work in two ways. First, serum

14   measures were used to estimate cumulative TCDD with methodology that has been applied to

15   several other cohorts of workers exposed to TCDD. Second, they used regression analyses that

16   examined individual-level TCDD exposures in relation to various outcomes as part of the

17   internal cohort comparisons. For noncancer outcomes, no dose-response associations with

18   TCDD were observed with the internal comparisons. Also, as found with earlier analyses of this

19   same cohort, no excess noncancer mortality relative to the New Zealand general population was

20   observed.

21   Associations between TCDD and diabetes have been found previously in TCDD-exposed

22   populations, most notably in the Ranch Hands cohort (Michalek and Pavuk, 2008). In this

23   cohort, only five deaths from diabetes were identified, and of these, only three occurred among

24   those who were exposed to TCDD. The study, therefore, has limited statistical power to

25   characterize associations between TCDD and mortality from diabetes. Further, the identification

26   of diabetes deaths is subject to misclassification errors due to under-reporting (McEwen et al.,

27   2006).

28

1   **C.1.2.1.8.4.3.**   Suitability of data for TCDD dose-response modeling

2   McBride et al. (2009b) found no statistically significant associations in any of the

3 noncancer causes of death. As all outcomes were based on mortality, dose-response modeling

4 was not conducted for this study.

5

6   **C.1.2.2.** *Feasibility of Dose-Response Modeling for Noncancer*

7   Relatively few study populations permit quantitative dose-response modeling to be

8 performed for noncancer outcomes. The serum collected among Seveso men and women

9 provide an opportunity to characterize risks for several health conditions in relation to TCDD

10 exposure. The collection of these serum samples, shortly after the accident does not require the

11 back-extrapolation of TCDD levels as in the occupational cohorts, which should reduce the

12 exposure assessment uncertainty and minimize the potential for exposure misclassification.

13   An added feature of the SWHS is the detailed collection of other risk factor data from

14 trained interviewers. These data allow for risk estimates to be adjusted for potential confounding

15 variables. For the evaluations of reproductive health outcomes, this adjustment is critical given

16 there are various documented risk factors for the different outcomes that were examined. For

17 some health outcomes, continued follow-up of the cohort is needed, given that several of the

18 Seveso studies suggest that those exposed at a very young age might be more susceptible to

19 subsequent adverse health effects.

20   The findings of positive associations and dose-response relationships with serum-based

21 measures of TCDD suggest several noncancer health outcomes could be associated with TCDD

22 exposure. These health outcomes include neonatal thyroid function, sex ratio, diabetes, and

23 semen quality. Although findings have suggested an association between TCDD and age at

24 menopause, they were not statistically significant and no dose-response trend was observed.

25 Weak or nonstatistically significant associations have been noted for endometriosis and

26 menstrual cycle characteristics and do not support quantitative dose-response analyses.

27   Associations between TCDD exposure and cardiovascular disease have been noted in

28 some, but not all, of the occupational cohorts, and also shortly after the accident among Seveso

29 residents. Findings from the cohort studies based on external comparisons using the SMR

30 statistic should be interpreted cautiously due to potential bias from the healthy worker effect.

31 Because the magnitude of the healthy worker bias is recognized to be larger for cardiovascular

1 diseases than for cancer outcomes, risk estimates in some occupational cohorts might be

2 underestimated for cardiovascular outcomes. Information on cardiovascular risk factors

3 generally was not captured in these studies, and sensitivity analyses were generally designed to

4 examine risk estimates generated for cancer outcomes.

5

6 **C.1.2.3.** *Summary of Epidemiologic Noncancer Study Evaluations for Dose-Response*
7   *Modeling*

8   All epidemiologic noncancer studies summarized above were evaluated for suitability of

9 quantitative dose-response assessment using the TCDD-specific considerations and study

10 inclusion criteria. The results of this evaluation are summarized in a matrix style array (see

11 Table C-3). The key epidemiologic noncancer studies suitable for further TCDD dose-response

12 assessment are presented in Table 2-2 in Section 2 of this document.

13

Table C-1. Summary of epidemiological cancer studies (key characteristics)

Publication	Length of follow-up	Latency period	Half-life for TCDD	Fraction of TEQs accounted for by TCDD
NIOSH Cohort				
Fingerhut et al. (1991a)	1942−1987	0, 20 years	N/A	N/A
Steenland et al. (1999)	1942−1993	0, 15 years	N/A	N/A
Steenland et al. (2001b)	1942−1993	0, 15 years	8.7 years (Michalek et al., 1996)	TCDD accounted for all occupational TEQ; 10% of background
Cheng et al. (2006)	1942−1993	0, 10, 15 years	8.7 years (Michalek et al., 1996), and CADM (Aylward et al., 2005a)	N/A
Collins et al. (2009)	1942−2003	None	7.2 years (Flesch-Janys et al., 1996)	N/A
BASF Cohort				
Thiess et al. (1982)	1953−1980	None	N/A	N/A
Zober et al. (1990)	1953−1987	Years since first exposure: 0−9, 10−19, and 20+	N/A	N/A
Ott and Zober (1996a)	1953−1991	None	5.8 years	N/A
Hamburg Cohort				
Manz et al. (1991)	1952−1989	None, used duration of employment (<20, >20 years)	N/A	N/A
Flesch-Janys et al. (1995)	1952−1992	None	7.2 years Flesch-Janys et al. (1994)	Mean TEQ without TCDD was 155 ng/kg; mean TEQ with TCDD was 296.5 ng/kg
Flesch-Janys et al. (1998)	1952−1992	None	7.2 years Flesch-Janys et al. (1996), also used decay rates that were function of age and fat composition	Mean concentration of TCDD was 101.3 ng/kg; for TEQ (without TCDD) mean exposure was 89.3 ng/kg
Becher et al. (1998)	1952−1992	0, 5, 10, 15 and 20 years	7.2 years Flesch-Janys et al. (1996) took into account age and fat composition	Not described

Table C-1. Summary of epidemiological cancer studies (key characteristics) (continued)

Publication	Length of follow-up	Latency period	Half-life for TCDD	Fraction of TEQs accounted for by TCDD
Seveso Cohort				
Bertazzi et al. (2001)	1976−1996	Periods postexposure: 0, 0−4, 5−9, 10−14, 15−19 years	N/A	N/A
Warner et al. (2002)	1976−1998	None	8 years (Pirkle et al., 1989)	N/A
Pesatori et al. (2003)	1976−1996	Period postexposure: 20 years	N/A	N/A
Baccarelli et al. (2006)	1976−1998	Period postexposure: 22 years	N/A	N/A
Consonni et al. (2008)	1976−2001	Periods postexposure: 0, 0−4, 5−9, 10−14, 15−19, 20−24 years	N/A	N/A
Chapaevsk Cohort				
Revich et al. (2001)	Cross-sectional study (1995−1998)	N/A	N/A	N/A
Ranch Hand Cohort				
Akhtar et al. (2004)	1962−1999	None	N/A	N/A
Michalek and Pavuk (2008)	1962−2004	None, but stratified by period of service	7.6 years	N/A
New Zealand Cohort				
t'Mannetje et al. (2005)	1969−2000 (herbicide producers); 1973−2000 (herbicide sprayers)	N/A	N/A	N/A
McBride (2009b)	1969−2004	None	N/A	N/A

Table C-1. Summary of epidemiological cancer studies (key characteristics) (continued)

Publication	Length of follow-up	Latency period	Half-life for TCDD	Fraction of TEQs accounted for by TCDD
McBride et al. (2009b)	1969−2004	None	7 years	N/A
Dutch Cohort				
Hooiveld et al. (1998)	1955−1991	Postexposure periods: 0−19 years, >19 years	7.1 years	N/A

Table C-2. Epidemiological cancer study selection considerations and criteria

Cancer	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect,	Individual-level exposures	Study size and follow-up adequate	Published in peer-reviewed literature.	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
	Considerations					**Criteria**			**Y/N**
NIOSH Cohort									
Fingerhut et al. (1991a) all cancer sites, site-specific analyses	√	X	X	X	√	√	X	√	N
Steenland et al. (1999) all cancer sites combined, site-specific analyses	√	√	√	√	√	√	√	√	N[a]
Steenland et al. (2001b) all cancer sites combined	√	√	√	√	√	√	√	√	Y
Cheng et al. (2006) all cancer sites combined	√	√	√	√	√	√	√	√	Y
Collins et al. (2009) all cancer sites combined, site-specific analyses	√	√	√	√	√	√	√	√	Y
BASF Cohort									
Thiess et al. (1982) all cancer sites combined, site-specific analyses	√	X	X	X	X	√	X	X	N

Table C-2. Epidemiological cancer study selection considerations and criteria (continued)									
	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect,	Individual-level exposures	Study size and follow-up adequate	Published in peer-reviewed literature.	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
Cancer	Considerations					Criteria			Y/N
BASF Cohort (continued)									
Zober et al. (1990) all cancer sites combined, site-specific analyses	√	√	X	X	X	√	X	X	N
Ott and Zober (1996a) all cancer sites combined	√	√	√	√	√	√	√	√	Y
Hamburg Cohort									
Manz et al. (1991) all cancer sites combines, site-specific analyses	√	√	√	√	√	√	X	√	N
Flesch-Janys et al. (1995) all cancer sites combined	√	√	√	√	√	√	√	X	N
Flesch-Janys et al. (1998) all cancer sites combined, site-specific analyses	√	√	√	√	√	√	√	√	N[b]
Becher et al. (1998) all cancer sites combined	√	√	√	√	√	√	√	√	Y
Seveso Cohort									
Bertazzi et al. (2001) all cancer sites combined, site-specific analyses	√	√	√	X	√	√	X	X	N
Pesatori et al. (2003) all cancer sites combined, site-specific analyses	√	√	X	X	√	√	X	X	N

Table C-2. Epidemiological cancer study selection considerations and criteria (continued)									
	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect,	Individual-level exposures	Study size and follow-up adequate	Published in peer-reviewed literature.	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
Cancer	**Considerations**					**Criteria**			**Y/N**
Consonni et al. (2008) all cancer sites combined, site-specific analyses	√	√	√	X	√	√	X	X	N
Seveso Cohort–Women's Health Study									
Baccarelli et al. (2006) site specific analysis	√	√	X	√	√	√	√	√	N[c]
Warner et al. (2002) breast cancer incidence	√	√	√	√	√	√	√	√	Y
Chapaevsk Cohort									
Revich et al. (2001) all cancer sites combined, site-specific analyses	X	X	X	X	√	√	X	X	N
Ranch Hands Cohort									
Akhtar et al. (2004) all cancer sites combined, site-specific analyses	√	√	√	√	√	√	√	√	Y
Michalek and Pavuk (2008) all cancer sites combined	√	√	√	√	√	√	√	√	Y
Dutch Cohort									
Hooiveld et al. (1998) all cancer sites combined, site-specific analyses	√	X	√	√	X	√	√	X	N

Table C-2. Epidemiological cancer study selection considerations and criteria (continued)									
	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect,	Individual-level exposures	Study size and follow-up adequate	Published in peer-reviewed literature.	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
Cancer	Considerations					Criteria			Y/N
New Zealand Cohort									
t'Mannetje et al. (2005) all cancer sites combined, site-specific analyses	√	X	√	√	√	√	X	X	N
McBride et al. (2009a) all cancer sites combined, site-specific analyses	√	X	X	√	X	√	X	X	N
McBride et al. (2009b) all cancer sites combined, site-specific analyses	√	√	X	√	√	√	√	X	N

[a]This study has been superseded and updated by Steenland et al. (2001b).
[b]Becher et al. (1998)) assessed this same cohort taking cancer latency into account, thereby superseding this study.
[c]It is unknown whether the frequency of t(14;18)translocations in lymphocytes relates specifically to an increased risk of non-Hodgkin lymphoma. Given this lack of obvious adverse effect, dose-response analyses for this outcome were not conducted.

√ = Consideration/criterion satisfied; X = Consideration/criterion not satisfied.

Table C-3. Epidemiological noncancer study selection considerations and criteria

	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect	Individual-level exposures	Study size and follow-up adequate		Published in peer-reviewed literature	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
Noncancer			**Considerations**					**Criteria**		**Y/N**
NIOSH Cohort										
Steenland et al. (1999) mortality (noncancer) -ischemic heart disease	√	X	√	√	√		√	√	X	N
Collins et al. (2009) mortality (noncancer)	√	√	X	√	√		√	√	X	N
BASF Cohort										
Ott and Zober (1996a) mortality (noncancer)	√	√	X	√	√		√	√	X	N
Hamburg Cohort										
Flesch-Janys et al. (1995) mortality (noncancer)	√	√	√	√	√		√	√	X	N
Seveso Cohort–Women's Health Study										
Eskenazi et al. (2002b) menstrual cycle characteristics	√	√	√	√	√		√	√	√	Y
Eskenazi et al. (2002a) endometriosis	√	√	X	√	X		√	√	X	N

Table C-3. Epidemiological noncancer study selection considerations and criteria (continued)									
	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect	Individual-level exposures	Study size and follow-up adequate	Published in peer-reviewed literature	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
Noncancer	**Considerations**					**Criteria**			**Y/N**
Seveso Cohort–Women's Health Study (continued)									
Eskenazi et al. (2003) birth outcomes	X	X	X	√	√	√	√	X	N
Warner et al. (2004) age at menarche	√	√	X	√	√	√	√	√	Na
Eskenazi et al. (2005) age at menopause	√	√	X	√	√	√	√	X	N
Warner et al. (2007) ovarian function	√	√	X	√	√	√	√	X	N
Eskenazi et al. (2007) uterine leiomyoma	√	√	√	√	√	√	√	X	N
Seveso Cohort–Other Studies									
Bertazzi et al. (2001) mortality (noncancer)	√	√	X	X	√	√	X	X	N
Consonni et al. (2008) mortality (noncancer)	√	√	X	X	√	√	X	X	N

Table C-3. Epidemiological noncancer study selection considerations and criteria (continued)										
	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect	Individual-level exposures	Study size and follow-up adequate		Published in peer-reviewed literature	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
Noncancer	**Considerations**						**Criteria**			**Y/N**
Seveso Cohort–Other Studies (continued)										
Mocarelli et al. (2000) sex ratio	√	√	√	√	√		√	√	X	N
Baccarelli et al. (2004; 2002) immunological effects	√	√	X	√	√		√	√	X	N
Landi et al. (2003) gene expression	√	√	X	√	X		√	X	X	N
Alaluusua et al. (2004) developmental dental defects	√	√	√	√	√		√	√	√	Y
Baccarelli et al. (2005) chloracne	√	√	√	√	√		√	√	√	N[b]
Baccarelli et al. (2008) neonatal thyroid function	√	√	√	√	√		√	√	√	Y
Mocarelli et al. (2008) semen quality	√	√	√	√	√		√	√	√	Y
Chapaevsk Study										
Revich et al. (2001) mortality (noncancer) and reproductive health	X	X	X	X	√		√	X	X	N
Ranch Hands Cohort										
Henriksen et al. (1997) diabetes	√	X	√	√	√		√	√	X	N

Table C-3. Epidemiological noncancer study selection considerations and criteria (continued)									
	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect	Individual-level exposures	Study size and follow-up adequate	Published in peer-reviewed literature	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
Noncancer	**Considerations**					**Criteria**			**Y/N**
Longnecker and Michalek (2000) diabetes	√	X	√	X	√	√	√	X	N
Michalek et al. (2001a) hematological effects	√	X	X	√	√	√	√	X	N
Michalek et al. (2001b) hepatic abnormalities	√	X	√	√	√	√	√	X	N
Ranch Hands Cohort (continued)									
Michalek et al. (2001c) peripheral neuropathy	√	X	√	√	X	√	√	X	N
Pavuk et al. (2003) thyroid function and disorders	√	√	X	√	X	√	√	X	N
Michalek and Pavuk (2008) diabetes	√	√	√	√	√	√	√	X	N
Ufa Cohort									
Ryan et al. (2002) sex ratio	X	X	X	X	√	X	X	X	N
Vietnam Veterans Cohort									
Kang et al. (2001) long-term health consequences	X	X	X	√	√	√	X	X	N
New Zealand Cohort									
McBride et al. (2009b) mortality (noncancer)	√	√	X	√	X	√	√	X	N
McBride et al. (2009a)									

Table C-3. Epidemiological noncancer study selection considerations and criteria (continued)									
	Methods clear and unbiased	Risk estimates not susceptible to biases	Association between TCDD and adverse health effect	Individual-level exposures	Study size and follow-up adequate	Published in peer-reviewed literature	Exposure primarily to TCDD	Effective exposure estimable	Pass for dose-response analyses?
Noncancer	**Considerations**						**Criteria**		**Y/N**
mortality (noncancer)	√	X	X	√	√	√	X	X	N

Table C-3. Epidemiological noncancer study selection considerations and criteria (continued)

[a]EPA cannot assess the biological significance of this finding and cannot establish a LOAEL for this effect.
[b]Chloracne is considered to be an outcome associated with high TCDD exposures; thus this study was not considered further in RfD derivation.
√ = Consideration/criterion satisfied. X = Consideration/criterion not satisfied.

C.2. EVALUATION TABLES FOR CANCER STUDIES

C.2.1. National Institute for Occupational Safety and Health (NIOSH) Cohort Studies

Table C-4. Fingerhut et al. (1991a)—All cancer sites, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The data sources to ascertain vital status and cause of death information were the Social Security death files, the National Death Index, and the Internal Revenue Service. Vital status could be determined for 98% of the cohort.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. While the authors provide compelling arguments that suggest risks are not unduly biased by lack of cigarette smoking data, they acknowledge potential biases that could exist for other occupational exposure (e.g., asbestos) for which data were lacking.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. There was not a statistically significant linear trend of increasing mortality with increased duration of exposure.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. This study used duration of exposure, at an individual level, as a surrogate measure of TCDD. Duration of exposure determined by number of years workers were involved in processes involving TCDD contamination. Exposure was determined by reviewing, at each plant, operating conditions, job duties, records of TCDD levels in industrial hygiene samples, intermediate reactants, products, and wastes. Exposure assessment was limited and the uncertainty related to exposure measures not fully addressed.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. This is the largest of the occupational cohorts that has been exposed to TCDD. The cohort consisted of 5,172 workers and a total of 265 cancer deaths. Site-specific mortality analyses, including soft tissue sarcoma ($n = 4$), was limited by small numbers.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. New England Journal of Medicine, 1991; 324:212–218. Authors address the possibility of bias from lack of control for potential confounders such as smoking and other occupational exposures. They address limitations of using death certificates for identifying certain causes of deaths, and limitations of using duration of employment as an exposure metric.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. Since this study used duration of exposure as the exposure metric, dose-response relationships cannot be quantified.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Models incorporated period of latency, and a surrogate measure of cumulative TCDD exposure was modeled. The follow-up interval was sufficiently long (1942–1987).

Conclusion	Overall, quantitative exposure data are lacking on an individual-level basis. Further dose-response analysis should consider updated data for this cohort that includes serum-based measures of TCDD, in addition to an extension of the follow-up period. Given these limitations, this study is not further evaluated for TCDD dose-response assessment.

Table C-5. Steenland et al. ([1999](#))—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The study evaluated mortality from all cancer sites (combined). As described in the paper, the sources of vital status and cause of death information were received from the Social Security death files, the National Death Index, and the Internal Revenue Service. Vital status was known for 99.4% of the cohort members, cause of death information is available for 98% of the decedents.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Occupational exposure to asbestos and 4-aminobiphenyl contributed to some excess cancer, but no evidence of confounding for the relationship between TCDD and all cancer mortality was detected following removal of workers who died of bladder cancer. No information is available for cigarette smoking, although dose-response patterns were stronger for nonsmoking related cancers. This finding suggests that smoking is not responsible for excess cancer risk that was observed in the cohort.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. When a 15-year lag interval was incorporated into the exposure metric a statistically significant dose-response pattern was observed for all cancer sites combined with both a continuous measure of TCDD ($p = 0.05$) as well as one that was log-transformed ($p < 0.001$).
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The study conducted detailed sensitivity analyses and evaluated different assumptions regarding latency, log-transformed TCDD exposures, and half-life values for TCDD.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. This is the largest of the occupational cohorts with exposures to TCDD. The cohort consisted of 5,132 male workers and a total of 377 cancer deaths. This permits characterization of risk for all cancer sites (combined).
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Journal of the National Cancer Institute, 1999; 91(9):779–786. The authors discussed the potential for bias from smoking, and other occupational exposures for which data for both were lacking at an individual basis.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.

Response	Criteria satisfied. Exposure scores assigned on an individual level using a job-exposure matrix (JEM). The job-exposure matrix was based on estimated factor of contact with TCDD in each job, level of TCCD contamination of materials at each plant over time, and proportion of day worker could be in contact with materials. These factors were multiplied together to derive a daily exposure score, which was accumulated over the working history of each worker to obtain a cumulative measure of TCDD.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. The follow-up of the cohort extended from 1942 until the end of 1993. Greater than 25 years of follow-up have accrued in cohort allowing for latency to be examined. Different assumptions on the half-life of TCDD were evaluated and produced similar results. Latency intervals were incorporated, with strongest associations noted with an interval of 15 years.
Conclusion	This study meets the criteria and considerations noted above but has been superseded and updated by Steenland et al.(2001b). Therefore, this study was not considered for further dose-response analyses.

Table C-6. Steenland et al. (2001b)—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The study evaluated mortality from all cancer sites (combined). As described by Steenland et al. (1999) the sources of vital status and cause of death information were received from the Social Security death files, the National Death Index, and the Internal Revenue Service. Vital status was known for 99.4% of the cohort members, cause of death information is available for 98% of the decedents.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Occupational exposure to asbestos and 4-aminobiphenyl contributed to some excess cancer, but no evidence of confounding for the relationship between TCDD and all cancer mortality was detected following removal of workers who died of bladder cancer. No information is available for cigarette smoking, although dose-response patterns were similar between smoking and nonsmoking related cancers. There is no available information in the study to determine how representative the 199 workers were of the overall workers in that plant, or the potential for this to result in exposure misclassification.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Increased risk estimates were observed in the higher cumulative exposure categories. The dose-response curve was not linear at higher doses.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.

Response	Consideration satisfied. Exposure metrics considered included cumulative TCDD, log10TCDD, average exposure, and a cubic spline model was also evaluated. Exposure response relationships were also evaluated using toxicity equivalences (TEQs). Exposure scores were assigned on an individual level using a job-exposure matrix. The job-exposure matrix was based on estimated factor of contact with TCDD in each job, level of TCCD contamination of materials at each plant over time, and proportion of day worker could be in contact with materials. Serum levels were measured in 199 workers at one of 8 plants in 1998. Different estimate of the half-life of TCDD were used, and similar results were produced. The paper presented a range in risk estimates thereby conveying the range of uncertainties in risk estimates derived using different measures of exposure.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. This is the largest of the occupational cohorts with exposures to TCDD. The cohort consisted of 3,538 male workers and a total of 256 cancer deaths.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied Am J Epidemiol, 2001, 154(5):451–458. However, additional details to assess uncertainties associated with characterizing serum data in a subset of workers to remainder of cohort are lacking.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. The metrics considered included cumulative TCDD, log10TCDD, average exposure, and a cubic spline model was also evaluated. Exposure response relationships were also evaluated using TEQs. Serum lipid TCDD measurements from 170 workers whose TCDD levels were greater than 10 ppt (the upper ranges of a background level) were used along with JEM information, work histories, and a pharmacokinetic elimination model to estimate dose rates per unit exposure score. In this regression model, the estimated TCDD level at the time of last exposure was modeled as a function of exposure scores. The coefficient relating serum levels and exposure scores was then used to estimate serum TCDD levels over time from occupational exposure (minus the background level) for all 3,538 workers. Time-specific serum levels were then integrated over time to derive a cumulative serum lipid concentration due to occupational exposure for each worker.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Greater than 25 years of follow-up have accrued in cohort allowing for latency to be examined. Different assumptions on the half-life of TCDD were evaluated producing similar results.
Conclusion	Overall, criteria have been satisfied. This study was modeled in the 2003 Reassessment and is considered for further dose-response evaluations herein.

Table C-7. Cheng et al. (2006)—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The study evaluated cancer mortality. The vital status and the information regarding the cause of death were extracted from the Social Security death files, the National Death Index, and the Internal Revenue Service (Steenland et al., 1999). Vital status was known for 99.4% of the cohort members, while cause of death information is available for 98% of the decedents.

2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. This is the same data set used in the Steenland et al. (2001b) paper. Occupational exposure to asbestos and 4-aminobiphenyl contributed to some excess cancer, but no evidence of confounding for the relationship between TCDD and all cancer mortality was detected following removal of workers who died of bladder cancer. No information is available for cigarette smoking, although dose-response patterns were similar between smoking and nonsmoking related cancers.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Slope coefficients are available for all cancers combined under a varying set of assumptions. Little evidence of an association was found when lag interval was not taken into account. Associations strengthened with incorporation of a 10 to 15 year lag interval. Dose response was nonlinear at higher exposures, suggesting a nonlinear relationship or increased exposure misclassification at higher levels.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Compared to the 1st order models, the concentration, and age dependent model (CADM) provided a better fit for the serum sampling data. CADM model exposure estimates are higher than those based on an age only, constant 8.7-year half-life model. As discussed by Aylward et al. (2005b), model exposure estimates are influenced not only by choice of elimination model, but also by choices in regression procedure (e.g., log transformation, use of intercept, and incorporation of background dose term). Other limitations or uncertainties in exposure assessment include the following Job-exposure matrix based on limited sampling data, and subjective judgment on contact times and factors Inability to take into account interindividual variability in TCDD elimination kinetics Dose-rate regressions are based on a small sample of the cohort with serum measures; therefore, regression results may not be representative of remainder of the cohort.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Largest cohort of TCDD exposed workers. The risk estimates are based on a total of 256 cancer deaths.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Risk Analysis, 2006; 4:1,059–1,071. Additional details to assess uncertainties associated with characterizing serum data can be found in Aylward et al. (2005b); Risk Anal. 25(4):945–956.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Cumulative serum lipid concentrations were estimated for each worker. No other DLCs were assessed in this analysis.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Concentration and age-dependence of TCDD elimination and two compartments (hepatic and adipose tissue) were taken into account when estimating TCDD exposures. Nearly 50 years of follow-up were available permitting an evaluation of latency.
Conclusion	This study met the main criteria and considerations. The study is considered for further dose-response analyses.

Table C-8. Collins et al. ([2009](#))—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Vital status complete for all but two workers.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. No information collected on smoking status, but no excess in lung cancer or nonmalignant respiratory diseases noted. Analyses took into account potential for exposure to pentachlorophenol.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. No dose-response pattern was observed with all cancer sites combined, however, a dose-response pattern was observed with soft tissue sarcoma. The study found no association between TCDD and death from most types of cancer.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The authors used serum from 280 former TCP workers to estimate historical exposure levels of TCDD, furans, and polychlorinated biphenyls (PCBs) for all 1,615 workers. Exposure assessment included detailed work history, industrial hygiene monitoring, and the presence of chloracne cases among groups of workers. This data was integrated into a 1-compartment, first-order pharmacokinetic to determine the average TCDD dose associated with jobs in each group, after accounting for the presence of background exposures estimated from the residual serum TCDD concentration in the sampled individuals. The authors did not evaluate departures from linearity, or examine skewness at higher exposures. Exposure levels were not provided.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Largest study of workers employed in one center, and a total of 177 deaths from cancer were observed. Limited precision in the relative risk estimate was noted for soft tissue sarcoma and TCDD exposures.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in Am J Epidemiol, 2009, 170(4):501–506. The authors discuss limitations of using death certificates for identifying deaths from soft tissue sarcoma for which a positive association was noted, assumptions in exposure characterization, and effects of cigarette smoking.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. This study has the largest number of serum samples obtained from a specific plant.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Although specific analyses of latency were not reported, this cohort had a sufficient length of follow-up for cancer mortality outcomes.
Conclusion	The authors found a statistically significant dose-response trend for soft tissue sarcoma mortality and TCDD exposures. The all-tumor results are not amenable to dose-response analysis because they found no effect. Therefore, this study is considered for quantitative dose-response analysis for the soft tissue sarcoma mortality results, only.

C.2.2. BASF Cohort Studies

Table C-9. Zober et al. (1990)—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. A large component of the cohort (94 out of 247 workers) was assembled by actively seeking out workers who were alive in 1986 through the "Dioxin Investigation Programme." As a result, it is likely a number of deaths were missed due to the recruitment of survivors. This underascertainment is supported by much lower all cancer standardized mortality ratio (SMR) one component of the cohort (SMR = 0.48, 95% CI = 0.13–1.23) relative to the general population.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. See above discussion of underascertainment in mortality for some of the cohort members. Although it is likely that other coexposures occurred (e.g., among firefighters), confounding could only occur if these coexposures were associated with both the endpoint and exposure (TCDD) being considered.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Workers were not categorized on the basis of their exposure, but rather their mortality experience compared to control cohort and the general population. The design of the study does not allow for dose response to be examined.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. Although years since first exposure was examined, exposure assessment was based on working in various occupational cohorts. Since there was no quantitative assignment of TCDD exposures, the associated uncertainties could not be evaluated.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration not satisfied. There were only 23 cancer deaths in the entire cohort. As such, this study lacked adequate statistical power to detect cancer mortality differences that were moderate in magnitude.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Int Arch Occup Environ Health, 1990, 62:139–157. The authors address issues related to the healthy worker effect, multiple comparisons, smoking, and small size of the cohort.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. Risks were derived by comparing mortality rates of the three cohort subsets relative to a control cohort and the general population by time since first exposure categories. Workers were not assigned exposures. There were no quantitative estimates of TCDD exposure.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. While the study was able to indirectly look at variations in risk estimates related to latency by using time since exposure, there were no quantitative estimates of TCDD exposure.

Conclusion	This study is not suitable for dose-response analysis, as it failed the inclusion criteria. Most notably, the lack of exposure data does not permit the use of these data for a dose-response analysis.

Table C-10. Ott and Zober (1996a)—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Mortality ascertainment appeared to be fairly complete. The ascertainment of cancer incidence is more difficult to judge as geographical area not covered by a cancer registry.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Information was collected on smoking status, body mass index (BMI), and other occupational exposures, however a large portion of the cohort was firefighters who may have been exposed to other occupational carcinogens. However, the recruitment of survivors may results in under-ascertainment of mortality.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Increased cancer incidence was observed in the highest TCDD cumulative exposure category. Risks were most pronounced when a period of 20 years since first exposure was incorporated into the model.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Cumulative measure of TCDD expressed was derived from serum measures. Exposure was also estimated by chloracne status of the cohort members. The authors have not addressed the potential implication of deriving TCDD exposure estimates for the whole cohort using sera data that were available for only about half of the cohort.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 31 deaths. It is the smallest of the occupational cohorts, but the deaths can be grouped into quartiles to allow for evaluation of dose-response relationships.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Occupational and Environmental Medicine, 1996, 53:606–612. A large component of the cohort (94 out of 247 workers) was assembled by actively seeking out workers who were alive in 1986 through the "Dioxin Investigation Programme." As a result, it is likely a number of deaths were missed due to the recruitment of survivors. This underascertainment is supported by much lower all cancer SMR one component of the cohort (SMR = 0.48, 95% CI = 0.13–1.23) relative to the general population (Zober et al., 1990).
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum samples, taken in 1989, were available for 138 surviving workers out of 254 and allowed for cumulative TCDD levels to be estimated using regression techniques in the remainder of the cohort.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.

Response	Criteria satisfied. Exposure assignment took into the affect that body mass index had on TCDD half-lives. TCDD levels estimates through back-extrapolation of serum levels based on half-life estimates obtained from previous studies. Latency was considered with stronger association observed in external comparisons incorporating a latency of 20 years. The follow-up of the cohort was lengthy (>50 years).
Conclusion	Given a part of the cohort was based solely on survivors in the in the mid-1980s, the SMR statistic derived from this study underestimates excess mortality relative to the general population. The cohort also includes some firefighters who are recognized to be exposed to other carcinogenic agents—these exposures may be confounding the associations that were reported. However, exposure to TCDD was quantified and the effective dose and oral exposure estimable. Overall, criteria have been satisfied. This study was modeled in the 2003 Reassessment and is considered for further dose-response evaluations herein.

1 ## C.2.3. The Hamburg Cohort

Table C-11. Manz et al. (1991)—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Deaths were identified through medical records of the cohort members. A review of death certificates of the identified cancer deaths found a high degree of concordance (51/54). One of the 136 noncancer death certificates examined indicated an "occult" neoplasm.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Smoking data were similar between exposed and nonexposed cohort based on independent samples. Occupational exposures for which individual data are lacking are unlikely to explain dose response with TCDD. The potential impacts of any exposure misclassification is hard to gauge, but the authors reported that some misclassification was likely given that 5 of the 37 workers classified in the high exposure group had adipose levels lower than background (20 ng/kg).
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Dose-response patterns across three levels of exposure observed among those who started work before 1954, and among those who worked for 20 years or longer. Dose-response patterns not evident across whole cohort, among those with less than 20 years of employment, or among those who started after 1954.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures..
Response	Consideration satisfied. Categorical exposures were based on TCDD concentrations in precursor materials, products, waste, and soil from the plant grounds, measured after the plant closed in 1984. Exposure uncertainty examined using a separate group of 48 workers who provided adipose tissue samples. Other surrogate measures of exposure were considered in this study, including duration of exposure and year of first employment.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 65 cancer deaths for the comparison to the comparison cohort of gas workers. The study is underpowered to look at site-specific cancers.

1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Lancet 1991, 338:959–964. The authors discussed the potential for misclassification from the use of death certificates, the healthy worker effect and the related use of a comparison cohort of gas supply workers, other occupational exposures present at the plant, potential impact and the lack of smoking data.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. Exposure consisted of a large DLC component that was not quantified. Given crude TCDD exposure categorization data, no quantitative exposure metric was derived.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Exposure metrics were constructed that took into account duration of exposure, and periods when exposure was highest. However, exposure estimates did not consider lagged exposure.
Conclusion	This study is not amenable to further TCDD dose-response analysis and is not considered further here because it consisted of a large DLC component that was quantified and no quantitative exposure metric was derived. The dose-response patterns of risks observed across the three exposure groups provide compelling support for an association between TCDD and cancer mortality, particularly, given the associations observed when analyses restricted to those who were hired when TCDD exposures were known to be much higher, and among those who worked for at least 20 years. Subsequent studies improved the exposure assessment through the use of serum measures.

Table C-12. Flesch-Janys et al. (1995); Flesch-Janys et al. (1996) erratum— All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Medical records used to identify deaths over the period 1952–1992.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Similarity in smoking rates between control cohort and the exposed workers was similar based on independent surveys. Occupational exposures to benzene, and dimethyl sulfate were unlikely to bias dose-response pattern observed as these exposures occurred in production departments with low-medium levels of exposure.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Dose-response relationship observed across 6 exposure categories, with the cohort of gas supply workers used as the referent.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.

Response	Consideration satisfied. For all cancer sites combined, there were 124 deaths in the exposed cohort, and 283 in the cohort of gas supply workers. No site-specific cancers were examined in this paper.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 1995, 1442:1165–1175. The authors discuss the potential role of other occupational exposures (i.e., dimethyl sulfate, solvents, and benzene), smoking, and suitability of the comparison cohort of gas supply workers.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum and adipose tissues were used to estimate TCDD exposure in 190 workers. A one-compartment first-order kinetic model was used to estimate exposure at end of exposure for these workers. Regression methods were then used to estimates TCDD exposures for all workers.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Exposure was based on half-life estimates from individuals with repeated serum measures. Other dioxin-like compounds were considered with the toxic equivalencies of polychlorinated dibenzo-p-dioxins and furans (TOTTEQ) exposure metric. No consideration, however, was given to latency or lagged exposures.
Conclusion	The exposure data used within this study are well-suited to a dose-response analysis given the associations observed, the characterization of exposure using serum, and quality of ascertainment of cancer outcomes. However, subsequent methods have been applied to the cohort to derive different exposures to TCDD using area under the curve approaches, which updates the analysis herein. Therefore, subsequent studies (i.e., Becher et al., 1998) will supersede this evaluation.

Table C-13. Flesch-Janys et al. (1998)—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Mortality follow-up was extended until the end of 1992, an increase in 3 years from previous analyses of the cohort.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Exposure was well characterized using sera data. While serum samples provided only from a subsample of surviving workers, these levels were consistent with expected levels in different production departments. The authors examined other potential occupational coexposures (e.g., β-hexachlorocyclohexane) and indirectly examined the potential effect of smoking on the associations that were detected.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. A dose-response relationship across quartiles of TCDD was observed with cancer mortality based on the SMR statistic (SMRs = 1.24, 1.34, 1.34, 1.73), and a linear test for trend was statistically significant ($p = 0.01$).

4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The exposure measure was an integrated TCDD concentration over time estimate that back-calculated TCDD exposures to the end of the employment. Categorical and continuous TCDD exposures were examined in relation to the health outcome. These efforts improve the exposure assessment of earlier studies.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 124 cancer deaths.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Environ Health Perspect, 1998, 106(2):655–662. The authors address uncertainties in the estimation of exposure, describe the potential for confounding from β-2,4,5-T, hexachlorocyclohexane, and cigarette smoking. In fact, they showed that blood levels of TCDD were not associated with smoking in a subsample suggesting little bias from lack of smoking data.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum samples, taken from 190 workers were used to derive TCDD levels for the entire cohort. Methods used to estimate exposure took into account elimination of TCDD during employment periods when exposure took place, and the methods of the area under the curve was used as it takes into account variations in concentration over time, and reflects cumulative exposure.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Exposure estimated based on half-lives observed in individuals with repeated samples. Area under the curve approach was used which is an improvement from past characterizations of exposure in this cohort.
Conclusion	The study provides data suitable for dose-response modeling. Derivation of exposure was done using current understanding of elimination of TCDD. Estimates of risks were derived from external comparisons to the general population that are unlikely to be biased by healthy worker effect, but risks generated using internal cohort comparisons would be preferable. Becher et al., (1998) assessed this same data taking cancer latency into account, therefore Flesch-Janys et al., (1998) will not be further considered for dose-response modeling.

Table C-14. Becher et al. (1998)—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Medical records used to identify deaths over the period 1952–1992. The follow-up interval was lengthy.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Risks adjusted for exposures to TEQ, β-hexachlorobenzene, and employment characteristics. Smoking was shown to be similar to the comparison cohort of gas workers.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. A variety of exposure measures for both TCDD and TEQs found positive associations with cancer mortality.

4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The exposure measure was an integrated TCDD concentration over time estimate that back-calculated TCDD exposures to the end of the employment. Categorical and continuous TCDD exposures were examined in relation to the health outcome. Different models explored the shape of the dose-response curve. These efforts improve the exposure assessment of earlier studies.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 124 cancer deaths.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Environ Health Perspect, 1998, 106(2):663–670. The authors discuss uncertainties associated with their use of exposure metrics, inability to evaluate effects for polychlorinated dibenzo-p-dioxin (PCDD)/polychlorinated dibenzofurans (PCDF) other than dioxin due to high correlations with β-HCH, and inability to characterize risks associated with exposures in children.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. The authors derived a measure of cumulative dose as a time-dependent variable ("area under curve") using serum measures available in a sample of 275 workers.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. TCDD levels estimates through back-extrapolation of serum levels based on half-life estimates obtained from previous studies. Latency was considered, and a variety of exposure metrics including nonlinear relationships were evaluated.
Conclusion	In this paper, a variety of exposure metrics were found to be positively associated with cancer mortality. The additional lifetime risk of cancer corresponded to a daily intake of 1pg ranged between .01 and 0.001. This study was modeled in the 2003 Reassessment and is considered for further dose-response evaluations herein.

C.2.4. The Seveso Cohort Studies

Table C-15. Bertazzi et al. (2001)—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Mortality appears to be well captured from the vital statistics registries in the region (99% complete). Vital status was ascertained using similar methods for both the exposed and reference populations. Both cancer and noncancer mortality outcomes were evaluated. Ideally, would have evaluated incident rather than decedent outcomes for cancer.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Individual-level data on potential confounders (i.e., age, calendar period, and gender) were adjusted for. Information from other independent surveys suggests similarity between smoking behaviors across the regions. Comparison of cancer mortality rates before the time of the accident between the regions also revealed no differences.

3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied (for all cancers combined). No statistically significant excesses noted in Zone A, or Zone B relative to reference area. Evidence of an exposure-response relationship was detected for lymphatic and hematopoietic tissues by number of years since first exposure.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. Subjects were assigned to one of the zones (A, B, R, or reference) based on official residence on the day of the accident or at entry into the area. Exposure misclassification is likely and lack of individual-level data precludes an examination of this source of error.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. In total, 27, and 222, cancer deaths were found among residents of Zones A, and B, respectively. This allowed examined of gender-specific effects.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 2001 Jun 1; 153(11):1031−1044. Authors discuss completeness of mortality ascertainment, diagnostic accuracy of death certificates particularly with respect to diabetes, limited available of blood dioxin measures that did not permit estimation of TCDD dose on an individual-level basis.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. Individual-level exposure data are unavailable. Exposure based on place of residence at time of the explosion. Soil sampling performed indicated considerable variability in TCDD levels within each region. In addition, place of residency at time of explosion does not ensure individuals were at their home around the time of the accident.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. An ecological measure of exposure (region of residency at time of accident) was used to categorize individuals according to their possible exposure. Latencies were considered. While such an approach has value for identifying wherever excesses occurred among highly exposed populations, it is not precise enough to conduct a quantitative dose-response analysis.
Conclusion	The lack of individual-level exposure data precludes quantitative dose-response modeling using these data.

Table C-16. Pesatori et al. (2003)—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Mortality was ascertained from 1977−1996, and, as reported in other related manuscripts, appears to be well captured from the vital statistics registries in the region (99% complete). Cancer incidence data was available from 1977−1991.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Individual-level data on potential confounders (i.e., age, calendar period, and gender) were adjusted for.

3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Although risk of all cancer mortality was not associated with zone of residence, increased risk of cancer incidence was observed in Zone A. Among men, excess lymphatic and hematopoietic cancer incidence was observed in Zone A (primarily to non-Hodgkin lymphoma). Soft tissues sarcoma cancer incidence was also associated with residence in Zone R among males, but not the more highly exposed zones (A and B). Among females living in Zones A and B, higher rates were observed for multiple myeloma (RR = 4.9, 95% CI = 1.5−16.1), cancer of the vagina (RR = 5.5, 95% CI = 1.3−23.8), and cancer of the biliary tract (RR = 3.0, 95% CI = 1.1−8.2).
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. Subjects were assigned to one of the zones (A, B, R, or reference) based on official residence on the day of the accident or at entry into the area. Exposure misclassification is likely and lack of individual-level data precludes an examination of this source of error.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied for some endpoints, although several of the cancer specific mortality results among women were based on very small number of deaths (i.e., <5).
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Occup Environ Med, 1998; 55:126–131. Authors discuss limitations such as residency-based exposure assignment, absence of smoking, differential and death certification in exposed versus nonexposed areas.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. Individual-level exposure data are unavailable. Exposure based on place of residence at time of the explosion. Soil sampling performed indicated considerable variability in TCDD levels within each region. In addition, place of residency at time of explosion does not ensure individuals were at their home around the time of the accident.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. An ecological measure of exposure (region of residency at time of accident) was used to categorize individuals according to their possible exposure. Latencies were considered. While such an approach has value for identifying wherever excesses occurred among highly exposed populations, it is not precise enough to conduct a quantitative dose-response analysis.
Conclusion	No dose-response patterns evident in the study, and the study lacked quantifiable measures of TCDD at an individual-level basis. The data are not well suited for dose-response analysis.

Table C-17. Consonni et al. (2008)—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Mortality appears to be well captured from the vital statistics registries in the region (99% complete). Both cancer and noncancer mortality evaluated, although diagnostic accuracy of death certificates is likely low. Ideally, would have evaluated incident rather than decedent outcomes for cancer.

2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Individual-level data on potential confounders (i.e., age, calendar period, and gender) were adjusted for. Comparison of cancer mortality rates before the time of the accident between the regions also revealed no differences. Information from other independent surveys suggests similarity between smoking behaviors across the regions.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied for some outcomes. For all cancer sites combined, no evidence of dose response was observed relative to general population across Zones A, B and R. Only statistically significant excess found in Zone A was for chronic rheumatic disease but based on only three deaths. Higher cancer excesses were found in Zone A after a latency period was incorporated; however, no dose-response relationship observed with this latency period. Evidence of an exposure-response relationship was detected for lymphatic and hematopoietic tissues by zone of residence.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. Subjects were assigned to one of the zones (A, B, R, or reference) based on official residence on the day of the accident or at entry into the area. Exposure misclassification is likely and lack of individual-level data precludes an examination of this source of error.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. In total, 42, 244, and 1,848 cancer deaths were found among residents of Zones A, B, and R respectively.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 2008, 167:847–858. Authors discuss potential for selection bias, limitation of residential based measure of exposure, similarities of mortality ascertainment in exposed and referent populations, and multiple testing.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. Individual-level exposure data are unavailable. Exposure based on place of residence at time of the explosion. Soil sampling performed indicated considerable variability in TCDD levels within each region. In addition, place of residency at time of explosion does not ensure individuals were at their home around the time of the accident.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. An ecological measure of exposure (region of residency at time of accident) was used to categorize individuals according to their possible exposure. Latencies were considered. While such an approach has value for identifying wherever excesses occurred among highly exposed populations, it is not precise enough to conduct a quantitative dose-response analysis.
Conclusion	The lack of individual-level exposure data precludes quantitative dose-response modeling using these data.

Table C-18. Baccarelli et al. (2006)—Site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Polymerase chain reaction methods were used to describe outcome measures. The prevalence of t(14; 18) was estimated as those individuals having a t(14; 18) positive blood sample divided by the t(14; 18) frequency (number of copies per million lymphocytes).
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Questionnaire data were used to collect information on cigarette smoking. Other potential confounders (age, smoking status, and duration of smoking). In addition, both exposure and outcome were objectively and accurately measured.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Associations were detected between the frequency of t(14; 18) and plasma TCDD levels as well as zone of residence at the time of the explosion. No association was detected for these exposure measures and prevalence of t(14; 18). A dose-response trend was detected for TCDD and the mean number of t(14;18) translocations/10^6 lymphocytes, however the relevance of t(14; 18) in lymphocytes to non-Hodgkin lymphoma is uncertain.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The authors highlight that exposure metrics represent both past and current body burdens. They employ several different exposure metrics of TCDD: place of residence (Zone A, B, R or reference), categorical serum measures, a linear term, log (base 10) transformed TCDD, and individuals with chloracne diagnosed after the accident.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Analyses are made using 72 highly exposed, and 72 low exposed individuals.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Carcinogenesis, 2006, 27(10):2001–2007. The authors discuss the limitation of using t(14; 18) translocations as an outcome measure, and the uncertain role it plays in the development of non-Hodgkin lymphoma.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. A total of 144 subjects were included in the study. This included 72 subjects who had low exposures, and 72 who had high exposures based on serum concentrations.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. A variety of measures were employed including current TCDD levels, as well as surrogates of exposure at the time of the accident.
Conclusion	While an association was observed with the frequency of t(14; 18) translocation, it is uncertain whether this translates into an increased risk of non-Hodgkin lymphoma. Given the speculative nature of this endpoint and lack of demonstrated adverse effect, dose-response analyses for this outcome were not conducted.

Table C-19. Warner et al. ([2002](#))—Breast cancer incidence

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Diagnoses of incident breast cancer were based on interview and information from medical records appears thorough. Of the 15 cases of breast cancer, 13 were confirmed by pathology and the remaining 2 by surgery report only. Three cases of breast cancer were excluded which represents a large proportion of the total cases identified. This would reduce sample size and could result in bias if the exclusion was association with TCDD exposure.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Information was collected on an extensive series of risk factors by using an interviewer administered questionnaire. Participation rates for the survey were fairly good (80%).
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Limited evidence (not statistically significant) of a dose response when TCDD was analyzed as a categorical variable; only one breast cancer case was in the referent exposure category. In the analysis of TCDD as a continuous measure ($\log_{10}$TCDD), the hazard ratio associated with a 10-fold increase in TCDD serum levels was 2.1 (95% CI = 1.0–4.6).
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures..
Response	Consideration satisfied. Different exposure metrics were considered in these analyses (categorical, continuous, measures on a log-scale). Exposure data are of high quality as they are based on serum samples taken among women near the time of the accident. As such, exposure assignment is not dependent on as many assumption as used in occupational cohorts were back-extrapolation for many years had to be performed.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration somewhat satisfied. Inadequate follow-up for cancer limited the number of cases available. Sample size also limited the conclusions draw from the categorical analysis based on very few cases for some exposure categories.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Paper published in Environ Health Perspect, 2002 Jul, 110(7):625–628. A major limitation of the study is the small number of incident cases of breast cancer ($n = 15$), important strengths of the study include characterization of TCDD using serum collected near the time of the accident.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum was used to estimate TCDD levels in 981 of 1,271 eligible women who had lived in either of the two contaminated sites in 1976. Data represent an objective measure of TCDD near the time of the exposure. Data obtained near the time of exposure which minimized the potential for exposure misclassification.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Exposure characterized using serum measures obtained close to the time of the accident.

Conclusion	While characterization of exposure and availability of other risk factor data at an individual-level basis are important strengths of this study, small sample size ($n = 15$ cases) based on inadequate follow-up is a key limitation. Quantitative dose-response analyses were conducted using this study, but continued follow-up of the study population or consideration of all cancer outcomes would be valuable.

1 **C.2.5. The Chapaevsk Study**

Table C-20. Revich et al. (2001)—All cancer sites combined, and site-specific analyses

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration cannot be evaluated. Insufficient details are provided in the paper to gauge the completeness and coverage of the cancer registry and mortality data. Health outcomes were examined on the basis of information in the official medical statistics.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Given the aforementioned limitations of this ecological study, it is unclear to what extent the results may be subject to bias
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Dose response was not evaluated as exposure was based on residency in the region vs. no residency.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. No individual-level exposure estimates were used.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. A total of 476 cancer deaths were observed among males, and 376 cancer deaths observed among females. The precision of the SMRs is demonstrated with fairly narrow confidence intervals for many causes of death.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in Chemosphere, 2001, 43(4–7):951–966. Authors do not address the completeness of the mortality follow-up, and whether there are differences in mortality surveillance between regions. The authors do acknowledge, however, that new investigations being undertaken would characterize exposure using serum-based measures.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. It is a cross-sectional study that compares mortality rates between regions. No individual-level exposure data available.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. No individual-level exposure estimates were used in the study.
Conclusion	These cancer data are cross-sectional in nature; therefore, dose-response analyses were not conducted for this study.

C.2.6. The Air Force Health ("Ranch Hands") Study

Table C-21. Akhtar et al. ([2004](#))—All cancer sites combined and site-specific analyses

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Cancer incidence and mortality based on information from repeated medical examinations, medical records and death certificate.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. The risk estimates were adjusted for a number of factors measured on an individual level, including smoking.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. There is evidence of a dose response for all cancers and for some site-specific cancers (i.e., malignant melanoma, and prostate cancer).
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. High quality exposure data for most veterans was collected, so extrapolation to other members of the cohort was not required. The serum dioxin measurements also correlated well with reported skin exposure to herbicide in Vietnam, but collection of the samples 25 years later required back-extrapolation.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. In total, 117 incidence cancers identified in the Ranch Hands cohort. For those sites with a dose-response association, malignant melanoma and prostate cancer, there were 16 and 34 incident cases, respectively.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in J Occup Environ Med, 2004, 46(2):123–136. Authors highlight that this is only cancer incidence study in US veterans, and the lengthy interval of follow-up (35–40 years)—both important strengths of the study. They addressed potential bias from healthy-worker effect, and uncertainties surrounding the estimation of TCDD exposure (extrapolation 30 years after exposure), as well as exposure to other chemical exposures. Study uses incident outcomes for cancer.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Individual exposure estimates are based on measurements of dioxin serum lipid concentrations. They were available for 1,009 Ranch Hands and 1,429 in the comparison cohort.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. TCDD exposures at the end of duty were estimated by back-extrapolating 1987 serum values.
Conclusion	This study is suitable for TCDD dose-response modeling of cancer outcomes data.

Table C-22. Michalek and Pavuk ([2008])—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Cancer incidence was ascertained through the use of medical records. Death certificate were used to identify some malignancies. Little data is provided on the number of individuals lost to follow-up, however the same mechanisms of case ascertainment were applied to both the comparison and Ranch Hand cohorts.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Information collected from repeated physical examinations allowed for the adjustment of risk factors such as smoking and exposure related factors such military occupation and number of years served.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied for some comparisons. Statistically significant associations were noted with cancer incidence and TCDD when analyses were restricted to workers who served at most two years in Southeast Asia and those who sprayed more than 30 days before 1967.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Initial TCDD dose were estimated at the end of the tour of duty for the Ranch Hands. Individual-level serum dioxin measurements correlated well with correlated with days of spraying and calendar period of service, but collection of the samples roughly 20 years later required back-extrapolation.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. A total of 347 incident cases of cancer were used in the analyses. For stratified analyses, statistical power is more limited. For example, only 67 incident cancer in the subset of workers who spent less than 2 years in Southeast Asia, and sprayed for at least 30 days before 1967.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied J Occup Environ Med 2008; 50:330–340. The authors discuss issues related to exposure misclassification error, and suggest approaches for improving characterization of days of spraying. Congener specific data were unavailable, thereby not allowing for congener specific risks or adjustments to be made.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. TCDD data was available for 986 veterans in the Ranch Hand cohort, and 1,597 members of the comparison cohort.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. TCDD exposures at the end of duty were estimated by back-extrapolating 1987 serum values.
Conclusion	This study is suitable for TCDD dose-response modeling of cancer outcomes.

C.2.7. Other Studies of Potential Relevance to Dose-Response Modeling

Table C-23. 't Mannetje et al. ([2005](#))—All cancer sites combined, site specific analyses

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. National records for death registrations through the New Zealand Health Information Service. Subjects not registered as having died during the study period were confirmed to be actually alive and resident in New Zealand using the New Zealand Electoral Roll, drivers' license, and social security records.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Seventeen percent of workers were lost to follow up but it is unclear if bias resulted. The dichotomous exposure measure was based on exposure to TCDD, chlorinated dioxins and phenoxy herbicides, so confounding is a possibility by these coexposures.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Dose-response evidence for duration of employment and elevated mortality noted only in synthesis workers.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Exposure measures were limited to duration of employment and exposed/unexposed.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For all cancer sites combined, there were 43 cancer deaths among the production workers, and 35 such deaths among the sprayers. Site-specific cancer analyses are limited by small sample sizes.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria not satisfied. Occup Environ Med, 2005; 62:34–40. A high percentage of the cohort was lost to follow-up (17%). The authors fail to mention this important limitation in this paper.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. This study used duration of exposure, at an individual level, as a surrogate measure of TCDD.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Exposure was defined according to duration, and not concentrations of TCDD. Latency intervals were not evaluated.
Conclusion	Overall, quantitative exposure data are lacking for TCDD and limited dose-response relationships were observed across duration of exposure categories. Furthermore, confounding by coexposures is a possibility. Taken together, these data are not suitable for inclusion in a dose-response analysis

Table C-24. McBride et al. ([2009a](#))—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The New Zealand Health Information Service Mortality Collection and the Registrar-General's Index to Deaths. Additional searches were based on the last known address from the work record; the electoral roll and the habitation index; the telephone book; the internet; and Terranet property information database. An additional search was carried out through the Births, Deaths, and Marriages office of the New Zealand Department of Internal Affairs. Lastly, automated personnel and pension records were also used to locate past New Plymouth workers and identify some deaths.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Considerable amount of workers were lost to follow up (22%), but it is unclear if bias resulted. The dichotomous exposure measure was based on exposure to TCDD, chlorinated dioxins and phenoxy herbicides, so confounding is a possibility by these coexposures.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Some SMRs for site-specific cancers were elevated but not statistically significant. There was no examination of dose-response effects.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Dichotomous exposure (exposed/unexposed) and duration of employment were examined from job exposure classification assessed via occupational history records industrial hygienists/factory personnel knowledge and questionnaires. Authors discuss limitations in the assignment of exposure among cohort members.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration not satisfied. A low number of deaths ($n = 76$) may have limited ability to detect effects small in magnitude and exposure-response relationships.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in Occup Medicine, 2009; 59(4):255–263. The authors highlight cohort lost to follow-up (22%), the limited size of the cohort, differences in cohort definitions between sprayers and producers, and the potential for other exposures during employment at the plant.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. TCDD exposures were not quantified.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Effective dose could not be estimated given the lack of individual-level TCDD exposure data.
Conclusion	The study lacks the quantification of exposures at an individual level, precluding dose-response analysis. This study is not considered further in the dose-response modeling analysis.

Table C-25. McBride et al. ([2009b](#))—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The New Zealand Health Information Service Mortality Collection and the Registrar-General's Index to Deaths were used to identify deaths. Additional searches were based on the last known address from the work record; the electoral roll and the habitation index; the telephone book; the internet; and several other public databases in New Zealand. An additional search was carried out through the Births, Deaths, and Marriages office of the New Zealand Department of Internal Affairs. Lastly, automated personnel and pension records were also used to locate past New Plymouth workers and identify some deaths.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Workers lost to follow-up (21%) were an unlikely source of bias since there was no evidence that this loss was differential in the internal analyses of workers. Confounding by sex, hire year, and birth year was addressed by adjustment in regression models. Potential confounding by other coexposures (e.g., 2,4,6-TCP) unlikely to have resulted in bias, due to presumed poor correlation with TCDD.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Although not statically significant, elevated SMRs (≥ 1.6) were noted for soft tissue sarcoma, non-Hodgkin Lymphoma, multiple myeloma and rectal cancer. The linear test for trend for TCDD exposure was not statistically significant for all cancer sites (combined), as well as lung cancer mortality. Dose-response relationships were not apparent across quartiles of TCDD exposure for all cancer sites combined, digestive cancers, lung cancer, soft tissue sarcomas or non-Hodgkin Lymphoma.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Cumulative exposure to TCDD as a time-dependent metric was estimated for each worker from serum samples, but the authors did not examine a continuous measure of TCDD exposure (lagged or unlagged).
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. The adequate statistical power to detect associations that were present was a strength of the study owing to the large sample size (n=1,599 workers), extensive follow-up period (35 years) and considerable exposure gradient.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in J Occup Environ Med 51:1049−1056. This paper discussed the strengths and limitation of the study
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum measures available for 346 workers were used to derive TCDD exposures for the entire cohort using the area under the curve approach.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Although, effective dose could be estimated from serum-derived cumulative exposure estimates, the exposure models did not consider different latency periods.
Conclusion	Given that no dose-response relationships were found, the data are not suited to dose-response analysis.

Table C-26. Hooiveld et al. ([1998](#))—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Outcomes were mortality. Few deaths expected to be missed since only 5% of the cohort was lost to follow-up or had emigrated.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Although dioxin-like compounds (PCDDs, PCDFs, and PCBs) were measured in the serum samples, these were not incorporated into the analysis. Therefore, confounding cannot be ruled out as an explanation of the reported association.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. A dose-response pattern was observed for internal cohort comparison for all cancer mortality, with RRs of 5.0 and 5.6 for the medium and high exposure, respectively. Dose-response patterns evident for lung cancer as well.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures..
Response	Consideration satisfied. Detailed occupational histories to assign dichotomous exposures (exposed/unexposed) based on maximum exposure levels. Although serum data also collected for TCDD and other coexposures (PCDDs, PCDFs, and PCBs), study only presents data for TCDD exposure. TCDD exposures at time of maximum exposure were extrapolated from measured serum.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration not satisfied for internal cohort comparisons in either men or women. Among men, only 7 cancer deaths were observed among those in the unexposed part of the cohort, and 51 among exposed workers. For external cohort comparisons, a total of 20 deaths were observed.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 1998, 147:891–901. The authors address potential limitations of estimating TCDD exposure from a subsample of surviving workers, lack of smoking data, the healthy worker effect, and relevance of other occupational exposures.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum samples were obtained from 94 of 144 subjects who were asked to participate in serum measurement study. Of these, a further 44 excluded due to absence due to holiday or work ($n = 22$), and nonexposed workers excluded because matching exposed worker not participating ($n = 20$). TCDD levels were extrapolated to the time of maximum exposure.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Exposures assigned based on levels at maximum exposure. Assignment of exposure based on nonrepresentative sample of 50 survivors among the occupational cohort.
Conclusion	The small number of identified cancer deaths, limitations in terms of the exposure assignment (based on nonrepresentative sample, and maximum exposure level) and concern over potential confounding by coexposures preclude using these data for a dose-response analysis.

1   **C.3. EVALUATION TABLES FOR NONCANCER STUDIES**

2   **C.3.1. NIOSH Cohort**

Table C-27. Steenland et al. (1999)—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased..
Response	Consideration satisfied. The study evaluated mortality from all cancer sites (combined). As described in the paper, the sources of vital status and cause of death information were received from the Social Security death files, the National Death Index, and the Internal Revenue Service. Vital status was known for 99.4% of the cohort members, cause of death information is available for 98% of the decedents.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. External comparisons for all-cause and cardiovascular mortality do not appear to be affected by the "healthy worker effect" as similar patterns were observed with internal cohort comparisons. Nonetheless, internal cohort comparisons are unable to adjust for many of the individual-level risk factors for cardiovascular disease.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. A dose-response relationship was observed with ischemic heart disease (linear test for trend $p = 0.05$), and with TCDD on a log-transformed scale the p-value was <0.001.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The study conducted detailed sensitivity analyses and evaluated different assumptions regarding latency, log-transformed TCDD exposures, and half-life values for TCDD. Associations were stronger for log-transformed values, and latency intervals of 15 years.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. This is the largest of the occupational cohorts with exposures to TCDD. The cohort consisted of 5,132 male workers and a total of 456 deaths from ischemic heart disease. This permits characterization of risk for all cancer sites (combined).
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Journal of the National Cancer Institute, 1999, 91(9):779–786. The authors discussed the potential for bias from smoking, and other occupational exposures for which data for both were lacking at an individual basis.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Exposure scores assigned at an individual level based on JEM. The JEM was based on estimated factor of contact with TCDD in each job, level of TCCD contamination of materials at each plant over time, and proportion of day worker could be in contact with materials. These factors were multiplied together to derive a daily exposure score, which was accumulated over the working history of each worker to obtain a cumulative measure of TCDD.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.

Response	Criteria not satisfied. The follow-up of the cohort extended from 1942 until the end of 1993. Greater than 25 years of follow-up have accrued in cohort allowing for latency to be examined. Different assumptions on the half-life of TCDD were evaluated and produced similar results. Latency intervals were incorporated, with strongest associations noted no lag. Suggests mechanisms occur at the same time as exposure. However, noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	TCDD exposures were quantified in this study, and a dose-response relationship was observed with ischemic heart disease mortality. The sample size was sufficient, and the follow-up interval was lengthy. However, no individual-level data were available for cardiovascular conditions, and the inability to adjust for these exposures introduces considerable uncertainty into the risk estimates. Furthermore, noncancer mortality is not considered a viable endpoint for dose-response analysis.

Table C-28. Collins et al. ([2009](#))—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Vital status complete for all but two workers.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. No information collected on smoking status, but no excess in lung cancer or nonmalignant respiratory diseases noted. Analyses took into account potential for exposure to pentachlorophenol. External cohort comparisons should be interpreted cautiously due to healthy worker effect, but internal cohort comparisons should not be influence by this bias.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. No statistically significant mortality excess for any noncancer mortality outcome evaluated. This included ischemic heart disease, stroke, nonmalignant respiratory disease, ulcers, cirrhosis, and external causes of death (accidents). Modeling of continuous measure of TCDD was not related to diabetes, ischemic heart disease, or nonmalignant respiratory mortality.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The authors used serum samples from 280 former TCP workers to estimate historical exposure levels of TCDD, furans, and polychlorinated biphenyls for all 1,615 workers. Exposure assessment included detailed work history, industrial hygiene monitoring, and the presence of chloracne cases among groups of workers. This data was integrated into a 1-compartment, first-order pharmacokinetic to determine the average TCDD dose associated with jobs in each group, after accounting for the presence of background exposures estimated from the residual serum TCDD concentration in the sampled individuals. The authors did not evaluate departures from linearity, or examine skewness at higher exposures. No presentation of exposure levels was provided.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. A total of 662 deaths were observed. Of these, 218 were from ischemic heart disease, and 16 from diabetes (two outcomes for which associations have been noted elsewhere).
1. Criteria	Study is published in the peer-reviewed scientific literature.

Response	Criteria satisfied. Published in Am J Epidemiol, 2009, 170(4):501−506. The authors discuss potential for exposure misclassification, large size of the cohort, lengthy follow-up interval, and large number of workers who provided serum from which TCDD exposures were estimated.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. This study has the greatest number of serum samples obtained from a specific plant.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusions	No dose-response associations were noted for noncancer mortality outcomes. The data are, therefore, not suited for dose-response modeling.

1   **C.3.2. BASF Cohort**

Table C-29. Ott and Zober ([1996a](#))—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Mortality ascertainment appeared to be fairly complete.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Information was collected on smoking status, body mass index, and other occupational exposures, however a large portion of the cohort was firefighters who may have been exposed to other occupational carcinogens. However, the recruitment of survivors may results in under-ascertainment of mortality.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. For external cohort comparisons across the three TCDD exposure categories, there was no dose-response pattern observed for any of the noncancer causes of death. Cox regression risk estimates for all cause or circulatory disease mortality when TCDD was modeled as a continuous variable were not statistically significant.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Cumulative measure of TCDD expressed was derived from serum measures. Exposure was also estimated by chloracne status of the cohort members. The authors have not addressed the potential implication of deriving TCDD exposure estimates for the whole cohort using sera data that were available for only about half of the cohort.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For all causes of death, there were 92 deaths, while 37 circulatory deaths. Many of the cause-specific death had less than 5 deaths in the upper exposure category.
1. Criteria	Study is published in the peer-reviewed scientific literature.

Response	Criteria satisfied. Occup Environ Med, 1996, 53:606–612. A large component of the cohort was assembled by actively seeking out workers who were alive in the mid 1980s. As a result, it is likely a number of deaths were missed. This is supported by much lower SMRs in this component of the cohort published in earlier studies of the cohort. This underascertainment of mortality results in biased SMR statistics (underestimated). The authors do highlight the value of the serum based measures to estimate TCDD exposure
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum samples, taken in 1989, were available for 138 surviving workers out of 254 and allowed for cumulative TCDD levels to be estimated using regression techniques in the remainder of the cohort.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Exposure assignment took into the affect that body mass index had on TCDD half-lives. TCDD levels estimates through back-extrapolation of serum levels based on half-life estimates obtained from previous studies. Latency was considered with stronger association observed in external comparisons incorporating a latency of 20 years. The follow-up of the cohort was lengthy (>50 years). However, noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	No associations noted with any noncancer deaths. External comparisons should be treated cautiously especially for cardiovascular mortality which is recognized to often be biased by the healthy-worker effect. In the absence of any outcome with an association with TCDD exposure, dose-response analyses of these data were not undertaken.

1   **C.3.3. Hamburg Cohort**

Table C-30. Flesch-Janys et al. (1995); Flesch-Janys et al. (1996) erratum— Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Medical records used to identify deaths over the period 1952−1992.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Similarity in smoking rates between control cohort and the exposed workers was similar based on independent surveys. Occupational exposures to benzene, and dimethyl sulfate were unlikely to bias dose-response pattern observed as these exposures occurred in production departments with low to medium levels of TCDD exposure.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Dose-response relationship observed for all-cause mortality, cardiovascular mortality, and ischemic heart disease mortality across 6 exposure categories, with the cohort of gas supply workers used as the referent. The linear tests for trend for these three outcomes were all statistically significant ($p < 0.05$).
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.

Response	Consideration satisfied. The exposure measures was an integrated TCDD concentration over time estimate that back-calculated TCDD exposures to the end of the employment. Categorical and continuous TCDD exposures were examined in relation to the health outcome. These efforts improve the exposure assessment of earlier studies.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For all causes of death combined, there were 414 deaths in the exposed cohort, and 943 in the cohort of gas supply workers. A total of 157 and 76 deaths from cardiovascular disease, and ischemic heart disease were noted. The corresponding number in the cohort of gas supply workers was 459, and 205, respectively.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 1995, 1442:1165–1175. The authors discuss the potential role of other occupational exposures (i.e., dimethyl sulfate, solvents, benzene), smoking, and suitability of the comparison cohort of gas supply workers.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum and adipose tissues were used to estimate TCDD exposure in 190 workers. A one-compartment first-order kinetic model was used to estimate exposure at end of exposure for these workers. Regression methods were then used to estimates TCDD exposures for all workers.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Exposure based on half-life estimates from individuals with repeated serum measures. Other DLCs were considered with the TOTTEQ exposure metric. Noncancer mortality, however, is not a viable endpoint to consider for further dose-response analysis.
Conclusion	Although, the exposure data used within this study are well-suited to a dose-response analysis for all-cause and cardiovascular mortality given the associations observed, use of noncancer mortality endpoint is not amenable for further dose-response analysis.

1   **C.3.4. The Seveso Women's Health Study**

Table C-31. Eskenazi et al. (2002b)—Menstrual cycle characteristics

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Information was also obtained from medical records for all obstetric and gynecologic conditions. Information on menstrual cycles was obtained from questionnaires. Women were asked about length of cycles, regularity, how many days flow lasted, and heaviness of menstrual flow (scanty, moderate, or heavy). Measurement error is likely for the subjective nature of self-reported menstrual parameters but specificity and sensitivity is difficult to ascertain due to lack of validation data for these measures.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Detailed risk factor information was collected from questionnaire, allowing for the potential confounding influence of many risk factors to be controlled for. The length of cycle study findings may have been affected by the presence of a few outliers.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.

Response	Consideration satisfied. A positive dose-response relationship was found with TCDD among women who were premenarcheal at time of the explosion and longer menstrual cycle. Increased TCDD exposure was associated with a lower relative risk of scanty menstrual flow. No association was noted with these two outcomes among postmenarcheal women. A decreased risk of irregular cycles was also observed with higher TCDD levels.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Cohort was large enough as analyses were conducted on 301 women.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 2002; 156(4) 383−392. Limitations included an inability to assess affects on menstrual cycle at time body burdens were the highest (at time of the accident). Also, TCDD was estimated for 1976, not concurrent with their cycles in the previous year, and a large number of women were excluded due to intrauterine device or oral contraceptive use. Strengths included population-based nature of study, with characterization of exposure using serum, and levels of other polychlorinated dibenzo-*p*-dioxins and dibenzofurans were at background levels. Findings for length of menstrual cycle may be unduly influenced by the presence of some outliers.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. The study population was based on 301 women as those who were over the age of 44 were excluded, as well as women with surgical of natural menopause, women with Turner's syndrome, those who had been pregnant or breastfed in the past year, and those who had used an intrauterine device or oral contraceptives. For 272 women, TCDD levels were based on serum data provided in 1976; TCDD levels were back-extrapolated to 1976 levels for the other 29 women.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Ideally, TCDD exposures would be concurrent with reporting of cycle characteristics. Herein, TCDD exposures were based on levels in 1976; however, given the long half-life of TCDD and the same follow-up interval for all women, TCDD exposures in 1976 should correlate well with levels near the time of interview. Further, the critical window of exposure can be estimated for the women that were premenarcheal at the time of the accident (12 years).
Conclusion	This study meets all of the criteria and considerations for further dose-response analysis. Although it is difficult to define the biologically relevant critical window of exposure for quantitative exposure calculations, the critical window of susceptibility is assumed to occur between birth and 13 years of age.

Table C-32. Eskenazi et al. (2002a)—Endometriosis

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.

Response	Consideration satisfied. Results of a pilot study showed that ultrasounds had excellent specificity and sensitivity for ovarian endometriosis. Those with uncertain case status were analyzed separately from cases.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Although more than half of the women were classified as 'uncertain' with respect to endometriosis disease status, these subjects were analyzed separately from those with endometriosis detected by laparoscopy or ultrasound. Bias is unlikely since disease misclassification is not likely to be differential with respect to TCDD exposure status.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. While an increased risk of endometriosis was observed across the 3 TCDD categories, these risks were not statistically significant relative to the lowest exposure category. The test for trend based on a continuous measure ($\log_{10}$TCDD) was also not statistically significant.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration not satisfied. Only a total of 19 cases of endometriosis were identified, and more than half of the subjects were listed as uncertain regarding endometriosis incidence.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Environ Health Perspect 2002; 110(7) 629–634. Author's highlight that this is the first study to examine the relationship between TCDD and endometriosis, and the availability of sera data to estimate TCDD levels. Limitations included the small number of women with endometriosis, and inability to confirm disease status for those without ultrasound or laparoscopy. Finally, young women may have been underrepresented due to cultural difficulties in examining women who had never been sexually active.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Eligible study subjects were women between 1 month and 40 years of age at time of accident. These analyses excluded virgins, those with Turner's syndrome, and women who refused the examination of ultrasound. Serum data were available for the 601 participants on which the analyses are based. Of these, 559 had serum measures taken in 1976/77, 25 between 1978 and 1981, and 17 women in 1996.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. TCDD exposure was estimated at the time of "conception attempt" using serum measures, with extrapolation from 1976 levels using half-life assumptions. It is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis. The critical window of exposure is unknown.
Conclusion	Various reasons preclude the use of these data to conduct dose-response analysis. This includes the lack of a statistically significant association, the large number of women for which endometriosis disease status was "uncertain", and uncertainty in estimating the critical period of exposure.

Table C-33. Eskenazi et al. (2003)—Birth outcomes

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration not satisfied. Outcomes were identified through self-reported questionnaires and subject to measurement error. Although there is no direct evidence of bias from differential reporting, women tended to over-report birth weight, and underreport birth defects in children. As a large number of women in Seveso underwent voluntary abortion in the first year after the explosion, an awareness bias may have contributed to differential reporting of pregnancy histories.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. See above.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. There was no association between spontaneous abortions and $\log_{10}$TCDD, or with small for gestational age. There was some suggestion of decreased mean birth weight and increased ORs for small for gestational age with TCDD exposure among pregnancies occurring in the first eight years following the accident; however, none of these achieved statistical significance at $p < 0.05$.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For spontaneous abortions there were 769 pregnancies. Fetal growth and gestational age analysis was carried out on 608 singleton births that occurred postexplosion.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Environ Health Perspect, 2003, 111(7):947–953. The authors highlight potential limitation of reliance on self-reported data to ascertain pregnancy outcomes. They also address the relevance of paternal exposures to TCDD on the developing fetus—such exposure data were not considered in this study.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. A total of 745 women in the SWHS had reported getting pregnant, of these 510 women were pregnant after the explosion (888 pregnancies). Analyses of spontaneous abortions based on 476 women (excludes those with voluntary abortion, ectopic pregnancy, or molar pregnancy). TCDD measured for 413 women in 1976/77, 12 women between 1978 and 1981, and 1996 for 19 women.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. TCDD exposures were extrapolated to 1976 values. However, there is considerable uncertainty in estimating exposure levels for narrow critical windows of exposure (e.g., trimesters during pregnancy) especially for pregnancies that occurred many years after the explosion in 1976.

Conclusion	The findings of the study are somewhat limited due to the reliance on self-reported information for pregnancy outcomes and possible awareness bias. The findings were not statistically significant. Considered together with the uncertainty in estimating exposure levels for narrow critical windows of exposure, dose-response analyses for this study were not conducted.

Table C-34. Warner et al. ([2004](#))—Age at menarche

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. In this study age at menarche was based on retrospective recall 5 to 19 years before the interview. Previous work suggests moderate to high correlations between actual and recalled menarche, misclassification of outcome would bias risk estimates towards the null (assuming nondifferential misclassification).
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Data collected from self-reported questionnaires allow for the potential confounding influence of many risk factors to be taken into account. Some misclassification of outcome may bias risk estimates towards the null.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. There was no association between TCDD levels and the age at menarche with either the continuous or categorical measures of TCDD in the primary publication, However, suggestive evidence of an association between serum TCDD concentrations and earlier age of menarche (HR = 1.20, 95% CI = 0.98−1.60, p for trend = 0.07) among 84 women under the age of 5 at the time of the accident was noted in a follow-up communication from Warner & Eskenazi ([2005](#))to be when analyses were restricted. The consideration is not satisfied because, in the context of the RfD derivation, considerable uncertainty remains as to whether associations with age at menarche represent an adverse health effect.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Cohort was large enough as analyses were performed using 282 women who were premenarcheal at the time of the explosion.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Environ Health Perspect, 2004, 112:1289–1292. Authors discuss use of pooled serum from residents of the unexposed zone, and that those in lowest exposure group had high exposures relative with contemporary levels for the area. Strengths of study include use of serum to estimate TCDD exposure.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. The SWHS included women between 1 month and 40 years of age at time of accident who attempted to get pregnant after the explosion ($n = 463$). This study is restricted to those who were premenarcheal at the time of the explosion ($n = 282$). Serum was collected for these women, primarily in 1976–1977 ($n = 257$), between 1978 and 1981 for 23, and in 1996–1997 for the 2 remaining women.

3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. TCDD exposures in 1976 were estimated by extrapolation serum levels obtained after this date using the Filser model. Both categorical and continuous measures of exposure were modeled. In utero measures of exposure are likely most relevant exposure based on findings from animal studies.
Conclusion	No association between TCDD levels and age at menarche was reported in the primary publication; however, a follow-up communication from Warner & Eskenazi (2005) reported a 10-fold increase in serum TCDD concentrations to be associated with an earlier age of menarche (HR = 1.20, 95% CI = 0.98−1.60, p for trend = 0.07) when analyses were restricted to 84 women under the age of 5 at the time of the accident. The TCDD exposure characterization of study subjects was based on serum data, and no major biases were introduced from the study design or analytical methods that were used. In the context of the RfD derivation, considerable uncertainty remains as to whether associations with age at menarche represents an adverse health effect, Therefore, dose-response analyses were not conducted for this study.

Table C-35. Eskenazi et al. (2005)—Age at menopause

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Outcome measures were obtained based on self-reported data collected from questionnaires. Studies have shown that self-reports of age at menopause are reported with accuracy and reliability, and among women with surgical menopause, the self-reported age correlated well with that on the medical records.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Data obtained from the questionnaire allow for the potential confounding influence of several potential confounders to be examined.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Risks of earlier menopause increased in the first four quintiles, with a statistically significant trend. No increased risk was noted in the highest exposure category (hazard ratio = 1.0 relative to lowest exposure group). The study authors suggest this is due to the "inverted U" dose response often seen with hormonally active compounds. Additionally, no statistically significant association was noted with log_{10}TCDD for the individual quintiles. More importantly, the biological significance of this result for the establishment of a LOAEL (that is needed in the context of the RfD derivation) could not be determined with confidence.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum concentrations of TCDD offer improved exposure assessment, although the critical exposure window is uncertain.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. The study included 616 women. Of these, 260 were premenopausal, 169 classified as natural menopause, 83 as surgical menopause, 24 as impending menopause, 33 as premenopausal, and 58 in an "other" category.
1. Criteria	Study is published in the peer-reviewed scientific literature.

Response	Criteria satisfied. Environ Health Perspect, 113:858–862 (2005). The authors highlight that this is first study to look at relationship between dioxin and age at menopause. Limitations of the study were that the lowest exposure group (≤20.4 ppt) included exposure levels that are far higher than background, and age at menopause was based on retrospective recall. A strength of study is ability to characterize TCDD using serum measures.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. The Seveso Women's Health Study collected serum sample which allowed TCDD exposures to be characterized. Those women ($n = 616$) who had not reached natural menopause at the time of the accident were included in the study. Serum measures collected in 1976/77 were available for 564 women, for 28 women, sera was collected between 1978 and 1981, while for 24 women, sera was collected in 1996/97.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. TCDD levels were estimated at the time of the explosion using available information on TCDD half-life. However, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis. The critical window of exposure can be estimated but is large and highly uncertain.
Conclusion	The biological significance of this result for the establishment of a LOAEL (that is needed in the context of the RfD derivation) could not be determined with confidence. Therefore, dose-response analyses were not conducted for this study.

Table C-36. Warner et al. (2007)—Ovarian function

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Ovarian cyst analysis based on women who underwent ultrasound ($n = 310$). Ovarian follicle analysis based on self-report on menstrual cycle and done in women in preovulatory cycle ($n = 96$) at time of ultrasound. Hormonal analysis based on women in last 14 days of cycle ($n = 129$).
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Data collected from self-reported questionnaires allow for the potential confounding influence of many risk factors to be taken into account. Some misclassification of outcome based on self-reports of menstrual cycle may bias risk estimates towards the null.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. There was no association between serum TCDD levels and the number or size of ovarian follicles. TCDD was also not associated with the odds of ovulation.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging given the nature of the very high initial exposure.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Cohort was large enough as analyses were performed using 129 women for ovulation outcome, and hormone analyses based on 87 women in luteal, and 55 in midluteal phases.

1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Environ Health Perspect, 2007,115:336–340. An important limitation cited by the authors was that women may not have been exposed at critical period (prenatally). Phases of the cycle may also have been misclassified as this was based on self-reported data. Strength, first study to have examined ovarian function and TCDD exposures.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. The SWHS included women between 1 month and 40 years of age at time of accident who were between 20–40 years of age and not using oral contraceptives at follow-up (*n* = 363).Of these, serum was collected for 330 women between 1976 and 1977, between 1978 and 1982 for 25 women, and between 1996 and 1997 for 8 women.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. There is a lack of a defined critical window of exposure in this study.
Conclusion	Because of the lack of a defined critical exposure window and absence of associations between TCDD and adverse health effects in this study, quantitative dose-response assessment was not conducted for this study. For these reasons, dose-response analyses were not conducted for this study.

Table C-37. Eskenazi et al. (2007)—Uterine leiomyoma

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Outcomes were determined using two definitions: current fibroids, or past diagnosis of fibroids. For past diagnosis of fibroids, self-reported data and medical records were used to determine whether women were previously diagnosed with fibroids, these were confirmed with medical records. A total of 25 women indicated they had never been diagnosed with fibroids. Medical records indicate a past diagnosis for these women, and they were classified as such. For current fibroids, this was determined at the time of the interview for 634 women using transvaginal ultrasound examinations.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. In the SWHS questionnaires were administered to the participants and detailed data for reproductive characteristics, smoking, body mass index, and alcohol use were collected so risks could readily be adjusted for these covariates.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied, but inverse associations reported. An inverse dose-response pattern with the percentage of women diagnosed (current and past history—combined) with fibroids across 3 categories of exposure. Namely, the percentages of women with fibroids in the ≤20, 20.1–75.0, and >75.0 ppt categories were 41.1%, 26.8%, and 20.0%, respectively.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. A variety of different exposure metrics were considered including linear, categorical, splines, and $\log_{10}$TCDD.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. A total of 251 women were found to have fibroids, and there were 62, 110, and 79 women with fibroids diagnosed in the 3 TCDD exposure categories.

1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 2007, 166:79–87. In this study, the authors found an inverse association between TCDD and uterine leiomyoma risk. The authors highlighted strengths of the study that included the longitudinal design, serum measures taken at an individual-level basis and most taken within 2 years of the accident, ability to include outcomes among those who did not take an ultrasound by using an adapted statistical approach. An important limitation that was the differences in risk by the stage of development could not be assessed as all women were exposed postnatally, and only 4 cases were observed among those who were premenarcheal at the time of exposure.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Final sample consisted of 956 women in the Seveso Women's Health Study without a history of fibroids. For 872 of these women, serum was collected in 1976 and 1977. For 56 women, TCDD was measured in women between 1978 and 1981, and for 28 women the serum was collected in 1996.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. TCDD exposures were back extrapolated to expected levels in 1976 (at the time of the accident). However, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis. The critical window of exposure is uncertain.
Conclusion	Because the critical window of exposure is uncertain, dose-response analyses were not conducted for this study.

1 **C.3.5. Other Seveso Noncancer Studies**

Table C-38. Mocarelli et al. (2008)—Semen quality

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Serum levels of TCDD were measured on an individual basis for men in exposed areas; pooled samples from men in uncontaminated areas were measured to assess background TCDD exposure levels.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. While compliance rates may have introduced some possible bias, this does not seem likely as different effects noted between the 22–31 and 32–39 year old age groups. Information collected for other risks factors, which have been used as adjustment factors in the models.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Figure 3 suggests dose-response relationship among those aged 1–9 at the time of the accident for sperm concentration and motility.

4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum concentrations of TCDD offer improved exposure assessment, although delineating the critical exposure window is challenging.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Analyses are based on 135 males exposed to TCDD.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Environmental Health Perspective s, 2008, 116(1):70–77. The authors describe strengths associated with characterization of exposure (using serum samples), and representativeness of study population. Limitation of study includes low compliance (but high for semen sample studies), namely, 60% among a group of healthy men. The compliance rate was higher among exposed group (69%).
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Involved males, <16 years old at time of accident.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. TCDD exposures were based on serum samples. Serum samples were drawn (in 1997/1998) from participants whose 1976 samples were above 15 ppt. Pooled samples obtained in 1997/98 were used to describe background TCDD levels in uncontaminated areas. The associated between TCDD exposure and semen quality was found statistically significant for the boys with 1 and 9 years of age at the time of the accident. This provides a critical window of exposure to estimate TCDD concentration.
Conclusion	Health outcomes are exposures are well characterized using serum data. However, the men exposed between the ages of 1 and 9 to elevated TCDD levels had reduced semen quality 22 years later. It is difficult to discern whether this effect is a consequence of the initial high exposure between 1 and 9 years of age or a function of the cumulative exposure for this entire exposure window beginning at the early age. Nonetheless, dose-response analyses for this outcome were conducted.

Table C-39. Mocarelli et al. (2000)—Sex ratio

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Birth records examined for those who lived in parents who lived in the area and who provided serum samples.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Paternal TCDD exposures were associated with an increased probability of female births ($p = 0.008$).
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum samples were used to estimate maternal and paternal TCDD levels. No discussion of exposure levels in reference population.

5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Statistically significant findings achieved.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. The Lancet, 2000, 355:1858–1863.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum levels of TCDD were obtained from parents using samples provided in 1976/77. Serum measures available for 296 mothers and 239 fathers.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Serum based measures of TCDD were obtained shortly after the accident. TCDD levels were also extrapolated to the time of conception. Although paternal pubertal exposures may be a key critical window for sex differentiation, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis.
Conclusion	The data from this study demonstrate a positive dose-response relationship with pubertal and pre-pubertal paternal TCDD levels at the time of the accident and increased likelihood for female births. However, it is difficult to identify the relevant time interval over which TCDD dose should be considered; specifically, it is difficult to discern whether this effect is a consequence of the initial high exposure during childhood or a function of the cumulative exposure for this entire exposure window beginning at the early age. Dose-response analysis for this outcome was not conducted, because EPA could not define the critical exposure window.

Table C-40. Baccarelli et al. (2008)—Neonatal thyroid function

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Measures of b-TSH are taken using a standardized protocol 72 hours after birth. These b-TSH measures are taken on all newborns born in the region of Lombardy which includes Seveso.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. For the comparisons involving place of residence at the time of the accident, exposure misclassification is likely given variability in soil TCDD exposure levels within these areas. For the individual TCDD measures (n=51) reported in the study figures, exposure misclassification is unlikely.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Mean neonatal b-TSH was 0.98μU/ml [0.90–1.08] in the reference area, 1.35μU/ml [1.22–1.49] in zone B, and 1.66μU/ml [1.19–2.31] in zone A ($p < 0.001$). The plotted frequency distributions have similar shapes, but have shifted to the right for areas of higher exposures. Neonatal b-TSH was correlated with current maternal plasma TCDD (β-0.47, $p < 0.001$) in the 51 newborns for which individual maternal serum TCDD values were available.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.

Response	Consideration satisfied. TEQs were measured among the 38 women for which serum samples were available and were defined for a mixture of dioxin-like compounds. Maternal mean total TEQs (PCDDs, PCDFs, coplanar PCBs, and noncoplanar PCBs) was 41.8 ppt. Two measures of exposure included place of residence at time of accident and plasma samples obtained from mothers at the time of delivery. Similarities in positive dose-response relationships give stronger weight to the findings.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For plasma based estimate of maternal TCDD there were 51 mother-child pairs. Only seven children in total were found to have b-TSH levels in excess of 5 μU/mL.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. PLOS Medicine 2008; 5(7)1133–1142. The authors discuss the strength of the study related to characterization of exposure using serum sampling, and ability to adjust for factors related to b-TSH or TCDD levels (gender, birth weight, birth order, maternal age, hospital and type of delivery). They also highlight that a limitation of study was that the influence of mother-child dioxin transfer through colostrum could not be assessed because no information on breast-feeding before b-TSH measurement was available.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. In the population-based study, eligible women who resided in zones A and B at the time of the accident ($n = 1,772$) were matched to nonexposed women. In the study based on plasma dioxin measurements, participants were the 51 children born to 38 women from zones A, B, R, or a reference zone for which plasma dioxin measurements were available.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Maternal TCDD levels were estimated at the time of delivery based on plasma samples, and the critical window of exposure was assumed to be the 9-month gestational period.
Conclusion	The data provide an opportunity for conducting dose-response analyses.

Table C-41. Alaluusua et al. (2004)—Developmental dental defects

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Ascertainment of dental health was done blind to place of residence, used standard protocol for caries developed by the WHO, and the clinical examination supplemented by radiographic examination.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Additional risk factor information was collected on questionnaires. These factors were considered as adjustment factors. The potential for participation bias is not possible to ascertain given the available information. The potential impact of exposure misclassification is also unknown, but the there is some suggestion that some individuals in the non-ABR zone may higher TCDD levels than expected based on background exposure concentrations.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.

Response	Consideration satisfied. Increased prevalence of developmental enamel effects found with increased TCDD serum measures. Namely, prevalence in unexposed region was 26%, whereas in the low, middle, and high TCCD groups the prevalence was 10%, 40%, and 60%, respectively.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. TCDD exposure level based on serum lipids. No discussion of exposure levels in reference population.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Despite small numbers, statistically significant findings were achieved.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Environmental Health Perspectives, 2004, 112(13):1313–1318. Authors mention two important strengths of the study: characterization of TCDD exposure using serum collected shortly after the time of the accident, and the fact that developmental defects are permanent in nature. Therefore, they represent a health outcome can evaluated years later. Little discussion was made of the impact of differential compliance rates between the exposed (74%) and nonexposed (58%) groups. Authors mention two important strength of the study: characterization of TCDD exposure using serum collected shortly after the time of the accident, and the fact that developmental defects are permanent in nature. Therefore, they represent a health outcome can evaluated years later. Little discussion was made of the impact of differential compliance rates between the exposed (74%) and nonexposed (58%) groups.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum levels of TCDD could be estimated for children in exposed areas. No serum levels were available for reference group of children, and assumption of zero exposure was made. This seems reasonable.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. It is difficult to discern whether this effect is a consequence of the initial high exposure during childhood or a function of the cumulative exposure of the entire exposure window beginning at early age. However, assumptions can be made regarding the critical window of exposure and the relevant dose can be calculated.
Conclusion	The considerations for conducting a dose-response analysis have been satisfied with the study population of only those subjects who lived in the ABR zone at the time of the accident; exposure data are unavailable for those in the referent area. While is difficult to identify the relevant time interval over which TCDD dose should be considered, dose-response analyses were conducted for this outcome.

Table C-42. Bertazzi et al. (2001)—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. For some causes of death methods highly specific mortality appears to be well captured from the vital statistics registries in the region (99% complete). Some health outcomes (e.g., diabetes) are subject to misclassification using death certificate data.

2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Although individual-level data for individual risk factors are not available, the potential for confounding is likely minimal. For e.g., independent surveys suggests similarity between smoking behaviors across the regions. Exposure misclassification based on place of residency likely to bias risk estimates towards the null.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. While a dose-response relationship was observed for chronic obstructive pulmonary disease across Zones A, and B, this relationship was not.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. Exposure classification was based on the address of the residence on the date of the accident or when the person first entered the area. Although TCDD blood levels were also measured, these were not examined with respect to health outcomes. The lack of individual-level data also precluded an examination of these uncertainties.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. A total of 494 noncancer deaths were found among residents of Zones A, and B, respectively. This allowed examined of gender-specific effects.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 2001, 153:1031–1044. Authors discuss lack of individual-level exposure data and other risk factors (e.g., smoking), difficulties in extrapolating to background levels, diagnostic accuracy of using death certificates. Strengths included similarities between exposed and comparison population for several risk factors, completeness of follow-up, and consistent methods to identify mortality outcomes in the exposed and comparison populations.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. Individual-level exposure data are unavailable. Exposure based on place of residence at time of the explosion. Soil sampling performed indicated considerable variability in TCDD levels within each region. In addition, place of residency at time of explosion does not ensure individuals were at their home around the time of the accident.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. An ecological measure of exposure (region of residency at time of accident) was used to categorize individuals according to their possible exposure. Latencies were considered. While such an approach has value for identifying whether excesses occurred among highly exposed populations, it is not precise enough to conduct dose-response analyses. Furthermore, noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	Study is not suitable for dose-response analysis due to mortality as endpoint and lack of individual-level exposure data.

Table C-43. Consonni et al. (2008)—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. For some causes of death detection methods were highly specific; mortality appears to be well captured from the vital statistics registries in the region (99% complete). Some health outcomes (e.g., diabetes) are subject to misclassification using death certificate data.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Although individual-level data for individual risk factors are not available, the potential for confounding is likely minimal. For e.g., information from other independent surveys suggests similarity between smoking behaviors across the regions. Exposure misclassification based on place of residency is likely to bias risk estimates towards the null.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Statistically significant association noted in most highly exposed area for chronic rheumatic disease and chronic obstructive pulmonary disease. Dose-response pattern noted across Zones A, B and R for circulatory disease mortality 5–9 years after the accident.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. Lack of individual-level data precludes an examination of these uncertainties.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied . However, only three deaths from diabetes occurred among residents of Zone A. The limitation related to statistical power is exacerbated for stratified analyses carried out by number of years since the accident.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Am J Epidemiol, 2008, 167:847–858. Authors discuss potential for selection bias, limitation of residential based measure of exposure, similarities of mortality ascertainment in exposed and referent populations, and multiple testing.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. Individual-level exposure data are unavailable. Exposure based on place of residence at time of the explosion. Soil sampling performed indicated considerable variability in TCDD levels within each region. In addition, place of residency at time of explosion does not ensure individuals were at their home around the time of the accident.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. An ecological measure of exposure (region of residency at time of accident) was used to categorize individuals according to their possible exposure. Latencies were considered. While such an approach has value for identifying whether excesses occurred among highly exposed populations, it is not precise enough to conduct dose-response analyses. Furthermore, noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	Study is not suitable further dose-response evaluation due to noncancer morality endpoint.

Table C-44. Baccarelli et al. (2005)—Chloracne

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Chloracne cases identified using standardized criteria.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Important potential confounders were included in the quantitative analyses conducted by the study authors.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. Plasma TCDD was associated with an increased risk of chloracne. The odds ratios increased in a dose-response pattern across zone of residence.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Authors discussed implications of differential elimination rates by age and body growth.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. A total of 101 chloracne cases were identified, and 211 controls were selected. Statistically significant findings were observed in several comparisons, although statistical power was limited to assess potential interactions.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. British Journal of Dermatology, 2005, 152, 459–465. The authors detail the limited statistical power they had available in the study. They also highlight study strengths that included uniqueness of age and sex distribution of chloracne cases, characterization of TCDD that could be done using sera samples, and availability of both clinical and epidemiological data.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. TCDD was estimated in both chloracne cases and control using serum measures.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria satisfied. Serum based measures of TCDD were obtained shortly after the accident. Chloracne is thought to be caused by the initial high exposure.
Conclusion	Exposure to TCDD at sufficiently high levels is recognized to cause chloracne. This study provides limited relevance to dose-response modeling of TCDD as exposure levels typically observed in the general population are much lower.

Table C-45. Baccarelli et al. (2004; 2002)—Immunological effects

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Common methods were used to describe blood levels of plasma immunoglobulins (IgA, IgG, and IgM) and complement components (C3 and C4).
2. Consideration	Risk estimates are not susceptible to important biases.

Response	Consideration satisfied. Both exposure and outcome were objectively and accurately measured.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. While plasma IgG levels were inversely related with TCDD, it is uncertain whether this outcome is adverse.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Both categorical (quintiles) and continuous measures of TCDD were examined in the dose-response analysis.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Analyses are made using 72 highly exposed, and 72 low exposed individuals.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Toxicology letters, 2004, 149:287–293 and Environ Health Perspect, 2002, 110(12):1169–1173. The authors highlight that few studies have looked at immunological effects of TCDD in humans, that the current study was able to exclude those with concurrent medical conditions, and the ability to characterize exposure using serum measures. Limitations addressed were the uncertainty about the clinical relevance of the dose-response pattern found, and the relatively small size of the study population.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. A total of 120 subjects were included in the study. This included 62 randomly selected from the high exposed zone, and 58 selected from the reference area.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Dose-response relationships were examined using current TCDD levels. However, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis.
Conclusion	An inverse dose-response relationship between IgG and TCDD was observed. However, the biological significance of a decrease in IgG for the establishment of a LOAEL (needed in the context of the RfD derivation) could not be determined with confidence. . Further the critical window of exposure that would cause an effect on IgG levels is not known and thus does not allow for estimation of the effective TCDD exposure. Therefore, dose-response analyses were not conducted for this outcome.

1 **C.3.6. Chapaevsk Study**

Table C-46. Revich et al. (2001)—Mortality (noncancer) and reproductive health

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration not satisfied. Insufficient details are provided in the paper to gauge the completeness and coverage of the cancer registry and the mortality data. Health outcomes were examined on the basis of information in the official medical statistics.

2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Given the aforementioned limitations of this ecological study, it is unclear to what extent the results may be subject to bias.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Dose response was not evaluated as exposure was based on residency in the region vs. no residency.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. No individual-level exposure estimates were used.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Population-based data over several years were used to make comparisons at the ecological level.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in Chemosphere, 2001, 43(4–7):951–966.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. It is a cross-sectional study that compares mortality rates between regions. No individual-level exposure data available.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. No individual-level exposure estimates were used in the study.
Conclusion	These cancer data are cross-sectional in nature; therefore, dose-response analyses were not conducted for this study.

1 **C.3.7. Air Force Health ("Ranch Hands") Study**

Table C-47. Henriksen et al. (1997)—Diabetes

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Newly diagnosed cases of diabetes following the completion of the veterans' tours of duty were identified from self-reported questionnaire data with verification from medical records, or by using a postchallenge glucose serum test. Disease severity was determined based on questionnaire, and review of medical records. Fasting glucose and 2-hour postprandrial glucose tests were used to identify glucose abnormalities among nondiabetics.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Adjustment was made for a number of risk factors related to diabetes (e.g., BMI, family history, smoking). However, variations in the solubility of dioxin due to between-subject differences in lipid fractions may account for the positive association observed. Many of the health outcomes under study (i.e., diabetes, impaired glucose tolerance, insulin resistance) are associated with lipid abnormalities.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.

Response	Consideration satisfied. There were statistically significant positive associations noted between TCDD and diabetes, as well as changes in serum glucose levels, reduced time to onset of diabetes, severity of diabetes, and glucose abnormalities among nondiabetics. While many of the comparisons are based on small numbers, overall, the associations are consistent across the outcomes that were examined.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The methods used to estimates TCDD levels are clearly described, and capture exposure at an individual-level many years before the health outcome was determined. The authors describe the limitations of the exposure assessment within the paper. Sensitivity analyses were undertaken for several of the key associations. The key limitation is that the associations may be caused by differences in lipid fractions between individuals.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. There were a total of 2,265 veterans and 315 cases of diabetes. There was very little attrition across the four physical examinations performed in 1982, 1985, 1987 and 1992.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. The paper was published in Epidemiology 1997;8:252-258. The discussion contains an appropriate discussion of the strengths and weaknesses of the study.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum was used to characterize TCDD exposure. While the quantification of TCDD levels at the time the tour of duty ended may be misspecified due to between-subject differences in lipid fractions, the methods used were able to reasonably discriminate between those veterans with high and low exposures.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. The nature of the data preclude identification of the critical window of exposure to be examined and a effective dose to be calculated for this endpoint.
Conclusion	While the health outcomes and TCDD exposures were characterized using valid methods, the nature of the data preclude identification of the critical window of exposure to be examined. Thus, dose-response modeling was not conducted for this study.

Table C-48. Longnecker and Michalek ([2000](#))—Diabetes

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Newly diagnosed cases of diabetes following the completion of the veterans' tours of duty were identified from self-reported questionnaire data with verification from medical records, or by using a postchallenge glucose serum test. Glucose and insulin measures were obtained among nondiabetics using fasting and 2-yr post challenge serum test.
2. Consideration	Risk estimates are not susceptible to important biases.

Response	Consideration not satisfied. Adjustment was made for a number of risk factors related to diabetes (e.g., BMI, family history, smoking). However, the analysis was cross-sectional in nature, and therefore was unable to take into account the timing of exposure in relation to diagnosis of diabetes. The increased solubility of dioxin in triglycerides, whose levels are higher in diabetics, may account for the positive association observed.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. There were statistically significant positive associations noted between TCDD and diabetes, as well between TCDD and serum glucose and insulin levels.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. The methods used to estimate TCDD levels are clearly described and are able to determine exposures at an individual level. However, the range of exposures is small given the exclusion of the more highly exposed Ranch Hand veterans. It is possible that between-subject difference in lipids and triglycerides may introduce an important source of exposure measurement error. The authors describe the limitations of the exposure assessment within the paper. The key limitations include the cross-sectional nature of the data, and the noncausal associations that may be caused by triglycerides.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. There were a total of 1,197 veterans and 169 cases of diabetes. Levels or participation across the multiple physical examinations were high.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. The paper was published in Epidemiology 2000;11(1):44-48. The discussion contains an appropriate discussion of the strengths and weaknesses of the study.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum-based measures are an objective and valid method to determine TCDD exposure levels.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. The diabetes cases were identified over a nearly 25-year interval. The nature of the data and analysis preclude identification of the critical window of exposure and estimation of an effective dose for this study.
Conclusion	While the health outcomes and TCDD exposures were characterized using valid methods, the data are essentially cross-sectional and thus are unable to evaluate associations between TCDD and diabetes that can take into account the timing of the exposure. Given the narrow range in TCDD exposures in this study, particularly given the Ranch Hand workers were excluded, these between-subject differences may introduce an important source of bias. Further, the nature of the analysis precludes identification of the critical window of exposure. Thus, dose-response modeling was not conducted for this study.

Table C-49. Michalek et al. (2001a)—Hematological effects

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Hematological measures were determined from serum samples obtained across four physical examinations.
2. Consideration	Risk estimates are not susceptible to important biases.

Response	Consideration not satisfied. Associations between TCDD and platelet counts may be influenced by other health conditions not accounted for by the study design. The positive association noted between TCDD and mean corpuscular volume may be noncausal. Specifically, this association may be due to raised triglycerides levels or increased prevalence of liver impairment among those more highly exposed to TCDD.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. Most hematological measures were not consistently associated with TCDD across the different physical examination periods. While positive associations between TCDD and platelet counts and mean corpuscular volumes were observed, they were not consistent with a dose-response relationship as statistically significant differences, relative to those in the lowest exposure group, were observed only among those in the highest exposure group.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The methods used to estimate TCDD exposure are clearly described, and capture exposure at an individual level prior to the diagnosis of the health outcome under study. The authors describe the limitations of the exposure assessment within the paper.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Continuous measures of hematological function approximately 2,200 veterans at four physical examinations. The study lacked adequate statistical power to perform the secondary analysis of the relationship between TCDD and abnormally high red blood cell counts.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. The paper was published in Archives of Environmental Health, 2001; 56(7):396-405.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum was used to characterize TCDD exposure at end of tour of duty. Given exposures dropped dramatically for the Ranch Hands following their tours of duty, exposure to TCDD prior to disease onset is reasonably characterized, though some misclassification between those in the comparison group and those in the lowest Ranch Hand exposure grouping is inevitable. Serum-based measures of hematological function were obtained at multiple examinations which permitted dose-response relationships to be evaluated at four time intervals.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. There is uncertainty in the critical window of exposure. This study analyzes the potential for associations between point-in-time measures of TCDD serum levels and changes in hematological measures that may have occurred at any time over approximately a 30-year interval. The clinical relevance of reported outcomes also is uncertain.
Conclusion	While the health outcomes and TCDD exposures were characterized using valid methods, most hematological measures were not associated with TCDD. For corpuscular volume and blood platelet levels an association with TCDD was detected. However, this association may be noncausal and the influence of other confounders cannot be entirely ruled out. The clinical relevance of these outcomes is also uncertain. Further, no dose-.response trend was observed with either of these two hematological measures. Additionally, there is uncertainty in the critical window of exposure. For these reasons, dose-response modeling was not conducted for this study.

Table C-50. Michalek et al. (2001b)—Hepatic abnormalities

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Hepatic function measures were determined from serum samples obtained across four physical examinations, and the prevalence of liver disorders was determined using self-reported data verified by medical records.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Associations between TCDD and liver function may be influenced by other health conditions not accounted for by the study design.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. No dose-response trend was observed with most measures of liver function. There was no association between TCDD and hepatomegaly or nonalcoholic chronis liver disease and cirrhosis. However, an association between TCDD was observed with γ-glutamyltransferase, and increased odds ratios of several hepatic disorders were observed among those in the highest TCDD exposure group relative to the comparison cohort.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The methods used to estimate TCDD exposure are clearly described, and capture exposure at an individual level prior to the diagnosis of the health outcome under study. The authors describe the limitations of the exposure assessment within the paper.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Continuous measures of liver function approximately 2,200 veterans during the 1992 physical examination. For some liver conditions, there were few prevalent cases across the exposure categories, however, statistically significant differences were observed for many conditions when comparisons where made between those in the highest exposure group relative to the lowest.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. The paper was published in Annals of Epidemiology 2001; 11:304-311.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum was used to characterize TCDD exposure at end of tour of duty. Given exposures dropped dramatically for the Ranch Hands following their tours of duty, exposure to TCDD prior to disease onset is reasonably characterized, though some misclassification between those in the comparison group and those in the lowest Ranch Hand exposure grouping is inevitable. Serum-based measures of liver function were obtained at the 1992 examination which permitted dose-response relationships to be examined.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. There is uncertainty in the critical window of exposure. This study analyzes the potential for associations between point-in-time measures of TCDD serum levels and liver disease that may have occurred at any time over approximately a 25-year interval the clinical relevance of the health endpoints that were examined is uncertain.

Conclusion	The results do not unequivocally support a relationship between liver damage and TCDD exposure. Confounding and reverse causality cannot be eliminated. Additionally, there is uncertainty in the critical window of exposure. This study analyzes the potential for associations between point-in-time measures of TCDD serum levels and liver disease that may have occurred at any time over approximately a 25-year interval, making it difficult to calculate a cumulative TCDD effective dose over time. For these reasons, dose-response modeling was not conducted for this study.

Table C-51. Michalek et al. (2001c)—Peripheral Neuropathy

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The outcomes were determined using a standardized neurological exam conducted by a board certified neurologist blinded to exposure status. A number of difference measures of peripheral neuropathy were obtained over multiple physical examinations.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Some of the observed associations may be due to residual confounding by diabetes.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. For some measures of peripheral neuropathy, the data were suggestive of a dose-response relationship, particularly for probable symmetrical peripheral neuropathy. However, only data from the 1997 examination yielded statistically significant increased odds ratio in the highest exposure category relative to the comparison cohort. Associations between TCDD and diagnosed peripheral neuropathy were evident in both 1992 and 1997, however, there were very few veterans diagnosed with this condition.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The methods used to estimate TCDD exposure are clearly described, and capture exposure at an individual level prior to the diagnosis of the health outcome under study. The authors describe the limitations of the exposure assessment within the paper.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration not satisfied. There were very few cases of peripheral neuropathy, particularly in the most highly exposed groups. Statistical significance was only achieved in a few instances, and in some cases, the odds ratios could not be estimated.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Neurotoxicology 2001: 22:479-490.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum was used to characterize TCDD exposure at end of tour of duty. Given exposures dropped dramatically for the Ranch Hands following their tours of duty, exposure to TCDD prior to disease onset is reasonably characterized, though some misclassification between those in the comparison group and those in the lowest Ranch Hand exposure grouping is inevitable.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.

Response	Criteria not satisfied. There is uncertainty in the critical window of exposure which impacts the ability to calculate an effective TCDD over time. This study analyzes the potential for associations between point-in-time measures of TCDD serum levels and peripheral neuropathy that may have occurred at any time over approximately a 30-year interval.
Conclusion	While an association was noted between peripheral neuropathy and TCDD levels, these comparisons were limited by a small number of outcomes particularly within the highest exposure group. Statistical significance was only achieved for some measures of peripheral neuropathy using data from the 1997 examination, but not in the other 4 examination periods. Residual confounding by undiagnosed diabetes may have distorted the measures of association, and this bias cannot be fully dismissed. Additionally, there is uncertainty in the critical window of exposure which precludes calculation of a cumulative TCDD effective dose over time. Multiple comparisons arising from conducting statistical tests of significant over multiple time periods, and measure of neuropathy raise the possibility of detecting a false-positive (spurious) association. For these reasons, dose-response modeling was not conducted for this study.

Table C-52. Pavuk et al. (2003) —Thyroid function and disorders

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Thyroid diseases among veterans in the Air Force Health Study were identified using questionnaire data collected in up to five examinations that were verified by a review of medical records. Measures of thyroid function were also determined using serum samples.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Exposure to TCDD was assessed using serum, and reasonably classified veterans based on their exposure prior to disease onset. Appropriate methods were used to analyze the data both longitudinally and cross-sectionally.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. There were no statistically significant associations between TCDD and thyroid diseases. No associations were noted between serum-based measures of thyroid function (T4, T3%, or FTI) and TCDD levels. While the data suggest a dose-response relationship between TCDD and TSH levels, the clinical implications are unclear. There were no statistically significant increased risks of abnormal TSH levels among those in the highest exposure group relative to the lowest for any of the five examination periods.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. The methods used to estimate TCDD exposure are clearly described, and capture exposure at an individual level prior to the diagnosis of the health outcome under study. The authors describe the limitations of the exposure assessment within the paper.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration not satisfied. There were 188 veterans who were diagnosed with a thyroid condition following their tour of duty, and comparisons between 6 different thyroid diseases and four TCDD exposure categories had poor statistical power. While there was a suggestion of increased TSH abnormalities among Ranch Hand in the highest exposure group, these findings did not achieve statistical significance for any of the 5 examination periods. Further follow-up of this cohort is needed as the age distribution of the cohort may be too young to detect associations between TCDD and thyroid function.

1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. The paper was published in Annals of Epidemiology 2003; 13:335-343. The authors have discussed the strengths and limitations of the study.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum was used to characterize TCDD exposure as of 1987. Given exposures dropped dramatically for the Ranch Hands following their tours of duty, exposure to TCDD prior to disease onset is reasonably characterized. Serum-based measures of thyroid function were obtained at multiple examinations which permitted dose-response relationships to be evaluated both cross sectionally and longitudinally.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. There is uncertainty in the critical window of exposure which impacts the ability to calculate an effective TCDD over time. This study analyzes the potential for associations between point-in-time measures of TCDD serum levels and thyroid conditions and measures of thyroid disorders that may have occurred at any time over approximately a 30-year interval.
Conclusion	While the health outcomes and TCDD exposures were characterized using valid methods, no associations were observed between TCDD and any of the six thyroid conditions studied. Additionally, no associations were noted with T4, FTI, or T3% in either cross-sectional or longitudinal analyses. There is some support for a dose-response relationship between TCDD and TSH, however, no statistically significant increase in abnormal TSH levels were observed among those in the highest exposure group at any of the 5 examinations. Therefore, the clinical implications of this dose-response relationship are unclear, particularly in light of the lack of associations between TCDD and any of the thyroid disorders examined. Additionally, there is uncertainty in the critical window of exposure, which precludes calculation of a cumulative TCDD effective dose over time. For these reasons, dose-response modeling was not conducted for this study.

Table C-53. Michalek and Pavuk (2008)—Diabetes

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. Prevalent diabetes identified from medical records from repeated medical check-ups. Preferred method of ascertaining outcome relative to use of death certificates.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Adjustment was made for a number of risk factors related to diabetes (e.g., BMI, family history, smoking) and other factors likely strongly associated with TCDD exposure (e.g., last calendar year of service, occupation, etc.).
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration satisfied. The RR for an increase in 10 units was 1.29 ($p < 0.001$), and the risks across the background, low and high exposure categories, relative to the unexposed were 0.86, 1.45, and 1.68.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.

Response	Consideration satisfied. Initial TCDD dose were estimated at the end of the tour of duty for the Ranch Hands. Individual-level serum dioxin measurements correlated well with correlated with days of spraying and calendar period of service, but collection of the samples roughly 20 years later required back-extrapolation.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. There were a total of 439 cases of diabetes identified.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. J Occup Environ Medicine, 2008, 50:330–340. The authors address strengths and limitations related to the accuracy of the one-compartment pharmacokinetic model, impact of the covariate time spent in Southeast Asia, and potential exposure misclassification on days sprayed.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. TCDD estimates were derived using serum samples.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. The nature of the data did not allow for latency or critical windows of exposure to be determined.
Conclusion	Because the nature of the data did not allow for the critical windows of exposure to be identified, dose-response modeling was not conducted for this study.

1 **C.3.8. Other Noncancer Studies of Dioxin**

Table C-54. McBride et al. (2009b)—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The New Zealand Health Information Service Mortality Collection and the Registrar-General's Index to Deaths were used to identify deaths. Additional searches were based on the last known address from the work record; the electoral roll and the habitation index; the telephone book; the internet; and Terranet property information database. An additional search was carried out through the Births, Deaths, and Marriages office of the New Zealand Department of Internal Affairs. Lastly, automated personnel and pension records were also used to locate past New Plymouth workers and identify some deaths.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration satisfied. Workers lost to follow-up (21%) were an unlikely source of bias since there was no evidence that this loss was differential in the internal analyses of workers. Confounding by sex, hire year, and birth year was addressed by adjustment in regression models. Potential confounding by other coexposures (e.g., 2,4,6-TCP) unlikely to have resulted in bias, due to presumed poor correlation with TCDD.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. There was no associations detected for mortality and the TCDD exposure surrogates. No dose-response trend was observed across the exposure categories of TCDD.

4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Cumulative exposure to TCDD as a time-dependent metric was estimated for each worker from serum samples, but the authors did not examine a continuous measure of TCDD exposure (lagged or unlagged).
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration not satisfied. Although the study had a large sample size (n=1,599 workers), extensive follow-up period (35 years) and considerable exposure gradient, a limited number noncancer deaths occurred. As such, mortality for some outcomes such as diabetes (based on 5 deaths) did not have adequate statistical power to examine potential associations. T he loss to follow-up of 21% of workers was also substantial. This would have impacted statistical power by reducing the number of deaths among the workers.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in J Occup Environ Med, 2009, 51:1049–1056. The other studies in the cohort highlight the 21% of the cohort lost to follow-up and the potential for other exposures during employment at the plant.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria satisfied. Serum measures available for 346 workers were used to derive TCDD exposures for the entire cohort using the area under the curve approach.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Effective dose could be estimated from serum-derived cumulative exposure estimates. Also, noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	A considerable portion of the cohort was lost to follow-up, and no dose-response associations were reported. In addition, since all outcomes were based on mortality, dose-response modeling was not conducted for this study

Table C-55. McBride et al. ([2009a](#))—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration satisfied. The New Zealand Health Information Service Mortality Collection and the Registrar-General's Index to Deaths were used to identify deaths. Additional searches were based on the last known address from the work record; the electoral roll and the habitation index; the telephone book; the internet; and Terranet property information database. An additional search was carried out through the Births, Deaths, and Marriages office of the New Zealand Department of Internal Affairs. Lastly, automated personnel and pension records were also used to locate past New Plymouth workers and identify some deaths.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. Considerable amount of workers were lost to follow up (22%), but it is unclear if bias resulted. The dichotomous exposure measure was based on exposure to TCDD, chlorinated dioxins and phenoxy herbicides, so confounding by these coexposures is possible.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.

Response	Consideration not satisfied. There was no associations detected for mortality and the TCDD exposure surrogates. Because no individual exposure estimates were available for these analyses, dose response could also not be evaluated.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Dichotomous exposure (exposed/unexposed) and duration of employment were examined from job exposure classification assessed via occupational history records industrial hygienists/factory personnel knowledge and questionnaires. Authors discuss limitations in the assignment of exposure among cohort members.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. The size of the cohort is large enough to characterize mortality risks relative to the general population for most common causes of deaths. A limitation of this study is the loss to follow-up of a substantial percentage of workers (22%). This would have impacted statistical power by reducing the number of deaths among the workers.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in Occup Medicine, 2009, 59(4):255–263. The authors highlight cohort lost to follow-up, the limited size of the cohort, differences in cohort definitions between sprayers and producers, and the potential for other exposures during employment at the plant.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. TCDD exposures were not quantified. The dichotomous exposure measure was based on exposure surrogates of TCDD, chlorinated dioxins and phenoxy herbicides.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. Effective dose could not be estimated given the lack of individual-level exposure data. Noncancer mortality is not a viable endpoint to consider for further dose-response analysis.
Conclusion	The study lacks the quantification of exposures at an individual level, and a considerable portion of the cohort was lost to follow-up. In addition, since all outcomes were based on mortality, dose-response modeling was not conducted for this study.

Table C-56. Ryan et al. (2002)—Sex ratio

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration not satisfied. Company records were used to identify births, the date of birth, and the sex of the child. No information was provided on the expected completeness of identifying births in this manner. Moreover, the study was expanded to include workers who heard about the study in a public forum. Therefore, the study could be influenced by participation bias.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. See above.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. The study compared birth ratios among men and women employed at the plant to the general population. No categories of exposure were examined.

4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration not satisfied. This is not relevant as no analyses were done in relation to exposure levels.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. For the categories of exposure used (yes/no), and the stratified analyses by sex and subcohort, the study allows for the birth ratios to be estimated with sufficient precision.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria not satisfied. Published in Environ Health Perspect, 2002, 110(11):A699–A701. The authors discussed the limitations of using serum collected many years after they stopped working to estimate TCDD exposures when the preferred metric would be TCDD levels at the time of conception. They did not address issues about the representativeness of the study participants to the entire cohort of workers, nor did they address the limitation of not being able to conduct dose-response analyses using individual-level TCDD data.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. While serum measures were available for 84 of the 198 participants of the study, birth ratios were compared between the cohort of 2,4,5-T and 2,4,5-trichlorphgenol workers relative to the city of Ufa. There was no attempt to derive birth ratios in relation to exposure levels. The serum data were only used to demonstrate that these workers, on average, had TCDD levels 30 times higher than Ufa residents.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. TCDD exposures were based on serum measures taken in some cases many years after children were born; no attempt was made to back-extrapolate to the time of conception.
Conclusion	Risk estimates have not been derived in relation to TCDD exposure levels. Uncertainties exist about the representativeness of the participants in relation to the cohort as a whole, and insufficient details are provided to evaluate the extent in which all births were identified. While these data could not be used for quantitative dose-response modeling, the much lower male:female birth ratio among exposed fathers is consistent with the finding by Mocarelli et al, and lends support to those findings. Dose-response modeling was not conducted for this study.

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Table C-57. Kang et al. (2002)—Long term health consequences

1. Consideration	Methods used to ascertain health outcomes are clearly identified and unbiased.
Response	Consideration not satisfied. Data collected from only half of the individuals in the study target population, thus, there is some potential for selection bias in this study. The study excluded those who had died before 1999, excluding potentially important TCDD-related adverse health effects that could result in death more than two decades after veterans had been actively spraying. Survey participation rates were modest: 72.9% for Vietnam veterans and 69.2% for non-Vietnam veterans. If those in poorer health were less inclined to participate, the prevalence of the selected chronic health conditions would be understated. The study relied on self-reported measures of disease prevalence increasing the possibility of recall bias.
2. Consideration	Risk estimates are not susceptible to important biases.
Response	Consideration not satisfied. See above.

3. Consideration	Study demonstrates an association between TCDD and adverse health effect.
Response	Consideration not satisfied. The data collected are cross-sectional, they are ill-suited for evaluating the relationship between the timing of exposure and the onset of disease.
4. Consideration	Exposure assessment methodology is clear and characterizes individual-level exposures.
Response	Consideration satisfied. Serum TCDD levels were available for 897 subjects, although the entire study population consisted of a group of 1,499 Vietnam veterans and a control group of 1,428 non-Vietnam veterans.
5. Consideration	Study size and follow-up adequate to estimate risk and ensure sufficient statistical power.
Response	Consideration satisfied. Size of study population likely provided sufficient study power to observe effects.
1. Criteria	Study is published in the peer-reviewed scientific literature.
Response	Criteria satisfied. Published in Chemosphere in 2001. The authors discussed the limitations of using collected sera.
2. Criteria	Exposure is primarily to TCDD and can be quantified to assess dose-response relationships.
Response	Criteria not satisfied. While serum TCDD measures were available for some of the study participants, there was no analysis of other contaminant exposures in the study population.
3. Criteria	Effective exposure is estimable latency and window(s) of exposure are examined.
Response	Criteria not satisfied. The critical exposure window could not be identified for the study.
Conclusion	A number of potential biases are present in this study. There is also potential confounding of results from exposures to other contaminants that have not been evaluated in the population. The critical exposure window cannot be determined. Dose-response modeling was not conducted for this study.

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C.4. REFERENCES

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APPENDIX D

Summaries and Evaluations of Cancer and Noncancer In Vivo Animal Bioassay Studies for Inclusion in TCDD Dose-Response Assessment

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NOTICE

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

CONTENTS—Appendix D: Summaries and Evaluations of Cancer and Noncancer In Vivo Animal Bioassay Studies for Inclusion in TCDD Dose-Response Assessment

DRAFT - DO NOT CITE OR QUOTE

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2 **IN VIVO ANIMAL BIOASSAY STUDIES FOR INCLUSION**
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5
6 **D.1. SUMMARY OF ANIMAL BIOASSAY STUDIES INCLUDED FOR TCDD**
7 **DOSE-RESPONSE MODELING**

8   This appendix summarizes studies that have already met the in vivo animal bioassay

9 TCDD study inclusion criteria (see Section 2.3.2). These studies are identified and described in

10 a tabular form in Section 2.4.2 of the main document in Tables 2-3 and 2-4, for cancer and

11 noncancer, respectively. Section D-2 of this appendix also provides a final list of the studies that

12 were selected (see Table D-1) and a list of those in vivo animal studies that were excluded (see

13 Table D-2), along with identification of the criteria that were not met for those studies. The

14 following study summary sections are organized by reproductive studies, developmental studies,

15 and general toxicity studies (subdivided by duration). They summarize the experimental

16 protocol, the results, and the NOAELs and LOAELs U.S. Environmental Protection Agency

17 (EPA) has identified for each included study.

18   To evaluate and discuss studies consistently, doses were converted to nanograms per

19 kilogram body weight per day (ng/kg-day) and were also adjusted for continuous exposure.

20 Some doses were adjusted based on daily dietary intake and body weight. For these studies,

21 EPA uses 10% of an animal's body weight as the daily feed rate. More commonly, doses were

22 adjusted from 5 days/week to a 7 days/week standard adjustment, in which case administered

23 doses were multiplied by 5 and divided by 7 to obtain continuous doses. To adjust for weekly

24 dosing, the weekly administered doses were multiplied by the administration frequency per week

25 (in days) and divided by 7 to give continuous doses.

26   Other exposure protocols used a single loading dose followed by weekly maintenance

27 doses. To adjust these doses, the loading dose was added to the maintenance doses multiplied by

28 the administration frequency, and this sum was divided by the exposure duration to give a

29 continuous dosing rate. The doses administered in single dose studies were not averaged over

30 the observation period.

31

D.1.1. Reproductive Studies

D.1.1.1. *Bowman et al. (1989a; 1989b) [and related Schantz and Bowman (1989); Schantz et al. (1986); Schantz et al. (1992)]*

Female rhesus monkeys (6 to 10 years old; 8 per treatment) were exposed to 0 or 5 ppt (for 3.5 years), or 25 ppt (for 4 years) TCDD (purity not specified) (Schantz et al., 1992; Bowman et al., 1989a; Bowman et al., 1989b; Schantz and Bowman, 1989; Schantz et al., 1986). Female monkeys were mated to unexposed males after 7 months (Cohort I) and 27 months (Cohort II) of exposure, and, then again 10 months postexposure (Cohort III). The average daily doses to mothers were equivalent to 0, 0.12, and 0.67 ng/kg-day. The 0.67 ng/kg-day dose group had reduced reproductive rates in both Cohorts I ($p < 0.001$) and II (Bowman et al., 1989b). The mean number of days of offspring survival ($p < 0.023$) also decreased. No effects on birth weight or growth, or physical evidence of toxicity (Bowman et al., 1989a) were observed. Behavioral effects were observed in the offspring (Cohort I: 7, 6, and 0 offspring, respectively; Cohort II: 3, 5, and 0 offspring, respectively; Cohort III: 6, 7, and 3, respectively). In the 0.67 ng/kg-day dose group, the number of offspring was insufficient to form a group in either Cohorts I or II. Offspring in the 0.12 ng/kg-day dose group had alterations in social behavior of the mother-infant pairs (mothers had increased care giving, which appeared to be an effect of the infants and not due to the treatment of the mother) and peer group of the offspring after weaning (Bowman et al., 1989a). The performance of learning tasks was inversely related to the level of TCDD in the body fat. Schantz and Bowman (1989) examined effects using discrimination-reversal learning (RL) and delayed spatial alteration (DSA). RL detected effects in the 0.12 ng/kg-day group as measured by retarded learning of the shape reversal ($p < 0.05$), but DSA did not. In another behavioral study, Schantz et al. (1992) placed two offspring (one male, one female) from the 0.12 ng/kg-day dose group of Cohort I into each of three peer groups that also consisted of two control monkeys tested in a large playroom for 1.5 hours/day, 5 days/week. Patterns of behavior were then watched beginning on the second day of socialization 4 days/week for 9 weeks. Play behavior, displacement, and self-directed behavior were significantly altered in the TCDD-exposed offspring. In a second experiment by Schantz et al. (1992) utilizing offspring from Cohort III (i.e., born after the cessation of maternal exposure to TCDD), four offspring from mixed treatment groups (i.e., control and 0.12 and 0.67 ng/kg-day dose groups; varying numbers of males and females per group) and 3−4 offspring from the same

1   treatment groups were placed into peer groups and assessed similarly as described above.

2   Behavioral changes were observed in peer groups containing only TCDD-exposed offspring, but

3   behavior was not altered in TCDD-exposed offspring socializing with control monkeys.

4   Additionally, Schantz et al. (1986) combined the cohorts and looked at 5, 5, and 3 mother-infant

5   pairs in the 0, 0.12, and 0.67 ng/kg-day groups, respectively. They found that TCDD-exposed

6   mother-infant pairs spent more time in close, social contact compared with the controls (mutual

7   ventral contact, $p < 0.025$; nipple contact, $p < 0.01$) and infants had reduced locomotor activity

8   ($p < 0.05$), but the dose effect was complex. Of note, the control groups contained fewer males

9   than did the TCDD-exposed groups.

10   From these reproductive studies in monkeys, a LOAEL of 0.12 ng/kg-day is established

11   for significantly altered social behavior in offspring from TCDD-exposed females (Schantz et al.,

12   1992). A NOAEL cannot be determined. However, there are several issues associated with

13   these data that confound their interpretation. For example, there were a small number of

14   TCDD-exposed offspring (only one male and one female) in a limited number of observed peer

15   groups (only three). The subjective nature of the experimental design (e.g., observing and

16   scoring the various social interactions and other behaviors among the offspring, the schematic of

17   the playroom apparatus, etc.) also contributes uncertainty to the data analysis. Additionally, the

18   biological significance of the alteration in social behaviors among the TCDD-exposed offspring

19   (e.g., increased initiation of social play as it pertains to overall social adjustment) is difficult to

20   assess. Furthermore, in a follow-up report by Rier et al. (2001b), DLC levels were quantified in

21   the sera of some of the maternal monkeys from the aforementioned studies 13 years after

22   termination of TCDD treatment. Rier et al. (2001b) reported that the animals had elevated serum

23   PCB77 and PCB126 levels and an increased serum TEQ. Although the cause of the elevated

24   PCB levels was unclear, the study authors speculated that "accumulation of PCBs in

25   TCDD-treated animals may have resulted from PCB exposure during TCDD administration due

26   to a contaminated TCDD solution or other inadvertent source." They also inferred that all the

27   animals may have been exposed to PCBs in their feed or other environmental sources. Taken

28   together, the multitude of confounding factors greatly decreases the confidence in the

29   dose-response data from aforementioned reproductive studies in monkeys.

30

D.1.1.1.1. *Supplemental published information on these rhesus monkeys [Rier et al. (1995; 1993)]*

Rier et al. (1995; 1993) examined the impact of chronic TCDD exposure on endometriosis. Female rhesus monkeys (eight animals per treatment group) were exposed to 0, 5, or 25 ppt TCDD (purity not specified) in feed for 4 years. Previously, Bowman et al. (1989a) determined that these dietary concentrations were equivalent to 0, 0.12, and 0.67 ng/kg-day, respectively. Ten years after termination of TCDD treatment, the presence of endometriosis was determined via laparoscopic surgical procedure, and the severity of the disease was assessed. The study authors reported that three monkeys in the 0.67 ng/kg-day exposure group died at 7, 9, and 10 years after termination of TCDD treatment. Autopsy results attributed the deaths to widespread and severe peritoneal endometriosis (all three monkeys) along with obstruction of the colon (one monkey) and blockage of the jejunum (one monkey). Other deaths also occurred in the control group (1 death from birthing complications and another from an unknown cause); in the 0.12 ng/kg-day dose group (1 death due to natural causes with no endometriosis), and in the 0.67 ng/kg-day dose group (1 death due to a breeding fight with no incidence of endometriosis). At study termination, 17 live animals and the 3 that had previously died of endometriosis were evaluated (total $n = 20$).

Incidence of endometriosis was significantly ($p < 0.05$) higher than in the control group with 71 and 86% incidence rates in the 0.12 and 0.67 ng/kg-day dose groups, respectively, compared with 33% in the control group. Severity of endometriosis was also significantly ($p < 0.001$) correlated with TCDD dose. Staging by rAFS indicated that untreated control animals had either minimal or no incidence of endometriosis. In comparison, endometriosis was absent in 2 of the 7 monkeys in the 0.12 ng/kg-day dose group, while only 1 of the 7 animals in the high-dose group was disease free. Moderate-to-severe disease was observed in 3 of the 7 animals in the 0.12 ng/kg-day dose group and 5 of the 7 animals in the 0.67 ng/kg-day dose group. Moderate-to-severe disease was not observed in the control group. The authors also compared the incidence and severity of endometriosis in TCDD-exposed animals with 304 normal, nonneutered females with no dioxin exposure and reported that the disease was not present in monkeys that were less than 13 years of age, while the disease rate was 30% among animals 13 years of age or older. The study authors report that these findings are in agreement

1 with human and rhesus studies demonstrating that the prevalence of detectable endometriosis can

2 increase with advanced age.

3 In a follow-up report, Rier et al. (2001b) examined the DLC and TCDD levels in sera

4 collected from 9 treated (*n* = 6, 0.12 ng/kg-day dose group; *n* = 3, 0.67 ng/kg-day dose group)

5 and 6 control female monkeys surviving from the Rier et al. (1995; 1993) study and 13 years

6 after termination of TCDD treatment. Additional studies were conducted on four monkeys that

7 died 7 to 11 years after TCDD exposure. Rier et al. (2001b) reported that treated animals in this

8 study had elevated serum TCDD, PCB77, and PCB126 levels, as well as an increased serum

9 TEQ; the fractional contribution of serum TCDD levels to total serum TEQ was 30% in treated

10 animals. Although the severity of endometriosis in the 15 monkeys examined was determined

11 previously (Rier et al., 1995; Rier et al., 1993), it was reevaluated and disease status was similar

12 between laparoscopies. Endometriosis severity corresponded to the serum PCB77

13 concentrations rather than total TCDD. As stated previously, the study authors speculated that

14 "accumulation of PCBs in TCDD-treated animals may have resulted from PCB exposure during

15 TCDD administration due to a contaminated TCDD solution or other inadvertent source." They

16 also inferred that all the animals may have been exposed to PCBs in their feed or other

17 environmental sources. Thus, in these studies, it is not possible to determine the contribution of

18 TCDD, alone, to the endometriosis due to the background contamination. These studies (Rier et

19 al., 1995; Rier et al., 1993), were not selected for TCDD dose-response modeling because

20 exposures were not to TCDD only.

21

22 **D.1.1.2.**   *Franc et al. (2001)*

23 To study the effects of subchronic, low-dose exposure to TCDD on the regulation and

24 expression of the aryl hydrocarbon receptor (AhR), Franc et al. (2001) used rodent models with

25 varying sensitivities to TCDD. Female Sprague-Dawley rats, inbred Long-Evans rats, and

26 outbred Han/Wistar rats (eight per dose group) were dosed via oral gavage with 0, 140, 420, or

27 1,400 ng/kg TCDD (>99% purity) dissolved in corn oil once every 2 weeks for 22 weeks (0, 10,

28 30, and 100 ng/kg-day average daily doses). Animals were sacrificed 10 days after the final

29 dosing. Body weights were recorded biweekly and just before sacrifice. After sacrifice, liver

30 and thymus weights were determined. Liver tissue samples were removed and either frozen for

31 RNA isolation followed by semiquantitative RT-PCR or homogenized and prepared for

1   subcellular fraction analysis. Radioligand binding and immunoblotting techniques were used to

2   measure AhR levels, and RT-PCR analysis was used to assess mRNA levels of AhR, aryl

3   hydrocarbon nuclear receptor (ARNT), and CYP1A1.

4   Long-Evans rats exhibited significant ($p < 0.001$) decreased weight gain over time as

5   compared with the Sprague-Dawley and Han/Wistar rats as determined by repeated measures

6   analysis of variance (ANOVA). Because body-weight gain varied indirectly with TCDD

7   exposure, liver and thymus tissue weights were normalized to body weight for data analysis.

8   TCDD exposure led to a significant ($p < 0.05$) increase in relative liver weights at all three

9   TCDD doses and in all three rat strains, compared with the control groups. At the upper end of

10 the TCDD dose range, Sprague-Dawley rats dosed with 100 ng/kg-day showed the greatest

11 increase in relative liver weights (160% of the control values), while the relative liver weights in

12 Long-Evans and Han/Wistar rats were similar to each other, and also were elevated above

13 control values by 10–20%. At the 30 and 100 ng/kg-day doses, the relative thymus weights were

14 significantly lower ($p < 0.05$) in all rat strains compared with their corresponding controls, but

15 the 10 ng/kg-day dose did not produce a statistically significant effect in any strain. However,

16 absolute thymus weight was higher at all doses in Han/Wistar rats, which also had a higher

17 control thymus weight.

18   Supporting observed differences in baseline TCDD sensitivity among the rat strains, liver

19 AhR levels in the control groups as measured by radioligand binding were similar for Sprague

20 Dawley and Han/Wistar rats, but were approximately twofold higher for Long-Evans rats. A

21 significant ($p < 0.05$) twofold, dose-dependent increase in radioligand binding of liver AhR was

22 observed at all TCDD doses relative to the control in Sprague-Dawley rats. At the 30 ng/kg-day

23 dose, the AhR level for Long-Evans rats was significantly ($p < 0.05$) increased to approximately

24 250% of the control level.

25   AhR protein levels measured in the liver cytosol by immunoblotting were highest in the

26 10 and 30 ng/kg-day TCDD dose groups for all three rat strains. Significant ($p < 0.05$) increases

27 in AhR levels were observed in the Sprague-Dawley rats that received 30 ng/kg-day, and in

28 Long-Evans rats that received either 10 or 30 ng/kg-day. A significant ($p < 0.05$) decrease in

29 AhR protein level was observed only at the 100 ng/kg-day dose in Han/Wistar rats. Liver AhR

30 protein was not detectable by immunoblotting in nuclear extracts for any strain or dose. The

1   study authors assert that AhR levels measured in cytosol correspond to measures in whole-tissue

2   lysates as demonstrated in their previous work.

3   Based on RT-PCR analysis, all three rat strains showed similar responses in liver AhR

4   mRNA following TCDD exposure. Liver AhR mRNA levels increased significantly ($p < 0.05$)

5   as compared with control levels in all rat strains at 10 and 30 ng/kg-day and in Long-Evans rats

6   at 100 ng/kg-day. The study authors observed that statistically significant increases in AhR

7   mRNA levels in the liver were not always associated with statistically significant increases in

8   AhR levels for a given strain and dose, but that the opposite (increases in AhR levels associated

9   with increases in AhR mRNA levels) was always true. Changes in liver ARNT mRNA levels

10   tended to increase with increasing TCDD dose, and the increases were significant ($p < 0.05$) in

11   the 30 ng/kg-day dose groups of Long-Evans and Han/Wistar rats. At the 100 ng/kg-day TCDD

12   dose, all rat strains showed a decrease in ARNT mRNA in the liver relative to controls with

13   significant ($p < 0.05$) differences for the 100 ng/kg-day TCDD dose groups of Sprague-Dawley

14   and Han/Wistar rats. Liver CYP1A1 mRNA induction was not detectable in control animals. A

15   significant ($p < 0.05$) increase in liver CYP1A1 mRNA was observed in all rat strains

16   administered 10 or 30 ng/kg-day TCDD. Liver CYP1A1 mRNA levels also were significantly

17   ($p < 0.05$) elevated above controls in the 100 ng/kg-day groups although not to the same extent

18   as in the 30 ng/kg-day groups. For all rat strains, the largest up-regulation for AhR and ARNT

19   mRNA levels occurred in the 30 ng/kg-day TCDD dose groups.

20   The NOAEL for TCDD identified in this study is 10 ng/kg-day TCDD. At 10 ng/kg-day

21   TCDD, the change in relative liver weight, while significantly ($p < 0.05$) increased in

22   Sprague-Dawley rats, was determined (Franc et al., 2001) to be less than 10% and judged by

23   EPA not to be biologically relevant. Also, at 10 ng/kg-day TCDD, the change in relative thymus

24   weight, was not statistically significantly decreased in Sprague-Dawley, Han-Wistar or

25   Long-Evans rats. The study LOAEL is 30 ng/kg-day based on statistically and biologically

26   significant increases in relative liver weight in Sprague-Dawley and Long-Evans rats and

27   statistically and biologically significant decreases in relative thymus weight in Sprague-Dawley,

28   Han-Wistar, and Long-Evans rats.

29

D.1.1.3.   *Hochstein et al. (2001)*

Adult female mink (12/treatment group) were administered dietary concentrations of 0.0006 (control), 0.016, 0.053, 0.180, or 1.40 ppb TCDD (purity >99.8%) for 132 days (Hochstein et al., 2001). This dose is estimated to be equivalent to 0.03 (control), 0.8, 2.65, 9, and 70 ng/kg-day assuming a food consumption of 5% of body weight per day. Females were mated with unexposed males beginning on treatment Day 35. Females were allowed to mate every fourth day during a 29-day mating period or until a confirmed mating. Mated females were presented with a second male either the day after initial mating or 8 days later. In the 70 ng/kg-day group, the treated animals were lethargic after 4 to 5 weeks, with several having bloody (tarry) stools near the end of the trial. Two animals in the 70 ng/kg-day dose group died prior to study termination. These animals had lost a large percentage of their body weight (24−43%), and had pale yellow livers and intestinal hemorrhages. Histopathology from both mink indicated marked diffuse hepatocellular vacuolation. The mean body weight decreased in all treatment groups including the control (losing an average of 3.29% of initial body weight), compared to a dose-dependent loss of up to 26% in the 70 ng/kg-day group. Mating and reproduction were considered subnormal in all groups. The number of females that gave birth in the 0.03 (control), 0.8, 2.65, 9, and 70 ng/kg-day dose groups were 5/12, 0/12, 3/12, 8/12, and 0/11, respectively. The study authors speculated that the subnormal breeding and reproductive performances in the control females likely were due to the indoor environment in which the mink were housed. In the three groups that gave birth, there was a dose-dependent decrease in kit body weight at birth, which was significant ($p < 0.05$) in the 9 mg/kg-day group compared with the controls. The body weight in the kits was not significantly different at 3 or 6 weeks after birth. The 3-week survival rates of 71, 47, and 11% were recorded for kits in the 0.03 (control), 2.65, and 9 ng/kg-day dose groups, respectively. Six-week kit survival rates were 62, 29, and 11% in the 0.03 (control), 2.65, and 9 ng/kg-day dose groups, respectively.

In the adult females, clinical signs of toxicity were noted in the 70 ng/kg-day group near the end of the study and included alopecia and notably thickened, deformed, and elongated toenails. There was a dose-dependent decrease in plasma total solids, total protein, and osmolality that reached statistical significance ($p < 0.05$) in the two highest exposure groups. Anion gap was significantly decreased ($p < 0.05$) and alanine aminotransferase was significantly increased in the 70 ng/kg-day group compared to the controls. At terminal sacrifice, there was a

1   dose-related decrease in body weight. There was a dose-related increase in liver weight that

2   reached statistical significance ($p < 0.05$) in the 70 ng/kg-day dose group. The brains of 42% of

3   the animals in the 70 ng/kg-day dose group had localized accumulation of lymphatic cells within

4   the meninges with mild extension into the adjacent neuropil and mild gliosis. Of the 10 mink

5   surviving to study termination in the 70 ng/kg-day group, 3 had periportal hepatocellular

6   vacuolation. These same brain and liver lesions were not observed in the control mink.

7   As there were no litters produced in the low-dose group and pregnancy outcomes were

8   not dose related, the 0.8 ng/kg-day exposure level does not inform the choice of NOAEL or

9   LOAEL. Thus, the LOAEL for this study is 2.65 ng/kg-day (132-day maternal exposure

10   duration) based on reduced kit survival (47% of control at 6 weeks). A NOAEL cannot be

11   determined for this study.

12

13   **D.1.1.4.   *Hutt et al. ([2008](#))***

14   Hutt et al. ([2008](#)) conducted a 3-month study investigating changes in morphology and

15   morphogenesis of preimplantation embryos as a result of chronic exposure to TCDD in female

16   rats. The study authors administered 0 or 50 ng/kg TCDD (>99% purity) in corn oil via oral

17   gavage to groups of three pregnant Sprague-Dawley rats on gestation days (GDs) 14 and 21 and

18   on postnatal days (PNDs) 7 and 14. The resulting female pups were divided into groups of 3 and

19   administered 0 or 50 ng/kg TCDD (>99% purity) in corn oil (equivalent TCDD doses of 0 and

20   7.14 ng/kg-day) on PND 21 and weekly thereafter until they reached 3 months of age. Pups

21   were then mated, fertilization was verified, and preimplantation embryos were harvested

22   4.5 days later. Preimplantation embryos were examined using immunofluorescence microscopy

23   to determine blastomere abnormalities.

24   No significant difference as compared with the control in preimplantation embryotoxicity

25   was observed following exposure to TCDD. Morphologically normal preimplantation embryos

26   were significantly ($p < 0.05$) reduced in the 50 ng/kg TCDD exposed rats (15 of 41, 36.6%)

27   compared with the control group (31 of 39, 79.5%). Preimplantation embryos of TCDD-exposed

28   rats included irregularities in mitotic spindles (13 of 18 were monopolar), chromosome patterns

29   in metaphase, blastomere size, and shape, blastomere nuclei shape in interphase, f-actin, and

30   cytokinesis. The study authors concluded that the compaction stage of preimplantation

31   embryogenesis is the most sensitive following exposure to TCDD.

1 A LOAEL for this study is 50 ng/kg (7.14 ng/kg-day adjusted dose) for a significantly

2 ($p < 0.05$) lower proportion of morphologically normal preimplantation embryos during

3 compaction stage in female Sprague-Dawley pups weekly for 3 months. A NOAEL cannot be

4 determined for this study.

5

6 **D.1.1.5.**   *Ikeda et al. ([2005b](#))*

7   Ikeda et al. ([2005b](#)) studied the effect of repeated TCDD exposure to F0 dams on the

8 male gonads of F1 generation and sex ratio in the F2 generation. Twelve female Holtzman rats

9 were treated with a single dose of 400 ng/kg TCDD (≥98% purity) orally, via gavage, followed

10 by weekly treatment doses of 80 ng/kg TCDD (16.5 ng/kg-day adjusted for continuous exposure

11 of 10 weeks; specified 2 weeks premating, assumed 1 week for successful mating, 3 weeks of

12 gestation, and specified 4 weeks to weaning) during mating, pregnancy, and lactational periods

13 (total exposure duration approximately 10 weeks). Corn oil served as the control in another

14 group of 12 dams. Four dams were sacrificed on GD 20 to evaluate the in utero toxicity of

15 TCDD. Litter sizes from the remaining eight dams were examined on PND 2, and some of the

16 F1 offspring were sacrificed to estimate TCDD tissue concentrations. The remaining offspring

17 were weaned on PND 28. Some of the F1 (number not specified) offspring were mated with

18 untreated females on PND 98, following which, litter size, sex ratio, weight, and anogenital

19 distance of F2 pups were examined on PND 2. Mated and unmated F1 males were sacrificed and

20 the testes, epididymis, seminal vesicle, and the ventral prostate were weighed; the cauda

21 epididymis was weighed and examined for sperm count.

22   All fetuses in the control and TCDD group as a result of in utero exposure in the

23 F0 generation survived. Litter size, sex ratio, and anogenital distance in the F1 generation on

24 PND 2 were not altered as a result of in utero TCDD exposure. Pup weight was significantly

25 ($p < 0.05$) lower in the TCDD-treated group than in controls. TCDD concentration in the

26 adipose tissue of the F0 dams on GD 20 was significantly ($p < 0.05$) higher than in the liver.

27 Adipose TCDD was significantly ($p < 0.01$) reduced at weaning, however, compared to

28 concentrations on GD 20. F1 pup liver TCDD concentration increased significantly ($p < 0.01$)

29 and was higher on PND 28 than PND2. The liver weight in F1 males increased by 14-fold at

30 PND 28 compared to PND 2, implying a transfer of approximately 850 pg of TCDD from the

31 dam to the F1 pup livers during lactation. TCDD also was detected in pup adipose tissue on

1 PND 28. Body weight of TCDD-exposed F1 males was significantly ($p < 0.001$) lower than

2 control males at weaning (PND 28). No significant differences in testis and cauda epididymis

3 weights were observed between the control and treated groups. Ventral prostate weight in the

4 F1 males exposed to TCDD, however, was approximately 60% lower than controls. No change

5 in weight of the body, brain, testes, cauda epididymis, or seminal vesicle was observed at

6 PND 120. Ventral prostate weight, however, was 16% lower than that of the control group

7 ($p < 0.001$). Sperm count in the cauda epididymis of the F1 males was not affected by TCDD

8 exposure.

9   Examination of F2 generation litters indicated no significant differences in litter size, pup

10 body weight, and anogenital distance between TCDD-treated or vehicle control groups. The

11 percentage of male F2 pups born to maternally and lactationally TCDD-exposed males was

12 significantly ($p < 0.05$) lower (38%) than those sired by control group males (52%). Every

13 female mated with maternally TCDD-exposed F1 males delivered more female than male pups.

14   A LOAEL for TCDD of 16.5 ng/kg-day for an estimated 10 week exposure duration in

15 F0 rat dams is identified in this study for decreased development of the ventral prostate in the

16 F1 generation (60% lower than controls) and for significantly ($p < 0.05$) altered sex ratio

17 (decreased percentage of males) in the F2 generation. A NOAEL cannot be determined for this

18 study.

19

20 **D.1.1.6.   *Ishihara et al. ([2007](#))***

21   Ishihara et al. ([2007](#)) examined the effect of repeated TCDD exposure of F0 males on the

22 sex ratio of F1 offspring. Seven-week-old male ICR mice ($n = 127$) were divided into three

23 groups and treated via gastric intubation with an initial loading dose of either 2 or 2,000 ng

24 TCDD/kg BW or an equivalent volume of sesame oil (vehicle) as control, followed by a weekly

25 maintenance doses of 0, 0.4, or 400 ng/kg until the animals were 12 weeks old. One week after

26 the last exposure, the animals were mated with untreated female mice. On the day a vaginal plug

27 was identified, F0 male mice were sacrificed and major organs including testes, epididymis, and

28 liver were removed and weighed. Organ tissues also were examined for histopathological and

29 immunohistochemical changes. Treatment levels, averaged over the 6 week period from start of

30 treatment to mating (five maintenance doses), were 0, 0.095, and 950 ng/kg-day for the control,

31 low dose and high dose groups, respectively.

1   All TCDD-treated males successfully impregnated untreated females and yielded viable

2   offspring. Mortality, pup weights, and mating and fertility indices were not affected by TCDD

3   exposure. There were no significant differences in body weights or in relative weights of testes,

4   epididymis, or livers in the TCDD-treated F0 males compared to the control group. The livers of

5   some animals (number not specified) in the high-dose group, however, were larger and heavier

6   than in the controls or the low-dose group. Hence, tissues from the high-dose animals were

7   selected for detailed immunohistochemical examination.

8   General histopathological findings in the TCDD-treated groups showed no changes in

9   cell morphology in germ, Sertoli, and Leydig cells of the testes. Arrangement of the germ cells

10   was normal and there was no difference in the epididymis spermatozoon number in either of the

11   TCDD-treated groups compared to controls. Livers of some of the animals in the high-dose

12   group however, showed enlarged and vacuolated areas in the centrilobular area when compared

13   to the low-dose group and the control group. Immunohistochemical and quantitative

14   immunohistological findings showed a marked increase in staining intensity for cytochrome

15   P450 (CYP)1A1 in the cytoplasm of the hepatocytes in the centrilobular area of the high-dose

16   TCDD group compared to the cells in the low-dose and the control groups. In addition,

17   proportions of immunoreactive CYP1A1 areas in the liver sections of the high-dose group were

18   higher than in the low-dose and control groups. The proportions of immunoreactive CYP1A1

19   also varied across animals ($n = 33$) in the high-dose group.

20   In addition to the above findings, there was a dose-related decrease in the male/female

21   sex ratio. The proportion of male offspring of the high-dose group was significantly lower

22   ($p < 0.05$) than that observed in controls (46.2% vs. 53.1%, respectively). Hepatic

23   immunoreactive CYP1A1 staining levels in individual F0 males were strongly correlated with

24   the sex ratio of their offspring.

25   A LOAEL for TCDD of 950 ng/kg-day for a 6 week exposure duration of F0 male mice

26   is identified for significantly ($p < 0.05$) decreased male/female sex ratio (i.e., higher proportion

27   of female offspring) in the F1 generation. The NOAEL is 0.095 ng/kg-day.

28

29   **D.1.1.7.**   *Latchoumycandane and Mathur ([2002](#)) [and related: Latchoumycandane et al.*
30   *([2003](#), [2002a](#); [2002b](#))]*

31   Latchoumycandane and Mathur ([2002](#)) conducted a study to determine whether treatment

32   with vitamin E protected rat testes from TCDD-induced oxidative stress. Groups of albino male

1 Wistar rats ($n = 6$) were administered an oral dose of 0 (vehicle alone) 1, 10, or 100 ng

2 TCDD/kg-day for 45 days, while another group of animals ($n = 6$) was coadministered TCDD at

3 the same doses, along with vitamin E at a therapeutic dose of 20 mg/kg-day for 45 days. At

4 study termination, animals were fasted overnight, weighed, and sacrificed. Testis, epididymis,

5 seminal vesicles, and ventral prostate were removed, weighed, and preserved for further

6 examination. The left testis was used to determine daily sperm production, while the right testis

7 was used for biochemical studies. Superoxide dismutase, catalase, glutathione reductase, and

8 glutathione peroxidase activity were measured in the testes, along with production of hydrogen

9 peroxide and lipid peroxidation. In a separate exposure protocol, groups of albino male Wistar

10 rats ($n = 4$) were administered an oral dose of 0 (vehicle alone) 100, 1,000, or 10,000 ng/kg-day

11 TCDD for 4 consecutive days (Latchoumycandane et al., 2003see summary in Appendix H); .

12   Body weights of TCDD-treated rats did not differ significantly from the control group.

13 Testis, epididymis, seminal vesicle, and ventral prostate weights in the TCDD-treated groups,

14 however, decreased significantly ($p < 0.05$) when compared with controls. None of these

15 changes were observed in the TCDD-exposed groups receiving vitamin E. There was a

16 dose-related decrease in daily sperm production ($p < 0.05$) in all three TCDD-treated groups

17 when compared with the control group. In contrast, the TCDD-treatment groups that also

18 received vitamin E did not show any significant changes in daily sperm production compared to

19 the controls. The TCDD-treated groups also showed significantly ($p < 0.05$) lower activities of

20 the antioxidant enzymes (superoxide dismutase, catalase, glutathione reductase, and glutathione

21 peroxidase) than the control group. Levels of hydrogen peroxide and lipid peroxidation

22 increased significantly ($p < 0.05$) in the testes of the rats treated with TCDD compared to the

23 corresponding controls. The TCDD-treated groups that had been coadministered vitamin E show

24 no difference in antioxidant enzyme activities or in reactive oxygen species production when

25 compared with controls.

26   A LOAEL for TCDD of 1.0 ng/kg-day for a 45-day exposure duration in rats is identified

27 in this study for significantly ($p < 0.05$) reduced sperm production and significantly ($p < 0.05$)

28 decreased reproductive organ weights. A NOAEL cannot be determined for this study.

29

1   **D.1.1.8.**   *Murray et al. (1979)*

2   Male (10−16 per treatment) and female (20−32 per treatment) Sprague-Dawley rats were

3   administered diets containing TCDD (purity >99%) to achieve daily dosages of 1, 10, or

4   100 ng/kg-day through three generations. After 90 days of treatment, F0 rats were mated to

5   produce F1a offspring. Thirty-three days after weaning of the last F1a litter, the F0 rats were

6   mated again to produce F1b offspring. Some F0 rats were mated a third time for a cross-mating

7   study. The F1b and F2 rats were mated at about 130 days of age to produce the F2 and

8   F3 generations. No clinical signs of toxicity or changes in body weight or food consumption

9   were observed in F0 rats during the 90 days of treatment before mating. The 100 ng/kg-day

10   group was discontinued due to the lack of offspring. In the three surviving offspring (all males),

11   no changes in appearance, body weight, or food consumption occurred. A dose of 10 ng/kg-day

12   caused a consistent decreased body weight in both sexes of F1 and F2 rats, which was associated

13   with decreased food consumption. A significant ($p < 0.05$) decrease in the fertility in the F1 and

14   F2 rats occurred in the 10 ng/kg-day group—but not in F0 rats. The number of live pups and

15   gestational survival index were significantly ($p < 0.05$) decreased in the 100 ng/kg-day F0 rats

16   and in the 10 ng/kg-day F1 and F2 rats. The gestational survival index also was significantly

17   ($p < 0.05$) decreased in F2 rats administered 1 ng/kg-day. Postnatal survival was significantly

18   ($p < 0.05$) reduced only in F2 rats administered 10 ng/kg-day. Growth (as measured by body

19   weight) was affected in the 10 ng/kg-day group only in the third generation. In the 10 ng/kg-day

20   group, a significant ($p < 0.05$) decrease in relative thymus weight and increase in liver weight

21   also occurred in F3 rats (weights were not measured in F2 rats). Additionally, mating

22   100 ng/kg-day TCDD-treated females with untreated males increased the percent of implants

23   resorbed as assessed by uterine histopathology.

24   The reproductive LOAEL is 10 ng/kg-day based on a significant ($p < 0.05$) decrease in

25   fertility (33−37% lower than controls); decrease in the number of live pups (18−27% lower than

26   controls); decrease in gestational survival (10−11% lower than controls); decrease in postnatal

27   survival (32% lower than controls); and decreased postnatal body weight (14−19% lower than

28   controls at weaning) in one or more generations. The reproductive NOAEL is 1 ng/kg-day.

29

D.1.1.9. *Shi et al. (2007)*

Pregnant Sprague-Dawley rat dams (3 per treatment group) were administered 0, 1, 5, 50, or 200 ng/kg TCDD (purity >99%) in corn oil by gavage on GD 14 and GD 21 and on PND 7 and PND 14 for lactational exposure to pups (Shi et al., 2007). Ten female pups per treatment were selected and administered TCDD weekly at the same dose levels through their reproductive lifespan (approximately 11 months). The corresponding equivalent daily TCDD doses are 0, 0.14, 0.71, 7.14, and 28.6 ng/kg-day. Vaginal opening was slightly—but significantly ($p < 0.05$)—delayed in the 28.6 ng/kg-day females. Vaginal opening was also delayed—but not significantly—in the 0.14 and 7.14 ng/kg-day females. Reproductive senescence with normal cyclicity was significantly ($p < 0.05$) accelerated beginning at 9 months in 7.14 and 28.6 ng/kg-day females. Serum estradiol concentrations were decreased at all time points across the estrous cycle in a dose-dependent manner with a statistically significant decrease ($p < 0.05$) in all but the lowest dose group. TCDD exposure, however, did not affect the number or size distribution of ovarian follicles; responsiveness of the pituitary gland to gonadotropin-releasing hormone, or serum profiles of FSH, LH, or progesterone.

A LOAEL for TCDD of 0.71 ng/kg-day for an 11-month exposure duration was identified in this study based on significantly ($p < 0.05$) decreased estradiol levels in offspring. The NOAEL for this study is 0.14 ng/kg-day.

D.1.1.10. *Yang et al. (2000)*

Yang et al. (2000) studied the impact of TCDD exposure on the incidence and severity of endometriosis in female rhesus monkeys. Groups of 7- to 10-year old nulliparous cynomolgus monkeys were treated with 0 ($n = 5$), 1, 5, or 25 ($n = 6$ per group) ng/kg BW TCDD 5 days per week via gelatin capsules for 12 months. Because the monkeys received 1 capsule 5 days per week, the doses adjusted for continuous exposure were 0, 0.71, 3.57, and 17.86 ng/kg-day. Prior to TCDD administration, all animals had endometriosis induced during Days 12–14 of the menstrual cycle by auto-transplantation of endometrial-strips in multiple abdominal sites. All TCDD-treated and control groups were laparoscopically examined during months 1, 3, and 6 to monitor the survival of endometrial implantations and to obtain peritoneal fluid to determine the concentration and immunotype of endometrial growth regulator cytokines interleukin-6 (IL-6) and interleukin-6 soluble receptor (IL-6sR). Because insufficient peritoneal fluids were present

1   in the treated and control monkeys, however, the study authors collected blood samples at 6 and

2   12 months during laparoscopy for routine hematology and to assess the circulating levels of IL-6

3   and IL-6sR. All animals were sacrificed at 12 months, and circulating levels of gonadal steroids

4   also were measured at the time of necropsy.

5   No changes were observed among treatment levels in general toxicological endpoints

6   such as body weight changes, food consumption, hematological endpoints, general activity

7   levels, and caretaker interaction. In addition, TCDD did not impact circulating levels of gonadal

8   steroids measured during necropsy. Similarly, there were no differences in the number of

9   menstrual cycles, the length of the menstrual cycle, or bleeding intervals. Endometrial implants

10   were found in at least one site in all TCDD-treated and control monkeys during the

11   first laparoscopic examination. Follow-up laparoscopies revealed that there was a continuous

12   loss of endometrial implants over time in each dose group. At the 1-, 3-, and 6-month

13   examination, the number of endometrial losses was not significantly different among different

14   dose groups. At the 12-month examination, however, a significantly ($p < 0.05$) higher rate of

15   survival of endometrial implants was observed in the 3.57 and 17.86 ng/kg-day dose groups

16   compared to the control group. The highest rate of endometrial implant survival was observed in

17   the ovaries regardless of the dose group. In contrast, all lesions disappeared from the left broad

18   ligament, whereas two on the right broad ligament and one on the uterine fundus survived.

19   There was a dose-dependent divergence in the growth response of endometrial implants

20   following TCDD exposure. Both the maximum and minimum implant diameters in the

21   17.86 ng/kg-day dose group were significantly ($p < 0.05$) larger compared to controls. In

22   contrast, the maximum and minimum implant diameters in the 0.71 ng/kg-day dose group were

23   significantly ($p < 0.05$) smaller compared to controls. TCDD did not impact implant diameters

24   in the 3.57 ng/kg-day dose group when compared to controls. Histological examinations

25   revealed that endometrial glands and stromal cells were present in all surviving implants.

26   Sections examined in the 17.86 ng/kg-day of TCDD possessed cystic endometrial glands that

27   were more frequently observed in this dose group compared to other groups including controls.

28   In addition, the circulating levels of IL-6 were significantly ($p < 0.05$) lower in monkeys exposed

29   to 17.86 ng/kg-day TCDD both at 6 and 12 months compared to the control group. In contrast,

30   the circulating levels of IL-6sR were significantly ($p < 0.05$) higher in animals treated with 3.57

1   and 17.86 ng/kg-day TCDD at 6 months, while the levels were higher only in the

2   17.86 ng/kg-day TCDD group at 12 months.

3   A LOAEL for TCDD of 17.86 ng/kg-day for a 1 year exposure duration was identified in

4   this study for significantly ($p < 0.05$) increased endometriosis induced by endometrial implant

5   survival, significantly ($p < 0.05$) increased maximum and minimum implant diameters, and

6   growth regulatory cytokine dysregulation (as assessed by significantly decreased IL-6 levels,

7   $p < 0.05$). A NOAEL of 3.57 ng/kg-day is identified in this study.

8

9   **D.1.2.   Developmental Studies**

10 **D.1.2.1.   *Amin et al. (2000)***

11   Amin et al. (2000) studied the impact of in-utero TCDD exposure on the reproductive

12 behavior in male pups. Groups of pregnant Harlan Sprague-Dawley rats ($n = 108$ divided into

13 4 cohorts; number of animals in the TCDD treatment group is ~3 per dose group) were dosed via

14 gavage with 0, 25, or 100 ng/kg-day TCDD (purity >98%) in corn oil on GDs 10−16. On the

15 day of birth (PND 0), pups were examined for gross abnormalities and the number of live pups,

16 their weights, and sex were recorded from each litter. Litters consisting of more than eight pups

17 were reduced to eight, composed of four males and four females when possible. Litters

18 consisting of fewer than five pups were excluded from the study to minimize between-litter

19 differences in growth rate, maternal behavior, and lactational exposure. After this exclusion,

20 approximately 10 to 11 litters per exposure group remained. All pups were weaned on Day 21

21 and one male and one female were retained to assess reproductive development, play behavior,

22 reproductive behavior, and saccharin preference behavior. Both male and female pups were

23 tested for saccharin preference between 189 and 234 days of age. A saccharin preference test

24 was conducted for 8 days. For the first 4 days, rats were provided bottles containing tap water,

25 and on Days 5 and 6 the animals were provided a bottle containing water and a bottle containing

26 0.25% saccharin solution. On Days 7 and 8, the animals were provided water and a bottle

27 containing 0.50% of saccharin solution. A 0.50% saccharin solution was used because previous

28 studies have reported that male rats exhibited a greater reduction in preference for this saccharin

29 concentration compared to females, hence the sex difference in preference is more marked at this

30 saccharine dose.

1   None of the treated dams exhibited any signs of toxicity as a result of exposure to TCDD.
2   Gestational body weight, liver weight, litter size, and percent live births were all comparable to
3   the corresponding control group. Birth rate and weaning weight of the pups also were not
4   affected by TCDD exposure. Sex-related water consumption, however, was significantly
5   ($p < 0.001$) affected during the first 4 days with female pups drinking more water per 100 g of
6   body weight compared to the respective male counterparts. Saccharin consumption was
7   significantly ($p < 0.001$) affected, with females consuming greater amounts of saccharin solution
8   per 100 g body weight compared with the corresponding males. Additionally, both male and
9   female pups drank significantly ($p < 0.001$) more of the 0.25% saccharin solution compared with
10   the 0.50% saccharin solution. Females of all exposure groups consumed less of both the 0.25
11   and 0.50% saccharin solution compared to the same-sex control group. Comparisons of each
12   exposure group to the control group indicated that only the high TCDD exposure group
13   (100 ng/kg-day) different significantly ($p < 0.05$) compared to control in the consumption of
14   0.25% saccharin solution. In contrast, for the 0.50% saccharin solution, both the low- and high-
15   TCDD-dose groups differed significantly ($p < 0.05$ and $p < 0.01$, respectively) compared to the
16   control group. The saccharin preference of TCDD-exposed male rats did not differ from that of
17   the male control group. The TCDD-exposed females' preference for saccharin solution,
18   however, was significantly reduced in both the 25 ($p < 0.05$) and the 100 ng/kg-day ($p < 0.005$)
19   dose group compared to that of the female controls. The study authors state that the reduction in
20   saccharin consumption and preference in females could be due to the antiestrogenic action of
21   TCDD and that recent research reports suggest that TCDD can decrease the level of estrogen
22   receptor (ER) mRNA by blocking the ability of ER to transactivate from the estrogen response
23   element.
24   A LOAEL for TCDD of 25 ng/kg-day for 7 days of gestational exposure is identified for
25   significantly ($p < 0.05$) decreased preference in the consumption of 0.25% saccharin solution. A
26   NOAEL cannot be determined for this study.
27

28 **D.1.2.2.** *Bell et al. (2007c)*
29   Bell et al. (2007c) examined the reproductive effects of TCDD in rats exposed during
30   development. Female CRL:WI (Han) rats were treated with TCDD (99% purity; dissolved in
31   acetone) in the diet at concentrations of 0 (acetone alone; $n = 75$), 28, 93, or

1   530 ($n = 65$/group) ng TCDD/kg diet, which provided average doses of 0, 2.4, 8, or

2   46 ng/kg-day, respectively. Rats were exposed to TCDD 12 weeks prior to mating, during

3   mating, and through pregnancy. Dams were switched to the control diet after parturition. Litters

4   from pregnant dams were reduced to a maximum size of eight on PND 4 and to five males (if

5   possible) on PND 21. These males were left untreated until sacrificed (25/group, one/litter) on

6   PND 70, while all remaining animals were sacrificed on PND 120. All sacrificed animals were

7   necropsied and received a seminology examination. Prior to sacrifice, during Weeks 12 and 13,

8   20 animals from each dose group were tested for learning ability and motor activity, and were

9   also administered a functional observation battery. During postnatal Week 16, groups of 20 male

10   F1 rats from each treatment group were paired with untreated virgin females for 7 days, and

11   mated females were killed on GD 16 and examined for terminal body weights, pregnancy status,

12   number of corpora lutea, and number of intrauterine implantations.

13   The study authors found no evidence of direct maternal toxicity from exposure to TCDD.

14   In the high-dose groups, 8 of 27 dams suffered complete litter loss compared with 3 dams in the

15   control group, but the difference was not statistically significant. Pup survival at PND 4 was also

16   lower in the high-dose group, but the difference again was not statistically significant.

17   A dose-related decrease in mean pup body weight was observed on PND 1, and this trend

18   continued throughout the lactation period. High-dose male pups had lower body weights when

19   compared to controls at PND 21, with this trend continuing over the course of the study.

20   Balanopreputial separation (BPS) was significantly ($p < 0.05$) delayed compared to controls in

21   all three treatment groups by 1.8, 1.9, and 4.4 days in the low-, medium-, and high-dose groups,

22   respectively. The study authors reported that adjustment for lower body weights observed at

23   PND 21 and PND 42 did not affect the estimate of delay in BPS. No adverse effects from

24   maternal treatment were observed on learning or in functional observational battery performance.

25   Offspring in the high-dose group exhibited less activity when compared to controls ($p < 0.05$)

26   when they were subjected to a test of motor activity for 30 minutes.

27   The median precoital time was 2−3 days for all 20 F1 males that were mated during

28   postnatal Week 16. The uterine and implantation data were similar in all dose groups and there

29   were no significant differences in the proportion of male offspring between groups. Epididymal

30   sperm counts and sperm motility did not differ significantly between dose groups in animals

31   sacrificed during postnatal Week 10. The mean number of spermatids was significantly lower

1 (14%; $p < 0.05$), and the proportion of abnormal sperm was significantly ($p < 0.05$) higher in the

2 high-dose group when compared to controls on PND 70. These effects, however, were not seen

3 in animals sacrificed on PND 120.

4   Terminal body weights were significantly ($p < 0.05$) decreased in the high-dose group

5 (6.9 %) compared to controls on PND 120, while the depression in body weight in the

6 medium-dose group (5.5%) was not statistically significant. At PND 70, the relative and

7 absolute testis weight of the high-dose group was less than the controls (12 and 18%,

8 respectively). Absolute spleen weight in the high-dose group was significantly higher (8%) on

9 PND 70, and increased significantly ($p < 0.05$) by 1−3% on PND 120 in all dose groups

10 compared to controls. Kidney weight in the low and medium-dose groups was significantly

11 ($p < 0.05$) greater than in controls (~2%) at PND 120. In addition to these organs, ventral

12 prostate (9.4%) and relative liver (~4.5%) weights were significantly ($p < 0.05$) higher than

13 controls on PND 120 in the medium- and low- and high-dose groups, respectively. On

14 PND 120, absolute brain weight was significantly ($p < 0.05$) less than the control in the

15 medium-dose group, while relative brain weight was significantly ($p < 0.05$) higher than the

16 control in the low- and high-dose group. Histological examination revealed no unusual findings.

17   A LOAEL for TCDD of 2.4 ng/kg-day following an estimated 17-week exposure

18 duration of dams was identified in this study for significantly ($p < 0.05$) delayed BPS. A

19 NOAEL was not identified in this study.

20

21 **D.1.2.3.**   *Franczak et al. ([2006](#))*

22   Franczak et al. ([2006](#)) examined the impact of chronic TCDD exposure on the onset of

23 reproductive senescence in female rats. Pregnant Sprague-Dawley rats ($n = 2$–3/dose group)

24 were fed 50 or 200 ng/kg TCDD (>99% purity) or corn oil vehicle (4 mL/kg) orally on GD 14

25 and 21 and PND 7 and 14 to provide in utero and lactational exposure to TCDD. On PND 21,

26 female pups ($n = 7$/dose group) were weaned and were subsequently given weekly doses of

27 either 50 or 200 ng/kg-week TCDD by gavage (7.14 or 28.6 ng/kg-day adjusted for continuous

28 exposure; administered doses divided by 7) or corn oil vehicle. Exposure continued for up to

29 8 months, and the animals were observed for changes in estrus cycle at 4, 6, and 8 months. Rats

30 were sacrificed at 8 months of age when the TCDD-treated animals had entered the transition to

1   reproductive senescence. Following sacrifice, diestrus concentrations of serum LH, FSH,

2   progesterone, and estradiol were measured, and the ovaries were collected for examination.

3   Estrus cycles at 4 months exhibited normal cyclicity in both TCDD-exposed groups and

4   did not differ significantly from the control group. At 6 months, however, there was a tendency

5   ($p < 0.1$) toward loss of normal estrus cyclicity in animals treated with TCDD. At the 8 month

6   observation, estrus cyclicity was significantly ($p < 0.05$) different in both dioxin-exposed groups

7   compared to controls (cumulative TCDD exposure is reported as 1.7 and 8 µg/kg for the 50 and

8   200 ng/kg dose groups, respectively). The study authors noted that although the low-dose

9   animals showed an increased prevalence of prolonged cycles, persistent estrus or diestrus was

10   observed in only 10% of the rats. Conversely, approximately 50% of the rats exhibited loss of

11   cyclicity in the high-dose group. There were no changes in the number and size distribution of

12   ovarian follicles or the number of corpora lutea at either dose. Progesterone levels at 8 months

13   tended to be higher ($p < 0.08$) in animals receiving either 7.14 or 28.6 ng/kg-day TCDD

14   compared to controls, while serum estradiol concentrations were significantly ($p < 0.03$) lower at

15   diestrus. Serum LH levels in TCDD-treated animals were comparable to those in the control

16   group, while FSH levels were elevated in rats receiving 7.14 ng/kg-day TCDD—but not in the

17   28.6 ng/kg-day dose group.

18   A LOAEL for TCDD of 7.14 ng/kg-day for an 8-month exposure duration was identified

19   for significantly ($p < 0.03$) decreased serum estradiol levels. A NOAEL cannot be determined

20   for this study.

21

22   **D.1.2.4.**   *Hojo et al. (2002) [and related: Zareba et al. (2002)]*

23   Hojo et al. (2002) studied the impact of prenatal exposure to TCDD on sexually

24   dimorphic behavior in rats. Thirty-six pregnant Sprague-Dawley rats were assigned according to

25   a randomized block design to groups receiving 0, 20, 60, or 180 ng/kg TCDD (98% purity) on

26   GD 8. Litters from pregnant dams were culled to 5 females and 5 males on PND 4 and allowed

27   to wean normally, at which time 5, 5, 6, and 5 litters from the 0, 20, 60, and 180 ng/kg TCDD

28   treatment groups, respectively, were maintained for examination of behavioral response.

29   Offspring were exposed to TCDD (from a single maternal exposure) for about 35 days through

30   gestation and lactation. After weaning at PND 21, offspring were fed ad libitum until PND 80, at

31   which time a fixed amount of food was supplied daily to maintain constant body weights. At

1   90 days old, the rats in these treatment groups were trained to press a lever to obtain food pellets

2   using two operant behavior procedures. Initially, each lever press was reinforced. The fixed

3   ratio (FR) requirement was then increased every fourth session from the initial setting of 1 to

4   values between 6 and 71. The responses for 30 days were studied under a multiple schedule

5   combining FR 11 and another schedule requiring a pause of at least 10 seconds between

6   responses (differential reinforcement of low rate, or DRL 10-seconds)

7   Pup and dam body weights were not affected by TCDD exposure, and all pups were

8   successfully trained in the lever-press response within 3–4 days. Analyses of the FR procedure

9   data indicated that the male pups responded at a lower rate at all TCDD doses when compared to

10 the control group. In case of female pups, all TCDD-treated groups responded at a higher rate

11 than controls. None of these results was, by itself, however, statistically significant.

12 Examination of the FR 11 and DRL 10-second data indicated that when considering the FR

13 component of this multiple procedure, males from all three treatment groups responded at lower

14 rates when compared to the controls. Conversely, all female pups responded at higher rates than

15 controls. In addition, the treatment-by-sex interaction was significant ($p = 0.036$), with the

16 60 ng/kg female pups responding at a higher rate than the 60-ng/kg male pups. Examination of

17 the delayed response component in the multiple FR 11 and DRL 10-seconds procedures

18 indicated that almost all TCDD treatment groups were affected. Like the FR component, male

19 pups at all TCDD dose groups responded at a lower rate compared to controls, while female pups

20 at all dose groups responded at a higher rate than controls. There was also a significant

21 ($p = 0.001$) sex-by-treatment interaction for the DRL 10-seconds similar to the FR component.

22 Following behavioral testing, the animals were sacrificed and cortical depth measurements were

23 taken in selected right and left brain regions. Reduced cortical thickness and altered brain

24 morphometry were observed in both male and female offspring in the 180-ng/kg exposure group

25 when compared to controls (Zareba et al., 2002).

26   A nominal LOAEL for TCDD of 20 ng/kg for a single exposure on GD 8 is established

27 for this study based on abrogation of sexually dimorphic neurobehavioral responses. A NOAEL

28 cannot be derived for this study.

29

D.1.2.5. *Kattainen et al. (2001)*

Pregnant Line A, B, and C rats derived from Han/Wistar and Long-Evans rats (4−8 pregnant dams/strain/treatment group) were administered a single gavage dose of 0, 30, 100, 300, or 1,000 ng/kg TCDD (purity >99%) in corn oil on GD 15 (Kattainen et al., 2001). On PND 1, the litters were culled to three males and three females. Offspring were weaned on PND 28. Female pups were sacrificed on PND 35 and male pups were sacrificed on PND 70. TCDD treatment did not affect body weight or cause clinical signs of toxicity in the dams. In Line B offspring, body weights in the 1,000 ng/kg group were slightly decreased during PND 1−7, while Line C offspring had slightly decreased body weights throughout the study period (data were not provided). The development of the third molar was affected the most in Line C offspring. In 5 of 10 Line C females and 6 of 10 Line C males treated with 1,000 ng/kg TCDD, the lower third molar did not develop. In comparison, 1 of 19 Line A females and 1 of 18 Line B females administered 1,000 ng/kg TCDD lacked the third molar at sacrifice. Third molars were present in all the controls and all male Line A and B offspring administered 1,000 ng/kg. Due to the lack of eruption of the third molar in the majority of Line B and C control females (only 30% erupted), however, the effects of TCDD on third molar eruption could only be evaluated in Line A female offspring (with 94% eruption). There was a dose-dependent decrease in the eruption of the lower third molar in Line A female offspring with a significant ($p < 0.05$) decrease observed in the 300 and 1,000 ng/kg dose groups. In the male offspring, any third molar that developed erupted by PND 70. The mesiodistal length of the existing lower third molar was reduced in a dose-dependent manner in both genders of all three rat lines. In Line A and C females, the decrease was significant ($p < 0.05$) at all doses. The size of the second molars was also significantly decreased with 1,000 ng/kg ($p < 0.05$) in all but Line C males.

A developmental LOAEL for TCDD of 30 ng/kg for maternal exposure on GD 15 is established for this study, based on impaired tooth development (significantly reduced mesiodistal length of the lower third molar by approximately 12% to 38% [$p < 0.05$]). A NOAEL could not be determined.

D.1.2.6.   *Keller et al. (2008a; 2008b; 2007c)*

Keller et al. (2008a; 2008b; 2007c) conducted three separate experiments to assess the impact of TCDD on molar tooth development using different mouse strains. In Experiment 1, Keller et al. (2007c) used six inbred mouse strains (C57BL/6J, BALB/cByJ, A/J, CBA/J, C3H/HeJ, and C57BL/10J) known to possess high affinity ligand-binding aryl hydrocarbon receptor alleles (*b*), two with *b1* alleles (C57BL/6J and CBA/J), and four with *b2* alleles (BALB/cByJ, A/J, C3H/HeJ, and CBA/J). Females (number not specified) from each strain were mated with males of the same strain. On GD 13, each pregnant female was assigned to one of the four dose groups and treated with 0, 10, 100, or 1,000 ng TCDD/kg BW via oral gavage. The control group received corn oil. GD 13 was chosen for dosing because the first morphological signs of tooth development occur on GD 11. The first visible signs of the M1 (molar) occur on GDs 13–14 followed by final cuspal morphology, which is determined on GD 15. The F1 offspring of females from each strain were weaned and separated by sex at PND 28 and were euthanized at PND 70. Each F1 mouse was examined for the presence or absence of both maxillary (M^3) and mandibular third molars (M_3) on both the left and right sides. In addition, all mice were scored as either normal or variant in M_1 morphology for both molar rows.

In Experiment 2 (Keller et al., 2008b), dams from six inbred mouse strains (C57BL/6J, BALB/cByJ, A/J, CBA/J, C3H/HeJ, and C57BL/10J) were orally dosed on GD 13 with 0, 10, 100, or 1,000 ng TCDD/kg BW in corn oil. GD 13 was used as the dosing day because it coincided with the formation of Meckel's cartilage (a major signal center) in the mouse mandible that is followed shortly by intramembranous bone formation on GD 15. The A/J mouse strain was abandoned because the authors had difficulty rearing the offspring from this strain. All offspring (*n* = 4 or 5 per treatment group) from the remaining strains were euthanized at 70 days of age. Mandible size and shape from all selected offspring were examined using geometric morphometric methods to assess the impact of TCDD exposure.

In Experiment 3 (Keller et al., 2008a), dams from six inbred mouse strains (C57BL/6J, BALB/cByJ, A/J, C3H/HeJ, CBA/J, and C57BL/10J) were treated with a single oral dose of 0, 10, 100, or 1,000 ng TCDD/kg-BW in corn oil. GD 13 was chosen as the dosing day because the first visible signs of the first molar (M_1) occurs on GDs 13–14 and the final cuspal morphology (the pattern of projections on the chewing surface of the tooth) is not determined until after GD 15. Similar to Experiment 2, the A/J mouse strain was abandoned due to difficulty in rearing

1   offspring. All offspring ($n = 107–110$ in each of the five strains for all treatment groups) were

2   euthanized at 70 days of age and their molar size, shape, and asymmetry traits were examined

3   using geometric morphometric methods.

4   In Experiment 1, all four M_3s were present in all dose groups in mice from C57BL/6J,

5   BALB/cByJ, and C57BL/10J strains. A similar response was observed in the A/J strain mice

6   with only 3 of 51 F1 mice exhibiting missing third molars. Approximately one-third of the mice

7   from the CBA/J and C3H/HeJ strains, however, were missing at least one M^3 or M_3 molar. The

8   numbers of CBA/J mice missing one or both M_3 or M^3 molars were 0/29, 2/21, 6/29, and 30/30

9   in the 0, 10, 100, and 1,000 ng/kg groups, respectively. In the C3H/Hej animals, the numbers

10   missing one or both molars were 1/24, 3/28, 1/26, and 30/36, respectively.

11   Maternal TCDD exposure was also found to affect the frequency of M_1 variants, but only

12   in the C57BL/10J strain, and the dose-response relationship was nonmonotonic. The proportions

13   of variants observed in the 0, 10, 100, and 1,000 ng/kg dose groups were 33, 68, 59, and 58%,

14   respectively.

15   A LOAEL for TCDD of 10 ng/kg maternal exposure on GD 13 is identified for this study

16   for increased incidence (33%) of the M_1 variant in the C57BL/10J mouse strain. A NOAEL

17   cannot be determined in this study.

18   In Experiment 2, TCDD exposure of dams did not affect offspring survival or 10-week

19   body weight in any of the inbred mouse strains used. Analysis of variance (ANOVA) indicated

20   that although mandible size in both male and female offspring varied significantly ($p < 0.0001$)

21   among strains, it was not affected by TCDD exposure. In contrast, analysis of covariance

22   indicated that TCDD exposure significantly ($p = 0.0033$) decreased the mandible size in male

23   offspring in the C3H/HeJ strain at all treatment groups. The mean mandible size was similar

24   across all treatment groups in both sexes in all strains with male offspring exhibiting larger

25   mandibles compared to females. Males in the C3H/HeJ strain exhibited a significant (level not

26   reported) downward trend in mandible size throughout all treatment groups. Females in the

27   C3H strain also showed a similar trend in mandible size—but the trend was not significant.

28   ANOVA on mandible shape indicated that males had significantly ($p < 0.0001$) different

29   mandible shape in strain × treatment groups. In contrast, in female offspring, although the

30   mandible shape was significantly ($p < 0.0001$) different due to strains, treatment groups, and

31   litter, the strain × treatment interaction was not significant. Male offspring from the C3H/HeJ

1   and C57BL/6J mouse strains appear to be more sensitive to TCDD than BALB/cByJ or

2   CBA/J mice, with the C57BL/10J strain exhibiting intermediate sensitivity. In addition to these

3   analyses, Procrustes distance analysis also indicated that C3H/HeJ mice had the greatest

4   response to the highest dose of TCDD, followed by the C57BL/6J strain. Female offspring in the

5   C3H/HeJ and C57BL/6J strains also exhibited the largest change in Procrustes distance with

6   TCDD exposure. This trend, however, was not statistically significant ($p = 0.29$).

7   A LOAEL for TCDD of 10 ng/kg maternal exposure on GD 13 was identified for this

8   study for significantly ($p = 0.0033$) decreased mandible shape and size in male C3H/HeJ mice.

9   A NOAEL cannot be determined in this study.

10   In Experiment 3, the effect of TCDD exposure on offspring survival or body weight was

11 not reported. Three-way ANOVA results showed significant ($p < 0.0001$) differences in molar

12 size among strains, sexes, and litters—but not among treatment groups. Molar size difference in

13 sex × strain interaction was significant ($p = 0.03$), whereas differences in sex × treatment and

14 sex × strain × treatment were not significant. Additionally, molar size in treatment × strain

15 interaction also was not statistically significant. Based on these results, the authors reported that

16 molar size varied significantly ($p < 0.0001$) among all five strains tested, with all strains

17 exhibiting similar trends in all four treatment groups. Strain differences in molar size were more

18 apparent in male offspring. A hormesis-like trend in molar size was observed in all strains

19 (except in BALBc/ByJ) and sexes with an increase at the 100 ng/kg dose and a decrease in the

20 1,000 ng/kg dose. In addition to lack of difference in molar size for all treatment groups in all

21 strains, fluctuating asymmetry in molar size also did not increase with increasing doses of

22 TCDD.

23   In contrast to these results on molar size, the Procrustes ANOVA indicated that molar

24 shape was significantly ($p < 0.0001$) affected by strain, sex, treatment, and litter size. Molar

25 shape in sex × strain and sex × strain × treatment interactions was also highly significant

26 ($p < 0.0001$). Based on these results, the authors concluded that differences between males and

27 females varied based on the strain, and that the effect of TCDD exposure on each strain also

28 differed for male and female offspring. Because molar shape in treatment × strain interaction

29 was significant ($p < 0.0001$), differences in molar shape between the three treatment groups and

30 the control group were analyzed for each strain using nonorthogonal contrasts. In male

31 offspring, contrasts between the control group and 1,000 ng/kg were statistically significant only

1   in the C3H/HeJ ($p < 0.0001$) and CBA/J ($p < 0.03$) strains. These results suggest that these

2   two strains are most susceptible to TCDD effect on molar shape, and similar results were

3   observed in female offspring of these two strains. The contrast in molar shape between the

4   control and the 100 ng/kg treatment group for the female C57BL/6J mice also was statistically

5   significant ($p = 0.0096$). On the whole, when considering Procrustes distance results for molar

6   shape, the C3H/HeJ male offspring had the largest response at the low and high doses, while the

7   female offspring had the largest response at low and mid doses. This observation in male

8   C3H/HeJ mice is consistent with that of TCDD-induced changes in mandible size from Keller

9   et al. (2008b).

10   A LOAEL for TCDD of 10 ng/kg maternal exposure on GD 13 is identified for this study

11 for significant ($p < 0.0001$) differences in molar shape in male C3H/HeJ mice. A NOAEL

12 cannot be determined in this study.

13

14 **D.1.2.7.   *Kuchiiwa et al. (2002)***

15   Kuchiiwa et al. (2002) studied the impact of in utero and lactational TCDD exposure on

16 serotonin-immunoreactive neurons in raphe nuclei on F1 male mouse offspring. Twenty-one

17 adult female ddY mice (seven per treatment group) were administered TCDD (99.1% purity) by

18 oral gavage once per week, for 8 weeks, at doses of 0, 4.9, or 490 ng/kg (0, 0.7, or 70 ng/kg-day

19 average daily dose; administered doses divided by 7) or an equivalent volume of olive oil vehicle

20 (6.7 mL/kg) by gavage. Immediately following the final treatment, the mice were housed with

21 untreated male mice for mating. At approximately 20–21 days after mating, 3 female mice from

22 each dose group, including the control group gave birth to 10–12 offspring. One day after birth,

23 each litter was culled to 10 offspring to accommodate similar lactational TCDD exposure. On

24 PND 28, the offspring were weaned, and three offspring from each TCDD exposed group and

25 the control group were selected for an immunocytochemical examination at 42 days of age.

26 Following sacrifice of these offspring, the brain of each animal was removed and every second

27 serial section of the brain was processed for immunocytochemistry. In addition to the serial

28 sections of the brain, cells from 18 offspring (6 males per treatment group) were used to assess

29 the number of cells in the dorsal and median raphe nucleus, the supralemniscal area, and the

30 Nucleus raphe magnus.

Examination of external morphology, birth, and postnatal body weights indicated that there were no differences between the male TCDD-exposed offspring and the control male offspring. TCDD-exposed males, however, were aggressive toward other normal mice and were also hypersensitive to soft touch.

Serotonin-immunoreactive neurons were found to be distributed throughout the entire brainstem in 42-day-old males, and the general pattern in the TCDD-exposed animals was consistent with those observed in control male offspring. Serotonergic neurons were identified and counted in the caudal linear nucleus, the median and dorsal raphe nucleus, Nucleus raphe pontis, interpeduncular nucleus, supralemniscal area, pedunculopontine segmental nuclei, deep mensencephalic nucleus, Nucleus raphe magnus, pallidus, and obscurus, dorsal and medial to the facial nucleus and the ventrolateral medulla. Results from computerized cell counts ($n = 6$) showed an average of 1,573.3 immunoreactive neurons in the raphe nuclei from the control group versus 716.3 and 419.8 neurons in the low- and high-dose offspring, respectively. The numbers of immunoreactive neurons in the individual raphe nuclei (dorsalis, medianus, magnus, and B9) from the TCDD-exposed offspring were significantly ($p < 0.01$) lower than control values, with the degree of reduction being dose-related.

A lowest-observed-adverse-effect level (LOAEL) of 0.7 ng/kg-day for an 8-week exposure duration is identified in this study for a significantly ($p < 0.01$) lower number of serotonin-immunoreactive neurons in the raphe nuclei of male offspring. A NOAEL cannot be determined for this study.

D.1.2.8.   *Li et al. (2006)*

Pregnant and pseudopregnant (obtained by mating normal estrous female mice with vasectomized male mice) NIH mice (10 per treatment group) were exposed to 0, 2, 50, or 100 ng/kg-day of TCDD (purity 99%) during early gestation (GDs 1–8), preimplantation (GDs 1−3), or peri-implantation to postimplantation (GDs 4–8) (Li et al., 2006). On GD 9, animals were evaluated. The two highest TCDD doses (50 and 100 ng/kg-day) caused significant ($p < 0.05$) early embryo loss independent of gestational exposure time. At 100 ng/kg-day, however, the embryo loss was greater when administered during GDs 1–8 or GDs 1–3 compared to GDs 4–8 ($p < 0.01$). Uterine weight was significantly decreased in the pseudopregnant mice when administered 50 or 100 ng/kg-day TCDD during GDs 1–8

1   ($p < 0.001$) or 1–3 ($p < 0.01$), but was only decreased at 100 ng/kg-day in pseudopregnant mice

2   when administered during GDs 4–8 ($p < 0.01$). Estradiol levels were increased at all TCDD

3   treatment levels (100% at the lowest dose), but statistical significance was not indicated. All

4   doses at all treatment times resulted in a significant reduction ($p < 0.01$) in serum progesterone

5   levels, with a 45% decrease at the lowest dose. Because the hormone effects were observed

6   following 4 days of treatment, the nominal doses were averaged over the entire test period of

7   8 days prior to measurement. The resulting average daily doses of TCDD were 0, 1, 25, and

8   50 ng/kg-day.

9   A LOAEL of 2 ng/kg-day administered for 4 to 8 days is established in this study for a

10 significant ($p < 0.01$) decrease in progesterone (45% above control) and an approximate twofold

11 increase in estradiol levels (significance not indicated). A NOAEL cannot be determined.

12

13 **D.1.2.9.**   *Markowski et al. (2001)*

14   Pregnant Holtzman rats (4–7 per treatment group) were administered a single gavage

15 dose of 0, 20, 60, or 180 ng/kg TCDD (purity not specified) in olive oil on GD 18 (Markowski et

16 al., 2001). One female rat from each litter (4–7 per treatment group) was assigned to training on

17 a wheel apparatus to respond on a lever for brief opportunities to run. Once animals responded

18 to an FR1 schedule of reinforcement, the requirement for lever pressing was increased to FR2,

19 FR5, FR10, FR20, and FR30 schedules. After each training session, the estrous cycle stage was

20 determined. Maternal body weight, length of gestation, number of pups per litter, and sex

21 distribution within litters were unaffected by treatment. For each of the FR schedules, there was

22 a significant dose-related ($p = 0.0001$) decrease in the number of earned run opportunities, lever

23 response rate, and total number of revolutions in the wheel in the adult female offspring. There

24 was no correlation between estrous cycle and responding for access to wheel running.

25   The developmental LOAEL for this study is a single dose of 20 ng/kg administered on

26 GD 18 for neurobehavioral effects. A NOAEL cannot be determined for this study.

27

28 **D.1.2.10.**   *Miettinen et al. (2006)*

29   Miettinen et al. (2006) administered a single oral dose of 0, 30, 100, 300, or 1,000 ng/kg

30 TCDD (purity >99%) in corn oil on GD 15 to pregnant Line C rats. The offspring (24–32 per

31 treatment group) were assigned to a sugar-rich cariogenic diet (via feed and drinking water) and

1   were orally inoculated three separate times with fresh cultures of *Streptococcus mutans*. Three

2   control groups varied with regard to TCDD exposure and administration of a cariogenic diet.

3   Two of the control groups received no TCDD, and the offspring were either maintained on a

4   normal diet without inoculation with *S. mutans* (C1; $n = 48$) or were given the cariogenic diet

5   with *S. mutans* inoculation (C2; $n = 42$). The final control group was maternally exposed to

6   1,000 ng/kg TCDD with offspring fed a normal diet without *S. mutans* inoculation (C3; $n = 12$).

7   TCDD did not affect the maternal or offspring body weight. Survival of the offspring was

8   reduced in the 1,000 ng/kg dose group (50–58% survival compared to 83–95% in C1 and C2,

9   respectively). All offspring administered 1,000 ng/kg were missing all lower third molars.

10   Two animals (8%) in the 100 ng/kg group were missing one of their lower third molars. All

11   doses—except the 100 ng/kg dose— caused a significant ($p < 0.05$) increase in the number of

12   caries lesions compared to group C2 (60, 79, 76, 83, and 91% in the C2, 30, 100, 300, and

13   1,000 ng/kg groups, respectively). Group C3 (1,000 ng/kg TCDD exposure, normal diet)

14   animals also had increased caries lesions compared to C1 (8 vs. 0%, respectively). There were

15   no detectable changes in tooth mineral composition that could explain the increase in caries

16   susceptibility.

17   The developmental LOAEL from this study is a single dose of 30 ng/kg administered on

18   GD 15 based on the significant ($p < 0.05$) increase in dental caries in pups (30% above control).

19   A NOAEL cannot be determined from this study.

20

21   **D.1.2.11.   *Nohara et al. (2000b)***

22   Pregnant Holtzman rats were administered 0, 12.5, 50, 200, or 800 ng/kg TCDD in corn

23   oil by gavage on GD 15 (Nohara et al., 2000b). On PND 2, five males were randomly selected

24   from each litter and dose group. TCDD was detected in the thymus, spleen, and bone marrow of

25   the male pups on PND 21 and PND 49. TCDD was still detected in the thymus and spleen on

26   PND 120 but the levels decreased over time. The TCDD concentration was highest in the

27   thymus at all time points. There were no changes in the body, thymus, or spleen weights of the

28   male offspring on PND 5, PND 21, PND 49, or PND 120. On PND 5, there was a 200-fold

29   increase in CYP1A1 in the thymus of the high-dose male pups. CYP1A1 was only slightly

30   increased in the spleen. This induction decreased through PND 49. There was a slight (not

31   statistically significant) dose-dependent decrease in thymus cellularity in the male offspring at

1 PND 120. Spleen cellularity at PND 49 decreased in a dose-dependent manner (15–50% of the

2 control), with a statistically significant ($p < 0.05$) decrease observed in the high-dose group. A

3 slight but not significant reduction in spleen cellularity was noted in the high-dose group at

4 PND 21. The same effect was not observed at PND 120, nor was there any change in the percent

5 of B or T cells in the spleen. No changes in cytokine levels were observed in the 800-ng/kg

6 group.

7   Although a change in spleen cellularity on PND 49 (puberty) was observed, this effect

8 was transient, and there were no coexisting changes in the percentage of splenic lymphocytes,

9 spleen weight, and cytokine levels. Therefore, a developmental NOAEL of a single dose of

10 800 ng/kg administered on GD 15 is identified for this study. A LOAEL is not established.

11

12 **D.1.2.12.   *Ohsako et al. (2001)***

13   Pregnant Holtzman rats (6 per treatment group) were administered 0, 12.5, 50, 200, or

14 800 ng/kg TCDD (purity >99.5%) in corn oil by gavage on GD 15 (Ohsako et al., 2001). On

15 PND 2, five males were randomly selected from each litter. Two male offspring from each litter

16 were sacrificed on PND 49 and PND 120. Neither maternal nor male offspring body weight was

17 affected by TCDD treatment. TCDD was detected in both the fat and testes at all dose levels

18 (including controls) with highest levels found in fat. There were no apparent treatment-related

19 effects on testicular weight, epididymal weight, daily sperm production, cauda epididymal sperm

20 reserves, luteinizing hormone, follicle stimulating hormone, or testosterone levels. There was,

21 however, a clear dose-dependent decrease in urogenital complex weight and ventral prostate

22 weight at both PND 49 and PND 120. For male offspring, statistically significant ($p < 0.05$)

23 decreases were noted in urogenital complex weight at PND 120 in the 200 and 800 ng/kg groups,

24 in ventral prostate weight at PND 49 in 800 ng/kg group, and at PND 120 in the 200 and

25 800 ng/kg groups. There was also a dose-dependent decrease in anogenital distance (the length

26 between the base of the genital tubercle and the anterior edge of the anus); the decrease was not

27 statistically significant at PND 49. At PND 120, however, male offspring in all but the lowest

28 dose group had significantly ($p < 0.05$) reduced anogenital distance compared to the control

29 animals. There was also a dose-dependent increase in 5αR-II mRNA expression in the ventral

30 prostate on PND 49 with significant increases ($p < 0.05$) in the 200 and 800 ng/kg animals.

31 There was a significant ($p < 0.01$) decrease in the androgen receptor mRNA in the ventral

1 prostate on PND 49 at all doses tested. Similar effects were not observed on PND 120 or in the

2 caput epididymis on PND 49.

3   The developmental LOAEL for this study is a single dose of 50 ng/kg administered on

4 GD 15 for significantly ($p < 0.01$) reduced anogenital distance in male offspring (approximately

5 14%). The NOAEL for this study is 12.5 ng/kg.

6

7 **D.1.2.13.**   *Schantz et al. ([1996](#))*

8   Schantz et al. ([1996](#)) studied the impact of in utero TCDD exposure on spatial learning in

9 male and female pups. Groups of pregnant Harlan Sprague-Dawley rats ($n = 108$, divided into

10 4 cohorts; number of animals in each TCDD group approximately 4 per treatment group) were

11 dosed via gavage with 0, 25, or 100 ng/kg-day TCDD (purity >98%) in corn oil on GDs 10−16.

12 On the day of birth (PND 0), the pups were examined for gross abnormalities and the number of

13 live pups, weight, and sex were recorded for each litter. On PND 2, litters were culled to eight

14 animals and were balanced to include four males and four females whenever possible. To

15 minimize litter-size effects, litters with fewer than five pups were excluded from the study. The

16 exclusion of these litters resulted in 10−11 litters per treatment group. Pups were weaned on

17 PND 21 and one male and one female pup from each litter were maintained for the learning tests.

18 Pups were tested 5 days per week for spatial learning and memory in a radial arm maze and a

19 T-maze. A radial arm maze working memory test and a T-maze DSA task were used a part of

20 the testing process.

21   TCDD treatment did not affect dam gestational weight gain, dam liver weight, gestation

22 length, litter size, percentage of live births, birth weight, or postnatal growth of the pups

23 observed during the course of the study. Exposed pups, however, exhibited some signs of

24 toxicity in all exposure groups. Thymus weight was decreased and liver weight was increased in

25 the 100 ng/kg-day TCDD dose group. Also, liver microsomal 7-ethoxyresorufin-O-deethylase

26 (EROD) activity was markedly induced in pups from both the 25 and 100 ng/kg-day dose

27 groups. In the radial maze test, rats from all TCDD exposure groups displayed a significant

28 ($p < 0.01$) learning behavior as shown by progressively fewer errors from the first block of

29 sessions through the fourth session. The treatment by sex and treatment by session block

30 interactions were not significant. Comparisons between the average number of errors per session

31 block in the TCDD-exposed and control group indicated that both the 25 and the 100 ng/kg-day

1   dose groups made significantly ($p < 0.05$ and $p < 0.001$, respectively) fewer errors compared to

2   the control group. TCDD did not significantly affect adjacent arm selection behavior as

3   measured by C statistic; hence the reduction in errors observed did not appear to be accounted

4   for by an increased tendency to run into adjacent arms. Female pups had a significant ($p < 0.05$)

5   shorter radial arm maze latency, however, compared to the male pups. In the T-maze test,

6   TCDD did not significantly affect the percent of correct performance. All exposure groups

7   performed best at the shortest delay, which showed a decline as the length of the intertrial delay

8   interval was increased. Additionally, all treated groups improved their performance over a

9   three-block session period. This finding indicated that animals in all groups could learn the task.

10   These observations were confirmed by a highly significant main effect of delay ($p < 0.001$) and

11   highly significant main effect of session blocks ($p < 0.001$). At the shortest 15-second delay,

12   average percent correct performance increased from 75 to 92%, while at the longest 40-second

13   delay, the average percent correct performance increased from 62 to 82%. A significant

14   ($p < 0.05$) main effect of exposure was evident in latency to respond in the T-maze.

15   Comparisons of the exposed group to control group, however, indicated that none of the

16   individual exposure groups differed significantly from the controls. Because no clear pattern

17   was observed in the various exposure groups, differences in latency to respond had no impact on

18   learning of the task.

19   Based on these results, the study authors state that the fact TCDD seems to have a

20   facilitatory effect on radial arm maze learning in rats should be interpreted with caution and

21   needs further evaluation using different and more varied learning tasks. No toxicologically

22   adverse endpoints were concurrently examined. Thus, a LOAEL and a NOAEL cannot be

23   determined for this study.

24

25   **D.1.2.14.** *Seo et al. ([1995](#))*

26   To study developmental effects of TCDD on thyroid hormone levels, time-mated female

27   Sprague-Dawley rat dams ($n = 10-14$/treatment group) were administered either 25 or

28   100 ng/kg-day of TCDD (>98% pure) in corn oil via gavage from GDs 10–16. Vehicle controls

29   received equivalent amounts of corn oil. The study also investigated PCB treatment outcomes.

30   At birth, pups were weighed and grossly examined for abnormalities. At 2 days of age, litters

31   with fewer than 5 pups were excluded from the analysis and the remaining litters were culled to

1   4 males and 4 females. Each treatment group contained 10 or 11 litters. Pups remained with the

2   dams until weaning. At weaning, 4−6 pups were retained for neurobehavioral tests (which were

3   not reported as part of this study). The remaining offspring were sacrificed, which provided

4   5−9 litters per treatment group. Data were collected from one male and one female when

5   possible. No signs of toxicity were evident in the dams; measurements on dams included

6   gestational weight gain, liver weight, litter size, and live births. Pup birth weight and weaning

7   weight were unaffected by treatment. In pups sacrificed at weaning (21 days old), a significant

8   ($p < 0.05$) decrease occurred in thymus weight for the high-dose group, but not in thyroid, liver,

9   or brain weight. A significant ($p < 0.05$) decrease (20.4%) was observed in T4 in high-dose

10 females. Thyroid stimulating hormone and T_3 were unaffected by treatment. Uridine

11 diphosphate (UDP)-glucuronosyl transferase activity towards 4-nitrophenol significantly

12 ($p < 0.05$) increased in both treatment groups over control values, and the increase in the

13 high-dose group was significantly ($p < 0.05$) greater than in the low-dose group. Liver

14 microsomal EROD activity was significantly ($p < 0.05$) increased in both treatment groups, but

15 is considered to be an adaptive response and not adverse.

16   A LOAEL of 100 ng/kg-day for decreased thymus weights and decreased thyroxine is

17 identified for this study. A NOAEL of 25 ng/kg-day is established.

18

19 **D.1.2.15.   *Sparschu et al. ([1971](#))***

20   Sparschu et al. ([1971](#)) studied the teratogenic and developmental effects of TCDD

21 exposure in rats. Groups of pregnant Sprague-Dawley rats were dosed via gavage with 0

22 ($n = 31$), 30, 125, 500, 2,000, or 8,000 (n = 10-14 per group) ng/kg-day TCDD (purity 91%) in

23 corn oil on GDs 6−15. Maternal body weights were assessed on GD 0, 6, 13, and 20, and all

24 dams were observed for clinical signs of toxicity throughout the test period. On GD 20, the

25 dams were sacrificed and evaluated for the numbers of pregnancies, implantation sites, corpora

26 lutea, and viable and dead fetuses. All removed fetuses were individually weighed, sexed, and

27 examined for external malformations as well as intestinal hemorrhage. One-third of the fetuses

28 were examined for skeletal alterations, and two-thirds for visceral abnormalities.

29   Clinical signs of toxicity in the dams included vaginal hemorrhage at ≥2,000 ng/kg-day at

30 various intervals throughout gestation. The study authors described dams in the 8,000 ng/kg-day

31 dose group as "thin" and showing "signs of debilitation." Maternal body weight gain was

1 significantly ($p < 0.01$) reduced compared to control values at doses ≥500 ng/kg-day on GD 13,

2 as well as at 500 ($p < 0.01$), 2,000 ($p < 0.001$), and 8,000 ng/kg-day ($p < 0.001$) on GD 20. No

3 significant differences were observed in fertility or the number of implantation sites or corpora

4 lutea at any dose tested. The mean number of viable fetuses per litter was significantly

5 ($p < 0.05$) decreased at 500 ng/kg-day compared to control. Only 7 viable fetuses were found

6 and occurred in 4 of the 11 total litters examined in the 2,000 ng/kg-day dose group, and there

7 were no viable fetuses in the 8,000 ng/kg-day dose group. The mean number of resorption sites

8 per litter was significantly increased at 500 ($p < 0.05$), 2,000 ($p < 0.001$), and 8,000 ng/kg-day

9 ($p < 0.001$).

10 No significant differences were observed in the fetal sex ratios at any dose tested. Mean

11 fetal body weight was significantly decreased compared to control values at 125 ($p < 0.01$), 500

12 ($p < 0.05$), and 2,000 ng/kg-day ($p < 0.001$) for males, and at 125 ($p < 0.01$) and 2,000 ng/kg-day

13 ($p < 0.001$) for females. Incidence of intestinal hemorrhage was increased on a per-fetus and

14 per-litter basis at doses ≥125 ng/kg-day. The incidence of tail and limb malformations was not

15 consistently increased over that of control. With respect to soft tissue abnormalities,

16 subcutaneous edema was observed at doses ≥125 ng/kg-day on a per fetus basis. Skeletal

17 abnormalities included delayed ossification of sternebrae and skull bones and wavy thirteenth

18 ribs, but these findings occurred throughout the various groups independent of dose and also in

19 controls.

20 The developmental LOAEL for TCDD of 125 ng/kg-day was identified for decreased

21 body weight in dams and male fetuses, as well as fetal intestinal hemorrhage and subcutaneous

22 edema. The developmental NOAEL in this study is 30 ng/kg-day. The maternal NOAEL and

23 LOAEL were 125 and 500 ng/kg-day, respectively, for decreased body weight gain.

24

25 **D.1.2.16.** *Smith et al. (1976)*

26 Smith et al. (1976) studied the teratogenic and developmental effects of TCDD exposure

27 in mice. Groups of pregnant CF-1 mice were dosed via gavage with 0, 1.0, 10, 100, 1,000, or

28 3,000 ($n = 14-41$ per group) ng/kg-day TCDD (purity not specified) in corn oil on GDs 6−15.

29 Maternal body weights were assessed on GD 6, 10, 16, and 18, and all dams were observed for

30 clinical signs of toxicity throughout the test period. On GD 18, the dams were sacrificed and

31 evaluated for the number of live, dead, and resorbed fetuses, and the livers were also removed

1   and weighed. All removed fetuses were individually weighed, sexed, measured, and examined

2   for external malformations. One-third of each litter was examined for soft tissue anomalies, and

3   all the fetuses were examined for skeletal anomalies. The litter was considered the experimental

4   unit of treatment and observation.

5   No significant differences were observed in maternal body weight at any time during

6   gestation at any dose tested. Relative liver weight in dams was significantly ($p < 0.05$) increased

7   in the 3,000 ng/kg-day dose group (13%) compared to control, but absolute liver weights were

8   not significantly changed at any dose tested. The percentage of resorptions per implantations

9   was significantly ($p < 0.05$) increased only at the 1,000 ng/kg-day dose compared to control.

10   There were no significant differences from control values at any dose in implantation sites per

11   litter, percentage of litters with resorptions, sex ratio, fetal body weight, and fetal length.

12   With respect to fetal anomalies among the litters, there was a significantly ($p < 0.05$)

13   increased incidence of cleft palate in the 1,000 and 3,000 ng/kg-day dose groups compared to

14   that of control. Additionally, there was a significantly ($p < 0.05$) increased incidence of litters

15   with bilateral dilated renal pelvis in the 3,000 ng/kg-day group compared controls. Although not

16   statistically significant, the incidence of exencephaly was greatest at the lowest dose level

17   (1.0 ng/kg-day). Because of this observation, an additional group of 30 mice were run through

18   the GD 6−15 treatment protocol at 1.0 ng/kg-day with another control group run concurrently

19   ($n = 24$). In this exposure, the incidence of exencephaly in the litters from treated dams was

20   comparable to that in the controls. The percentage of resorptions per implantations was

21   increased (12%, $p = 0.048$) over that of controls (8%); however, this effect was not observed in

22   the original 1.0 ng/kg-day exposure and the incidence was similar to that of the original control

23   animals (11%).

24   A maternal LOAEL of 3,000 ng/kg-day was identified for increased relative liver weight

25   in mouse dams. The maternal NOAEL is 1,000 ng/kg-day. A developmental LOAEL of

26   1,000 ng/kg-day was identified for increased incidence of cleft palate. The developmental

27   NOAEL is 100 ng/kg-day.

28

29   **D.1.2.17.   *Simanainen et al. ([2004b](#))***

30   Simanainen et al. ([2004b](#)) studied the impact of in utero and lactational TCDD exposure

31   on the male reproductive system in three rat lines that are differentially sensitive to TCDD.

1   Groups of 5 to 8 pregnant Line A, B, and C C57BL/6N CYP1A2 dams were given a single dose

2   of 0, 30, 100, 300, or 1,000 ng/kg of TCDD (purity >99%) in corn oil on GD 15 via oral gavage.

3   Control animals were similarly dosed with a corn oil vehicle. One day after birth, litters were

4   randomly culled to include three males and three females to allow uniform postnatal exposure.

5   Offspring were weaned on PND 28. Dam and pup viabilities were monitored throughout the

6   study. Pup body weights were determined on PNDs 1, 4, 7, 14, and 28. Anogenital distance and

7   crown-to-rump length were measured on PNDs 1 and 4. On Day 70, pups were sacrificed and

8   trunk blood was collected. Serum was collected for testosterone analysis. The testes, cauda of

9   the right epididymis, ventral prostrate, seminal vesicles, and thymus was dissected and weighed.

10   Absolute and relative organ weights were determined, and cauda epididymis and testes were also

11   preserved for sperm count analysis.

12   TCDD caused no mortality or overt signs of toxicity to the dams. Pup survival from

13   implantation to the day after birth also was not affected by TCDD exposure. Survival from the

14   day of implantation to the day after birth, however, was uncharacteristically lower in control

15   Line B rats (41%), resulting in a significant difference compared with the two lowest doses (30

16   and 100 ng/mg TCDD). The average survival percentage in the controls for Line A, B, and C

17   rats was 85% (range 80−86%); 64% (41−86%); and 74% (63−85%); respectively. Percentage of

18   male pup survival in each line between PND 1 and PND 28 was 99% except for Line B males

19   exposed to 30 ng/kg TCDD and Line C males exposed to 30 or 100 ng/kg, where male survival

20   rate averaged 81% (range 81−83%). On PND 70, a significant ($p < 0.05$) reduction in body

21   weight was observed only in Line B and C rats at 1,000 ng/kg. In pups exposed to 1,000 ng/kg

22   TCDD, both absolute and relative weight of the ventral, anterior, and dorsolateral prostrate

23   decreased in all three lines at most postnatal time points measured. The change was most

24   consistent and significant ($p < 0.05$) in the ventral lobe. Animals exposed to 1,000 ng/kg TCDD

25   had an average decrease in absolute weight of the anterior prostrate of 37, 32, and 34% in

26   Lines A, B and C, respectively. Additionally, the average dorsolateral prostrate weight was also

27   decreased by 34, 28, and 39% in Lines A, B, and C, respectively. The effect on the ventral

28   prostrate was reversible with the only significant ($p < 0.05$) decrease in weight observed in

29   Line B rats at PND 70 in the 1,000 ng/kg TCDD dose group. The authors reported that TCDD

30   had no consistent effects on the weight of seminal vesicles. The absolute weights of the testis

31   and epididymis showed a significant ($p < 0.05$) increase on PNDs 28−49, but the relative testis,

1   epididymis, and cauda epididymis weights remained unchanged. In pups exposed to

2   1,000 ng/kg TCDD, severe malformation, including small caput and cauda and degeneration of

3   corpus epididymis, was observed. Malformations in the epididymis were observed in 6 of

4   44 Line C male rat offspring and 3 of 47 Line A male rat offspring. In Line A, B, and C rats at

5   PND 70in the 1,000 ng/kg TCDD dose group, daily sperm production was reduced by 9, 25, and

6   36% and cauda epididymal sperm reserves were reduced by 18, 42, and 49%, respectively.

7   Daily sperm reduction (17%) was significant ($p < 0.05$) in Line C rats at a TCDD dose of

8   300 ng/kg and in Line B and C rats at 1,000 ng/kg. A reduction in cauda epididymal sperm

9   reserves (25%) was significant ($p < 0.05$) in Line C rats at 300 and 1,000 ng/kg TCDD.

10   A LOAEL for TCDD of 300 ng/kg is identified for reduction in daily sperm production

11   and cauda epididymal sperm reserves in Line C rats. A NOAEL of 100 ng/kg is identified for

12   this study.

13

14   **D.1.2.18.** *Sugita-Konishi et al. (2003)*

15   Sugita-Konishi et al. (2003) examined the immunotoxic effects of lactational exposure to

16   TCDD in newborn mice. Eight pregnant female C57BL/6NCji mice were administered 0, 1.8, or

17   18 ng/L of TCDD via drinking water from parturition to weaning of the offspring (for a total of

18   17 days). Based on an average water intake of 14–16 mL/day, the average daily intake of TCDD

19   for the dams was 1.14 and 11.3 ng/kg-day in the low- and high-dose groups, respectively. In

20   male offspring sacrificed at weaning (21 days after birth), there was a statistically significant

21   ($p < 0.05$) decrease in relative spleen weight and a statistically significant ($p < 0.005$) increase in

22   thymic CD4+ cells in the high-dose group. The changes in relative spleen weight and thymic

23   CD4+ cells were dose related, but effects in the low-dose group did not achieve statistical

24   significance. Changes in spleen weight and CD4+ cell numbers were not observed in the female

25   offspring. In a separate experiment, offspring infected with *Listeria monocytogenes* following

26   lactational TCDD exposure exhibited a statistically significant increase in serum tumor necrosis

27   factor alpha (TNF-α) 2 days after infection in both sexes in the low- ($p < 0.05$) and high-dose

28   ($p < 0.005$) groups. There was also a statistically significant increase in serum interferon gamma

29   in *Listeria*-infected high-dose females ($p < 0.05$). The number of bacteria in the spleen was also

30   significantly increased ($p < 0.05$) 2 days after infection in the high-dose females compared to the

1 controls, but not in males. *Listeria* levels in the spleen returned to control levels by 4 days after

2 infection in both sexes.

3 Based on these results, a LOAEL for TCDD of 11.3 ng/kg-day following a 17 day

4 exposure to dams was identified for significantly ($p < 0.05$) decreased spleen weight (in male

5 pups), a significant ($p < 0.005$) increase in thymic CD4+ cells (in male pups), and for increased

6 susceptibility to *Listeria monocytogenes* (in male and female pups). The NOAEL for this study

7 is 1.14 ng/kg-day.

8

9 **D.1.3. Acute Studies**

10 **D.1.3.1. *Burleson et al. (1996)***

11 Burleson et al. (1996) studied the impact of TCDD exposure on mice that were

12 challenged with the influenza virus 7 days after treatment with TCDD. Groups of 8-week-old

13 female B6C3F$_1$ mice ($n = 20$, 2 replicate groups) were treated one time with 0, 1, 5, 10, 50, 100,

14 or 6,000 ng/kg TCDD (purity >99%, dissolved in corn oil) via oral gavage. In addition to the

15 treated groups, randomly selected animals were assigned as a sentinel group and screened for

16 numerous pathogens. Results of all tests performed on this sentinel group were negative.

17 Seven days after TCDD treatment, all animals were lightly anesthetized and infected intranasally

18 with a highly lethal influenza A/Hong Kong/8/68 virus (H3N1; passage 14). The animals were

19 infected with sufficient H3N1 virus to achieve a 30% mortality rate in the control animals.

20 Animals were observed for mortality and morbidity for 21 days following viral infection.

21 Six mice from each treatment group were sacrificed on Days 3, 9, and 12 postinfection, and

22 body, thymus, and wet lung weights were recorded. Influenza viral titers were examined by

23 sacrificing eight mice each at 2 hours and at 1, 4, 6, 7, 8, 9, 10, and 11 days post infection.

24 Exposure to TCDD resulted in significantly ($p < 0.05$) increased mortality in the 10, 50,

25 and 100 ng/kg dose groups. No statistically significant difference in the percentage alive was

26 observed between these dose groups. TCDD doses of 1 and 5 ng/kg did not alter mortality in

27 influenza infected animals. A time-related increase in the wet weights of the lungs in infected

28 mice as a result of increased edema also was reflected in an increase in the lung

29 weight-to-body-weight ratio. The study authors stated that this ratio was not altered as a result of

30 TCDD exposure. TCDD-only exposures at 1, 10, or 100 ng/kg did not affect thymus weight.

31 Similarly, animals infected with the influenza virus following TCDD exposure also showed no

1   loss in thymic weight. Enhanced mortality in TCDD-treated animals was not correlated with an

2   increase in influenza virus titers. Additionally, animals treated with 1, 10, 100, or 1,000 ng/kg

3   did not affect pulmonary viral titer assays on Days 6, 7, and 8 postinfection. The authors also

4   concluded that TCDD did not alter Hong Kong virus replication or clearance.

5   Although these results support immunotoxic effects induced by TCDD, the findings were

6   not reproduced by Nohara et al. (2002a) using the identical study design, and the translation of

7   these findings to humans is dubious. Thus, no LOAEL/NOAEL was established. A LOEL for

8   TCDD of 10 ng/kg for a single exposure is identified for significantly ($p < 0.05$) increased

9   mortality in mice infected 7 days later with the influenza virus. The NOEL for this study is

10   5 ng/kg.

11

12   **D.1.3.2.** *Crofton et al. (2005)*

13   Crofton et al. (2005) studied the impact of TCDD exposure in addition to the impact of

14   mixtures of thyroid disrupting chemicals and PCBs on serum total thyroxine (TT4)

15   concentration. Groups of female Long-Evans rats were dosed via oral gavage with 0, 0.1, 3, 10,

16   30, 100, 300, 1,000, 3,000, or 10,000 ng/kg-day TCDD (purity >99%) in corn oil ($n = 14, 6, 12,$

17   6, 6, 6, 6, 6, 6, and 4, respectively) for 4 consecutive days. On the day following the last dose,

18   animals were sacrificed, trunk blood was collected, and serum obtained via centrifugation was

19   assayed for TT4 concentration using standard radioimmunoassay methods.

20   No visible signs of toxicity or changes in animal body weight as a result of TCDD

21   exposure were observed. Serum T4 levels showed a dose-dependent decrease, with the levels

22   dropping sharply beginning at 100 ng/kg-day dose. Percent serum T4 levels were 96.3, 98.6,

23   99.8, 93.3, 70.9, 62.5, 52.7, 54.7, and 49.1% in the 0.1, 3, 10, 30, 100, 300, 1,000, 3,000, and

24   10,000 ng/kg-day groups, respectively.

25   A LOAEL for TCDD of 100 ng/kg-day for 4 consecutive days of exposure is identified in

26   this study for a reduction in serum T4 levels (70.9% compared to 100% in controls). The

27   NOAEL for this study is 30 ng/kg-day.

28

29   **D.1.3.3.** *Kitchin and Woods (1979)*

30   Female Sprague-Dawley rats (nine per control and four per treatment group) were

31   administered a single dose of 0, 0.6, 2, 4, 20, 60, 200, 600, 2,000, 5,000, or 20,000 ng/kg TCDD

1   (purity >99%) in corn oil. Animals were sacrificed 3 days after treatment and CYP level and

2   benzo[*a*]pyrene hydroxylase activity in the liver were measured. A significant ($p < 0.05$)

3   increase in cytochrome P450 levels occurred with doses of 600 ng/kg or greater and in

4   benzo[*a*]pyrene hydroxylase activity with doses of 2 ng/kg or greater. Cytochrome P450 was

5   significantly ($p < 0.05$) higher 1 month after a single exposure of 2,000 ng/kg (the only dose

6   measured), but not after 3 or 6 months. Aryl hydrocarbon hydralase (AHH; $p < 0.05$) and EROD

7   ($p < 0.01$) were both significantly increased through 3 months after treatment, and although

8   elevated at 6 months, the results were not significant.

9   CYP induction alone is not considered a significant toxicologically adverse effect given

10 that CYPs are induced as a means of hepatic processing of xenobiotic agents. Thus, no LOAEL

11 or NOAEL was established for this study because adverse endpoints (e.g., indicators of

12 hepatotoxicity) were not measured. The acute LOEL, however, is 2 ng/kg based on a significant

13 ($p < 0.05$) increase in benzo[*a*]pyrene hydroxylase activity (37% above control). The NOEL is

14 0.6 ng/kg.

15

16 **D.1.3.4.   *Li et al. ([1997](#))***

17   Female Sprague-Dawley rats (22 days old; 10 per treatment) were administered a single

18 oral dose of TCDD (>98% pure) in corn oil via gavage at doses of 3, 10, 30, 100, 300, 1,000,

19 3,000, 10,000, or 30,000 ng/kg. Vehicle controls received equivalent amounts of corn oil, while

20 naïve controls were sham-treated only. In a preliminary time-course study, animals received a

21 single dose of 10,000 ng/kg and were sacrificed at 1, 2, 4, 8, 16, 24, 48, and 72 hours. The

22 time-course study showed two peaks in LH and FSH levels at 1 hour and 24 hours, with a

23 decrease to control values by 48 hours. Thus, in the dose-response study, animals were

24 sacrificed at 1 or 24 hours after treatment, blood was collected, and serum FSH and LH were

25 measured. The dose-response study demonstrated that the peak at 1 hour was related to the

26 vehicle as the peak also occurred in the vehicle controls, but did not occur in the naïve controls.

27 At 24 hours, FSH was increased at 10 ng/kg and higher (>fourfold increase at 10 ng/kg). Doses

28 of 10 to 1,000 ng/kg showed similar increases (not all reached statistical significance; $p < 0.05$).

29 A dose-dependent increase occurred for doses ≥3,000 ($p < 0.05$) with a maximum increase of

30 20-fold over the vehicle control. At 24 hours, the LH response significantly ($p < 0.05$) increased

31 only for doses ≥300 ng/kg with a maximum increase of 15-fold above the vehicle control. The

1   study authors calculated an ED_{50} of 500 ng/kg for gonadotropin increase. The dose-dependent

2   release of LH was confirmed in in vitro studies, but did not occur with the same magnitude. The

3   increase did not occur in calcium-free medium and was unrelated to gonadotropin releasing

4   hormone.

5   Based on the increase in serum FSH, the LOAEL was 10 ng/kg and the NOAEL was

6   3 ng/kg.

7

8   **D.1.3.5.** *Lucier et al. ([1986](#))*

9   Adult female Sprague-Dawley rats (six per treatment) were administered a single gavage

10   dose of TCDD (purity not specified) in either corn oil or contaminated soil at doses of 15, 40,

11   100, 200, 500, 1,000, 2,000, 5,000 (corn oil), or 5,500 (contaminated soil) ng/kg. Animals were

12   sacrificed 6 days later and livers were removed for analysis. No clinical signs of acute toxicity

13   or changes in body weight were observed at any dose. AHH increased in a dose-dependent

14   manner with significant ($p < 0.05$) increases observed at 15 ng/kg or greater in corn oil or

15   40 ng/kg or greater in contaminated soil. Cytochrome P450 was significantly ($p < 0.05$)

16   increased with doses of 1,000 ng/kg or greater in corn oil or 500 ng/kg or greater in contaminated

17   soil. A dose-dependent increase was observed for UDP glucoronyltransferase (significance of

18   individual doses not reported), with the results twice as high with corn oil than with

19   contaminated soil. The authors state that the results indicate bioavailability from soils is 50%.

20   Because the association between AHH activity and TCDD-mediated hepatotoxicity is

21   unknown and no adverse endpoints were measured, a LOAEL or NOAEL was not determined

22   for this study. The acute LOEL for this study is 15 ng/kg, based on the significant ($p < 0.05$)

23   increase (80% above control) in AHH. No NOEL is established.

24

25   **D.1.3.6.** *Nohara et al. ([2002a](#))*

26   Male and female $B6C3F_1$ (C57BL/6 × C3H), BALB/c, C57BL/6N, and DBA2 mice

27   (10−40 per treatment group) were administered a single dose of 0, 5, 20, 100, or 500 ng/kg

28   TCDD in corn oil via gavage. Seven days following TCDD treatment, mice were infected with a

29   mouse-adapted strain of influenza (A/PR/34/8; H1N1) at a plaque forming unit dose designed to

30   target approximately 30% mortality in each strain. TCDD did not affect the body weight or

31   survival in any of the infected mouse strains at any dose.

1   Therefore, no LOAEL is established in this study. The NOAEL is 500 ng/kg.

2

3   **D.1.3.7.   *Simanainen et al. ([2003](#))***

4   Simanainen et al. ([2003](#)) studied the short-term effects of TCDD exposure to determine

5   the efficacy and potency relationships among three differentially susceptible rat lines. The three

6   rat lines used were A, B, and C, and they were selectively bred from TCDD-resistant Han/Wistar

7   and TCDD-sensitive Long-Evans rats. The study authors reported that Line A rats were most

8   resistant to TCDD acute lethality followed by Line B and C. Groups of five or six randomly

9   selected rats (sex not specified) were treated with a single oral dose of TCDD (purity >99%) in

10   corn oil by oral gavage. The dose of TCDD was reported to range between 30 ng/kg and

11   3,000 µg/kg for Line A, 30 ng/kg and 1,000 µg/kg in Line B, and 30 ng/kg and 100 µg/kg for

12   Line C. Control animals were similarly dosed with a corn oil vehicle. Rats were sacrificed on

13   Day 8 postexposure, and trunk blood was collected and serum separated. Liver and thymus were

14   removed and weighed, and liver samples were collected and preserved. Liver EROD activity,

15   serum aspartate aminotransferase (ASAT) activity, free fatty acid (FFA) concentration, and total

16   bilirubin concentration were determined. Teeth were also examined.

17   Relative thymus weights were reduced 25% at 300 ng/kg relative to controls in Line B

18   rats. Liver enzyme (CYP1A1) induction, as measured by EROD activity, was evident at all

19   exposure levels; CYP induction is considered to be an adaptive effect and not adverse in itself.

20   No other endpoints were affected below 1 µg/kg in any of the three rat lines.

21   A LOAEL for TCDD of 300 ng/kg is identified for decreased relative thymus weight in

22   Line B rats. A NOAEL of 100 ng/kg is identified for this study.

23

24   **D.1.3.8.   *Simanainen et al. ([2002](#))***

25   To study the short-term effects of TCDD on hormone levels, adult female Long-Evans

26   (TCDD-sensitive) and Han/Wistar (TCDD-resistant) rats ($n = 9{-}11$/treatment) were administered

27   a single dose of TCDD (>99% pure) in corn oil via gavage at doses ranging from 30 ng/kg to

28   100 µg/kg. Vehicle controls received an equivalent amount of corn oil. The study also

29   examined other polychlorinated dibenzo-*p*-dioxins outcomes. Rats were sacrificed on Day 8

30   postexposure, and trunk blood was collected and serum separated. Liver and thymus were

31   removed and weighed, and liver samples were collected and preserved. Liver EROD activity,

1 serum ASAT activity, FFA concentration, and total bilirubin concentration were determined.

2 Teeth were also examined.

3   Neither FFA nor ASAT levels in Han/Wistar rats showed a dose-response relationship.

4 In Long-Evans rats, however, a significant ($p < 0.05$) dose-dependent increase in FFA occurred

5 at 300 ng/kg TCDD. Serum ASAT sharply increased in Long-Evans rats between 3,000 and

6 10,000 ng/kg. Body weight change and relative thymus weights were significantly decreased

7 ($p < 0.05$) in Han/Wistar rats with doses ≥10,000 ng/kg and in Long-Evans rats with doses

8 ≥1,000 ng/kg. Liver EROD activity was significantly ($p < 0.05$) increased with all doses in both

9 strains. Serum T4 was significantly ($p < 0.05$) decreased in Long-Evans rats at concentrations

10 ≥300 ng/kg, but were not significantly affected in Han/Wistar rats. Serum bilirubin was

11 significantly ($p < 0.05$) increased with doses ≥10,000 ng/kg in Long-Evans rats and

12 ≥30,000 ng/kg in Hans/Wistar rats. Both strains of rat showed a dose-dependent increase in

13 mean severity of incisor tooth defects. The results indicate that TCDD was the most potent

14 congener tested in both rat strains.

15   A LOAEL of 300 ng/kg for decreased T4 in the Long-Evans rat is identified for this

16 study. A NOAEL of 100 ng/kg is established.

17

18 **D.1.3.9.   *Smialowicz et al. ([2004](#))***

19   Smialowicz et al. (2004) examined the impact of TCDD exposure on immunosuppression

20 in mice. Groups of female (number not specified) C57BL/6N CYP1A2 (+/+) wild-type mice

21 were administered a single dose of 0, 30, 100, 300, 1,000, 3,000, or 10,000 ng/kg TCDD (purity

22 >99%) in corn oil via oral gavage. Control animals were similarly dosed with a corn oil vehicle.

23 To assess immune function, 7 days after TCDD administration, all mice were immunized with

24 sheep red blood cells (SRBCs) via injection into the lateral tail vein. Five days after

25 immunization, mice were sacrificed, blood was collected, and enzyme-linked immunosorbant

26 assays were performed. Additionally, spleen, thymus, and liver weights also were measured.

27   Body and spleen weights of the wild-type mice were unaffected by the TCDD exposure.

28 A decrease in thymus weights of the mice appeared to be dose related. Only mice treated with

29 10,000 ng/kg TCDD, however, showed a statistically significant ($p < 0.05$) decrease in thymus

30 weights compared to corresponding controls. Liver weights also showed a dose-related increase

31 with only animals treated with 3,000 and 10,000 ng/kg TCDD showing statistical significance

1 ($p < 0.05$) compared to the control group. The antibody response to SRBCs indicated a

2 dose-related suppression in the wild-type mice, with animals treated with 1,000, 3,000, and

3 10,000 ng/kg TCDD showing statistically significant ($p < 0.05$) suppression compared to the

4 controls.

5 　　　　A LOAEL for TCDD of 1,000 ng/kg is identified in female C57BL/6N CYP1A2 (+/+)

6 wild-type mice for significant ($p < 0.05$) suppression of SRBCs. The NOAEL for this study is

7 300 ng/kg.

8

9 **D.1.3.10.   *Vanden Heuvel et al. (1994)***

10 　　　　Vanden Heuvel et al. (1994) examined the dose-response relationship between TCDD

11 exposure and induction of hepatic mRNA. Groups of 10-week-old female Sprague-Dawley rats

12 were administered TCDD (purity ~99%) in corn oil once at 0, 0.1, 0.05, 1, 10, 100, 1,000, or

13 10,000 ng/kg-BW. Four days after TCDD treatment, animals were sacrificed and livers were

14 excised and preserved. Total hepatic RNA was extracted using guanidine thiocyanate and DNA

15 was removed using standard phenol-chloroform-isoamyl alcohol partitioning procedures.

16 Quantitative competitive RNA-PCR method was used to analyze CYP1A1,

17 UDP-glucuronosyltransferase I (UGT1), plasminogen activator inhibitor 2 (PAI2), β-actin, and

18 transforming growth factor α (TGFα). In addition to hepatic mRNA levels, microsomal protein

19 was assayed for EROD activity and livers were tested for TCDD concentration.

20 　　　　CYP1A1 mRNA induction levels in the TCDD-treated groups were low in the low-dose

21 region and sharply increased to plateaus at higher doses. The lowest dose that showed a

22 statistically significant ($p < 0.05$) difference compared to controls was the 1 ng/kg dose, which

23 showed a threefold increase in CYP1A1 mRNA levels. In contrast, a 130-fold increase occurred

24 at 100 ng/kg and a 4,000- and 7,000-fold increase occurred at 1,000 and 10,000 ng/kg,

25 respectively. A slight increase in the CYP1A1/β-actin levels was observed in the 0.1 ng/kg

26 group, but this increase was not significant. EROD activity exhibited a pattern similar to

27 CYP1A1 activity. EROD activity, however, was approximately 100-fold less sensitive

28 compared to mRNA levels in TCDD-treated groups. Statistical significance (*p*-value not

29 provided) in CYP1A1 level was observed at the 100 ng/kg dose compared to the 1 ng/kg dose.

30 The study authors reported that, despite this difference in CYP1A1 and EROD activity, the

31 correlation between CYP1A1 enzyme activity and mRNA levels was good. Dose-response

1 relationships for the induction of UGT1, PAI2, and TGFα mRNA differed from what had been

2 observed for CYP1A1 mRNA. UGT1 mRNA was induced, but at the much higher dose of

3 1,000 ng/kg. Additionally, the fivefold maximum induction of UGT1 mRNA was much less

4 than the 7,000-fold induction observed for CYP1A1 mRNA at the 10,000 ng/kg dose. The

5 authors state that this could be a result of the constitutive level of UGT1, which is much higher

6 than CYP1A1, which makes detecting induction of UGT1 in the low dose regions more difficult.

7 PAI2 and TGFα mRNA were not affected by TCDD in rat liver in the dose range tested. These

8 results indicate that dioxin-inducible genes have a quite dissimilar dose-response relationship.

9   Induction of CYP1A1 expression is not considered an adverse effect, as the role of

10 CYP1A1 in TCDD-mediated hepatotoxicity is unsettled. Therefore, in the absence of other

11 indicators of hepatotoxicity, a NOAEL/LOAEL cannot be determined for this study. A LOEL

12 for TCDD of 1 ng/kg for a single exposure was identified for statistically significant ($p < 0.05$)

13 increase in CYP1A1 mRNA levels. The NOEL for this study is 0.1 ng/kg.

14

15 **D.1.3.11.   *Weber et al. (1995)***

16   Weber et al. (1995) studied the effects of TCDD on intermediary metabolism in inbred

17 mice. Following establishment of dose ranges via LD50 studies, male C57BL/6 inbred mice

18 (4-7 per dose group) were administered a single gavage dose of 0, 30, 100, 300, 1,000, 3,000,

19 9,400, 37,500, 75,000, 100,000, 133,00, or 235,000 ng/kg TCDD (purity not specified) dissolved

20 in corn oil (on Day 0 of the experiment). Male DBA/2 inbred mice (4-7 per dose group) were

21 treated with 0, 1,000, 10,000, 97,500, 375,000, 1,500,000, 1,950,000, or 3,295,000 ng/kg TCDD

22 delivered in two gavage doses (on Days -1 and 0). All mice were sacrificed and weighed on

23 Day 8 after dosing, trunk blood was collected and pooled for each dose group for serum

24 preparation, and livers and kidneys were removed, weighed, and snap frozen. In both strains of

25 mice, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G-6-Pase)

26 activities were measured in the liver, and EROD activity was measured in the liver and kidneys.

27 Liver tryptophan 2,3-dioxygenase (TdO) activity and serum tryptophan levels were measured in

28 C57BL/6 mice. Additionally, glucose concentrations and thyroxine (T4) and triiodothyroxine

29 (T3) levels were measured in the pooled serum of both mouse strains.

30   On Day 8 after dosing, the study authors reported that food consumption and body weight

31 were unchanged from control values in C57BL/6 mice at any dose tested, but a significant

1 ($p < 0.05$) reduction in food consumption and body weight at doses $\geq$1,500,000 ng/kg-day in

2 DBA/2 mice (data not shown). Relative liver weight was significantly ($p < 0.05$) increased

3 above control values at doses $\geq$ 3,000 ng/kg-day in C57BL/6 mice and $\geq$97,500 ng/kg-day in

4 DBA/2 mice. Relative kidney weight was not affected by any dose of TCDD in C57BL/6 mice,

5 but was significantly ($p < 0.05$) decreased at 1,950,000 and 3,295,000 ng/kg in DBA/2 mice

6 (data not shown).

7   In both mouse strains tested, basal EROD activities in the kidneys were only about

8 one-tenth of those in the liver. In the liver of C57BL/6 mice, EROD activity was significantly

9 ($p < 0.05$) induced over control values at doses $\geq$300 ng/kg-day. Maximum induction occurred

10 at 37,500 ng/kg-day (58-fold), but then decreased by 28% in mice exposed at higher doses.

11 Kidney EROD activity in C57BL/6 mice was significantly ($p < 0.05$) induced over control values

12 at doses $\geq$ 37,500 ng/kg-day, and no decrease was observed at the higher doses. In the liver of

13 DBA/2 mice, EROD activity was significantly ($p < 0.05$) induced over control values at doses

14 $\geq$10,000 ng/kg-day. Maximum induction occurred at 375,000 ng/kg-day, but then decreased by

15 57% in mice exposed at higher doses. Kidney EROD activity in DBA/2 mice was significantly

16 ($p < 0.05$) induced over control values at doses $\geq$375,000 ng/kg-day, with a 3% and 29%

17 decrease below the level of maximum induction (1,500,000 ng/kg-day) at the two highest doses,

18 respectively. Liver PEPCK activity was significantly ($p < 0.05$) decreased below control values

19 at doses $\geq$100 ng/kg-day in C57BL/6 mice, and $\geq$10,000 ng/kg-day in DBA/2 mice. In contrast

20 to the PEPCK dose response, liver G-6-Pase activity was significantly ($p < 0.05$) decreased

21 below control values at doses $\geq$75,000 ng/kg-day in C57BL/6 mice, and $\geq$375,000 ng/kg-day in

22 DBA/2 mice. Liver TdO activity in C57BL/6 mice increased by ~20% over that of control at

23 300 ng/kg-day, and this magnitude of induction did not change throughout doses tested.

24   With respect to serum measurements, there were no dose-dependent changes in

25 tryptophan levels in either mouse strain tested. Serum glucose levels followed the course of

26 PEPCK activity in both strains of mice, with sharp decreases observed only in the high dose

27 range. Thyroid hormone (T3 and T4) levels exhibited a dose-dependent decrease over the entire

28 dose range in both strains of mice; the lowest T3 and T4 levels were 35% of controls at the

29 133,000 ng/kg-day dose in C57BL/6 mice, and 40% (T3) and 20% (T4) of controls at the highest

30 dose in DBA/2 mice.

TCDD-induced hepatic and renal enzyme alterations are not considered significant toxicologically adverse effects in and of themselves. Additionally, because the serum determinations were performed in pooled serum samples, statistical analysis could not be performed. Thus, this precludes these effects from being used to identify a NOAEL or LOAEL. However, a LOAEL for TCDD of 3,000 ng/kg-day was identified for increased relative liver weight in C57BL/6 mice. The NOAEL is 1,000 ng/kg-day for C57BL/6 mice in this study. In DBA/2 mice, a LOAEL for TCDD of 97,500 ng/kg-day was identified for increased relative liver weight, and the NOAEL is 10,000 ng/kg-day for this mouse strain.

D.1.4. Subchronic Studies

D.1.4.1. *Chu et al. (2001)*

Adult female Sprague-Dawley rats (five per treatment group) were administered TCDD (purity >99%) in corn oil by gavage at doses of 0, 2.5, 25, 250, or 1,000 ng/kg-day for 28 days (Chu et al., 2001). The 1,000 ng/kg-day dose of TCDD caused a significant ($p \leq 0.05$) decrease in body weight gain (36% lower than the control), increase in relative liver weight (40% greater than the control), and decrease in relative thymus weight (50% lower than the control). There was a significant ($p \leq 0.05$) increase in EROD activity, methoxy resoufin-O-deethylase (MROD) activity, and UDP-glucuronosyl transferase (UDPGT) activity in the liver of female rats receiving 250 or 1,000 ng/kg-day TCDD. In addition, significant ($p \leq 0.05$) increases in serum cholesterol were observed in the 250 and 1,000 ng/kg-day dose groups, and liver ascorbic acid (AA) also was significantly increased in the 1,000 ng/kg-day dose group. There was ~1.5-fold increase in liver glutathione-*S*-transferase (GST), which was not statistically significant. Other significant ($p \leq 0.05$) findings for the 1,000 ng/kg-day group included a decrease in liver vitamin A (51% lower than the control), an increase in kidney vitamin A (15.5-fold increase above the control), an increase in liver benzyloxy resoufin-O-deethylase (BROD, 30-fold increase above control), a decrease in liver pentoxyresoufin-O-deethylase (PROD, 37% lower than the control), increase in serum albumin (18% above the control), and a decrease in mean corpuscular hemoglobin (MCH, 7% below the control) and mean corpuscular volume (MCV, 7% below the control).

Based on the numerous significant ($p \leq 0.05$) liver-related biochemical changes and significant ($p \leq 0.05$) increased relative liver weight, as well as significantly decreased body

1 weight and relative thymus weight, the LOAEL for 28 days of exposure in this study is

2 1,000 ng/kg-day and the NOAEL is 250 ng/kg-day.

3

4 **D.1.4.2.   *Chu et al. ([2007](#))***

5   Chu et al. ([2007](#)) examined the potential impact of TCDD on various organs and the

6 toxicological impacts as a result of interactions between TCDD and PCBs in rats. Groups of

7 female Sprague-Dawley rats ($n = 5$ per treatment group) were treated daily for 28 days via

8 gavage with 0, 2.5, 25, 250, or 1,000 ng/kg-day TCDD (purity not specified) dissolved in corn

9 oil. Body weights were determined three times per week, and clinical observations were made

10 daily. At study termination, all animals were sacrificed and blood was analyzed for various

11 biochemical and hematological parameters. Liver, spleen, heart, thymus, brain, and kidneys

12 were removed and weighed. A small portion of the liver was homogenized and assayed for

13 BROD; EROD; MROD; and PROD. UDPGT, GST, and ascorbic acid levels also were

14 measured. Vitamin A levels in the liver, kidney, and lungs were analyzed as free retinol

15 (vitamin A), and histopathological analysis was conducted on various tissues.

16   Growth rate and thymic weights in rats treated with 1,000 ng/kg-day TCDD were

17 significantly ($p \leq 0.05$) inhibited compared to the control group. Enzyme analysis indicated that

18 measured levels of TCDD in the liver correlated with hepatic microsomal enzyme activity. The

19 authors reported that liver microsomal EROD and MROD activities were significantly ($p < 0.05$

20 for EROD activity, significance level for MROD not reported) increased in the 250 and

21 1,000 ng/kg-day TCDD dose groups compared to the control group. UDPGT levels were

22 significantly (significance level not reported) increased in the 250 and 1,000 ng/kg-day TCDD

23 dose groups compared to the controls. Serum albumin levels were significantly ($p < 0.05$)

24 increased in the 1,000 ng/kg-day TCDD dose group compared to the control group. Serum

25 cholesterol levels were significantly (level not reported) increased compared to the control group

26 at 250 ng/kg-day TCDD dose, while liver ascorbic acid concentrations were significantly (level

27 not reported) increased in the 1,000 ng/kg-day dose group. Hematological analysis indicated that

28 hemoglobin, packed cell volume, MCH, MCV, and platelet values were decreased in the

29 1,000 ng/kg-day TCDD dose group. Significant ($p \leq 0.05$) differences were observed only in

30 MCH and MCV levels compared to the control. Vitamin A levels in the liver and kidney were

31 significantly ($p < 0.05$) lower in the 1,000 ng/kg-day TCDD group compared to the control

1   group. Histopathological evaluation of various tissues indicated that liver, thyroid, and thymus

2   were the target organs. No TCDD-related affects were found in other tissues. A dose-dependent

3   alteration in the thymus consisted of reduced thymic cortex and increased medullar volume with

4   more animals exhibiting these changes at the 250 and 1,000 ng/kg-day dose level compared to

5   the control group. Alterations in thyroid included reduced follicles, reduced colloid density, and

6   increased epithelial height. A dose-dependent change in the thyroid was observed, with the

7   highest impact evident in reduced follicles and reduced colloid density beginning at a dose of

8   25 ng/kg-day TCDD. Changes in liver were characterized by accentuated hepatic zones,

9   anisokaryosis of hepatocytes, increased cytoplasmic density, and vacuolation. These changes

10   were also dose dependent, with more animals exhibiting these histopathological changes with

11   increasing TCDD dose. Based on these results, the study authors concluded that exposure to

12   TCDD resulted in a wide range of adverse effects with the thyroid proving to be most sensitive.

13   A LOAEL for TCDD of 25 ng/kg for a 28-day exposure is identified for alterations in

14   thyroid, thymus, and liver histopathology. The NOAEL for this study is 2.5 ng/kg-day.

15

16   **D.1.4.3.   *DeCaprio et al. ([1986](#))***

17   Hartley guinea pigs (10 per sex per dose) were administered TCDD (purity not specified)

18   in the diet for 90 days at concentrations of 0, 2, 10, 76, or 430 ppt (equivalent to 0, 0.12, 0.61,

19   4.9, and 26 ng/kg-day in males and 0, 0.12, 0.68, 4.86, and 31 ng/kg-day in females calculated by

20   the study authors using food consumption and body weights). Other animals were administered

21   the high-dose diet (i.e., 430 ppt) for 11, 21, or 35 days and then administered the control diet

22   (i.e., no exposure) for the remainder of the 90 days for recovery analysis. Four high-dose males

23   died and two were sacrificed moribund by Day 45; the remaining four animals were sacrificed on

24   Day 46 for necropsy. Four high-dose females also died and two were sacrificed moribund by

25   Day 55 with the remaining females sacrificed on Day 60 for necropsy. Animals in the 76- and

26   430-ppt groups had significantly ($p < 0.05$) reduced body weights. Organ weights were not

27   obtained in the 430-ppt group due to the early sacrifice, but in the 76-ppt group a significant

28   decrease in relative thymus weight ($p < 0.05$) was observed, and relative liver ($p < 0.01$) and

29   brain ($p < 0.05$) weights in males increased. Although a similar trend occurred in the females,

30   the results were not statistically significant. Males administered 76 ppt in the diet also had a

31   53% increase in triglycerides ($p < 0.05$). The same increase was observed in females, but was

1   not statistically significant. In the recovery groups, mortality during the recovery period after 11

2   or 21 days of treatment was 10% and after 35 days of treatment was 70%. Animals lost weight

3   during the treatment period. Although the body weight increased during the recovery period, the

4   body weight remained low compared to the control for the study duration.

5   The LOAEL from this study is 4.9 ng/kg-day for 90 days of exposure, based on

6   decreased body weight (12−15%; $p < 0.05$) and changes in organ weights (10−30%, significant

7   only in the males). The NOAEL is 0.61 ng/kg-day.

8

9   **D.1.4.4.   *Devito et al. ([1994](#))***

10   Female B6C3F$_1$ mice (5 per treatment) were administered 0, 1.5, 4.5, 15, 45, or

11   150 ng/kg TCDD (98% pure) in corn oil via gavage, 5 days a week, for 13 weeks. This dose is

12   equivalent to 0, 1.07, 3.21, 10.7, 32.1, 107 ng/kg-day (adjusted for continuous exposure,

13   administered dose multiplied by 5 and divided by 7). Body weight was recorded weekly and

14   animals were sacrificed 3 days after the last treatment. Examinations were performed on the

15   lung, skin, uterus, and liver. No differences were observed in the liver or uterus weights or in the

16   estrogen receptor levels in these two tissues. A dose-dependent increase in EROD activity (an

17   indicator of CYP1A1 [CYP] induction) in the lung, skin, and liver was observed, with significant

18   ($p < 0.05$) increases even at the lowest dose. The TCDD doses used did not achieve maximal

19   EROD induction. A significant ($p < 0.05$) increase in liver acetanilide-4-hydroxylase (ACOH;

20   an indicator of CYP1A2 induction) also was observed with all doses. A maximum induction of

21   ACOH occurred with doses of 3.21 ng/kg-day and greater. A dose-dependent increase in

22   specific phosphotyrosyl protein (pp) levels also was observed. Levels of pp34 and pp38 were

23   significantly ($p < 0.05$) increased even at the lowest dose, while pp32 reached statistical

24   significance ($p < 0.05$) with doses of 4.5 ng/kg-day and above.

25   The role of CYPs and phosphorylated pp32, pp34, and pp38 in TCDD-mediated toxicity

26   is unknown, and changes in the activity or function of these proteins are not considered adverse.

27   Therefore, no LOAEL or NOAEL is established. The 13-week LOEL is 1.07 ng/kg-day, based

28   on a significant ($p < 0.05$) increase in EROD, ACOH, pp34, and pp38 levels (all increased by at

29   least twofold). No NOEL is established for this study.

30

D.1.4.5. *Fattore et al. ([2000](#))*

Fattore et al. ([2000](#)) examined TCDD-induced reduction of hepatic vitamin A levels in a

subchronic rat bioassay on Sprague-Dawley rats. Four experiments were conducted;

Experiments 1, 2, and 3 were conducted in both male and female rats, while Experiment 4 was

conducted only in female rats. The dosing regimens for each experiment were as follows:

Experiment 1—Groups of six Iva:SIV 50 rats (male and female) were maintained on a diet
consisting of 0, 200, 2,000, or 20,000 ng TCDD/kg diet and 3-μg vitamin A/kg diet for
13 weeks. Assuming food consumption of 10% of body weight per day, the average daily
doses are 0, 20, 200, and 2,000 ng/kg-day TCDD.

Experiment 2—Groups of six male and female rats were treated with 0 or
200 ng TCDD/kg-day and 3 μg vitamin A/kg diet for 13 weeks.

Experiment 3—Groups of six male and female rats were fed 0, 200, or
1,000 ng TCDD/kg-day and 3 μg vitamin A/kg diet for 13 weeks.

Experiment 4—Groups of female rats (number not specified; IVA;SIV 50 Sprague-Dawley
strain) were treated with TCDD for 26 and 39 weeks in addition to a 13-week dietary
treatment with 0 or 100 ng TCDD/kg-day and 3 μg vitamin A/kg diet for 13 weeks.

For a 13-week exposure duration employed in all four experiments, male and female rats

were treated at 0, 20, 100 (females only), 200, 1,000, or 2,000 ng/kg-day. In all

four experiments, the livers from the control and treated animals were analyzed at termination

for free retinol content to determine hepatic vitamin A levels.

Results

Experiment 1—Liver and body weights in both treated males and females were significantly
affected at all but the lowest dose tested (20 ng/kg-day). Liver injury was severe, particularly
in female rats treated with 2,000 ng TCDD/kg-day. Dietary intake of vitamin A in male rats
was comparable to intake in controls—except in the 2,000 ng/kg-day group, which showed a
reduction of 16% in the dietary intake of vitamin A compared to controls. There was no
effect of TCDD on vitamin A intake in female rats. Hepatic vitamin A levels showed a
dose-dependent reduction with levels dropping sharply in the 200 and 2,000 ng/kg-day dose
groups, particularly in treated females. The reduction was significant at 200 ng/kg-day
($p < 0.05$) and 2,000 ng/kg-day ($p < 0.01$) in males and at 200 ng/kg-day ($p < 0.5$) and
2,000 ng/kg-day ($p < 0.001$) in females. The reductions ranged from 68–99% in males and
72–99% in females when compared to corresponding controls.

Experiment 2—Changes in liver and body weights were not reported. Hepatic vitamin A level in males and females were reduced by 70% and 99%, respectively, compared to controls, in rats receiving 20 ng/kg-day (significance level in females: $p < 0.01$).

Experiment 3—Similar to the results of Experiments 1 and 2, a dose-related trend of significantly ($p < 0.001$) reduced hepatic vitamin A level was observed in both males and females, with males exhibiting a particularly sharp drop at the 1,000 ng/kg-day dose compared to controls.

Experiment 4—Females treated with 100 ng/kg-day showed significant reductions in hepatic vitamin A levels ($p < 0.05$–0.001) at all three treatment durations (13, 26, and 39 weeks).

A LOAEL for TCDD of 20 ng/kg-day for a 13-week subchronic exposure was identified in this study for decreased hepatic vitamin A levels (27 and 24% lower than the corresponding control in female and male rats, respectively). This LOAEL is determined using data from Experiment 1. A NOAEL was not identified in this study.

D.1.4.6.   *Fox et al. (1993)*

Sprague-Dawley rats (6 per sex per dose) were gavaged with TCDD (purity not specified) in corn oil using a dose-loading regime to achieve and maintain steady-state levels of 0.03, 30, or 150 ng/g in the liver. The regime consisted of an initial loading dose of 5, 2,500, or 12,000 ng/kg followed every 4 days with a maintenance dose of 0.9, 600, or 3,500 ng/kg. Averaging the doses over the 14 days provides average daily doses of 0.55, 307, and 1,607 ng/kg-day (e.g., 5 ng/kg-day on Day 1 and 0.9 ng/kg-day on Days 5, 9, and 13 is $5 + 0.9 + 0.9 + 0.9/14 = 0.55$ ng/kg-day). Body weight, liver weight, and liver gene expression were measured at 7 and 14 days. A significant ($p < 0.05$) decrease in body weight occurred in high-dose males (at 14 weeks only) and females (at 7 and 14 days). A significant ($p < 0.05$) increase in absolute and relative liver weights was observed in mid- and high-dose males and females at both 7 and 14 days. Although the liver of treated animals indicated moderate vacuolization and swelling, there was no indication of necrosis. An increase in gene expression (clone 1, CYP1A1, CYP1A2, and albumin) was observed in the mid- and high-dose groups. A significant ($p < 0.05$) decrease in labeling index (indication of cell proliferation) occurred in both females (all doses) and males (high-dose only) during Week 1—but not during Week 2.

The 14-day LOAEL is 307 ng/kg-day for significant ($p < 0.05$) increases in absolute and relative liver weights (25─34%). The NOAEL is 0.55 ng/kg-day.

D.1.4.7. *Hassoun et al. (1998)*

Female B6C3F$_1$ mice (number not specified) received TCDD (>98% pure) in corn oil 5 days per week for 13 weeks via gavage at doses of 0, 0.45, 1.5, 15, or 150 ng/kg (equivalent to 0, 0.321, 1.07, 10.7, and 107 ng/kg-day adjusted for continuous exposure; administered dose multiplied by 5 and divided by 7). Three days after the final dose, animals were sacrificed and their brains were removed for oxidative stress testing. Biomarkers for oxidative stress included production of superoxide anion, lipid peroxidation, and DNA single-strand breaks. A significant ($p < 0.05$) increase was observed in superoxide anion production, lipid peroxidation as measured by thiobarbituric acid-reactive substances (TBARS), and DNA single-strand breaks with all doses tested.

No other indicators of brain pathology were assessed, and it is unfeasible to link the markers of oxidative stress to a TCDD-induced toxicological outcome in the brain. Thus, no LOAEL/NOAEL was established. The subchronic (13-week) LOEL is 0.32 ng/kg-day, based on significant ($p < 0.05$) increases in superoxide anion production (80% above control); lipid peroxide production (25% above the control); and DNA single-strand breaks (twofold over the control). No NOEL is established.

D.1.4.8. *Hassoun et al. (2000)*

Hassoun et al. (2000) examined the effect of subchronic TCDD exposure on oxidative stress in hepatic and brain tissues. Groups of 8-week-old female Harlan Sprague-Dawley rats (6 rats/group) were administered TCDD (98% purity, dissolved in 1% acetone in corn oil) via gavage at 0, 3, 10, 22, 46, or 100 ng/kg-day, 5 days/week, for 13 weeks (0, 2.14, 7.14, 15.7, 32.9, or 71.4 ng/kg-day adjusted for continuous exposure; administered doses were multiplied by 5 and divided by 7 days/week). Animals were sacrificed at the end of the study period, and the brain and liver tissues were collected and used to determine the production of reactive oxygen species, lipid peroxidation, and DNA single-strand breaks (SSBs).

A dose-dependent effect was observed in both the liver and brain tissue as a result of TCDD treatment. Based on the maximal induction of superoxide anion by various doses, more production of superoxide anion was observed in the liver tissue when compared with the brain tissue with an observed increase of 3.1- and 2.2-fold respectively, when compared to the control group. A similar dose-dependent effect was observed in the induction of lipid peroxidation in

1 TCDD-treated animals with an approximately 1.8-fold increase in lipid peroxidation in both

2 tissues relative to the corresponding controls. A dose-dependent relationship was also observed

3 for DNA SSBs in both the hepatic and brain tissues at all TCDD-treated doses compared to

4 controls. Increases were statistically significant ($p \leq 0.05$) beginning at the lowest administered

5 dose.

6 　　　　Similar to the statement above, because no adverse endpoints were measured, no

7 LOAEL/NOAEL was established. However, a LOEL for TCDD of 2.14 ng/kg-day for a

8 13-week exposure duration was identified in this study for significant increases ($p \leq 0.05$) in

9 superoxide anion, lipid peroxidation, and DNA SSBs in the liver and brain tissues. A NOEL

10 cannot be determined for this study.

11

12 **D.1.4.9.** *Hassoun et al. (2003)*

13 　　　　Hassoun et al. (2003) examined the role of antioxidant enzymes in TCDD-induced

14 oxidative stress in various regions of the rat brain after subchronic exposure. Groups of

15 8-week-old female Harlan Sprague-Dawley rats (12 rats/group) were administered TCDD (98%

16 purity, dissolved in 1% acetone in corn oil) via gavage at 0, 10, 22, or 46 ng/kg-day (0, 7.14,

17 15.7, or 32.9 ng/kg-day adjusted for continuous exposure; administered doses were multiplied by

18 5 and divided by 7) daily for 13 weeks. Animals were sacrificed at the end of the study period

19 and the brain was immediately removed and dissected to the following regions: cerebral cortex

20 (Cc), hippocampus (H), cerebellum (C), and brain stem including midbrain, pons, and medulla.

21 Four pooled samples from each region per dose (i.e., 3 animals/pooled sample) were used in the

22 study. Dissected regions were subsequently assayed for lipid peroxidation (thiobarbituric acid

23 reactive substances, or TBARS), superoxide dismutase, catalase, and glutathione peroxidase.

24 Because the cytochrome c reduction method was used to determine superoxide anion (SA)

25 production in brain tissues, superoxide dismutase (SOD) was added to some of the brain tissue

26 samples that had the highest SA production (tissue homogenates from Cc and H from rats treated

27 with 46 ng/kg-day TCDD).

28 　　　　A dose-dependent increase in the production of SA was observed in the Cc and H, but

29 significant changes in SA production were not observed in either the C or the mid-brain, pons, or

30 medulla brain stem cells. Similar to SA production, there was a dose-dependent increase in the

31 production of TBARS in the Cc and H regions of the brain, but no significant changes were

1 observed in either the C or the B sections of the brain. The study authors also measured the

2 activities of various enzymes as a result of TCDD treatment and reported a dose-dependent

3 increase in SOD activity in the C and B sections, while there was dose-dependent suppression in

4 SOD activity in Cc and H. In contrast, catalase activity was significantly ($p < 0.05$) increased in

5 H and Cc at the 10 ng/kg-day TCDD dose level compared to controls and the mid- and high-dose

6 animals. Catalase activity also was increased in a dose-dependent manner in the C section, but

7 no significant changes in the activity of this enzyme were observed in the B section at any of the

8 three TCDD tested doses. The effects of subchronic exposure to different doses of TCDD on

9 glutathione stimulating hormone peroxidase (GSH-Px) showed a different response compared to

10 other enzymes. There was a dose-dependent increase in the activity of this enzyme in the C and

11 B regions of the brain, while a significant increase in the activity of GSH-Px occurred in Cc and

12 H only at the 10 ng/kg-day TCDD dose. In addition, the activity of this enzyme was suppressed

13 in a dose-dependent manner in the Cc and H at 22 and 46 ng/kg-day TCDD doses. Based on

14 these results, the study authors concluded that induction of oxidative stress by TCDD in the rat

15 brain occurs mainly in the Cc and H regions.

16   Similar to the statement above, because no adverse endpoints were measured, no

17 LOAEL/NOAEL was established. However, a LOEL for TCDD of 7.14 ng/kg-day for a

18 13-week exposure duration was identified for this study for increases in superoxide anion and

19 lipid peroxidation production, as well as increased activity in SOD, catalase, and GSH-Px.

20

21 **D.1.4.10. *Kociba et al. ([1976](#))***

22   Adult Sprague-Dawley rats (12 per sex per treatment group) were administered TCDD

23 (purity not reported) in corn oil via gavage 5 days per week at doses of 0, 1, 10, 100, or

24 1,000 ng/kg-day (equivalent to 0, 0.71, 7.14, 71.4, or 714 ng/kg-day averaged over 7 days; 5/7 of

25 dose). Five animals per group were sacrificed at the end of treatment, and the remaining animals

26 were observed over 13 weeks post treatment (only initial results for the post-treatment period

27 were provided in the report). Body weights and food consumption were measured semiweekly.

28 Hematology and clinical chemistry were measured after 36−37 or 85−86 days of treatment and

29 59−60 days after termination of treatment. Forty-eight hour urine samples were collected from

30 select rats from 85−89 days of treatment and 52−56 days after cessation of treatment. Gross and

31 histopathological exams were conducted on the tissues.

1   Four high-dose females died during treatment. Two high-dose females and

2   two high-dose males died during the post-treatment period. Animals treated with 714 ng/kg-day

3   were less active during the treatment period, which became less evident during the posttreatment

4   period. Yellow discoloration of the external pinnae also was noted in this group, both during

5   treatment and during the post-treatment period. A significant ($p < 0.05$) reduction in body

6   weight and food consumption was observed in the 71.4 and 714 ng/kg-day groups. The

7   following significant ($p < 0.05$) hematology changes were observed in the high-dose

8   (714 ng/kg-day) males at all measured time points: decreased packed cell volume, decreased red

9   blood cells, decreased hemoglobin, increased reticulocytes, and decreased thrombocytes.

10   Significant ($p < 0.05$) changes also occurred in the high-dose females, but the only consistent

11   observation was a decrease in thrombocytes and increased leukocytes. Significant changes in

12   clinical chemistry ($p < 0.05$) and urinalysis ($p < 0.05$) were more consistent between the sexes in

13   the high-dose group and included increases in total and direct serum bilirubin; increase in serum

14   alkaline phosphatase; decreased urinary creatinine; and increased urinary coproporphyrin,

15   uroporphyrin, and delta-amino-levulinic. The following significant ($p < 0.05$) changes were

16   observed in the 71.4 ng/kg-day group: decreased packed cell volume (4−9%) in males; decreased

17   red blood cells (2−10%) in males; decreased hemoglobin (2−13%) in males; increased urinary

18   coproporphyrin (2.2-fold increase during treatment) in females; increased urinary

19   delta-amino-levulinic (47% increase during treatment) in females; increased total and direct

20   serum bilirubin (48−61%) in females; and increased serum alkaline phosphatase (twofold) in

21   females. The following significant ($p < 0.05$) changes in relative organ weights were observed

22   increased brain weight in 714 ng/kg-day males and females; increased liver weight in males

23   (71.4 and 714 ng/kg-day) and females (7.14, 71.4, and 714 ng/kg-day); increased spleen weight

24   in 714-ng/kg-day males and females; decreased thymus weight in 71.4 and 714 ng/kg males and

25   females; and increased testes weight in 714 ng/kg-day males. Microscopic changes were

26   observed in the thymus, and in other lymphoid tissues, and in the liver in rats treated with

27   71.4 ng/kg-day or greater.

28   The subchronic (13-week) LOAEL is 71.4 ng/kg-day, based on the numerous changes

29   noted in body weight, hematology, clinical chemistry, urinalysis, and histopathology. The

30   NOAEL is 7.14 ng/kg-day.

31

D.1.4.11. *Mally and Chipman (2002)*

Female F344 rats (3 per treatment group) were administered TCDD at concentrations of 0, 2.5, 25, or 250 ng/kg in corn oil via gavage for either 3 consecutive days or 2 days per week for 28 days (Mally and Chipman, 2002). The average daily doses for the 28-day study when adjusted for 7 days a week were 0, 0.71, 7.1, and 71 ng/kg-day (i.e., 2/7 of administered dose). No clinical signs of toxicity were observed. Histological examination of the liver revealed no abnormalities. All doses of TCDD reduced the number of connexin (Cx) 32 plaques and Cx32 plaque area in the liver, which was considered the target tissue. The reductions were not statistically significant after the 3-day treatment, but were significant after the 28-day treatment ($p < 0.05$). TCDD also caused a reduction in the Cx32 plaque number and area in the thyroid after 28 days, but the results were not statistically significant. Although the reduction in Cx32 plaque number and plaque area in the liver and thyroid occurred at all dose levels, there was no relation to dose. TCDD did not induce hepatocyte proliferation.

In the absence of additional indicators of hepatotoxicity, changes in Cx32 plaques are not clearly linked to TCDD-mediated hepatotoxicity, nor are they considered an adverse effect. Additionally, no toxicologically relevant endpoints were examined. Therefore, a NOAEL or LOAEL cannot be determined. A 28-day LOEL at the lowest dose of 0.71 ng/kg-day for significantly ($p < 0.05$) decreased Cx32 plaque area is evident (approximately 70% of the controls).

D.1.4.12. *Slezak et al. (2000)*

Slezak et al. (2000) studied the impact of subchronic TCDD exposure on oxidative stress in various organs of B6C3F$_1$ female mice. Groups of 8- to 10-week-old female B6C3F$_1$ mice (number not specified) were administered TCDD (purity >98%, dissolved in corn oil) via gavage at 0, 0.15, 0.45, 1.5, 15, or 150 ng/kg-day (0, 0.11, 0.32, 1.07, 10.7, or 107.14 ng/kg-day adjusted for continuous exposure) 5 days per week for 13 weeks. Three days after the last treatment, the animals were sacrificed and organs were removed for the measurement of oxidative stress indicators including superoxide anion (SA), lipid peroxidation (TBARS), ascborbic acid (AA), and total glutathione (GSH). Tissue TCDD concentrations also were measured.

The study authors reported that TCDD dose range resulted in overlapping tissue concentrations for liver, lung, kidney, and spleen. Liver had the highest TCDD concentration,

1   with each tissue demonstrating a dose-dependent increase in TCDD concentration. Compared to

2   controls, SA production in the liver was significantly ($p < 0.05$) lower at the 0.15 ng/kg-day

3   TCDD dose, while it was significantly ($p < 0.05$) higher at 15 and 150 ng/kg-day. A dose-

4   dependent increase in hepatic TBARS production was observed, although the rate of production

5   was significant ($p < 0.05$) only at the highest TCDD administered dose (150 ng/kg-day)

6   compared to controls. AA also followed the same pattern observed for hepatic SA and TBARS

7   with AA production significantly ($p < 0.05$) increased at the 15 and 150 ng/kg-day TCDD doses.

8   Contrary to the SA, TBARS, and AA responses, liver GSH levels were decreased at

9   0.15 ng/kg-day, were increased at 0.45 and 150 ng/kg-day, and did not change at 1.5 or

10   15 ng/kg-day when compared to the control group. Unlike the liver, there was no significant

11   increase in SA production in the lung at any of the TCDD tested doses; a dose dependent

12   reduction, however, was observed at 0.45, 15, and 150 ng/kg-day compared to controls. GSH

13   and AA production in the lung was decreased at 0.15 ng/kg-day, while AA production was

14   significantly ($p < 0.05$) increased at 15 and 150 ng/kg-day. Kidney SA production showed a

15   statistically significant ($p < 0.05$) increase only at the 15 and 150 ng/kg-day doses. GSH, like in

16   the liver and the lung, exhibited a decrease in production in the kidney following treatment at

17   0.15 ng/kg-day with this trend continuing at 0.45 and 1.5 ng/kg-day. AA levels in the kidney

18   were significantly ($p < 0.05$) lower at all subchronic doses, except at 1.5 ng/kg-day dose. SA

19   levels in the spleen differed little from the control group at any of the TCDD doses. Total GSH

20   in the spleen was higher only at the 150 ng/kg-day dose level, while the AA levels were

21   significantly ($p < 0.05$) decreased at 0.15, 1.5, and 150 ng/kg-day.

22   Similar to the statements regarding the Hassoun et al. studies above, because no adverse

23   endpoints were measured, no LOAEL/NOAEL was established. Therefore, a NOAEL or

24   LOAEL cannot be determined. However, a NOEL and LOEL of 1.07 and 10.7 ng/kg-day,

25   respectively, are identified in this study for increases in superoxide anion in the liver.

26

27   **D.1.4.13.   *Smialowicz et al. ([2008](#))*

28   Female B6C3F$_1$ mice (8–15 per treatment group) were administered TCDD (purity

29   >98%) in corn oil by gavage at doses of 0, 1.5, 15, 150, or 450 ng/kg-day, 5 days a week, for

30   13 weeks (1.07, 10.7, 107, or 321 ng/kg-day, adjusted for continuous exposure; i.e., 5/7 of the

31   dose) (Smialowicz et al., 2008). Mice were immunized 3 days after the final TCDD exposure

1   with an intravenous injection of an optimal concentration of 4×10^7 SRBCs and sacrificed 4 days

2   later. No TCDD-related effects on body weight were observed. There was a dose-related

3   decrease in relative spleen weight (9–19% lower than control values) with statistically significant

4   ($p < 0.05$) decreases at all but the lowest dose. Additionally, there was a statistically significant

5   ($p < 0.05$) increase in relative liver weight (5–21%) in all treatment groups compared to controls.

6   Statistically significant dose-dependent decreases were observed in the antibody response to

7   SRBCs (24–89% lower than control values), as measured by both the number of plaque forming

8   cells per 10^6 cells and plaque forming cells per spleen.

9   The 13-week LOAEL for this study is 1.07 ng/kg-day based on a significant ($p < 0.05$)

10   increase in relative liver weight (10%) and a significant ($p < 0.05$) decrease in antibody response

11   to SRBCs (24%). A NOAEL cannot be determined for this study.

12

13   **D.1.4.14.   *Van Birgelen et al. ([1995a](); [1995b]())***

14   Van Birgelen et al. ([1995a](); [1995b]()) studied the impact of TCDD exposure on various

15   biochemical endpoints in rats. In Van Birgelen et al.([1995b]()) groups of 7-week-old female

16   Sprague-Dawley rats ($n = 8$ per treatment group) were treated with 0, 200, 400, 700, 5,000, or

17   20,000 ng/kg TCDD (purity >99%) in the diet for 13 weeks. Daily TCDD intake based on food

18   consumption, diet level, and mean weight was estimated to be 0, 14, 26, 47, 320, or 1,024 ng/kg-

19   day. Blood samples were collected from treated animals and assayed for retinol (vitamin A),

20   triiodothyronine, and total (TT4) and free (FT4) thyroxine. At study termination, the animals

21   were sacrificed, and the liver, thymus, spleen, and kidneys were removed and weighed. Parts of

22   the liver were homogenized and assayed to determine EROD; CYP1A1; CYP1A2; and UDPGT

23   activity. Liver samples also were analyzed for retinol content. Van Birgelen et al. ([1995a]())

24   analyzes in greater detail the effects of TCDD on thyroid hormone metabolism, and both papers

25   are based on the same materials and methods.

26   TCDD-treated animals showed a dose-related decrease in food consumption. Animals

27   treated with 1,024 ng/kg-day TCDD consumed 32% less food compared to controls. Similarly, a

28   dose-related decrease in body weight gain was observed in all animals treated with TCDD.

29   Animals treated with ≥47 ng/kg-day of TCDD showed a statistically significant ($p < 0.05$)

30   decrease in body weight gain. Relative liver weights were significantly ($p < 0.05$) increased in

31   the 320 and 1,024 ng/kg-day TCDD dose groups compared to the controls. Absolute and relative

1 thymus weights were significantly ($p < 0.05$) decreased at all TCDD dose groups compared to

2 the control group. Relative kidney and spleen weights were significantly ($p < 0.05$) higher in

3 animals dosed with ≥47 ng/kg-day of TCDD compared to the control group, with the greatest

4 increase occurring in animals treated with 1,024 ng/kg-day TCDD (121 and 173% higher than

5 controls for kidney and spleen, respectively). Cytochrome P450 enzymes, including EROD,

6 CYP1A2, CYP1A1, and UDPGT, exhibited statistically significant ($p < 0.05$) increases in

7 activity at all TCDD dose groups compared to the control group. TT4 and FT4 thyroid hormone

8 concentrations were statistically significantly ($p < 0.05$) decreased only at TCDD doses

9 ≥47 ng/kg-day. A dose-dependent increase was observed in the plasma retinol concentrations

10 with significant ($p < 0.05$) increases occurring at ≥47 ng/kg-day TCDD after a 13-week

11 exposure. A dose-dependent reduction in liver retinoid levels also was observed after 13 weeks

12 of TCDD exposure with the levels dropping significantly ($p < 0.05$) at all TCDD-treated doses

13 compared to the control group.

14   A LOAEL for TCDD of 14 ng/kg for a 13-week exposure is identified for significantly

15 ($p < 0.05$) decreased absolute and relative thymus weights and significantly ($p < 0.05$) decreased

16 liver retinoid levels. A NOAEL cannot be determined for this study.

17

18 **D.1.4.15.   *Vos et al. (1973)***

19   Vos et al. (1973) conducted a study to examine the immune response in laboratory

20 animals treated with TCDD. In one experiment, 10 female Hartley strain guinea pigs were orally

21 treated with 8 weekly doses of 0, 8, 40, 200, and 1,000 ng/kg TCDD in corn oil (purity of TCDD

22 not specified) (0, 1.14, 5.71, 28.6, and 143 ng/kg-day adjusted for continuous exposure;

23 administered dose divided by 7). At study termination, the animals were sacrificed, and heart

24 blood was used to determine total leukocyte and differential leukocyte counts. In another

25 experiment, the effect of TCDD on humoral immunity was determined by injecting 0.1 mL of

26 tetanus toxoid into the right hind-foot pad on Day 28 (1 left foot tetanus toxoid, aluminum

27 phosphate-adsorbed) and again on Day 42 (1 left foot tetanus toxoid, unadsorbed). Blood was

28 collected ($n = 10$) on Days 35 and 49, and the serum tetanus-antitoxin concentrations were

29 determined using a modified single radial immunodiffusion technique.

30   All guinea pigs receiving 1,000 ng/kg-day TCDD either died or were killed when

31 moribund between 24 and 32 days. These animals showed severe weight loss, lymphopenia, and

depletion of the lymphoid organs, especially the thymus. Microscopic observations revealed severe atrophy of the thymic cortex with substantial destruction of lymphocytes, with the nuclear debris being engulfed by macrophages. Large cystic Hassall bodies, filled with polymorphonuclear leukocytes, were observed in the medulla. All animals treated with 0, 8, 40, or 200 ng/kg-day TCDD survived until study termination. Body weight gain was significantly ($p < 0.01$) lower in the 200 ng/kg-day group. Absolute thymus weight was significantly reduced in the 40 and 200 ng/kg-day treatment groups ($p < 0.01$ and $p < 0.05$, respectively). In contrast, relative thymus weight was significantly ($p < 0.01$) reduced only in the 200 ng/kg-day dose group. The absolute weight of the superficial cervical lymph nodes was significantly ($p < 0.05$) decreased in the 200 ng/kg-day group, while the relative adrenal weight was significantly ($p < 0.05$) increased in the 200 ng/kg-day dose group. Total leukocyte count was significantly ($p < 0.05$) decreased in the 40 ng/kg-day dose group and total lymphocyte count was significantly decreased at 8, 40, and 200 ng/kg-day ($p < 0.01$, $p < 0.05$, and $p < 0.05$, respectively). A significant (p-values not provided) monotonic dose-response relationship was determined for body weight (decrease), relative thymus weight (decrease), relative adrenal weight (increase), and total leukocyte and lymphocyte count (decrease). Microscopic examination of the lymphoid organs and adrenals showed no effects, while slight cortical atrophy of the thymus was observed at the 200 ng/kg-day dose.

Animals receiving the tetanus toxoid injection showed a small but significant increase in serum tetanus antitoxin concentrations at the 8 and 40 ng/kg-day dose ($p < 0.05$ and $p < 0.01$, respectively). Measurement at Days 49 and 56 indicated that serum antitoxin levels had decreased sharply and the significant ($p < 0.05$ on Day 49 and $p < 0.01$ on Day 56) effect was seen only at the 200 ng/kg-day dose level.

A LOAEL for TCDD of 5.71 ng/kg-day for an 8-week exposure is identified in this study for significantly ($p < 0.01$) reduced absolute thymus weight, significantly ($p < 0.05$) reduced leukocyte and lymphocyte count, and significantly ($p < 0.01$) increased serum tetanus antitoxin concentration. The NOAEL for this study is 1.14 ng/kg-day.

D.1.4.16.   *White et al. (1986)*

White et al. (1986) studied the impact of TCDD exposure on serum complement levels. Groups of female (C57BL/6 $\times$ C3H)F1(B6C3F$_1$) mice were treated for 14 consecutive days with

TCDD in corn oil (purity of TCDD not specified) at doses of 0, 10, 50, 100, 500, 1,000 or 2,000 ng/kg-day via gastric intubation ($n = 6-8$). At study termination, blood was collected from anesthetized animals and assayed for serum complement activity and complement component C3 levels.

Serum complement activity between the 10 and 100 ng/kg-day doses was between 69 and 59% compared to the vehicle control group, with all treatment groups being significantly ($p < 0.05$) low compared to the vehicle control. In contrast, C3 levels were comparable to the vehicle control with levels ranging between 98 and 94% of the control group. The higher doses of 500, 1,000, and 2,000 ng/kg-day, however, produced a marked decrease of the component hemolytic activity (45, 35, and 19% of the vehicle control) and of C3 levels (91, 81, and 74% of the vehicle control, respectively; significance level at $p < 0.05$).

A LOAEL for TCDD of 10 ng/kg-day for a 14-day exposure is identified in this study for significantly ($p < 0.05$) lower serum complement activity. A NOAEL cannot be determined for this study.

D.1.5.   Chronic Studies (Noncancer Endpoints)

D.1.5.1.   *Cantoni et al. ([1981](#))*

CD-COBS rats (4 per treatment) were orally administered TCDD (purity not specified) dissolved in acetone:corn oil (1:6) at doses of 0 (vehicle alone), 10, 100, or 1,000 ng/kg per week (equivalent to 1.43, 14.3, and 143 ng/kg-day adjusted for continuous exposure, administered dose by dividing the dose by 7) for 45 weeks. Urine was collected several times during treatment and tested for porphyrin excretion. Twenty-four hours after the final dose, animals were sacrificed and their livers, spleens, and kidneys were removed for analysis of total porphyrins. All treatment groups had a significant ($p < 0.05$) increase in coproporphyrin excretion beginning at 6, 3, or 2 months, respectively. Uroporphyrin excretion was significantly ($p < 0.05$) increased in the 14.3 ng/kg-day group at 10 months and in the 143 ng/kg-day group beginning at 6 months. The high-dose group also had a significant ($p < 0.05$) increase in excretion of heptacarboxylic methyl ester beginning at 6 months. The high-dose group had a marked porphyric state beginning at 8 months as indicated by a 70-fold increase above controls in total urinary porphyrin excretion. This group also had a significant ($p < 0.05$) increase in total porphyrins in the liver, kidneys, and spleen.

1   The 45-week LOAEL for this study is 1.43 ng/kg-day, based on a two- to threefold

2   increase in urinary coproporphyrin excretion. No NOAEL was established for this study.

3

4   **D.1.5.2.   *Croutch et al. (2005)***

5   Croutch et al. (2005) examined the impact of TCDD exposure on body weight via

6   insulin-like growth factor (IGF) signaling. Female Sprague-Dawley rats were randomly assigned

7   in groups of five to initial loading doses of TCDD (purity >98.5%, dissolved in corn oil) at 0,

8   12.5, 50, 200, 800, or 3,200 ng/kg-day, followed by treatment with maintenance doses equivalent

9   to 10% of the initial loading dose every third day to maintain a pharmacokinetic steady state

10   throughout the entire study (equivalent to 14-day average = 0, 1.25, 5, 20, 80, or 320 ng/kg-day;

11   28-day average = 0, 0.85, 3.4, 13.6, 54.3, or 217 ng/kg-day; 63-day average = 0, 0.60, 2.4, 9.5,

12   38, or 152 ng/kg-day; and 128-day average dose = 0, 0.51, 2.0, 8.1, 32.5, or 130 ng/kg-day).

13   Following 2, 4, 8, 16, 32, 64, or 128 days of initial dosing, the animals were sacrificed, the livers

14   were removed and weighed, and the trunk blood was collected to analyze glucose content. Rat

15   liver phosphoenolpyruvate carboxykinase (PEPCK) mRNA and protein levels also were

16   analyzed, and PEPCK activity was measured.

17   Body weights of TCDD-treated animals decreased after the second week of the

18   3,200 ng/kg-day TCDD loading dose, with significant differences beginning at Week 9. There

19   was also a statistically significant ($p \leq 0.05$) difference in body weights at Weeks 10, 11, 13, 18,

20   and 19 at the highest loading dose (3,200 ng/kg-day). PEPCK activity in the liver was also

21   decreased in a dose-dependent manner following TCDD administration at approximately

22   16 days. PEPCK inhibition was statistically significant ($p \leq 0.05$) on Day 4 in rats treated with

23   either 800 or 3,200 ng/kg-day TCDD when compared to animals treated with a loading dose of

24   200 ng/kg-day. A similar statistically significant change was observed in animals treated with

25   3,200 ng/kg-day on Day 16 when compared to the 200 ng/kg-day treatment group. In contrast,

26   differences in PEPCK activity at other doses or time points were not statistically significant. In

27   TCDD-treated animals, there was also a dose-dependent decrease in PEPCK mRNA expression

28   along with a decrease in PEPCK protein levels in the liver. In addition to body weight and

29   PEPCK activity changes, animals treated with 3,200 ng/kg-day TCDD showed a sharp decline in

30   circulating IGF-I levels on Day 8 compared to the control group (corn oil) and TCDD-treated

31   animals at lower doses. In the highest dose animals, IGF-I levels continued to decline to 42% of

the control group by Day 16 of the study. The IGF-I levels at the highest dose plateaued at an average decrease of 66% through Day 128 when compared to controls. Beginning at Day 8, the decrease in IGF-I was statistically significant at every time point through Day 128 compared to the control group, as well as groups treated with either 12.5 or 50 ng/kg-day TCDD. Similar statistically significant decreases also were observed for the 800 ng/kg-day TCDD-treated groups with an initial decrease of 37% on Day 16 followed by a further decline to approximately 45% thereafter compared to controls and the 12.5, 50, and 200 ng/kg-day dose groups. In contrast to these results, circulating levels of insulin and glucose were unaffected by TCDD treatment, while the active or phosphorylated form of AMPK-α protein increased with dose as a result of TCDD treatment.

A LOAEL for TCDD of 217 ng/kg-day for a 28-day exposure duration (because this represented the most sensitive time for elicitation of effects) was identified in this study for decreased body weight, significant ($p \leq 0.05$) inhibition of PEPCK activity, and reduced IGF-I levels (42% lower than the control group). A NOAEL of 54.3 ng/kg-day was identified in this study.

D.1.5.3. *Hassoun et al. (2002)*

Hassoun et al. (2002) examined the potential of TCDD and other dioxin-like chemicals to induce oxidative stress in a chronic rat bioassay. Groups of six Harlan Sprague-Dawley female rats were treated with 0, 3, 10, 22, 46, or 100 ng/kg-day TCDD (98% purity), 5 days a week via gavage for 30 weeks. The administered doses adjusted for continuous exposure were 0, 2.14, 7.14, 15.7, 32.9, and 71.4 ng/kg-day, respectively (administered doses were multiplied by 5 and divided by 7). At study termination, hepatic and brain tissues from all treated rats were divided into two portions and examined for the production of reactive oxygen species and SSBs in DNA.

When compared to controls, there was a dose-dependent increase in the production of superoxide anion in TCDD-treated animals ranging from 21–998% and 66–257% in hepatic and brain tissues, respectively. Hepatic tissues had statistically significant ($p < 0.05$) increases in superoxide anion production at doses ≥7.14 ng/kg-day, while the brain tissue had a statistically significant ($p < 0.05$) increase over controls at all doses. Similarly, increases in lipid peroxidation were observed in hepatic and brain tissues with a 481% increase ($p < 0.05$) at 71.4 ng/kg-day in the hepatic tissue when compared to controls. The increase in lipid oxidation

1　in brain tissue ranged from 33–188% ($p < 0.05$) in the 2.14–71.4 ng/kg-day dose groups. DNA

2　SSBs were also observed in both hepatic and brain tissue in all treated groups. When compared

3　to the control group, there was a dose-dependent statistically significant ($p < 0.05$) increase in

4　DNA SSBs ranging from 58–322% and 29–137% in hepatic and brain tissues, respectively.

5　Nonmonotonic dose-response relationships were observed for superoxide production and lipid

6　peroxidation in liver tissues, with greater-than-linear increases in effect between the two highest

7　dose levels.

8　　　　As stated above, because no adverse endpoints were measured, no LOAEL/NOAEL was

9　established. However, a LOEL for TCDD of 2.14 ng/kg-day for a 30-week exposure duration is

10　identified in this study for significant ($p < 0.05$) increases in superoxide anion, lipid peroxidation

11　production, and DNA SSBs in the liver and brain tissues. A NOEL cannot be determined for this

12　study.

13

14　**D.1.5.4.** *Hong et al. (1989)*

15　　　　Hong et al. (1989) studied the immunotoxic effects associated with chronic exposure to

16　TCDD in rhesus monkeys. Female rhesus monkeys (seven to eight animals per treatment group)

17　were exposed to 0, 5, or 25 ppt TCDD (purity not specified) in feed for 4 years. As described

18　previously (Bowman et al., 1989a; 1989b), these dietary concentrations were equivalent to 0,

19　0.12, and 0.67 ng/kg-day, respectively. These adult females were tested for immune

20　abnormalities 4 years after cessation of exposure. Additionally, offspring from exposed mothers

21　born into Cohort I ($n = 7$, 6, and 1, respectively), Cohort II ($n = 5$, 6, and 2, respectively), and

22　Cohort III ($n = 6$, 6, and 3, respectively) (as described by Bowman et al. (1989b)) were also

23　tested. Monoclonal antibodies with flow cytometry were used to enumerate cells in the various

24　leukocyte populations. A proliferative response to mitogens (phytohemagglutinin, pokeweed,

25　concanavalin A) as well as allo- and xeno-transplantation antigens was measured. Natural

26　killing capacity and a T cell dependent response to immunization with tetanus toxoid was also

27　assessed. The range of normal immune responses in rhesus monkeys was obtained from 45

28　healthy animals unrelated to the TCDD exposure studies.

29　　　　In adult monkeys, an increased number of T lymphocytes were observed in the

30　0.67 ng/kg-day dose group. However, there was not a proportional increase in each of the T cells

31　subsets, which was represented by increased numbers of cytotoxic/suppressor cells and

1 decreased numbers of helper/inducer cells. Although this resulted in a lower helper/suppressor

2 ratio in the 0.67 ng/kg-day group, the values were within the measured normal range. Peak

3 antibody level and antibody response to tetanus toxoid immunization was not altered compared

4 to control values at either dose tested. Macrophage depletion in the 0.12, and 0.67 ng/kg-day

5 groups resulted in the absence of amplification in a mixed lymphocyte response assay, compared

6 to a fivefold amplification in control monkeys. As previously reported, the 0.67 ng/kg-day dose

7 group had reduced reproductive rates (Bowman et al., 1989b) and the mean number of days of

8 offspring survival also decreased.

9   The surviving offspring from the TCDD-exposed mothers were examined using the same

10 immune panel used on the mothers and described above. The only material finding was an

11 immune hyperresponsiveness to tetanus toxoid immunization which correlated with TCDD tissue

12 levels ($r = 0.40$). However, this effect seems to be driven by only two of the offspring, and its

13 biological significance is unknown. There was no correlation between TCDD body burdens in

14 the offspring with a mother monkey's TCDD dose (i.e., offspring with the highest TCDD tissue

15 levels were born as often to mothers exposed to 0.12 ng/kg-day as 0.67 ng/kg-day).

16   In the absence of any relevant immunotoxicity endpoints or functional decrements of

17 immune function following TCDD exposure, neither a NOAEL nor a LOAEL can be established

18 for this study.

19

20 **D.1.5.5.   *Kociba et al. (1978)***

21   Sprague-Dawley rats (50 per sex per treatment group) were administered TCDD (purity

22 >99%) in the diet at doses of 0, 1, 10, or 100 ng/kg-day for 2 years. Body weights and food

23 consumption were routinely measured. Hematology, clinical chemistry, and urinalysis were

24 measured after 3, 12, or 23 months of treatment. Animals were routinely palpitated for tumors.

25 Gross and histopathological exams were conducted on the tissues of dead or dying animals or at

26 terminal sacrifice. Specific organs also were weighed.

27   The high-dose females had a statistically significant ($p < 0.05$) increase in mortality

28 compared to the controls during the second half of the study. Mortality changes in males were

29 variable and of questionable toxicological significance. A significant ($p < 0.05$) reduction in

30 body weight occurred in the 100 ng/kg-day males and females beginning at 6 months. Mid-dose

31 females also had reduced body weight, but to a lesser degree during the same time frame. There

1   were no consistent changes in food consumption. The following significant ($p < 0.05$)

2   hematology changes were observed in the high-dose animals: decreased packed cell volume in

3   males after 3 months and in females after 1 year, decreased red blood cells in females after

4   1 year and in males at terminal sacrifice, decreased hemoglobin in males after 3 months and in

5   females after 1 year, and decreased total white blood cell count in females after 1 year. Changes

6   in clinical chemistry ($p < 0.05$) occurred only in high-dose females and consisted of an increase

7   in serum alkaline phosphatase and gamma glutamyl transferase. Significant changes in

8   urinalysis occurred only in females and included increased urinary coproporphyrin in the mid-

9   and high-dose groups, increased urinary uroporphyrin in the mid- and high-dose groups, and

10 increased urinary delta-amino-levulinic acid in the high-dose group. Significant ($p < 0.05$)

11 changes in relative organ weights were observed, including increased liver weight in mid- and

12 high-dose females and decreased thymus weight in high-dose females. Mid- and high-dose rats

13 showed hepatocellular degeneration and inflammatory and necrotic changes in the liver. Thymic

14 and splenic atrophy were noted in high-dose females. An increase in non-neoplastic lung lesions

15 was noted in mid-dose females and high-dose males and females. High-dose females had an

16 increase in uterine changes. High-dose males had a significant ($p < 0.05$) increase in the

17 incidence of stratified squamous cell carcinomas of the tongue. High-dose males and females

18 had a significant ($p < 0.05$) increase in the incidence of squamous cell carcinomas of the hard

19 palate/turbinates.

20   The chronic (2-year) LOAEL is 10 ng/kg-day, based on the numerous significant

21 ($p < 0.05$) changes noted in coproporphyrin excretion (67% increase above control) and an

22 increase in liver and lung lesions in female rats. The NOAEL is 1 ng/kg-day.

23

24 **D.1.5.6.** *Maronpot et al. (1993)*

25   An initiation-promotion study was performed in female Sprague-Dawley rats (8−10 rats

26 per group). The rats were initiated with saline or diethylnitrosamine (DEN), followed 2 weeks

27 later by promotion with biweekly administration of TCDD (purity not specified) in corn oil via

28 gavage for 30 weeks. The doses were stated to be equivalent to 3.5, 10.7, 35.7, or

29 125 ng/kg-day. The rats were sacrificed 7 days after the final treatment. A significant ($p < 0.05$)

30 decrease in body weight occurred in the 125 ng/kg-day group. A significant ($p < 0.05$) increase

31 in relative liver weight occurred in the 35.7 and 125 ng/kg-day groups. There was a significant

1 ($p < 0.05$) increase in the labeling index in the 125 ng/kg-day group, but only with DEN

2 initiation. In the TCDD-alone group, a twofold increase in labeling index occurred in the

3 125 ng/kg-day group that did not reach statistical significance. A significant ($p < 0.05$) trend test

4 for increased alkaline phosphatase levels was observed in TCDD-treated animals; despite a

5 50% increase in the highest dose group, the increase was not statistically significant from

6 controls via a pairwise comparison. Total cholesterol and triglycerides were significantly

7 ($p < 0.05$) higher in the 125 ng/kg-day TCDD-alone group. A significant ($p < 0.05$) increase in

8 5'-nucleotidase occurred in the 35.7 and 125 ng/kg-day TCDD-alone groups. A dose-dependent

9 increase in the incidence and severity of liver toxicity as measured by microscopic lesions was

10 observed.

11   The 30-week LOAEL is 35.7 ng/kg-day, based on a significant ($p < 0.05$) increase in

12 relative liver weight (12%, accompanied by increases in incidence and severity of liver lesions).

13 The 30-week NOAEL is 10.7 ng/kg-day.

14

15 **D.1.5.7.**   *National Toxicology Program (1982)*

16   National Toxicology Program (NTP, 1982) conducted a carcinogenic bioassay of TCDD

17 on rats and mice. Fifty male and female Osborne-Mendel rats and male and female B6C3F$_1$

18 mice were treated twice per week with TCDD (purity not specified) in corn oil via oral gavage at

19 doses of 0, 5, 25, or 250 ng/kg for rats and male mice (1.4, 7.1, 71 ng/kg-day adjusted for

20 continuous exposure; administered doses multiplied by 2 and divided by 7) and 0, 20, 100, or

21 1,000 ng/kg for female mice (5.7, 28.6, or 286 ng/kg-day adjusted for continuous dosing;

22 administered doses multiplied by 2 and divided by 7) for 104 weeks. Seventy-five rats and mice

23 of each sex served as vehicle controls. One untreated control group of 25 rats and mice of each

24 sex was present in the TCDD treatment room and one untreated control group consisting of

25 25 rats and mice of each sex were present in the vehicle-control room. Animals surviving until

26 study termination were sacrificed at 105 or 108 weeks. A complete histopathological evaluation

27 was conducted on all animals.

28   Survival rates were not affected by TCDD exposure in rats or mice of either sex. Male

29 rats exhibited a dose-related depression in mean body weight after Week 55, while the females

30 exhibited a dose-related body-weight depression after 45 weeks of TCDD exposure. However,

31 the magnitude of the body weight response is not indicated. Mean body weights in male and

1   female mice were comparable to the vehicle control group throughout the bioassay. Noncancer

2   histopathologic findings included increased incidences of liver lesions (termed toxic hepatitis)

3   from TCDD exposure, and were detected in the high-dose rats and high-dose mice of each sex.

4   A LOAEL for TCDD of 1.4 ng/kg-day for a 104-week exposure duration is identified for

5   increased incidences of liver lesions in mice of both sexes. A NOAEL cannot be determined for

6   this study.

7

8   **D.1.5.8.** *National Toxicology Program (2006)*

9   Female Sprague-Dawley rats (81 control; 82 treatment group) were administered TCDD

10   (purity >98%) in corn oil:acetone (99:1) via gavage at doses of 0, 3, 10, 22, 46, or

11   100 ng/kg-day, 5 days per week for 105 weeks (0, 2.14, 7.14, 15.7, 32.9, or 71.4 ng/kg-day,

12   adjusted for continuous exposure) (NTP, 2006). In addition to this primary group, a stop group

13   of 50 animals was administered 100 ng/kg-day TCDD in corn oil:acetone (99:1) via gavage for

14   30 weeks and then just the vehicle for the remainder of the study. Up to 10 rats per dose group

15   were sacrificed and evaluated at 14, 31, or 53 ($n = 8$) weeks for biologically noteworthy changes

16   in the incidences of neoplasms or non-neoplastic lesions in the liver, lung, oral mucosa, uterus,

17   pancreas, thymus, adrenal cortex, heart, clitoral gland, ovary, kidney, forestomach, bone marrow,

18   mesentery gland, and pituitary gland. All interim sacrifice animals also received a complete

19   necropsy and microscopic examination, and the following organs were weighed: the left kidney,

20   liver, lung, left ovary, spleen, thymus (14 weeks only), and thyroid gland. Out of 53 control

21   animals and 53 or 54 animals per treatment group not used for interim sacrifice analyses, at study

22   termination the number of surviving animals had declined to 25 in the control group and to 21,

23   23, 19, 22, and 21 in five treatment groups, respectively, due to accidental deaths, moribund

24   animals, or death due to natural causes.

25   Survival rate was not affected by TCDD treatment. Mean body weights in the high dose

26   primary study group and the 100 ng/kg stop group were less than the vehicle control group after

27   Week 13 of the study. The mean body weights of animals in the 46 ng/kg-day group were less

28   than in the vehicle control at study termination (2 years), whereas animals in the 22 ng/kg-day

29   had lower mean body weights compared to controls during the last 10 weeks of study. In

30   addition to body weight changes, liver weights were also impacted as a result of TCDD

31   exposure. Absolute and relative liver weights were significantly (either $p \leq 0.01$ or $p \leq 0.05$)

1   higher in all dose groups compared to controls at the 14- and 31-week evaluation period, whereas

2   the relative liver weights were significantly (either $p \leq 0.01$ or $p \leq 0.05$) higher only at

3   ≥ 10 ng/kg-day at 53 weeks.

4   No clinical findings associated with TCDD treatment were observed. TCDD caused

5   changes in thyroid hormone levels at 14, 31, and 53 weeks. The following changes were

6   statistically significant ($p \leq 0.05$) compared to the vehicle control: decrease in TT4 at doses

7   ≥ 22 ng/kg-day at 14 and 31 weeks and at doses ≥ 46 ng/kg-day at 53 weeks; decrease in FT4 at

8   doses ≥ 22 ng/kg-day at 14 and 31 weeks; increase in total T_3 at doses ≥ 46 ng/kg-day at 14 and

9   31 weeks and at doses ≥ 10 ng/kg-day at 53 weeks; and increase in TSH at doses ≥ 46 ng/kg-day

10   at 14 weeks. There was a statistically significant ($p \leq 0.05$) increase in hepatocyte proliferation

11   at 14 weeks (22 ng/kg-day group only); 31 weeks (all doses); and 53 weeks (≥ 46 ng/kg-day).

12   There were statistically significant ($p \leq 0.01$) dose-dependent increases in liver (includes EROD

13   [CYP1A1-associated] activity; 7-pentoxyresorufin-O-deethylase [PROD; CYP2B-associated]

14   activity; and acetanilide-4-hydroxylase [CYP1A2-associated] activity) and lung (EROD)

15   cytochrome P450 enzyme activities in all treatment groups at all three evaluation periods

16   compared to the vehicle control group. The largest effect was an 82-fold induction of hepatic

17   EROD activity in the 46 ng/kg-day group at 31 weeks.

18   TCDD was detected at the greatest concentration in the liver, followed by fat tissue, with

19   tissue concentration increasing in both of these tissues in a dose-dependent manner. TCDD

20   tissue levels generally remained constant after the first measurement at Week 14. Pathological

21   examination at Week 14 revealed increased incidences of hepatocellular hypertrophy in animals

22   administered ≥ 10 ng/kg-day TCDD. Examinations at Weeks 31 and 53 indicated that incidence

23   and or severity of hepatocellular hypertrophy was increased at all treatment doses although

24   incidences were statistically significant ($p \leq 0.05$) only at ≥ 10 ng/kg-day doses. The incidence of

25   non-neoplastic hepatic lesions (including inflammation, necrosis, multiple eosinophilic focus,

26   diffuse fatty change, pigmentation, toxic hepatopathy) in the liver increased at doses

27   ≥ 22 ng/kg-day beginning at 14 weeks. The severity of the lesions increased at 14 weeks at doses

28   ≥ 46 ng/kg-day, but lesions were also observed at lower dose levels during later evaluation

29   periods (31 and 53 weeks). By terminal sacrifice, numerous non-neoplastic changes were noted

30   in TCDD treated rats, even at the lowest dose tested.

1   Noncancer cardiovascular and pulmonary effects were evident after 2 years of TCDD

2   exposure. Significantly increased incidences of minimal to mild cardiomyopathy were seen in

3   male and female rats at ≥ 10 ng/kg-day. In the lung, there was a significant ($p \leq 0.01$)

4   dose-dependent increase, when compared to the vehicle control, in the incidence of bronchiolar

5   metaplasia of the alveolar epithelium at all dose groups in the primary study.

6   A LOAEL for TCDD of 2.14 ng/kg-day adjusted dose for a 105-week exposure duration

7   is identified in this study for significantly (either $p \leq 0.01$ or $p \leq 0.05$) increased absolute and

8   relative liver weights, increased incidence of hepatocellular hypertrophy, and increased incidence

9   of alveolar to bronchiolar epithelial metaplasia. A NOAEL cannot be determined for this study.

10

11   **D.1.5.9.   *Sewall et al. (1993)***

12   Sewall et al. (1993) examined the impact of TCDD exposure on the hepatic epidermal

13   growth factor receptor (EGFR) as a critical effect in hepatocarcinogenicity. In two separate

14   experiments, groups of 6- to 8-week-old female Sprague-Dawley rats were randomly assigned to

15   the following groups: control group, receiving saline and corn oil; a promoted group that

16   received four different doses of TCDD along with saline; a DEN-only initiated control group;

17   and a DEN and TCDD initiated and promoted group that received four different doses of TCDD.

18   DEN was administered via intraperitoneal injection at a dose of 175 mg/kg [saline (S) vehicle] as

19   the initiating agent to animals that were 70 days old. The control animals received saline only.

20   In the first experiment, each treatment group (S/TCDD and DEN/TCDD) that included

21   sham-operated or ovariectomized and intact animals were treated with TCDD (purity >98%) at

22   125 ng/kg-day. In the second dose-response experiment, DEN-initiated and saline control

23   treatment groups (intact animals, 84 days old) were administered TCDD (purity >98%) in corn

24   oil via oral gavage once every 2 weeks for 30 weeks at doses equivalent to 0, 3.5, 10.7, 35.7, or

25   125 ng/kg-day ($n = 9$). A week after the last treatment, all animals were sacrificed and livers

26   were harvested and fixed for immunohistochemistry. Sections of the fixed liver were tested for

27   EGFR binding, EGFR autophosphorylation, immunolocalization of EGFR, and hepatic cell

28   proliferation.

29   In the first experiment, intact animals treated with 125 ng/kg-day TCDD exhibited a

30   65% reduction in EGFR binding capacity. In contrast, the EGFR equilibrium maximum binding

31   capacity (B_{max}) of the ovariectomized rats was not statistically different from the ovariectomized

1   control rats, and no changes in the K_d were detected in any treatment group. In the

2   dose-response experiment with intact animals, a significant ($p < 0.05$) TCDD dose-dependent

3   decrease in the B_{max} of EGFR was shown. A two-factor, five-level ANOVA indicated that the

4   effect of TCDD exposure on EGFR B_{max} was significant ($p = 0.0001$), whereas, the effect of

5   DEN treatment on EGFR B_{max} was not significant. Comparative analysis using Fisher's

6   protected least significant difference test indicated that the lowest TCDD dose resulting in a

7   statistically significant ($p < 0.05$) decrease in the EGFR B_{max} was 10.7 ng/kg-day S/TCDD

8   group. At the highest TCDD dose of 125 ng/kg-day, the EGFR B_{max} was reduced by 38%

9   compared to controls in both the DEN initiated and noninitiated groups. A two-factor, five-level

10   ANOVA showed no significant effect on EGFR K_d in either the DEN- or the TCDD-treated

11   groups. The EGFR autophosphorylation assay indicated that, with increasing TCDD dose, the

12   amount of EGFR autophosphorylation in DEN/TCDD-treated animals decreased. The study

13   authors state that this decrease is similar to the dose-response alterations observed for the EGFR

14   B_{max}. Additionally, EGFR autophosphorylation in control and 125 ng/kg-day noninitiated

15   animals was similar to the corresponding dose levels for the DEN-treated animals, suggesting

16   that DEN treatment did not affect the EGFR or the EGFR response to TCDD under the

17   experimental conditions. The immunolocalization assay indicated that staining was more

18   apparent in the centrilobular and midzonal regions of the liver in the DEN initiated control

19   animals, whereas, the amount of hepatocyte plasma membrane staining in DEN/TCDD treated

20   animals substantially decreased. The cell proliferation assay showed a decrease in the cell

21   labeling index in the 3.5 ng/kg-day DEN/TCDD dose group that was statistically less ($p \le 0.05$)

22   than the labeling index for the control group. In contrast, the labeling index for the

23   125 ng/kg-day DEN/TCDD treatment group was significantly ($p \le 0.05$) higher compared to

24   controls. Except for the low-dose (3.5 ng/kg-day) group, a clear dose-response trend

25   (two mid-level doses were not statistically significant) was observed in the other three TCDD

26   treated groups.

27   The role of EGFR in TCDD-mediated hepatotoxicity is unknown, and as such, this

28   endpoint cannot be unequivocally linked to TCDD-induced hepatotoxicity nor labeled as

29   adverse. Thus, no LOAEL/NOAEL was established. A LOEL for TCDD of 3.5 ng/kg-day for a

30   30-week exposure duration was identified in this study for a significant ($p = 0.0001$ using

31   ANOVA) decrease in EGFR B_{max} levels. A NOEL cannot be determined for this study.

D.1.5.10. *Sewall et al. ([1995a](#))*

Sewall et al. ([1995a](#)) studied the dose-response relationship for thyroid function alterations in female rats as a result of TCDD exposure. Groups of female Sprague-Dawley rats were initiated with DEN at 70 days of age at a dose of 175 mg/kg in a saline vehicle via an i.p. injection. DEN was administered as a liver-initiating agent for a concurrent study to determine TCDD promotion of hepatic preneoplastic foci. Saline-treated animals served as controls. At 84 days of age, both the DEN-initiated and the saline-noninitiated groups of animals were administered TCDD (purity >98%) or corn oil vehicle via oral gavage once every 2 weeks for 30 weeks at dose levels equivalent to 0, 0.1, 0.35, 1.0, 3.5, 10.7, 35.7, or 125 ng/kg-day ($n = 9$ per group). One week after the last TCDD treatment, the animals were sacrificed and the thyroid was removed and fixed for further analysis. Blood was drawn from the abdominal aortic vein, and the serum was isolated and preserved for hormone analysis. Liver was also removed and prepped for further analysis. Thyroid hormone analysis was performed to determine serum TSH, T3, and T4 levels using radioimmunoassay kits. Histological examination was conducted on eosin-stained sections of the thyroid tissue. RNA level in the hepatic tissue was determined using a reverse transcription polymerase chain reaction (RT-PCR) technique.

TCDD treatment did not affect thyroid weight. A dose-dependent decrease in serum T4 levels was observed in both noninitiated and DEN-initiated animals with T4 levels dropping significantly ($p < 0.05$) at the 35 and 125 ng/kg-day TCDD doses in the noninitiated group. Compared to the noninitiated control group, DEN alone did not significantly affect T4 levels. Serum T3 level in the 125 ng/kg-day treatment group was slightly elevated but was not significantly different from levels in the control group. TSH levels in DEN initiated rats were increased at a dose of 3.5 ng/kg-day. In the noninitiated group, TSH level in the 125 ng TCDD/kg-day group was 3.27 ± 0.34 ng/mL ($n = 9$) compared to 1.3 ± 0.18 ng/mL in the corn oil control group ($n = 7$). This result, in conjunction with the T4 data, demonstrates that TCDD had a similar effect on thyroid hormone levels in both the noninitiated and DEN initiated groups. Histological sections examined for nodular lesions or neoplasms exhibited thyroid follicular adenoma in one DEN/corn oil control animal. The DEN/TCDD-treated animals exhibited diffuse follicular hyperplasia, with the size of colloidal follicles decreasing with TCDD treatment. Other qualitative DEN/TCDD-related changes included increased frequency of abnormally shaped follicles. The study authors reported that image analysis demonstrated a

1 significant ($p = 0.013$) TCDD dose-related decrease in mean follicle size along with a significant

2 ($p = 0.001$) TCDD dose-related increase in parenchymal area. Additionally, like T4 and TSH

3 levels, DEN treatment alone or in combination with TCDD did not influence thyroid follicular or

4 C-cell morphology.

5   RT-PCR results for UGT1 and CYP1A1 mRNA levels indicated that the amount of

6 UGT1 mRNA at the 125 ng/kg-day dose was approximately 2.5-fold higher compared to the

7 concurrent controls. The study authors also stated that the maximal response for the UGT1

8 mRNA levels was reached at a dose between 1.0 and 3.5 ng TCDD/kg-day. In contrast, the

9 maximum induction of CYP1A1 mRNA was 260-fold higher at the 125 ng/kg-day compared to

10 the concurrent controls.

11   A LOAEL for TCDD of 35 ng/kg-day for a 30-week exposure duration was identified in

12 this study for a significant ($p < 0.05$) decrease in T4 levels. The NOAEL for this study is

13 10.7 ng/kg-day.

14

15 **D.1.5.11. *Toth et al. (1979)***

16   Toth et al. (1979) examined the impact of TCDD exposure on the formation of liver

17 tumors in male mice. Ten-week-old, outbred Swiss/H/Riop male mice were administered

18 sunflower oil or TCDD (purity not specified; in sunflower oil) at 0, 7, 700 or 7,000 ng/kg (0, 1,

19 100, or 1,000 ng/kg-day adjusted for continuous dosing; administered dose divided by 7; $n = 38$,

20 44, 44, and 43, respectively) once per week via gastric tube for 1 year. Once exposure had

21 ceased, animals were followed for the rest of their lives. After spontaneous death or when mice

22 were moribund, autopsies were performed and all organs were examined histologically.

23   Average life span in the 1,000 ng/kg-day dose group decreased considerably (72%) when

24 compared to the control group. TCDD also caused dose-dependent, severe chronic and ulcerous

25 skin lesions (12, 30, and 58% in the 1, 100, and 1,000 ng/kg-day dose groups, respectively) that

26 was followed by generalized lethal amyloidosis (12, 23, and 40% in the 1, 100, and

27 1,000 ng/kg-day dose groups, respectively).

28   A LOAEL for TCDD of 1 ng/kg-day for 1-year exposure duration was identified in this

29 study for severe chronic and ulcerous skin lesions (12% higher than controls), and generalized

30 lethal amyloidosis (12% higher than controls). A NOAEL cannot be determined for this study.

31

D.1.5.12. *Tritscher et al. ([1992](#))*

An initiation-promotion study was performed in female Sprague-Dawley rats (at least nine rats per group). Rats were initiated with an i.p. injection of diethylnitrosamine (DEN, 175 mg/kg) or saline, followed 2 weeks later by promotion with biweekly administration of TCDD (purity not specified) in corn oil via gavage for 30 weeks. The doses were stated to be equivalent to 3.5, 10.7, 35.7, or 125 ng/kg-day; control animals received corn oil. Rats were sacrificed 7 days after the final treatment and the livers were removed for further analysis. Liver TCDD concentrations were analyzed in DEN-initiated rats by gas chromatography-mass spectrometry. Hepatic cytochrome P450 levels (CYP1A1 and CYP1A2) and EROD activity were quantified in DEN/TCDD-treated rats, and immunohistochemical detection of CYP1A1 and CYP1A2 in liver was also conducted.

A linear relationship between administered dose of TCDD and liver TCDD concentration on a wet weight ($r = 0.999$) and lipid-adjusted basis ($r = 0.993$) was observed. A significant ($p < 0.01$) dose-response trend for increased CYP1A1 and CYP1A2 protein in the liver (hepatic microsomes) was observed in initiated and noninitiated rats. However, there were higher constitutive levels of the two CYP isozymes in noninitiated rats which produced a lower magnitude of induction by TCDD compared to the TCDD-alone group; there were no statistically significant differences between initiated and noninitiated rats at any dose tested. A strong relationship between liver TCDD concentration and CYP1A1 and CYP1A2 protein levels and EROD activity was also observed in DEN/TCDD-treated rats. Immunohistochemical staining of the serial liver sections for CYP1A1 and CYP1A2 protein from initiated and noninitiated rats exhibited a dose-dependent increase consistent with that observed via microsomal quantification. Immunolocalization and pattern of induction were also similar for both CYP isozymes. However, distribution pattern of positive immunoreactivity of the two CYP isozymes was varying, with the most intense staining observed around central veins.

CYP induction alone is not considered a significant toxicologically adverse effect given that CYPs are induced as a means of hepatic processing of xenobiotic agents. Thus, no LOAEL or NOAEL was established for this study because adverse endpoints (e.g., indicators of hepatotoxicity) were not measured.

D.1.6. Chronic Studies (Cancer Endpoints)

D.1.6.1.   *Della Porta et al. (1987)*

Della Porta et al. (1987) studied the long-term carcinogenic effects of TCDD in B6C3F$_1$

(C57BL/6JDp × C3Hf/Dp) mice. Six-week-old male and female mice (initially about

15/sex/dose, and increased by approximately 30 to 40 per group within a few weeks) were

administered 0, 2,500, and 5,000 ng/kg TCDD (purity not provided) in corn oil by oral gavage

once per week for 52 weeks (0, 357, and 714 ng/kg-day adjusted for continuous exposure). At

ages 31 to 39 weeks, 41 male mice and 32 female mice in the 2,500 ng/kg dose group were

mistakenly administered a single dose of 25,000 ng/kg TCDD. TCDD treatment for the

2,500 ng/kg dose group was halted for 5 weeks (beginning the week after the 25,000 ng/kg dose

was administered in error) and resumed until exposure was terminated at 57 weeks. Mortality

was observed and body weights recorded at unspecified intervals until 110 weeks of age, when

all surviving animals were sacrificed and necropsied. Histopathological analysis was conducted

on the following organs and tissues: Harderian glands, pituitary, thyroid, adrenals, tongue,

esophagus, and trachea; lungs, liver, pancreas; spleen, kidneys, and bladder; testes, ovaries, and

uterus, mesenteric lymph nodes, small intestine, and all other organs with presumed pathological

changes.

The body weights of both male and female mice exposed to 2,500 and 5,000 ng/kg

TCDD were markedly lower than in the corresponding control groups (statistical significance not

reported). Relative to the controls, a significant ($p < 0.001$), dose-related decrease in survival

occurred in animals treated with either dose of TCDD. In the subset of animals treated

inadvertently with a single dose of 25,000 ng/kg TCDD, mortality in male mice increased shortly

after this treatment; females, however, did not show a mortality increase following the

inadvertent treatment. This mortality in male mice was associated with subcutaneous edema,

degenerative hepatocyte changes, and bile duct hyperplasia. The incidence of non-neoplastic

lesions (such as amyloidosis of the liver, spleen, adrenals, and pancreas), liver necrosis, and

nephrosclerosis, was increased in mice exposed to TCDD compared to controls (statistical

significance not reported).

The study authors used two statistical tests to analyze tumor incidence. Because of the

increased mortality in treated groups compared to controls, one test, which assumes all tumors

are fatal, overestimated the differences between the treated and control groups. The second test

1   assumes that all tumors are incidental and resulted in an underestimation of TCDD effects. Both

2   tests were used to analyze the results for nonthymic lymphomas and hepatic adenomas and

3   carcinomas. Incidence of nonthymic lymphomas (6/45, 4/51, and 3/50 in the 0, 2,500, and

4   5,000 ng/kg dose groups, respectively in males and 17/49, 21/42, and 17/48 in the 0, 2,500, and

5   5,000 ng/kg dose groups, respectively in females) was significantly ($p < 0.05$ in males and

6   $p < 0.01$ in females) higher in TCDD-treated animals compared to the corresponding controls

7   using the fatal tumor test. However, the incidental tumor test showed that this higher incidence

8   was not significant. Similarly, a significantly ($p < 0.001$) higher incidence of hepatocellular

9   adenomas occurred in male mice using the fatal tumor test (10/43, 11/51, and 10/50 in the 0,

10 2,500, and 5,000 ng/kg dose groups, respectively), but the incidence was not significant when

11 assessed using the incidental tumor test. Hepatocellular carcinomas in males were significant,

12 ($p < 0.001$) using either the fatal or incidental tumor tests (5/43, 15/51, and 33/50 in the 0, 2,500,

13 and 5,000 ng/kg dose groups, respectively). In female mice, hepatocellular adenomas were

14 significant using both the fatal ($p < 0.01$) and incidental ($p < 0.001$) tumor tests (2/49, 4/42, and

15 11/48 in the 0, 2,500, and 5,000 ng/kg dose groups, respectively). Similar results for female

16 mice were obtained for incidence of hepatocellular carcinomas (1/49, 12/42, and 9/48 in the 0,

17 2,500, and 5,000 ng/kg dose groups, respectively), which also were significant using both the

18 fatal ($p < 0.01$) and incidental ($p < 0.05$) tumor tests. TCDD-related incidences of other tumor

19 types in both sexes were uniformly low and comparable in the treatment and control groups.

20   These results indicate that TCDD is carcinogenic in male and female B6C3F$_1$ mice,

21 causing hepatocellular adenomas and carcinomas in both sexes.

22   In addition to the long term bioassay results in mice described by Della Porta et al.

23 ([1987](#)), carcinogenic effects of TCDD in a neonatal bioassay were reported in the same

24 publication. Briefly, groups of male and female B6C3F$_1$ and B6CF1 (C57/BL6J × BALB/c)

25 mice were treated with 0, 1,000, 30,000 or 60,000 ng/kg BW TCDD via intraperitoneal (i.p.)

26 injection beginning at PND 10. Animals were treated once weekly for 5 weeks and then

27 observed until 78 weeks of age. However, because this study utilized i.p. injection as the route

28 of TCDD exposure, it does not qualify for further consideration based on the study selection

29 criterion that the study design consist of orally administered TCDD.

30

D.1.6.2. *Kociba et al. (1978)*

As discussed above, Kociba et al. (1978) conducted a lifetime (2-year) feeding study of male and female Sprague-Dawley rats using doses of 0, 1, 10, and 100 ng/kg-day. There were 50 males and 50 females in each group.

With respect to the cancer endpoints examined, the most significant finding was an increase in hepatocellular hyperplastic nodules and hepatocellular carcinomas in female rats. The incidence of hepatocellular carcinomas was significantly elevated above the control incidence at the 100 ng/kg-day dose, whereas increased incidence of hyperplastic nodules was evident in the 10 ng/kg-day dose group.

There have been two reevaluations of slides of liver sections from the Kociba et al. study (Goodman and Sauer, 1992; Sauer, 1990; Squire, 1990). The Squire Review was requested by EPA as an independent review of the slides. The Sauer Review was carried out using refined criteria for the diagnosis of proliferative hepatocellular lesions (Maronpot et al., 1989; Maronpot et al., 1986). Liver tumor incidences for the three evaluations are compared in Appendix F. Although there are some quantitative differences between the evaluations, the lowest detectable effect for liver tumor incidence is consistently observed at 10 ng/kg-day.

In the 10 ng/kg-day dose group, significant increases in the incidence of hyperplastic nodules of the liver were observed in female rats (18/50 in the Kociba evaluation, 27/50 in the Squire evaluation). Two females (2/50) had hepatocellular carcinomas. In the 1990 reevaluation (Goodman and Sauer, 1992; Sauer, 1990), nine females (9/50) were identified with hepatocellular adenomas and none with carcinomas; thus only one-third of the previously observed "tumors" were identified when using the refined diagnostic criteria. As discussed below, the tumor reclassification of Goodman and Sauer (1992) was used in the dose-response modeling for the Kociba et al. (1978) data set.

In addition to nodules in the liver, increased incidence of stratified squamous cell carcinoma of the tongue and nasal turbinates/hard palate, and keratinizing squamous cell carcinoma of the lung were also observed in female rats in the 100 ng/kg-day dose group. One possible cause for the induction of lung tumors in the Kociba feeding study may have been the aspiration of dosed feed into the lungs. However the promotion of lung tumors has been observed in mice treated systemically by intraperitoneal (i.p.) injections of TCDD (Beebe et al., 1995). In addition the induction of hyperplastic and metaplastic lesions in rats has been observed

1   following chronic oral gavage treatment with TCDD (Tritscher et al., 2000). More recently,

2   chronic oral exposure to HCDD resulted in the induction of lung tumors in treated female rats

3   (Rozman, 2000). These data indicate that the induction of lung tumors in the Kociba study was

4   most likely primarily the result of systemic chronic dietary exposure to TCDD rather than due to

5   a localized exposure to aspired dosed feed.

6   There was no detectable increase in liver tumor incidences in male rats in any of the dose

7   groups. The mechanism responsible for dioxin-mediated sex specificity for

8   hepatocarcinogenesis in rats is not clear, but may involve ovarian hormones (Lucier et al., 1991).

9   Although there was no increase in liver tumors in male rats in this study, in the

10   100 ng/kg-day group, there was an increased incidence of stratified squamous cell carcinoma of

11   the hard palate/nasal turbinate, stratified squamous cell carcinoma of the tongue, and adenoma of

12   the adrenal cortex.

13   Kociba et al. (1978) had reported that chemically related increases in preneoplastic or

14   neoplastic lesions were not found in the 1 ng/kg-day dose group. However, Squire identified two

15   male rats in the 1 ng/kg-day dose group with squamous cell carcinoma of the nasal

16   turbinates/hard palate, and one of these male rats had a squamous cell carcinoma of the tongue.

17   These are both rare tumors in Sprague-Dawley rats, and these sites are targets for TCDD,

18   implying that 1 ng/kg-day may not represent a NOEL. However, no dose-response relationships

19   were evident for tumors at these sites (Huff et al., 1991).

20   There is considerable controversy concerning the possibility that TCDD-induced liver

21   tumors are a consequence of cytotoxicity. Goodman and Sauer (1992) have extended the

22   reevaluation of the Kociba slides to include liver toxicity data and have reported a correlation

23   between the presence of overt hepatotoxicity and the development of hepatocellular neoplasms in

24   female rats. With the exception of two tumors in controls and one each in the low- and mid-dose

25   groups, all liver tumors occurred in livers showing clear signs of toxicity. However, male rat

26   livers exhibit cytotoxicity in response to high TCDD doses, yet they do not develop liver tumors.

27   Moreover, both intact and ovariectomized female rats exhibit liver toxicity in response to TCDD,

28   yet TCDD is a more potent promoter in intact but not ovariectomized rats (Lucier et al., 1991).

29   Therefore, if cytotoxicity is playing a role in liver tumorigenesis, other factors must also be

30   involved. Also, there is little information on the role of cytotoxicity in TCDD-mediated cancer

31   at other sites such as the lung and thyroid.

1 **D.1.6.3.** *Toth et al. (1979)*

2   In a study of 10-week-old outbred male Swiss/H/Riop mice, Toth et al. *(1979)*

3 administered oral gavage TCDD doses of 0, 7, 700, and 7,000 ng/kg-day in sunflower oil weekly

4 for 1 year (0, 1, 100, or 1,000 ng/kg-day adjusted for continuous dosing; see details above). All

5 mice (100/group) were followed for their entire lives. The study authors identified the effective

6 number of mice in each group to be the number of surviving animals when the

7 first tumor-bearing animal was identified. The average lifespan of the control, low, mid and high

8 dose groups was 588, 649, 633, and 424 days, respectively.

9   In the 100 ng/kg-day dose group, liver tumor incidence was twice that of the control

10 group and was statistically significant ($p < 0.01\%$). A dose-related increase in liver tumor

11 incidence was observed (18, 29, 48, and 30% in the control and three TCDD-treated groups,

12 respectively) in all treated mice. Increases were not statistically significant, however, at 1 and

13 1,000 ng/kg-day. The study authors also stated that spontaneous and induced liver tumors were

14 not histologically different. Additionally, the ratio of benign hepatomas to hepatocellular

15 carcinomas in the control group was not affected by treatment and an increase was observed only

16 in the absolute number of liver tumors. Cirrhosis was not observed with the tumors.

17

18 **D.1.6.4.** *NTP (1982)*

19   As discussed above, the NTP (1982) study was conducted using Osborne-Mendel rats

20 and B6C3F$_1$ mice (NTP, 1982). Groups of 50 male rats, 50 female rats, and 50 male mice

21 received TCDD as a suspension in corn oil:acteone (9:1) by gavage twice each week at doses of

22 0, 5, 25, or 250 ng/kg-day (daily averaged doses of 0, 1.4, 7.1, or 71 ng/kg-day for rats and male

23 mice and doses of 0, 5.7, 28.6, or 286 ng/kg-day for female mice.

24   There were no statistically significant dose-related decreases in survival in any

25 sex-species group. TCDD-induced malignant liver tumors occurred in the high-dose female rats

26 and in male and female mice. These can be considered to result from TCDD exposure because

27 they are relatively uncommon lesions in control Osborne-Mendel rats (male, 1/208; female,

28 3/208), are seen in female rats and mice of both sexes, and their increasing incidence with

29 increasing dose is statistically significant (Cochran-Armitage trend test, $p = 0.004$). Because

30 liver tumors were increased in both sexes of mice, this effect is not female-specific as was

31 observed in rats. Interestingly, liver tumor incidences were decreased in female rats in both the

1 NTP and Kociba low doses (not statistically significant compared with controls). For example,

2 the combined control incidence data were 11/161 (7%) compared with 4/99 (4%) in the low-dose

3 group.

4 The incidences of thyroid gland (follicular cell) tumors were increased in all three dose

5 groups in male rats. Because the responses in the two highest dose groups are highly significant,

6 the statistically significant elevation of incidence in the lowest dose group (Fisher exact

7 p-value = 0.042) is considered to be caused by exposure to TCDD, suggesting that thyroid tumor

8 incidence may be the most sensitive site for TCDD-mediated carcinogenesis. Because

9 71 ng/kg-day is above the maximum tolerated dose (MTD) (Huff et al., 1991), thyroid tumors

10 occur at doses more than 50 times lower than the MTD.

11 TCDD-induced neoplasms of the adrenal gland were observed in the 7.1 ng/kg-day/dose

12 group in male rats and in high-dose female rats. Fibrosarcomas of the subcutaneous tissue were

13 significantly elevated in high-dose female mice and female rats. One additional tumor type,

14 lymphoma, was seen in high-dose female mice. Lung tumors were elevated in high-dose female

15 mice; the increase was not statistically significant when compared with concurrent controls, but

16 the increase was dose related (Cochran-Armitage trend test, $p = 0.004$).

17 Huff (1992) concluded, based on the NTP bioassay results, that TCDD was a complete

18 carcinogen and induced neoplasms in rats and mice of both sexes. As was observed in the

19 Kociba study (1978), liver tumors were observed with greater frequency in treated female rats,

20 but in male rats the thyroid appears to be the most sensitive (increased tumor incidence at doses

21 as low as 1.4 ng/kg-day).

22

23 **D.1.6.5.** *NTP (2006)*

24 As discussed above, female Sprague-Dawley rats (53 control; 53 or 54 animals per

25 treatment group) were administered TCDD (purity >98%) in corn oil:acetone (99:1) via gavage

26 at doses of 0, 3, 10, 22, 46, or 100 ng/kg-day, 5 days per week for 105 weeks (0, 2.14, 7.14, 15.7,

27 32.9, or 71.4 ng/kg-day, adjusted for continuous exposure) (NTP, 2006). In addition to this

28 primary group, a stop-dose group of 50 animals was administered 100 ng/kg-day TCDD in corn

29 oil:acetone (99:1) via gavage for 30 weeks and then just the vehicle for the remainder of the

30 study. At study termination, the number of surviving animals had declined to 25 in the control

1   group and to 21, 23, 19, 22, and 21 in five treatment groups, respectively, due to accidental

2   deaths, moribund animals, or death due to natural causes.

3   Incidence of hepatocellular adenomas was significantly ($p < 0.001$) increased in the

4   100 ng/kg-day dose group in the primary study and exceeded incidences seen in historical

5   vehicle control range at study termination. A dose-related increase in the incidence of

6   cholangiosarcoma was seen in the primary study group in animals receiving 22 ng/kg-day or

7   higher doses of TCDD. The high dose group of 100 ng/kg-day had the highest incidence of

8   cholangiosarcoma with a significant ($p < 0.001$) number of animals exhibiting multiple

9   cholangiosarcomas. Such an incidence was not seen in historical vehicle controls. In contrast,

10 only two cholangiosarcomas and hepatocellular adenomas were seen in the 100 ng/kg-day group

11 in the stop-exposure study.

12   In the lung, at 2 years, there was a significantly ($p = 0.002$) increased incidence of cystic

13 keratinizing epithelioma in the 100 ng/kg-day dose group of the primary study, while there were

14 no epitheliomas in the 100 ng/kg-day group of the stop-exposure study. There was also a

15 significant ($p \leq 0.01$) dose-dependent increase, when compared to the vehicle control, in the

16 incidence of bronchiolar metaplasia of the alveolar epithelium at all dose groups in the primary

17 study. Squamous metaplasia was also present in the 46 and 100 ng/kg-day dose groups in the

18 primary study, and was also observed in the 100 ng/kg-day dose group in the stop-exposure

19 study.

20   A positive trend in the incidence of gingival squamous cell carcinoma of the oral cavity

21 was seen at all doses (except 22 ng/kg-day), with the incidence significantly ($p = 0.007$) high in

22 the 100 ng/kg-day dose group. In addition, the occurrence of this lesion in the 46 and

23 100 ng/kg-day group of the primary study and 100 ng/kg-day group of the stop-exposure study

24 exceeded the historical control range. The incidence of gingival squamous hyperplasia was

25 significantly (either $p \leq 0.01$ or $p \leq 0.05$) increased in all dose groups of the primary study as

26 well as the 100 ng/kg-day group of the stop-exposure study.

27   In the uterus, at 2 years, there was a significantly ($p = 0.032$) higher rate of squamous cell

28 carcinoma in the 46 ng/kg-day group compared to vehicle controls. In addition there were

29 two squamous cell carcinomas in the 100 ng/kg-day group of the stop-exposure study. No

30 squamous cell carcinomas have been reported in historical vehicle controls.

1   These results indicate that TCDD is carcinogenic to female Sprague-Dawley rats and

2   causes tumors at multiple sites.

3

4   **D.2. EVALUATION OF STUDIES**

5   Based on the results of EPA's literature search and collection activities (see Section 2.2

6   and Figure 2-1), a total of 1,441 studies were examined for their potential to be used in TCDD

7   quantitative dose-response analysis (see Figure 2-4 of the main document). Of the 1,441 studies,

8   49 were epidemiologic cancer or noncancer studies (see Appendix C for their summaries and

9   evaluations). In addition, there were 637 studies eliminated from consideration because they

10 were not suitable study types; these included, in vitro bioassays, review articles, PBPK modeling

11 studies, and studies that evaluated PCBs or other dioxin-like compounds other than TCDD. A

12 list of these studies is not provided in this appendix; results of the initial literature review can be

13 found online at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=199923#Download.

14 A total of 755 animal studies were evaluated (4 studies contained both cancer and noncancer

15 endpoints). The results are shown and discussed in the remainder of this Section D.2.

16

17 **D.2.1.   Evaluation of Animal Cancer Bioassays**

18   A total of eight animal cancer bioassays were available for evaluation (see Figure 2-4)

19 using EPA's study selection criteria (see Section 2.3.2 and Figure 2-3). Table 2-3 of the

20 document presents the 6 studies that met these criteria and are considered suitable for

21 quantitative TCDD dose-response modeling. Only two of the available cancer bioassays did not

22 meet EPA's study selection criteria, and, therefore, are not summarized in this document. These

23 include Eastin et al. (1998) because a genetically altered mouse strain is tested and Rao et al.

24 (1988), because an intraperitoneal injection was used instead of oral route of exposure.

25

26 **D.2.2.   Evaluation of Animal Noncancer Bioassays**

27   Table D-1. Summary of studies included in the dioxin reanalysis

28
29   provides the list of 78 studies that were selected as key studies for TCDD noncancer

30 dose-response analyses. These studies are peer-reviewed, noncancer, in vivo mammalian studies

31 that assessed TCDD dose response, and they meet EPA's study selection criteria (see Section

1   2.3.2 and Figure 2-3). Information on each of these studies is provided in Section D.1 of this

2   appendix and in Table 2-4 of the main document.

3   An additional 673 studies were excluded from analysis based on one or more of the

4   following reasons (see Figure 2-4): (1) 66 studies used genetically altered animals;

5   (2) 370 studies had a lowest tested dose that was too high (i.e., greater than 30 ng/kg-day);

6   (3) 142 studies tested chemicals that were not TCDD-only or used an unspecified TCDD dose;

7   and (4) 135 studies employed a nonoral dosing method. Table D-2 shows these studies and

8   identifies the study inclusion criteria that were not met. For many studies, more than one reason

9   for exclusion was found. Conversely, in some cases at least one criterion was not met and was

10   identified, but, given that the study had already been excluded based on one criterion, not all of

11   the other criteria for exclusion were further evaluated and identified.

12

13   **D.3. CROSS-SPECIES CONCORDANCE OF SELECTED HEALTH ENDPOINTS**

14   This appendix presents a cross-species comparison of NOAELs and LOAELs for selected

15   endpoints from the animal bioassay and human epidemiology studies that passed the noncancer

16   study selection criteria outlined in Section 2. The tables and figures are intended to illustrate the

17   degree of qualitative and quantitative concordance of effects across species and the consistency

18   of observation of those effects across studies within species. Tables D-3 through D-8 provide

19   these comparison for male reproductive, female reproductive, thyroid, developmental dental,

20   immune system, and neurological effects, respectively (also illustrated in Figures D-1 through

21   D-6). This analysis goes beyond the one presented in Section 4 (Tables 4-3 and 4-5) in that

22   effects at doses higher than the study LOAELs (for most sensitive effect) are included.

23   Quantitative concordance is considered in terms of modeled equivalent human exposures, as

24   displayed on the figures, and actual administered doses (tables only). Results from animal

25   bioassays that did not pass the low-dose-maximum selection criterion are not included here, but

26   may provide additional relevant information.

27   The endpoints evaluated here were chosen because they have been observed in both

28   human epidemiologic studies and animal bioassays (i.e., male and female reproductive effects,

29   thyroid hormone levels, and developmental dental effects) and quantified by EPA for RfD POD

30   consideration, or are sensitive effects in animals but not in humans (i.e., immunological and

31   neurological effects). Hepatic effects, which are not included here, are evident in all rodent

1   studies that looked for them and are often severe; hepatic effects reported for humans were not as

2   severe (Michalek et al., 2001b). Diabetes may be a sensitive health effect in humans(Michalek

3   and Pavuk, 2008), but no animal bioassays included in this analysis address diabetes or glucose

4   metabolism. Other animal studies that did not meet the dose-limit selection criterion may show

5   effects of interest at higher doses.

6   Male reproductive effects have been reported in all species (mice, rats and humans) in

7   which they were evaluated (Table D-3 and Figure D-1). Sperm effects, one of the co-critical

8   effects in humans selected for the RfD, is observed in more than one rat study, but not in mice, in

9   the studies selected for this analysis. Altered sex ratios (i.e., decreased proportion of male

10 offspring) have been reported for both mice and rats and in one human study (Mocarelli et al.,

11 2000); the human study was not considered for a POD (see Appendix C for study evaluation

12 details), and thus is not included in Figure D-1.

13   Female reproductive effects also have been reported for all species (mice, rats, monkeys

14 and humans) in which they were evaluated (Table D-4 and Figure D-2). Of particular note are

15 the more severe effects (i.e., reduced fertility, embryo loss and reduced offspring survival; see

16 Table D-4) that have been observed in animal species as compared to humans. Adverse birth

17 outcomes were not observed for the Seveso Women's Cohort as reported by Eskenazi et al.

18 (2003).   Other female reproductive effects observed in humans included lengthened menstrual

19 cycle reported by Eskenazi et al., (2002) which is the only study that passed the selection criteria

20 (and is shown in Figure D-2).Other female reproductive effects were unable to be evaluated for

21 RfD POD consideration because a critical exposure window could not be identified for these

22 effects (see Appendix C); these other health outcomes included early menopause (Eskenazi et al.,

23 2005) and possible anti-estrogenic effects (Eskenazi et al., 2007).

24   Effects of TCDD on thyroid hormones have been reported for rats and humans (Table

25 D-5 and Figure D-3) but have not been evaluated in other species in the selected data sets.

26 Increased neonatal TSH, the other co-critical effect for the RfD, has only been evaluated for

27 humans; rat studies have reported decreased serum levels of T3 and T4 in adults.

28   Developmental dental defects have also been observed in mice, rats and humans (Table

29 D-6 and Figure D-4) but are not a particularly sensitive endpoint for humans, as they are for mice

30 and rats. Other relatively sensitive endpoints reported in animal bioassays, such as

31 immunotoxicity (Table D-7 and Figure D-5) and neurotoxicity (Table D-8 and Figure D-6) do

1 not appear to be sensitive human health outcomes associated with TCDD exposure. Baccarelli et

2 al. (2004; 2002) reported decreased IgG levels for some individuals in the Seveso cohort and

3 concluded that the levels were far above those associated with immunodeficiency disorders.

4 Michalek et al. (2001c) found no evidence of peripheral neuropathy in Vietnam veterans exposed

5 to TCDD during operation Ranch Hand.

6   Overall, the analysis presented here supports the conclusion that there is a substantial

7 amount of qualitative concordance of effects between laboratory animal species and humans, but

8 lower quantitative concordance.

Table D-1. Summary of studies included in the dioxin reanalysis

Author (year)	Title of study
Amin et al. (2000)	Gestational and Lactational Exposure to TCDD or Coplanar PCBs Alters Adult Expression of Saccharin Preference Behavior in Female Rats
Bell et al. (2007c)	Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Developing Male Wistar(Han) Rat. II: Chronic Dosing Causes Developmental Delay
Bowman et al. (1989a)	Behavioral Effects in Monkeys Exposed to 2,3,7,8-TCDD Transmitted Maternally During Gestation and for Four Months of Nursing
Bowman et al. (1989b)	Chronic Dietary Intake of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) at 5 or 25 ppt in Monkey: TCDD Kinetics and Dose-effect Estimate of Reproductive Toxicology
Burleson et al. (1996)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Influenza Virus Host Resistance in Mice
Cantoni et al. (1981)	Porphyrogenic Effect of Chronic Treatment with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Female Rats. Dose–Effect Relationship Following Urinary Excretion of Porphyrins
Chu et al. (2001)	Mixture Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Polychlorinated Biphenyl Congeners in Rats
Chu et al. (2007)	Combined Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Polychlorinated Biphenyl Congeners in Rats
Crofton et al. (2005)	Thyroid-Hormone-Disrupting Chemicals: Evidence for Dose-Dependent Additivity or Synergism
Croutch et al. (2005)	2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and 1,2,3,4,7,8-Hexachlorodibenzo-*p*-Dioxin (HxCDD) Alter Body Weight by Decreasing Insulin-Like Growth Factor I (IGF-I) Signaling
DeCaprio et al. (1986)	Subchronic Oral Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Guinea Pig: Comparisons with a PCB-containing Transformer Fluid Pyrolysate
DeVito et al. (1994)	Dose-response Relationships in Mice Following Subchronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: CYP1A1, CYP1A2, Estrogen Receptor, and Protein Tyrosine Phosphorylation
Fattore et al. (2000)	Relative Potency Values Derived from Hepatic Vitamin A Reduction in Male and Female Sprague-Dawley Rats Following Subchronic Dietary Exposure to Individual Polychlorinated Dibenzo-*p*-dioxin and Dibenzofuran Congeners and a Mixture Thereof
Fox et al. (1993)	Gene Expression and Cell Proliferation in Rat Liver After 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure
Franc et al. (2001)	Persistent, Low-dose 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure: Effect on Aryl Hydrocarbon Receptor Expression in a Dioxin-Resistance Model

Table D-1. Summary of studies included in the dioxin reanalysis (continued)

Author (year)	Title of study
Franczak et al. (2006)	Effects of Acute and Chronic Exposure to the Aryl Hydrocarbon Receptor Agonist 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on the Transition to Reproductive Senescence in Female Sprague-Dawley Rats
Hassoun et al. (1998)	Induction of Oxidative Stress in Brain Tissues of Mice after Subchronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
Hassoun et al. (2000)	The Relative Abilities of TCDD and its Congeners to Induce Oxidative Stress in the Hepatic and Brain Tissues of Rats After Subchronic Exposure
Hassoun et al. (2002)	Induction of Oxidative Stress in the Tissues of Rats after Chronic Exposure to TCDD, 2,3,4,7,8-Pentachlorodibenzofuran, and 3,3',4,4',5-Pentachlorobiphenyl
Hassoun et al. (2003)	The Role Of Antioxidant Enzymes In TCDD-Induced Oxidative Stress in Various Brain Regions of Rats After Subchronic Exposure
Hochstein et al. (2001)	Chronic Toxicity of Dietary 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin to Mink
Hojo et al. (2002)	Sexually Dimorphic Behavioral Responses to Prenatal Dioxin Exposure
Hong et al. (1989)	Immune Abnormalities Associated With Chronic TCDD Exposure in Rhesus
Hutt et al. (2008)	The Environmental Toxicant 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Disrupts Morphogenesis of the Rat Pre-implantation Embryo
Ikeda et al. (2005b)	Repeated In Utero and Lactational 2,3,7,8-TCDD Exposure Affects Male Gonads in Offspring, Leading to Sex Ratio Changes in F2 Progeny
Ishihara et al. (2007)	Does Paternal Exposure to 2,3,7,8-TCDD Affect the Sex Ratio of Offspring?
Kattainen et al. (2001)	In Utero/Lactational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure Impairs Molar Tooth Development in Rats
Keller et al. (2007)	Qualitative Effects of Dioxin on Molars Vary Among Inbred Mouse Strains
Keller et al. (2008a)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Molar Development Among Non-resistant Inbred Strains of Mice: A Geometric Morphometric Analysis
Keller et al. (2008b)	Genetic Differences in Sensitivity to Alterations of Mandible Structure Caused by the Teratogen 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin
Kitchin and Woods (1979)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Effects on Hepatic Microsomal Cytochrome P-448-mediated Enzyme Activities
Kociba et al. (1976)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD): Results of a 13-week Oral Toxicity Study in Rats
Kociba et al. (1978)	Results of a Two-year Chronic Toxicity and Oncogenicity Study of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Rats. Long-term Toxicologic Studies of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Laboratory Animals
Kuchiiwa et al. (2002)	In Utero and Lactational Exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin Decreases Serotonin-immunoreactive Neurons in Raphe Nuclei of Male Mouse Offspring
Latchoumycandane and Mathur (2002)	Effects of Vitamin E on Reactive Oxygen Species-mediated 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Toxicity in Rat Testis

Table D-1. Summary of studies included in the dioxin reanalysis (continued)

Author (year)	Title of study
Latchoumycandane et al.(2002b)	Induction of Oxidation Stress in Rat Epidermal Sperm After Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
Latchoumycandane et al. (2002a)	The Effect of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on the Antioxidant System in Mitochondrial and Microsomal Fractions of Rat Testis
Latchoumycandane et al. (2003)	2,3,7,8-Tetrachlorodibenzo-*p* -dioxin (TCDD) Induces Oxidative Stress in the Epididymis and Epididymal Sperm of Adult Rats
Li et al. (1997)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Increases Release of Luteinizing Hormone and Follicle-Stimulating Hormone from the Pituitary of Immature Female Rats In Vivo and In Vitro
Li et al. (2006)	The Early Embryo Loss Caused by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin May be Related to the Accumulation of this Compound in the Uterus
Lucier et al. (1986)	Ingestion of Soil Contaminated with 2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin (TCDD) Alters Hepatic Enzyme Activities in Rats
Mally and Chipman (2002)	Non-genotoxic Carcinogens: Early Effects on Gap Junctions, Cell Proliferation and Apoptosis in the Rat
Markowski et al. (2001)	Altered operant Responding for Motor Reinforcement and the Determination of Benchmark Doses Following Perinatal Exposure to Low-level 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
Maronpot et al. (1993)	Dose Response for TCDD Promotion of Hepatocarcinogenesis in Rats Initiated with DEN: Histologic, Biochemical, and Cell Proliferation Endpoints
Miettinen et al. (2006)	The Effect of Perinatal TCDD Exposure on Caries Susceptibility in Rats
Murray et al. (1979)	Three-generation Reproduction Study of Rats Given 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in the Diet
Nohara et al. (2000b)	The Effects of Perinatal Exposure to Low Doses of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Immune Organs in Rats
Nohara et al. (2002a)	Effect of Low-dose 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Influenza A Virus-induced Mortality in Mice
NTP (1982)	NTP Technical Report on Carcinogenesis Bioassay of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in Osborne-Mendel Rats and $B6C3F_1$ Mice (Gavage Study)
NTP (2006)	NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Female Harlan Sprague-Dawley Rats (Gavage Studies)
Ohsako et al. (2001)	Maternal Exposure to a Low Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Suppressed the Development of Reproductive Organs of Male Rats: Dose-Dependent Increase of mRNA Levels of 5a-reductase Type 2 in Contrast to Decrease of Androgen Receptor in the Pubertal Ventral Prostate
Schantz and Bowman (1989)	Learning in Monkeys exposed Perinatally to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)

Table D-1. Summary of studies included in the dioxin reanalysis (continued)

Author (year)	Title of study
Schantz et al. (1986)	Maternal Care by Rhesus Monkeys of Infant Monkeys Exposed to Either Lead or 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)
Schantz et al. (1992)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Behavior of Monkeys in Peer Groups
Schantz et al. (1996)	Effects of Gestational and Lactational Exposure to TCDD or Coplanar PCBs on Spatial Learning
Seo et al. (1995)	Effects of Gestational and Lactational Exposure to Coplanar Polychlorinated Biphenyl (PCB) Congeners or 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Thyroid Hormone Concentrations in Weanling Rats
Sewall et al. (1993)	TCDD-mediated Changes in Hepatic Epidermal Growth Factor Receptor May be a Critical Event in the Hepatocarcinogenic Action of TCDD
Sewall et al. (1995a)	Alterations in Thyroid Function in Female Sprague-Dawley Rats Following Chronic Treatment with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
Shi et al. (2007)	Ovarian Endocrine Disruption Underlies Premature Reproductive Senescence Following Environmentally Relevant Chronic Exposure to the Aryl Hydrocarbon Receptor Agonist 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin
Simanainen et al. (2002)	Structure-Activity Relationships and Dose Responses of Polychlorinated Dibenzo-*p*-dioxins for Short-Term Effects in 2,3,7,8- Tetrachlorodibenzo-*p*-dioxin-Resistant and -Sensitive Rat
Simanainen et al. (2003)	Dose-response Analysis of Short-term Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Three Differentially Susceptible Rat Lines
Simanainen et al. (2004b)	Pattern of Male Reproductive System Effects After In Utero and Lactational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Exposure in Three Differentially TCDD-Sensitive Rat Lines
Slezak et al. (2000)	Oxidative Stress in Female B6C3F$_1$ Mice Following Acute and Subchronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)
Smialowicz et al. (2004)	CYP1A2 is Not Required for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-induced Immunosuppression
Smialowicz et al. (2008)	Relative Potency Based on Hepatic Enzyme Induction Predicts Immunosuppressive Effects of a Mixture of PCDDS/PCDFS and PCBS
Smith et al. (1976)	Teratogenicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in CF-1 Mice
Sparschu et al. (1971)	Study of the Teratogenicity of 2,3,7,8-Tetrachiorodibenzo-*p*-dioxin in the Rat
Sugita-Konishi et al. (2003)	Effect of Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on the Susceptibility to *Listeria* Infection
Tritscher et al. (1992)	Dose-response Relationships for Chronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in a Rat-tumor Promotion Model: Quantification and Immunolocalization of CYP1A1and CYP1A2 in the Liver
Toth et al. (1979)	Carcinogenicity Testing of Herbicide 2,4,5-Trichlorophenoxyethanol Containing Dioxin and of Pure Dioxin in Swiss Mice

Table D-1. Summary of studies included in the dioxin reanalysis (continued)

Author (year)	Title of study
Van Birgelen et al. (1995a)	Subchronic Dose-response Study of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Female Sprague-Dawley Rats
Van Birgelen et al. (1995b)	Subchronic Effects of 2,3,7,8-TCDD or PCBs on Thyroid Hormone Metabolism: Use in Risk Assessment
Vanden Heuvel et al. (1994)	Dioxin-responsive Genes: Examination of Dose-response relationships Using Quantitative Reverse Transcriptase-polymerase Chain Reaction
Vos et al. (1973)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on the Immune System of Laboratory Animals
Weber et al. (1995)	Correlation Between Toxicity and Effects on Intermediary Metabolism in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-treated Male C57BL/6L and DBA/2J Mice
White et al. (1986)	Modulation of Serum Complement Levels Following Exposure to Polychlorinated Dibenzo-*p*-dioxins
Yang et al. (2000)	Subchronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Modulates the Pathophysiology of Endometriosis in the Cynomolgus Monkey
Zareba et al. (2002)	Sexually Dimorphic Alterations of Brain Cortical Dominance in Rats Prenatally Exposed to TCDD

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
		Reason for excluding study			
Abbott and Birnbaum (1989)	TCDD Alters Medial Epithelial Cell Differentiation During Palatogenesis	-	X	-	-
Abbott and Birnbaum (1990)	Effects of TCDD on Embryonic Ureteric Epithelial EGF Receptor Expression and Cell Proliferation	-	X	-	-
Abbott and Probst (1995)	Developmental Expression of Two Members of a New Class of Transcription Factors: II. Expression of Aryl Hydrocarbon Receptor Nuclear Translocator in the C57BL/6N Mouse Embryo	-	-	X	-
Abbott et al. (1987b)	TCDD Alters the Extracellular Matrix and Basal Lamina of the Fetal Mouse Kidney	-	X	-	-
Abbott et al. (1987a)	TCDD-Induced Hyperplasia of the Ureteral Epithelium Produces Hydronephrosis in Murine Fetuses	-	X	-	-
Abbott et al. (1999a)	AhR, ARNT, and CYP1A1 mRNA Quantitation in Cultured Human Embryonic Palates Exposed to TCDD and Comparison with Mouse Palate In Vivo and in Culture	-	X	-	-
Abbott et al. (1999b)	RT-PCR Quantification of AHR, ARNT, GR, and CYP1A1 mRNA in Craniofacial Tissues of Embryonic Mice Exposed to 2,3,7,8-Tetrachlorodibenzo-p-dioxin and Hydrocortisone	-	X	-	-
Abbott et al. (2003)	EGF and TGF-α Expression Influence the Developmental Toxicity of TCDD: Dose Response and AhR Phenotype in EGF, TGF-α , and EGF+ TGF- α Knockout Mice	-	X	-	-
Abernethy et al. (1985)	2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Promotes the Transformation of C3H/10T1/2 Cells	-	-	-	X
Abraham et al. (1988)	Pharmacokinetics and Biological Activity of 2,3,7,8-Tetrachlorodibenzo-p-dioxin. 1. Dose-dependent Tissue Distribution and Induction of Hepatic Ethoxyresorufin o-deethylase in Rats Following a Single Injection	-	-	-	X

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Ackermann et al. (1989)	Selective Inhibition of Polymorphonuclear Activity by 2,3,7,8-Tetracholordibenzo-*p*-dioxin	-	X	-	-
Adamsson et al. (2008)	The Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Fetal Male Rat Steroidogenesis	-	X	-	-
Agrawal et al. (1981)	3,4,3N,4N-Tetrachlorobiphenyl Given to Mice Prenatally Produces Long-term Decreases in Striatal Dopamine and Receptor Binding Sites in the Caudate Nucleus	-	-	X	-
Aitio et al. (1979)	Different Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Glucuronide Conjugation of Various Aglycones: Studies in Wistar and Gunn Rats	-	X	-	-
Albro et al. (1978)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Lipid Profiles in Tissues of the Fischer Rat	-	X	-	-
Allen and Carstens (1967)	Light and Electron Microscopic Observations in *Macaca mulatta* Monkeys Fed Toxic Fat	-	X	-	-
Allen and Leamy (2001)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Affects Size and Shape, but Not Asymmetry, of Mandibles in Mice	-	X	-	-
Alsharif and Hassoun (2004)	Protective Effects of Vitamin A and Vitamin E Succinate Against 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-induced Body Wasting, Hepatomegaly, Thymic Atrophy, Production of Reactive Oxygen Species and DNA Damage in C57BL/6J Mice	-	X	-	-
Alsharif et al. (1990)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-induced Decrease in the Fluidity of Rat Liver Membranes	-	X	-	-
Alsharif et al. (1994b)	Oxidative Stress Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin is Mediated by the Aryl Hydrocarbon (Ah) Receptor Complex	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Alsharif et al. (1994c)	Stimulation of NADPH-dependent Reactive Oxygen Species Formation and DNA Damage by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin TCDD in Rat Peritoneal	-	X	-	-
Alsharif et al. (1994a)	The Effects of Ani-TNF-alpha Antibody and Dexamethasone on 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-induced Oxidative Stress in Mice	-	X	-	-
Altmann et al. (1995)	Maternal Exposure to Polychlorinated Biphenyls Inhibits Long-term Potentiation in the Visual Cortex of Adult Rats	-	-	X	-
Altmann et al. (1998)	Inhibition of Long-term Potentiation in Developing Rat Visual Cortex but Not Hippocampus by In Utero Exposure to Polychlorinated Biphenyls	-	-	X	-
Andersson et al. (2002)	A Constitutively Active Dioxin/Aryl Hydrocarbon Receptor (AhR) Induces Stomach Tumors	X	-	-	-
Aoa et al. (2009)	Comparison of Immunotoxicity Among Tetrachloro-, Pentachloro-, Tetrabromo- and Pentabromo-dibenzo-*p*-dioxins in Mice	-	-	X	-
Aragon et al. (2008a)	In Utero and Lactational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure: Effects on Fetal and Adult Cardiac Gene Expression and Adult Cardiac and Renal Morphology	-	X	-	-
Aragon et al. (2008b)	Perinatal 2,3,7,8-TCDD Exposure Sensitizes Offspring to Angiotensin II-induced Hypertension	-	X	-	-
Ashida et al. (1996)	Protective Action of Dehydroascorbic Acid on the Ah Receptor-dependent and Receptor-independent Induction of Lipid Peroxidation in Adipose Tissue of Male Guinea Pig Caused by TCDD Administration	-	-	-	X
Ashida et al. (2000)	2,3,7,8-TCDD-induced Changes in Activities of Nuclear Protein Kinases and Phosphatases Affecting DNA Binding Activity of c-Myc and AP-1 in the Livers of Guinea Pigs	-	X	-	X

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Astroff et al. (1987)	6-Methyl-1,3,8-Trichlorodibenzofuran as a 2,3,7,8-TCDD Antagonist: Inhibition of the Induction of Rat Cytochrome P-450 Isozymes and Related Monooxygenase Activities	-	-	-	X
Aubert et al. (1985)	Ontogeny of Hypothalamic Luteinizing Hormone-releasing Hormone (GnRH) and Pituitary GnRH Receptors in Fetal and Neonatal Rats	-	-	-	X
Aulerich et al. (2001)	Short Communications: Dietary Exposure to 3,3',4,4',5 -Pentachlorobiphenyl (PCB 126) or 2,3,7,8-TCDD Does Not Induce Proliferation of Squamous Epithelium or Osteolysis in Jaws of Weanling Rats	-	X	-	-
Badawi et al. (2000)	Effect of Chlorinated Hydrocarbons on Expression of Cytochrome P450 1A1, 1A2 and 1B1 and 2- and 4-Hydroxylation of 17β-estradiol in Female Sprague-Dawley Rats	-	X	-	-
Badesha et al. (1995)	Immunotoxic Effects of Prolonged Dietary Exposure of Male Rats to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Bagchi et al. (1993)	Time-dependent Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Serum and Urine Levels of Malondialdehyde, Formaldehyde, Acetaldehyde, and Acetone in Rats	-	X	-	-
Bagchi et al. (2002)	Comparative Effects of TCDD, Endrin, Naphthalene and Chromium (VI) on Oxidative Stress and Tissue Damage in the Liver and Brain Tissues of Mice	-	X	-	-
Bars and Elcombe (1991)	Dose-dependent Acinar Induction of Cytochromes P450 in Rat Liver. Evidence for a Differential Mechanism of Induction of P4501A1 by Beta-naphthaflavone and Dioxin	-	-	-	X
Barsotti et al. (1979)	Hormonal Alterations in Female Rhesus Monkeys Fed a Diet Containing 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Barter and Klaassen (1992)	UDP-glucuronosyltransferase Inducers Reduce Thyroid Hormone Levels in Rats by an Extrathyroidal Mechanism	-	-	X	-
Bastomsky (1977)	Enhanced Thyroxine Metabolism and High Uptake Goiters in Rats After a Single Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Beckett et al. (2005)	Squamous Epithelial Lesion of the Mandibles and Maxillaw of Wild Mink Naturally Exposed to Polychlorinated Biphenyls	X	-	-	X
Beebe et al. (1995)	Promotion of N-nitrosodimethylamine-initiated Mouse Lung Tumors Following Single or Multiple Low Dose Exposure to 2,3,7,8- Tetrachlorodibenzo-*p*-dioxin	-	-	-	X
Beguinot et al. (1985)	Phorbol Esters Induce Internalization Without Degradation of Unoccupied Epidermal Growth Factor Receptors	-	-	X	-
Bell et al. (2007b)	Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Developing Male Wistar(Han) Rat. I: No Decrease in Epididymal Sperm Count after a Single Acute Dose	-	X	-	-
Bell et al. (2007a)	Relationships Between Tissue Levels of 2,3,7,8-Tetrachlorodibenzop-dioxin (TCDD), mRNAs, and Toxicity in the Developing Male Wistar(Han) Rat	-	X	-	-
Bemis et al. (2007)	TCDD-Induced Alterations in Gene Expression Profiles of the Developing Mouse Paw Do Not Influence Morphological Differentiation of This Potential Target Tissue	-	-	-	X
Besteman et al. (2005)	Tetrachlorodibenzo-*p*-Dioxin (TCDD) Inhibits Differentiation and Increases Apoptotic Cell Death of Precursor T-Cells in the Fetal Mouse Thymus	-	X	-	-
Besteman et al. (2007)	2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) or Diethylstilbestrol (DES) Cause Similar Hematopoietic Hypocellularity and Hepatocellular Changes in Murine Fetal Liver, but Differentially Affect Gene Expression	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Biegel et al. (1989)	2,2N4,4N5,5N-Hexachlorobiphenyl as a 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Antagonist in C57BL/6 Mice	-	X	-	-
Birnbaum et al. (1985)	Toxic Interaction of Specific Polychlorinated Biphenyls and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: Increased Incidence of Cleft Palate in Mice	-	-	X	-
Birnbaum et al. (1986)	Synergistic Interaction of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Hydrocortisone in the Induction of Cleft Palate in Mice	-	X	-	-
Birnbaum et al. (1987a)	Teratogenic Effects of Polychlorinated Dibenzofurans in Combination in C57BL/6N Mice	-	-	X	-
Birnbaum et al. (1987b)	Teratogenicity of Three Polychlorinated Dibenzofurans in C57BL/6N Mice	-	-	X	-
Birnbaum et al. (1989)	Retinoic Acid and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Selectively Enhance Teratogenesis in C57BL/6N Mice	-	X	-	-
Birnbaum et al. (1990)	Differential toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in C57Bl/6 mice congenic at the Ah locus	-	X	-	-
Birnbaum et al. (1991)	Teratogenic Effects of 2,3,7,8-Tetrabromodibenzo-*p*-dioxin and Three Polybrominated Dibenzofurans in C57BL/6N Mice	-	-	X	-
Bjerke and Peterson (1994)	Reproductive Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Male Rats: Different Effects of In Utero Versus Lactational Exposure	-	X	-	-
Bjerke et al. (1994a)	Effects of In Utero and Lactational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure on Responsiveness of the Male Rat Reproductive System to Testosterone Stimulation in Adulthood	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Bjerke et al. (1994b)	Partial Demasculinization and Feminization of Sex Behavior in Male Rats by In Utero and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin is Not Associated with Alterations in Estrogen Receptor Binding or Volumes of Sexually Differentiated Brain	-	X	-	-
Blaylock et al. (1992)	Exposure to Tetrachlorodibenzo-*p*-dioxin (TCDD) Alters Fetal Thymocyte Maturation	-	X	-	-
Bohn et al. (2005)	Increased Mortality Associated with TCDD Exposure in Mice Infected with Influenza A Virus is Not Due to Severity of Lung Injury or Alterations in Clara Cell Protein Content	-	X	-	-
Boverhof et al. (2005)	Temporal and Dose-Dependent Hepatic Gene Expression Patterns in Mice Provide New Insights into TCDD-Mediated Hepatotoxicity	X	-	-	-
Boverhof et al. (2008)	Inhibition of Estrogen-Mediated Uterine Gene Expression Responses by Dioxin	-	X	-	-
Bowers et al. (2006)	Short Report: 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Reduces Leishmania Major Burdens In C57Bl/6 Mice	-	X	-	-
Brewster et al. (1987)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on the Guinea Pig Heart Muscle	-	-	-	X
Brewster and Matsumura (1984)	TCDD (2,3,7,8-Tetrachlorodibenzo-*p*-dioxin) Reduces Lipoprotein Lipase Activity in the Adipose Tissue of the Guinea Pig	-	-	-	X
Brouillette and Quirion (2008)	The Common Environmental Pollutant Dioxin-induced Memory Deficits by Altering Estrogen Pathways and a Major Route of Retinol Transport Involving Transthyretin	-	X	-	X
Brouwer and van den Berg (1983)	Early Decrease in Retinoid Levels in Mice After Exposure to Low Doses of Polychlorinated Biphenyls	-	-	X	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Brouwer and van den Berg (1984)	Early and Differential Decrease in Natural Retinoid Levels in C57Bl/Rij and DBA/2 Mice by 3,4,3N,4N-Tetrachlorobipheny	-	-	X	-
Brouwer et al. (1985)	Time and Dose Responses of the Reduction in Retinoid Concentrations in C57BL/Rij and DBA/2 Mice Induced by 3,4,3N,4N-Tetrachlorobiphenyl	-	-	X	-
Brown and Lamartiniere (1995)	Xenoestrogens Alter Mammary Gland Differentiation and Cell Proliferation in the Rat	-	X	-	-
Brunnberg et al. (2006)	The Constitutively Active Ah Receptor (CA-AhR) Mouse as a Potential Model for Dioxin Exposure—Effects in Vital Organs	-	X	-	-
Bryant et al. (1997)	Effects of TCDD on Ah Receptor, ARNT, EGF, and TGF-alpha Expression in Embryonic Mouse Urinary Tract	-	X	-	-
Bryant et al. (2001)	Teratogenicity of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) in Mice Lacking the Expression of EGF and/or TGF-alpha	X	X	-	-
Buchmann et al. (1994)	Effects of 2,3,7,8-Tetrachloro- and 1,2,3,4,6,7,8-Heptachlorodibenzo-*p*- dioxin on the Proliferation of Preneoplastic Liver Cells in the Rat	-	-	X	-
Bushnell and Rice (1999)	Behavioral Assessments of Learning and Attention in Rats Exposed Perinatally to 3,3',4,4',5-Pentachlorobiphenyl (PCB 126)	-	-	X	-
Byers et al. (2006)	Association Between the Levels of Biogenic Amines and Superoxide Anion Production in Brain Regions of Rats After Subchronic Exposure to TCDD	-	X	-	-
Calfee-Mason et al. (2002)	Vitamin E Inhibits Hepatic NF-kB Activation in Rats Administered the Hepatic Tumor Promoter Phenobarbital	-	-	X	-
Camacho et al. (2004)	Effect of 2,3,7,8-TCDD on Maternal Immune Response During Pregnancy	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Cantoni et al. (1984)	Different Susceptibility of Mouse Tissues to Porphyrogenic Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Carney et al. (2004)	2,3,7,8-TCDD Activation of the AHR/AHR Nuclear Translocator Pathway Causes Developmental Toxicity Through a CYP1-A-independent Mechanism in Zebrafish	X	-	-	-
Chaffin et al. (1996)	In Utero and Lactational Exposure of Female Holtzman Rats to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: Modulation of the Estrogen Signal	-	X	-	-
Chaffin et al. (1997)	Alterations to the Pituitary-gonadal Axis in the Female Rat Exposed In Utero and Through Lactation to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Chahoud et al. (1989)	Reproductive Toxicity and Pharmacokinetics of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. I. Effects of High Doses on the Fertility of Male Rats	-	-	-	X
Chapman and Schiller (1985)	Dose-related Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in C57BL/6J and DBA/2J Mice	-	X	-	-
Chen et al. (1993)	In Utero Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Does Not Impair Testosterone Production by Fetal Rat Testis	-	X	X	-
Chen et al. (2001)	Disposition of Polychlorinated Dibenzo-*p*-dioxins, Dibenzofurans, and Non-ortho Plychlorinated Biphenyls in Pregnant Long Evans Rats and the Transfer to Offspring	-	-	X	-
Chen et al. (2002)	A Mixture of Polychlorinated Dibenzo-*p*-dioxins (PCDDs), Dibenzofurans (PCDFs), and Non-ortho Polychlorinated Biphenyls (PCBs) Changed the Lipid Content of Pregnant Long Evans rats	-	-	X	-
Chen et al. (2003)	The Effect of 2,3,7,8-TCDD on Chorionic Gonadotrophin Activity in Pregnant Macaques	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
		Reason for excluding study			
Cheng et al. (2002)	2,3,7,8-TCDD Treatment Induces c-Fos Expression in the Forebrain of the Long-Evans Rat	-	X	-	-
Cho et al. (2006)	Enhanced Expression of Plasma Glutathione Peroxidase in the Thymus of Mice Treated with TCDD and its Implication for TCDD-induced Thymic Atrophy	-	X	-	-
Choi et al. (2006)	In Utero Exposure to 2,3,7,8-TCDD Induces Amphiregulin Gene Expression in the Developing Mouse Ureter	-	-	-	X
Choi et al. (2008)	Effect of 2,3,7,8-TCDD on Testicular Spermatogenesis-related Panels and Serum Sex Hormone Levels in Rats	-	X	-	-
Chou et al. (1979)	Neuropathology of "Spinning Syndrome" Induced by Prenatal Intoxication with a PCB in Mice	-	-	X	-
Clark et al. (1981)	Enhanced Suppressor Cell Activity as a Mechanism of Immunosuppression by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	-	X
Clark et al. (1991a)	Tumor necrosis Factor involvement in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-mediated Endotoxin Hypersensitivity in C57Bl/6 Mice Congenic at the Ah Locus	-	X	-	-
Clark et al. (1991b)	Tumor Promotion by TCDD in Female Rats. In: Biological Basis for Risk Assessment of Dioxins and Related Compounds	-	X	-	X
Cohen et al. (1979)	Anticarcinogenic Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Benzo[a]pyrene and 7,12-Dimethylbenz[a]anthrene Tumor Initiation and its Relationship to DNA Binding	-	-	-	X
Collins and Capen (1980)	Fine Structural Lesions and Hormonal Alterations in Thyroid Glands of Perinatal Rats Exposed In Utero and by the Milk to Polychlorinated Biphenyls	-	-	X	-
Collins et al. (2008)	2,3,7,8-Tetracholorodibenzo-*p*-Dioxin Exposure Disrupts Granule Neuron Precursor Maturation in the Developing Mouse Cerebellum	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
		Reason for excluding study			
Comer and Norton (1982)	Effects of Perinatal Methimazole Exposure on a Developmental Test Battery for Neurobehavioral Toxicity in Rats	-	-	X	-
Courtney (1976)	Mouse Teratology Studies with Chlorodibenzo-*p*-dioxins	-	X	-	-
Courtney and Moore (1971)	Teratology Studies with 2,4,5-Trichlorophenoxyacetic Acid and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	X
Couture et al. (1989)	Developmental Toxicity of 2,3,4,7,8-Pentachlorodibenzofuran in the Fischer 344 Rat	-	-	X	-
Couture et al. (1990)	Characterization of the Peak Period of Sensitivity for the Induction of Hydronephrosis in C57BL/6N Mice Following Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Crofton and Rice (1999)	Low-frequency Hearing Loss Following Perinatal Exposure to 3,3',4,4',5-Pentachlorobiphenyl (PCB 126) in Rats	-	-	X	-
Cummings et al. (1996)	Promotion of Endometriosis by 2,3,7,8- Tetrachlorodibenzo-*p*-dioxin in Rats and Mice: Time-Dose Dependence and Species Comparison	-	X	-	-
Dalton et al. (2001)	Dioxin Exposure Is an Environmental Risk Factor for Ischamic Heart Disease-IP injection	-	-	-	X
D'Argy et al. (1984)	Teratogenicity of TCDD and Congener 3,3N,4,4N-Tetrachloroazoxybenzene in Sensitive and Nonsensitive Mouse stRains After Reciprocal Blastocyst Transfer	-	X	-	-
Davies et al. (2008)	Essential Role of the AH Receptor in the Dysfunction of Heme Metabolism Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Davis et al. (2000)	Ovarian Tumors in Rats Induced by Chronic 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Treatment	-	X	-	-
de Heer et al. (1995)	Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) to the Human Thymus after Implantation in SCID Mice	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
		Reason for excluding study			
Dearstyne and Kerkvliet (2002)	Mechanism of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-induced Decrease in Anti-CD3-activated CD4+ T cells: the Roles of Apoptosis, Fas, and TNF	-	X	-	-
Devito et al. (1992)	Antiestrogenic Action of 2,3,7,8-Tetrachloro- dibenzo-*p*-dioxin: Tissue Specific Regulation of Estrogen Receptor in CD1 Mice	-	-	-	X
Dhar and Setty (1990)	Changes in Testis, Epididymis and Other Accessory Organs of Male Rats Treated with Anandron During Sexual Maturation	-	-	X	-
Dienhart et al. (2000)	Gestational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Induces Developmental Defects in the Rat Vagina	-	X	-	-
Diliberto et al. (1999)	Effects of CYP1A2 on Disposition of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, 2,3,4,7,8-Pentachlorodibenzofuran, and 2,2',4,4',5,5'-Hexachlorobiphenyl in CYP1A2 Knockout and Parental (C57BL/6N and 129/Sv) Strains of Mice	-	X	-	-
Dong et al. (2002)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Zebra Fish Embryo: Local Circulation Failure in the Dorsal Midbrain is Associated with Increased Apoptosis	X	-	-	-
Dong et al. (2004)	Role of Aryl Hydrocarbon Receptor in Mesencephalic Circulation Failure and Apoptosis in Zebrafish Embryos Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	X	-	-	-
Dragan et al. (1991)	An initiation-promotion assay in rat liver as a potential complement to the 2-year carcinogenesis bioassay	-	-	X	-
Dragan et al. (1992)	Characterization of the Promotion of Altered Hepatic Foci by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Female Rat	-	-	-	X
Dragin et al. (2006)	For Dioxin-induced Birth Defects, Mouse or Human CYP1A2 in Maternal Liver Protects whereas Mouse CYP1A1 and CYP1B1 Are Inconsequential	X	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Dunlap and Matsumura (2000)	Analysis of Difference In Vivo Effects of TCDD Between c-src +/+ mice, c-src Deficient, -/+ and -/- B6, 129-Srctm l sor Mice and their Wild-type Littermates-IP Injection	X	-	-	-
Dunlap et al. (1999)	Differential Toxicities of TCDD In Vivo Among Normal, c-src Knockout, Geldanamycin-, and Quercetin-treated Mice	X	-	-	X
Dunlap et al. (2002)	Effects of Src-deficiency on the Expression of In Vivo Toxicity of TCDD in a Strain of c-src Knockout Mice Procured Through Six Generations of Backcrossings to C57BL/6 Mice-IP Injection	X	-	-	X
Ebner et al. (1988)	Effects of 2,3,7,8-Tetrachlorodibenzo-p-dioxin on Serum Insulin and Glucose Levels in the Rat	-	-	-	X
Eckle et al. (2004)	Immunohistochemical Detection of Activated Caspases in Apoptotic Hepatocytes in Rat Liver	X	-	-	-
Elder et al. (1976)	The Effect of Porphyrogenic Compound, Hexachlorobenzene, on the Activity of Hepatic Uroporphyrinogen Decarboxylase in the Rat	-	-	X	-
El-Sabeawy et al. (1998)	Treatment of Rats during Pubertal Development with 2,3,7,8-Tetrachlorodibenzo-p-dioxin Alters Both Signaling Kinase Activities and Epidermal Growth Factor Receptor Binding in the Testis and the Motility and Acrosomal Reaction of Sperm-IP injection	-	-	-	X
El-Tawil and Elsaieed (2005)	Induction of Oxidative Stress in the Reproductive System of Rats after Subchronic Exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin	-	X	-	-
Enan et al. (1992)	TCDD Causes Reduction in Glucose Uptake Through Glucose Transporters on the Plasma Membranes of the Guinea Pig Adipocyte	-	-	-	X
Enan et al. (1998)	Mechanism of Gender-Specific TCDD-induced Toxicity in Guinea Pig Adipose Tissue	-	X	-	X

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
		Reason for excluding study			
Eriksson et al. (1991)	Neonatal Exposure to 3,3N,4,4N-Tetrachlorobiphenyl: Changes in Spontaneous Behavior and Cholinergic Muscarinic Receptors in the Adult Mouse	-	-	X	-
Esser et al. (2005)	Effects of a Single Dose of 2,3,7,8-Tetrachlorodibenzo-p-dioxin, Given at Post-puberty, in Senescent Mice	-	-	-	X
Evans and Andersen (2000)	Sensitivity Analysis of a Physiological Model for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD): Assessing the Impact of Specific Model Parameters on Sequestration in Liver and Fat in the Rat	X	-	-	-
Faith and Moore (1977)	Impairment of Thymus-dependent Immune Function by Exposure of the Developing Immune System to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	-	X	-	-
Fan and Rozman (1994)	Relationship Between Acute Toxicity of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Distribution of Intermediary Metabolism in the Long-Evans Rat	-	X	-	-
Fan et al. (1996)	Effects of 2,3,7,8-Tetrachlorodibenzo-p-dioxin on Humoral and Cellmediated Immunity in Sprague-Dawley Rats	-	X	-	-
Faqi et al. (1998)	Reproductive Toxicity and Tissue Concentrations of Low Doses of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in Male Offspring Rats Exposed Throughout Pregnancy and Lactation	-	-	-	X
Fernandez-Salguero et al. (1995)	Immune System Impairment and Hepatic Fibrosis in Mice Lacking the Dioxinbinding Ah Receptor	X	-	-	-
Fernandez-Salguero et al. (1996)	Aryl-hydrocarbon Receptor-Deficient Mice Are Resistant to 2,3,7,8-Tetrachlorodibenzo-p-dioxin-Induced Toxicity	-	-	-	X
Fetissov et al. (2004)	Expression of Hypothalamic Neuropeptides After Acute TCDD Treatment and Distribution of Ah Receptor Repressor	-	X	-	-

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Fine et al. (1989)	Lymphocyte Stem Cell Alterations Following Perinatal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	X
Fine et al. (1990)	Prothymocyte Activity is Reduced by Perinatal 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure	-	X	-	X
Fisher et al. (2005)	Aryl Hydrocarbon Receptor-dependent Induction of Loss of Mitochondrial Membrane Potential in Epididydimal Spermatozoa by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	-	-	X
Flaws et al. (1997)	In Utero and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Induces Genital Dysmorphogenesis in the Female Rat	-	X	-	-
Fletcher et al. (2001)	Hepatic Vitamin A Depletion is a Sensitive Marker of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Exposure in Four Rodent Species	-	X	-	-
Fletcher et al. (2005a)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Alters the mRNA Expression of Critical Genes Associated with Cholesterol Metabolism, Bile Acid Biosynthesis, and Bile Transport in Rat Liver: A Microarray Study	-	X	-	-
Fletcher et al. (2005b)	Altered Retinoid Metabolism in Female Long-Evans and Han/Wistar Rats following Long-Term 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD)-Treatment-Subcutaneous administration	-	-	-	X
Flodstrom and Ahlborg (1992)	Relative Tumor Promoting Activity of Some Polychlorinated Dibenzo-*p*-dioxin-, Dibenzofuran-, and Biphenyl Congeners in Female Rats	-	-	-	X
Foster et al. (1997)	Morphologic Characteristics of Endometriosis in the Mouse Model: Application to Toxicology	-	-	-	X

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Frericks et al. (2006)	Transcriptional Signatures of Immune Cells in Aryl Hydrocarbon Receptor (AHR)-proficient and AHR-deficient Mice	X	X	-	X
Fritz et al. (2005)	In Utero and Lactational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure: Effects on the Prostate and Its Response to Castration in Senescent C57BL/6J Mice	-	X	-	-
Fujimaki et al. (2002)	Effect of a Single Oral Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Immune Function in Male NC/Nga Mice	-	X	-	-
Fujiwara et al. (2008)	Morphological and Immunohistochemical Studies on Cleft Palates Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Mice	-	X	-	-
Funatake et al. (2005)	Cutting Edge: Activation of the Aryl Hydrocarbon Receptor by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Generates a Population of CD4+ CD25+ Cells with Characteristics of Regulatory T Cells	X	X	-	-
Funseth et al. (2002a)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Trace Elements, Inflammation and Viral Clearance in the Myocardium During Coxsackievirus B3 Infection in Mice	-	-	-	X
Funseth et al. (2002b)	Effects of Coxsackievirus B3 Infection on the Acute-phase Protein Metallothionein and on Cytochrome P-4501A1 Involved in the Detoxification Processes of TCDD in the Mouse	-	-	-	X
Galijatovic et al. (2004)	The Human CYP1A1 Gene Is Regulated in a Developmental and Tissue-specific Fashion in Transgenic Mice	-	-	-	X
Gallo et al. (1986)	Interactive Effects of Estradiol and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Hepatic Cytochrome P-450 and Mouse Uterus	-	X	-	-
Gao et al. (2000)	Gonadotropin-releasing Hormone (GNRH) Partially Reverses the Inhibitory Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Ovulation in the Immature Gonadotropin-treated Rat	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Gao et al. (2001)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Decreases Responsiveness of the Hypothalamus to Estradiol as a Feedback Inducer of Preovulatory Gonadotropin Secretion in the Immature Gonadotropin-Primed Rat	-	X	-	-
Gao et al. (2004)	Lactational Exposure of Han/Wistar Rats to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Interferes with Enamel Maturation and Retards Dentin Mineralization	-	X	-	-
Garrett and Gasiewicz (2006)	The Aryl Hydrocarbon Receptor Agonist 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Alters the Circadian Rhythms, Quiescence, and Expression of Clock Genes in Murine Hematopoietic Stem and Progenitor Cells	-	X	-	-
Gasiewicz and Rucci (1984)	Cytosolic Receptor for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. Evidence for a Homologous Nature Among Various Mammalian Species	-	-	-	X
Gasiewicz et al. (1983)	Distribution, Excretion, and Metabolism of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in C57BL/6J, DBA/2J and B6D2F1/J Mice	-	-	-	X
Gasiewicz et al. (1986)	Changes in Hamster Hepatic Cytochrome P-450, Ethoxycoumarin *o*-deethylase, and Reduced NAD(P): Menadione Oxidoreductase Following Treatment with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. Partial Dissociation of Temporal and Dose-response Relationships From Elicited Toxicity	-	-	-	X
Gehrs and Smialowicz (1999)	Persistent Suppression of Delayed-type Hypersensitivity in Adult F344 Rats after Perinatal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Gehrs et al. (1997)	Alterations in the Developing; Immune System of the F344 Rat After Perinatal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. II. Effects on the Pup and the Adult	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Genter et al. (2006)	Comparison of Mouse Hepatic Mitochondrial Versus Microsomal Cytochromes P450 Following TCDD Treatment	-	-	-	X
Geusau et al. (2005)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Impairs Differentiation of Normal Human Epidermal Keratinocytes in a Skin Equivalent Model	X	-	-	-
Ghafoorunissa (1980)	Undernutrition and Fertility of Male Rats	-	-	X	-
Giavini et al. (1982)	Rabbit Teratology Studies With 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Giavini et al. (1983)	Embryotoxic Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Administered to Female Rats Before Mating	-	X	-	-
Goldey and Crofton (1998)	Thyroxine Replacement Attenuates Hypothyroxinemia, Hearing Loss, and Motor Deficits Following Developmental Exposure to Aroclor 1254 in Rats	-	-	X	-
Goldstein and Linko (1984)	Differential Induction of Two 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-inducible Forms of Cytochrome P-450 in Extrahepatic Versus Hepatic Tissues	-	-	-	X
Goldstein et al. (1973)	Hepatic Porphyria Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Mouse	-	X	-	-
Goldstein et al. (1982)	Induction of Porphyria in the Rat by Chronic Versus Acute Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Gonzalez et al. (1995)	Xenobiotic Receptor Knockout Mice	X	-	-	-
Gordon and Miller (1998)	Thermoregulation in Rats Exposed Perinatally to Dioxin: Core Temperature Stability to Altered Ambient Temperature, Behavioral Thermoregulation, and Febrile Response to Lipopolysaccharide	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Gordon et al. (1995)	Temperature Regulation and Metabolism in Rats Exposed Perinatally to Dioxin: Permanent Change in Regulated Body Temperature	-	X	-	-
Gordon et al. (1996)	Autonomic and Behavioral Thermoregulation in Golden Hamsters Exposed Perinatally to Dioxin	-	X	-	-
Gorski and Rozman (1987)	Dose-response and Time Course of Hypothyroxemia and Hypoinsulinemia and Characterization of Insulin Hypersensitivity in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-treated Rats	-	-	-	X
Gorski et al. (1990)	Reduced Gluconeogenesis in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-treated Rats	-	X	-	-
Gray et al. (1995b)	Exposure to TCDD During Development Permanently Alters Reproductive Function in Male Long Evans Rats and Hamsters: Reduced Ejaculated and Epididymal Sperm Numbers and Sex Accessory Gland Weights in Offspring With Normal Androgenic Status	-	X	-	-
Gray et al. (1995a)	Functional Developmental Toxicity of Low Doses of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and a Dioxin-like PCB (169) in Long Evans Rats and Syrian Hamsters: Reproductive, Behavioral and Thermoregulatory Alterations	-	X	-	-
Gray et al. (1997a)	A Dose-response Analysis of the Reproductive Effects of Single Gestational Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Male Long Evans Hooded Rat Offspring	-	X	-	-
Gray et al. (1997b)	In Utero 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Alters Reproductive Morphology and Function in Female Rat Offspring	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Gray et al. (1997b)	In Utero Exposure to Low Doses of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Alters Reproductive Development of Female Long Evans Hooded Rat Offspring	-	X	-	-
Greenlee et al. (1985)	Evidence for Direct Action of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Thymic Epithelium	X	-	-	-
Greig and DeMatteis (1973)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Drug Metabolism and Hepatic Microsomes of Rats and Mice	-	X	-	-
Guo et al. (2000)	Effect of TCDD on Maternal Toxicity and Chorionic Gonadotropin: Bioactivity in the Immediate Post-implantation Period of Macaque	-	X	-	-
Guo et al. (2007)	Toxic Effects of TCDD on Osteogenesis Through Altering IGFBP-6 gene Expression in Osteoblasts	-	X	-	X
Guo et al. (2008)	Anti-estrogenic Effect of Dioxin on Rat Skeleton Development	-	X	-	-
Haag-Gronlund et al. (1997)	Promotion of Altered Hepatic Foci by 2,3',4,4',5-Pentachlorobiphenyl in Sprague-Dawley Female Rats	-	-	-	X
Haake et al. (1987)	Aroclor 1254 as an Antagonist of the Teratogenicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Haavisto et al. (2001)	Prenatal Testosterone and Luteinizing Hormone Levels in Male Rats Exposed During Pregnancy to 2,3,7,8-TCDD and Diethylstilbestrol	X	-	-	-
Haavisto et al. (2006)	The Effects of Maternal Exposure to 2,3,7,8-TCDD on Testicular Steroidogenesis in Infantile Male Rats	-	X	-	-
Hahn et al. (1988)	The Role of the Ah Locus in Hexachlorobenzene-induced Porphyria: Studies in the Congenic C57BL/6J Mice	-	-	X	X
Håkansson and Hanberg (1989)	The Distribution of [14C]-2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and its Effect on Vitamin A Content in Parenchymal and Stellate Cells of Rat Liver	-	X	-	-

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Håkansson et al. (1989a)	2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin (TCDD)-induced Alterations in the Vitamin A Homeostasis and in the 7-Ethoxyresorufin *o*-deethylase (EROD)-activity in SD Rats and Hartley Guinea Pigs	-	X	-	-
Håkansson et al. (1989b)	Hepatic Vitamin A Storage in Relation to Paired Feed Restriction and TCDD-treatment	-	X	-	-
Håkansson et al. (1990)	Vitamin A Storage in Rats Subchronically Exposed to PCDDs/PCDFs	-	-	X	-
Håkansson et al. (1991)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on the Vitamin A Status of Hartley Guinea Pigs, SD Rats, C57Bl/6 Mice, DBA/2 Mice, and Golden Syrian Hamsters	-	-	-	X
Håkansson et al. (1994)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on the Hepatic 7-Ethoxyresorufin *o*-deethylase Activity in Four Rodent Species	-	-	-	X
Hamm et al. (2000)	In Utero and Lactational Exposure to 2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin Alters Postnatal Development of Seminal Vesicle Epithelium	-	X	-	-
Hamm et al. (2003)	A Mixture of Dioxins, Furans, and Non-ortho PCBs Based Upon Consensus TEQ Factors Produces Dioxin-like Reproductive Effects	-	-	X	-
Hanson and Smialowicz (1994)	Evaluation of the Effect of Low-level 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure on Cell Mediated Immunity	-	-	-	X
Hany et al. (1999)	Behavioral Effects Following Single and Combined Maternal Exposure to PCB 77 (3,4,3',4'-Tetrachlorobiphenyl) and PCB 47 (2,4,2',4'- Tetrachlorobiphenyl) in Rats	-	-	-	X

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Harper et al. (1991)	Ah Receptor in Mice Genetically "Nonresponsive" for Cytochrome P4501A1 Induction: Cytosolic Ah Receptor, Transformation to the Nuclear Binding State, and Induction of Aryl Hydrocarbon Hydroxylase by Halogenated and Nonhalogenated Aromatic Hydrocarbons in Embryonic Tissues and Cells	X	-	-	-
Harper et al. (1994a)	An Enzyme-linked Immunosorbent Assay (ELISA) Specific for Antibodies to TNP-LPS Detects Alterations in Serum Immunoglobulins and Isotype Switching in C57BL/6 and DBA/2 Mice Exposed to 2,3,7,8-Tetrachlorodibenzo-p-dioxin and Related Compounds	X	-	-	-
Harper et al. (1994b)	Inhibition of Estrogen-induced Progesterone Receptor in MCF-7 Human Breast Cancer Cells by Aryl Hydrocarbon (Ah) Receptor Agonists	X	-	-	-
Harris et al. (1973)	General Biological Effects of TCDD in Laboratory Animals	X	X	-	-
Hart (1972)	Manipulation of Neonatal Androgen: Effects on Sexual Responses and Penile Development in Male Rats	-	-	X	-
Harvey et al. (1993)	Spontaneous and Carcinogen-induced Tumorigenesis in P53 Deficient Mice	X	-	-	-
Hassoun et al. (1984a)	Teratogenicity of 2,3,7,8-Tetrachloro-dibenzofuran in BXD Recombinant Inbred Strains	-	-	X	X
Hassoun et al. (1984b)	Teratological Studies on the TCDD Congener 3,3N,4,4N-Tetrachloro-azoxybenzene in Sensitive and Nonsensitive Mouse Strains: Evidence for Direct Effect on Embryonic Tissues	-	-	X	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
		Reason for excluding study			
Hassoun et al. (1995)	Evidence of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-Induced Tissue Damage in Fetal and Placental Tissues and Changes in Amniotic Fluid Lipid Metabolites of Pregnant CF1 Mice	-	X	-	-
Hassoun et al. (1997)	Modulation of TCDD-induced Fetotoxicity and Oxidative Stress in Embryonic and Placental Tissues of C57BL/6J Mice by Vitamin E Succinate and Ellagic Acid	-	X	-	-
Hassoun et al. (2001)	Production of Superoxide Anion, Lipid Peroxidation and DNA Damage in the Hepatic and Brain Tissues of Rats after Subchronic Exposure to Mixtures of TCDD and its Congeners	-	-	X	-
Hassoun et al. (2004)	The Modulatory Effects of Ellagic Acid and Vitamin E Succinate on TCDD-Induced Oxidative Stress in Different Brain Regions of Rats after Subchronic Exposure	-	X	-	-
Hassoun et al. (2006)	The Effects of Ellagic Acid and Vitamin E Succinate on Antioxidant Enzymes Activities and Glutathione Levels in Different Brain Regions of Rats After Subchronic Exposure to TCDD	-	X	-	-
Hebert et al. (1990)	Relative Toxicity and Tumor-promoting Ability of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), 2,3,4,7,8-Pentachlorodibenzofuran (PCDF), and 1,2,3,4,7,8-Hexachlorodibenzofuran (HCDF) in Hairless Mice	-	-	-	X
Heimler et al. (1998)	Dioxin Perturbs, in a Dose- and Time-Dependent Fashion, Steroid Secretion, and Induces Apoptosis of Human Luteinized Granulosa Cells	X	-	-	-
Hemming et al. (1993)	Relative Tumor Promoting Activity of Three Polychlorinated Biphenyls in Rat Liver	-	-	-	X

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Hemming et al. (1995)	Liver Tumor Promoting Activity of 3,4,5,3',4'-Pentachloro-biphenyl and its Interaction with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	X	-
Henck et al. (1981)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: Acute Oral Toxicity in Hamsters	-	X	-	-
Henry and Gasiewicz (1987)	Changes in Thyroid Hormones and Thyroxine Glucuronidation in Hamsters Compared with Rats Following Treatment with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	-	X
Henry et al. (2006)	A Potential Endogenous Ligand for the Aryl Hydrocarbon Receptor Has Potent Agonist Activity In Vitro and In Vivo	X	-	-	-
Herbet et al. (1990)	Relative Toxicity and Tumor-promoting Ability of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), 2,3,4,7,8-Pentachlorodibenzofuran (PCDF), and 1,2,3,4,7,8-Hexachorodibenzofuran (HCDF) in Hairless Mice	-	-	-	X
Hermsen et al. (2008)	In Utero and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Affects Bone Tissue in Rhesus Monkeys	-	-	-	X
Herr et al. (1996)	Developmental Exposure to Aroclor 1254 Produces Low-frequency Alterations in Adult Rat Brainstem Auditory Evoked Responses	-	-	X	-
Herzke et al. (2002)	Kinetics and Organotropy of Some Polyfluorinated Dibenzo-*p*-dioxins and Dibenzofurans (PFDD/PFDF) in Rats	-	-	-	X
Hinsdill et al. (1980)	Immunosuppression in Mice Induced by Dioxin (TCDD) in Feed	-	X	-	-
Hochstein et al. (1998)	Effects of Dietary Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Adult Female Mink (*Mustela vison*)	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Hoegberg et al. (2005)	Retinoid Status and Responsiveness to 2,3,7,8,-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Mice Lacking Retinoid Binding Protein or Retinoid Receptor Forms- Exp 3	X	X	-	-
Hofer et al. (2004)	Simultaneous Exposure of Rats to Dioxin and Carbon Monoxide Reduces the Xenobiotic but Not the Hypoxic Response	-	X	-	-
Hoffer et al. (1996)	Dioxin Induces Transcription of Fos and Jun Genes by Ah Receptor-dependent and -Independent Pathways	X	-	-	-
Hogaboam et al. (2008)	The Aryl Hydrocarbon Receptor Affects Distinct Tissue	-	X	-	-
Hojo et al. (2006)	Sex-specific Alterations of Cerebral Cortical Cell Size in Rats Exposed Prenatally to Dioxin	-	X	-	-
Holcomb and Safe (1994)	Inhibition of 7,12-Dimethylbenzanthracene-induced Rat Mammary Tumor Growth by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	X	-
Holene et al. (1995)	Behavioral Effects of Pre- and Postnatal Exposure to Individual Polychlorinated Biphenyl Congeners in Rats	-	-	X	-
Holladay et al. (1991)	Perinatal Thymocyte Antigen Expression and Postnatal Immune Development Altered by Gestational Exposure to Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Holman et al. (2000)	Low-dose Responses to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Single Living Human Cells Measured by Synchrotron Infrared Spectromicroscopy	X	-	-	-
Hood et al. (2006)	Gestational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure Effects on Sensory Cortex Function	-	X	-	-
Hook et al. (1975)	Induction and Suppression of Hepatic and Extrahepatic Microsomal Foreign-compound-metabolizing Enzyme Systems by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
House et al. (1990)	Examination of Immune Parameters and Host Resistance Mechanisms in B6C3F$_1$ Mice Following Adult Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	-	X
Hung et al. (2006)	Protective Effects of Tea Melanin against 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-Induced Toxicity: Antioxidant Activity and Aryl Hydrocarbon Receptor Suppressive Effect	-	X	-	-
Hurst et al. (2000)	Acute Administration of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Pregnant Long Evans Rats: Association of Measured Tissue Concentrations with Developmental Effects	-	X	-	-
Hurst et al. (2002)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Disrupts Early Morphogenetic Events That Form the Lower Reproductive Tract in Female Rat Fetuses	-	X	-	-
Hushka et al. (1998)	Characterization of 2,3,7,8-Tetrachloro-dibenzofuran-dependent Suppression and AH Receptor Pathway Gene Expression in the Developing Mouse Mammary Gland	-	-	X	-
Huuskonen et al. (1994)	Developmental Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in the Most TCDD-resistant and -Susceptible Rat Strains	-	X	-	-
Hwang et al. (2004)	Panax Ginseng Improves Survival and Sperm Quality in Guinea Pigs exposed to 2,3,7,8-TCDD	-	-	-	X
Iba et al. (2001)	Pulmonary CYP1A1 and CYP1A2 Levels and Activities in Adult Male and Female Offspring of Rats Exposed During Gestation and Lactation to 2,3,7,8-TCDD	-	X	-	X
Ikeda et al. (2005a)	In Utero and Lactational Exposure to 2,3,7,8-TCDD in Rats Disrupts Brain Sexual Differentiation	-	X	-	-
Inouye et al. (2005)	T cell-derived IL-5 Production is a Sensitive Target of 2,3,7,8-TCDD	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Ioannou et al. (1983)	Toxicity and Distribution of 2,3,7,8-Tetrachlorodibenzofuran in Male Guinea Pigs	-	-	X	-
Ishida et al. (2004)	Reduction of the Toxicity of 2,3,7,8-TCDD in Mice Using an Antiulcer Drug, Geranylgeranylacetone	-	X	-	-
Ishimura et al. (2002)	Increased Glycogen Content and Glucose Transporter 3 mRNA Level in the Placenta of Holtzman rats After Exposure to 2,3,7,8-TCDD	-	X	-	-
Ishimura et al. (2006)	Suppressive Effect of 2,3,7,8-Tetrachlorodibenzo-p-dioxin on Vascular Remodeling That Takes Place in the Normal Labyrinth Zone of Rat Placenta during Late Gestation	-	X	-	-
Ishizuka et al. (2003)	Perinatal Exposure to Low Doses of 2,3,7,8-Tetrachlorodibenzo-p-dioxin Alters Sex-Dependent Expression of Hepatic CYP2C11	-	-	X	-
Ito et al. (1980)	The Effects of Various Chemicals on the Development of Hyperplastic Liver Nodules in Hepatectomized Rats Treated with N-nitrosodiethylamine or N-2-fluorenylacetamide	-	-	X	-
Ito et al. (2002)	Mechanism of TCDD-Induced Suppression of Antibody Production: Effect on T Cell-Derived Cytokine Production in the Primary Immune Reaction of Mice	-	-	X	-
Ito et al. (2008)	TCDD Exposure Exacerbates Atopic Dermatitis-related Inflammation in NC/Nga Mice	-	X	-	-
Jain et al. (1998)	Expression of ARNT, ARNT2, HIF1 Alpha, HIF2 Alpha and Ah Receptor mRNAs in the Developing Mouse	-	-	X	-
Jamsa et al. (2001)	Effects of 2,3,7,8-tetrachlorodibenzo-p-Dioxin on Bone in Two Rat Strains with Different Aryl Hydrocarbon Receptor Structures (subcutaneous exposure)	-	-	-	X

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Jang et al. (2007)	Antiteratogenic Effects of Alpha-naphthoflavone on 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Exposed Mice In Utero	-	X	-	-
Jang et al. (2008)	Antiteratogenic Effect of Resveratrol in Mice Exposed In Utero to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Janz and Bellward (1996)	In Ovo 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure in Three Avian Species	X	-	-	-
Jean-Faucher et al. (1982)	The Effect of Preweaning Under-nutrition Upon the Sexual Development of Male Mice. Biol Neonate 41:45-51	-	-	X	-
Jeong et al. (2008)	Accumulation of M1dG DNA Adducts After Chronic Exposure to PCBs, but Not From Acute Exposure to Polychlorinated Aromatic Hydrocarbons-mixtures Study	-	-	X	-
Jin et al. (2008a)	Enhanced TGF-β1 is Involved in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Induced Oxidative Stress in C57BL/6 Mouse Testis	-	X	-	-
Jin et al. (2008b)	In Utero Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Affects the Development of Reproductive System in Mouse-IP Injection	-	-	-	X
Jin et al. (2008c)	Toxic Effects of Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Development of Male Reproductive System: Involvement of Antioxidants, Oxidants, and p53 Protein	-	X	-	-
Jinno et al. (2006)	Induction of Cytochrome P450-1A by the Equine Estrogen Equilenin, a New Endogenous Aryl Hydrocarbon Receptor Ligand	-	-	X	X

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Johnson et al. (1992)	Reduced Leydig Cell Volume and Function in Adult Rats Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Without a Significant Effect on Spermatogenesis. Toxicology 76(2):103-118	-	X	-	X
Johnson et al. (1994)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Reduces the Number, Size, and Organelle Content of Leydig Cells in Adult Rat Testes	-	X	-	X
Johnson et al. (1997)	Promotion of Endometriosis in Mice by Polychlorinated Dibenzo-*p*- dioxins, Dibenzofurans, and Biphenyls	-	X	-	-
Johnson et al. (2000)	Sensitivity of the SRBC PFC Assay Versus ELISA for Detection of Immunosuppression by TCDD and TCDD-like Congeners	-	X	-	-
Jones and Greig (1975)	Pathological Changes in the Liver of Mice Given 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Kakeyama et al. (2001)	Changes in Expression of NMDA Receptor Subunit mRNA by Perinatal Exposure to Dioxin	-	X	-	-
Kakeyama et al. (2003)	Perinatal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Alters Activity-dependent Expression of BDNF mRNA in the Neurocortex and Male Rat Sexual Behavior in Adulthood	-	X	-	-
Kakeyama et al. (2008)	Perinatal Exposure of Female Rats to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Induces Central Precocious Puberty in the Offspring	-	X	-	-
Kamath et al. (1997)	Evidence for the Induction of Apoptosis in Thymocytes by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin In Vivo	-	-	-	X
Kamath et al. (1999)	Role of Fas-Fas Ligand Interactions in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-induced Immunotoxicity: Increased Resistance of Thymocytes From Fasdeficient (lpr)and Fas Ligand-defective (gld) Mice to TCDD-induced Toxicity	-	-	-	X

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Katz et al. (1984)	Characterization of the Enhanced Paw Edema Response to Carrageenan and Dextran in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-treated Rats	-	-	X	-
Kedderis et al. (1991)	Disposition of 2,3,7,8-tetrabromodibenzo-*p*-dioxin and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Rat: Biliary Excretion and Induction of Cytochromes CYP1A1 and CYP1A2	-	-	-	X
Keller et al. (2007a)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Affects Fluctuating Asymmetry of Molar Shape in Mice, and an Epistatic Interaction of Two Genes for Molar Size	-	X	-	-
Keller et al. (2007b)	The Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Molar and Mandible Traits in Congenic Mice: A Test of the Role of the Ahr Locus	-	X	-	-
Kelley et al. (1998)	Use of Model-based Compartmental Analysis to Study Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Vitamin A Kinetics in Rats	-	X	-	-
Kelley et al. (2000)	Mobilization of Vitamin A Stores in Rats After Administration of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: a Kinetic Analysis	-	X	-	-
Kelling et al. (1985)	Hypophagia-induced Weight Loss in Mice, Rats, and Guinea Pigs Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Kelling et al. (1987)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin treatment on Mechanical Function of the Rat Heart	-	X	-	-
Kerkvliet and Brauner (1990)	Flow Cytometric Analysis of Lymphocyte Subpopulations in the Spleen and Thymus of Mice Exposed to an Acute Immunosuppressive Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Kerkvliet and Oughton (1993)	Acute Inflammatory Response to Sheep Red Blood Cell Challenge in Mice Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD): Phenotypic and Functional Analysis of Peritoneal Exudate Cells	-	X	-	-
Kerkvliet et al. (1990)	Role of the Ah Locus in Suppression of Cytotoxic T Lymphocyte (CTL) Activity by Halogenated Aromatic Hydrocarbons (PCBs and TCDD): Structure-activity Relationships and Effects in C57Bl/6 Mice	-	X	-	-
Kerkvliet et al. (1996)	Inhibition of TC-1 Cytokine Production, Effector Cytotoxic T Lymphocyte Development and Alloantibody Production by 2,3,7,8- Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Kerkvliet et al. (2002)	T Lymphocytes Are Direct, Aryl Hydrocarbon Receptor (AhR)-Dependent Targets of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD):AhR Expression in Both CD4+ and CD8+ T Cells Is Necessary for Full Suppression of a Cytotoxic T Lymphocyte Response by TCDD	-	X	-	-
Khera (1992)	Extraembryonic Tissue Changes Induced by 2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin and 2,3,4,7,8-Pentachlorodibenzofuran with a Note on Direction of Maternal Blood Flow in the Labyrinth of C57BL/6N Mice	-	X	-	-
Khera and Ruddick (1973)	Polychlorodibenzo-*p*-dioxins: Perinatal Effects and the Dominant Lethal Test in Wistar rats. In: Chlorodioxins—Origin and Fate. Blair, EH, ed. Washington, DC: American Chemical Society; pp. 7084	-	X	-	-
Kim et al. (2003a)	Area Under the Curve as a Dose Metric for Promotional Responses Following 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure	-	X	-	-

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Kim et al. (2003b)	Effects of Benzo[a]pyrene, 2-Bromopropane, phenol and 2,3,7,8-TCDD on IL-6 Production in Mice After Single or Repeated Exposure-IP Injection	-	-	-	X
Kimmig and Schultz (1957)	Chlorierte Aromatische Zyklische Äther Als Ursache Der Sogenannten Chlorakne	-	-	-	X
Kitajima et al. (2004a)	Expression of the Arylhydrocarbon Receptor in the Peri-implantation Period of the Mouse Uterus and the Impact of Dioxin on Mouse Implantation-subcutaneous Injection	-	-	-	X
Kitajima et al. (2004b)	Histomorphometric Alteration and Cell-type Specific Modulation of Arylhydrocarbon receptor and Estrogen Receptor Expression by 2,3,7,8-TCDD and 17β-estradiol in Mouse Experimental Model of Endometriosis-subcutaneous Injection	-	-	-	X
Kitamura et al. (2006)	Mechanistic Investigation of the Cause for Reduced Toxicity of TCDD in wa-1 homozygous TGFα Mutant Strain of Mice as Compared its Matching Wild-type Counterpart, C57BL/6J Mice-IP Injection	-	-	-	X
Kleeman et al. (1990)	Inhibition of Testicular Steroidogenesis in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-treated Rats: Evidence That the Key Lesion Occurs Prior to or During Pregnenolone Formation	-	X	-	-
Ko et al. (2002)	In Utero and Lactational Exposure to 2,3,7,8-TCDD in the C57BL/6J Mouse Prostate: Lobe-specific Effects on Branching Morphogenesis	-	X	-	-
Ko et al. (2004)	Evidence that Inhibited Prostatic Epithelial Bud Formation in 2,3,7,8-TCDD-exposed C57BL/6J Fetal Mice is Not Due to Interruption of Androgen Signaling in the Urogenital Sinus	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Kopec et al. (2008)	Comparative Toxicogenomic Examination of the Hepatic Effects of PCB126 and TCDD in Immature, Ovariectomized C57BL/6 Mice	-	X	-	-
Kopf et al. (2008)	Hypertension, Cardiac Hypertrophy, and Impaired Vascular Relaxation Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin are Associated With Increased Superoxide	-	X	-	-
Korenaga et al. (2007)	Long-term Effects of Subcutaneously Injected 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on the Liver of Rhesus Monkeys-subcutaneous Injection	X	-	-	-
Korte et al. (1990)	Induction of Hepatic Monooxygenases in Female Rats and Offspring in Correlation with TCDD Tissue Concentrations After Single Treatment During Pregnancy	-	-	-	X
Kozak (1997)	ARNT-deficient Mice and Placental Differentiation	-	-	X	-
Kransler et al. (2007a)	Comparative Developmental Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Hamster, Rat, and Guinea Pig	-	X	-	-
Kransler et al. (2007b)	Gestational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Alters Retinoid Homeostasis in Maternal and Perinatal Tissues of the Holtzman Rat	-	X	-	-
Kransler et al. (2008)	Effects of Helicobacter infection on Developmental Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Holtzman rats	-	X	-	-
Kransler et al. (2009)	Lung Development in the Holtzman rat is Adversely Affected by Gestational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Kronenberg et al. (2000)	Generation of αβ T-cell receptor+ CD4- CD8+ cells in Major Histocompatibility Complex Class-I-deficient Mice Upon Activation of the Aryl Hydrocarbon Receptor by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-IP Injection	-	-	-	X

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Krowke et al. (1989)	Pharmacokinetics and Biological Activity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin. 2. Pharmacokinetics in Rats Using a Loading-Dose/Maintenance-dose Regime With High Doses	-	-	-	X
Kruger et al. (1990)	Induction of Caffeine-demethylations by 2,3,7,8-TCDD in Marmoset Monkeys Measured with a 14CO2-breath Test	-	-	-	X
Kwon et al. (2004)	Protective Effects of Ursodeoxycholic Acid Against 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-induced Testicular Damage in Mice-subcutaneous Injection	-	-	-	X
Laiosa et al. (2002)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Causes Alteration in Lymphocyte Development and Thymic Atrophy in Hemopoietic Chimeras Generated from Mice Deficient in ARNT2-IV Injection	-	-	-	X
Lakind et al. (2000)	Methodology For Characterizing Distributions Of Incremental Body Burdens Of 2,3,7,8-TCDD And DDE From Breast Milk In North American Nursing Infants	X	-	-	-
Lakshman et al. (1988)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on De Novo Fatty Acid and Cholesterol Synthesis in the Rat	-	X	-	-
Lakshman et al. (1989)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Lipid Synthesis and Lipogenic Enzymes in the Rat	-	-	-	X
Lakshman et al. (1991)	Mechanism of Action of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Intermediary Metabolism in the Rat	-	X	-	-
Latchoumycandane and Mathur (2002)	Effects of Vitamin E on Reactive Oxygen Species-mediated 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Toxicity in Rat Testis	-	-	X	-
Laurent et al. (2002)	Portal Absorption of 14C After Ingestion of Spiked Milk With 14C-Phenanthrene, 14C-Benzo[a]pyrene or 14C-TCDD in Growing Pigs	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Lawrence and Vorderstrasse (2004)	Activation of the Aryl Hydrocarbon Receptor Diminishes the Memory Response to Homotypic Influenza Virus Infection but Does Not Impair Host Resistance	-	X	-	-
Lawrence et al. (2000)	Fewer T lymphocytes and Decreased Pulmonary Influenza Virus Burden in Mice Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Lawrence et al. (2006)	Aryl Hydrocarbon Receptor Activation Impairs the Priming but Not the Recall of Influenza Virus-Specific CD8_ T Cells in the Lung	-	X	-	-
Lee et al. (2007)	Panax Ginseng Effects on DNA Damage, CYP1A1 Expression and Histopathological Changes in Testes of Rats Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-IP Injection	-	-	-	X
Lensu et al. (2006)	Assessment by c-Fos Immunostaining of Changes in Brain Neural Activity Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Leptin in Rats	X	-	-	-
Lewis et al. (2001)	In Utero and Lactational Treatment with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Impairs Mammary Gland Differentiation but Does Not Block the Response to Exogenous Estrogen in the Postpubertal Female Rat	-	X	-	-
Li et al. (1995a)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Estrous Cyclicity and Ovulation in Female Sprague-Dawley Rats	-	X	-	-
Li et al. (1995b)	Reproductive Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Female Rats: Ovulation, Hormonal Regulation, and Possible Mechanism(s)	-	X	-	-
Li et al. (1995c)	Toxicokinetics of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Female Sprague-Dawley Rats Including Placental and Lactational Transfer to Fetuses and Neonates	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Lilienthal and Winneke (1991)	Sensitive Periods for Behavioral Toxicity of Polychlorinated Biphenyls: Determination by Cross-fostering in Rats	-	-	X	-
Lilienthal et al. (1997)	Effects of Maternal Exposure to 3,3',4,4'-Tetrachlorobiphenyl or Propylthiouracil in Rats Trained to Discriminate Apomorphine From Saline	-	-	X	-
Lim et al. (2006)	Dihydroxy-, Hydroxyspirolactone-, and Dihydroxyspirolactone-urochlorins Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Liver of Mice	-	X	-	-
Lin et al. (1991)	The Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on the Hepatic Estrogen and Glucocorticoid Receptors in Congenic Strains of Ah Responsive and Ah Nonresponsive C57BL/6 Mice	-	X	-	-
Lin et al. (2001)	Role of the Aryl Hydrocarbon Receptor in the Development of Control and 2,3,7,8- Tetrachlorodibenzo-p-dioxin-Exposed Male Mice	-	X	-	-
Lin et al. (2002a)	Critical Window of Vulnerability for Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Prostate and Seminal Vesicle Development in C57BL/6 Mice	-	X	-	-
Lin et al. (2002b)	Effects of Aryl Hydrocarbon Receptor Null Mutation and In Utero and Lactational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure on Prostate and Seminal Vesicle Development in C57BL/6 Mice	-	X	-	-
Linden et al. (2005)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and Leptin on Hypothalamic mRNA Expression of Factors Participating in Food Intake Regulation in a TCDD-Sensitive and a TCDD-Resistant Rat Strain	-	X	-	-
Liu et al. (2003)	Induction of Aryl Hydrocarbon Receptor and CYP1A1 mRNA by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Rat Liver-IP Injection	-	-	-	X

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Loertscher et al. (2002)	In Utero Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Causes Accelerated Terminal Differentiation in Fetal Mouse Skin	-	X	-	-
Lucier et al. (1973)	TCDD-induced Changes in Rat Liver Microsomal Enzymes	-	X	-	-
Lucier et al. (1975a)	Nature of the Enhancement of Uridine Diphosphate Glucuronyltransferase Activity by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Rats	-	X	-	-
Lucier et al. (1975b)	Postnatal Stimulation of Hepatic Microsomal Enzymes Following Administration of TCDD to Pregnant Rats	-	X	-	-
Lucier et al. (1991)	Ovarian Hormones Enhance 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-mediated Increases in Cell Proliferation and Preneoplastic Foci in a Two-stage Model for Rat Hepatocarcinogenesis	-	-	X	-
Luebeck et al. (2000)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Initiation and Promotion of GST-P-Positive Foci in Rat Liver: A Quantitative Analysis of Experimental Data Using a Stochastic Model-subcutaneous injection	-	-	-	X
Luebke et al. (1994)	Assessment of Host Resistance to *Trichinella spiralis* in Mice Following Pre-infection Exposure to 2,3,7,8-TCDD	-	-	-	X
Luebke et al. (1995)	Host Resistance to *T. spiralis* infection in Rats Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	-	-	X
Luebke et al. (1999)	Effects of Aging on Resistance to *Trichinella spiralis* Infection in Rodents Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Luebke et al. (2001)	Suppression of Allergic Immune Responses to House Dust Mites in Rats Exposed to 2,3,7,8-TCDD-IP Injection	-	-	-	X

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Luebke et al. (2002)	Mortality in Dioxin-exposed Mice Infected With Influenza: Mitochondrial Toxicity (Reye's Like Symptoms) Versus Enhanced Inflammation as a Mode of Action-IP Injection	-	-	-	X
Lundberg et al. (1990)	Effects of 2,3,7,8-Tetrachlorodibenzo- p-dioxin (TCDD) Treatment In Vivo on Thymocyte Functions in Mice After Activation In Vitro	-	X	-	-
Luster et al. (1980)	Examination of Bone Marrow, Immunologic Parameters and Host Susceptibility Following Pre- and Postnatal Exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	-	X	-	-
Luster et al. (1985)	Acute Myelotoxic Responses in Mice Exposed to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	-	X	-	-
Ma et al. (2007)	Mouse Lung CYP1A1 Catalyzes the Metabolic Activation of 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)-IP Injection	-	-	-	X
Mably et al. (1990)	Hypergastrinemia is Associated With Decreased Gastric Acid Secretion in 2,3,7,8-Tetrachlorodibenzo-p-dioxin Treated Rats	-	X	-	-
Mably et al. (1991)	The Male Reproduction System is Highly Sensitive to In Utero and Lactational TCDD Exposure	-	X	-	-
MacLusky et al. (1998)	Hormonal Interactions in the Effects of Halogenated Aromatic Hydrocarbons on the Developing Brain	-	-	X	-
Madhukar et al. (1984)	Effects of In Vivo Administered 2,3,7,8-Tetrachloro-dibenzo-p-dioxin on Receptor Binding of Epidermal Growth Factor in the Hepatic Plasma Membrane of Rat, Guinea Pig, Mouse and Hamster	-	-	-	X
Madhukar et al. (1988)	2,3,7,8-Tetrachlorodibenzo-p-dioxin Causes an Increase in Protein Kinases Associated With Epidermal Growth Factor Receptor in the Hepatic Plasma Membrane	-	-	-	X

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Mann (1997)	Selected Lesions of Dioxin in Laboratory Rodents	-	-	-	X
Mantovani et al. (1980)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Macrophage and Natural Killer Cell Mediated Cytotoxicity in Mice	-	-	-	X
Markowski et al. (2002)	Impaired Cued Delayed Alternation Behavior in Adult Rat Offspring Following Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on GD 15	-	X	-	-
Marks (1985)	Exposure to Toxic Agents: the Heme Biosynthetic Pathway and Hemoproteins as Indicator	-	-	X	-
Marks and Staples (1980)	Teratogenic Evaluation of the Symmetrical Isomers of Hexachlorobiphenyl (HCB) in the Mouse. In: Proceedings of the 20th Annual Meeting of the Teratology Society, Portsmouth, NH, June 1980, p. 54A	-	-	X	-
Marks et al. (1981)	Influence of Symmetrical Polychlorinated Biphenyl Isomers on Embryo and Fetal Development in Mice	-	-	X	-
Massart and Meucci (2007)	Environmental Thyroid Toxicants and Child Endocrine Health	X	-	-	-
Matsumura et al. (1997)	Altered In Vivo Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in c-src Deficient Mice	-	-	-	X
Max and Silbergeld (1987)	Skeletal Muscle Glucocorticoid Receptor and Glutamine Synthetase Activity in the Wasting Syndrome in Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	X	-
McConnell and Moore (1979)	Toxicopathology Characteristics of Halogenated Aromatic Hydrocarbons	-	-	X	-
McConnell et al. (1978)	Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Rhesus Monkeys (*Macaca mulatta*) Following a Single Oral Dose	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
		Reason for excluding study			
McGrath et al. (1995)	Alternative Models for Low Dose-response Analysis of Biochemical and Immunological Endpoints for Tetrachlorodibenzo-*p*-dioxin	-	-	X	-
McKinley et al. (1993)	The Effect of Pretreatment on the Biliary Excretion of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, 2,3,7,8-Tetrachlorodibenzofuran, and 3,3',4,4'-Tetrachlorobiphenyl in the rat	-	-	X	-
McKinney et al. (1985)	Molecular Interactions of Toxic Chlorinated Dibenzo-*p*-dioxins and Dibenzofurans with Thyroxine Binding Prealbumin	-	-	X	-
McNulty (1977)	Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin for Rhesus Monkeys: Brief Report	-	X	-	-
McNulty (1984)	Fetotoxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) for Rhesus Macaques (*Macaca mulatta*)	-	X	-	-
McNulty (1985)	Toxicity and Fetotoxicity of TCDD, TCDF and PCB Isomers in Rhesus Macaques (*Macaca mulatta*)	-	-	X	-
McNulty et al. (1982)	Persistence of TCDD in Monkey Adipose Tissue	-	-	X	-
Mebus et al. (1987)	Depression of Rat Testicular 17-Hydroxylase and 17,20-Lyase After Administration of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Meulenbelt and de Vries (2005)	Toxicity of Dioxins in Humans	-	-	X	-
Meyer (2002)	Incidence of CTCL in Vietnam Veterans	-	-	X	-
Michalek (2008)	Diabetes and Cancer in Veterans of Operation Ranch Hand After Adjustment for Calendar Period, Days of Spraying, and Time Spent in Southeast Asia	-	-	X	-

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
		Reason for excluding study			
Michalek et al. (2001a)	Relation of Serum 2,3,7,8-Tetrachloro-p-dioxin (TCDD) Levels to Hematological Examination Results in Veterans of Operation Ranch Hand	-	-	X	-
Michalek et al. (2001c)	Serum Dioxin and Hepatic Abnormalities in Veterans of Operation Ranch Hand	-	-	X	-
Miettinen et al. (2002)	Effect of In Utero and Lactational 2,3,7,8-Tetrachlorodibenzo-p-dioxin Exposure on Rat Molar Development: The Role of Exposure Time	-	-	X	-
Miettinen et al. (2004)	Effects of Epidermal Growth Factor Receptor Deficiency and 2,3,7,8-Tetrachlorodibenzo-p-dioxin on Fetal Development in Mice	-	-	X	-
Miettinen et al. (2005)	Effects of In Utero and Lactational TCDD Exposure on Bone Development in Differentially Sensitive Rat Lines	-	-	X	-
Miller (1985)	Congenital PCB Poisoning: a Reevaluation	-	-	X	-
Miller et al. (1986)	Teratologic Evaluation of Hexabrominated Naphthalenes in C57BL/6N Mice	-	-	X	-
Mimura et al. (1997)	Loss of Teratogenic Response to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) in Mice Lacking the Ah (dioxin) Receptor	-	-	X	-
Mitchell and Lawrence (2003a)	Exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Renders Influenza Virus-Specific CD8_ T Cells Hyporesponsive to Antigen	-	-	X	-
Mitchell and Lawrence (2003b)	T cell Receptor Transgenic Mice Provide Novel Insights Into Understanding Cellular Targets of TCDD: Suppression of Antibody Production, but Not the Response of CD8+ T Cells, During Infection with Influenza Virus	X	-	-	-
Mitchell et al. (2006)	Sustained Aryl Hydrocarbon Receptor Activity Attenuates Liver Regeneration	-	-	X	-

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Mitrou et al. (2001)	Toxic Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Related Compounds	-	-	X	-
Mitsui et al. (2006)	Perinatal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Suppresses Contextual Fear Conditioning-accompanied Activation of Cyclic AMP Response Element-binding Protein in the Hippocampal CA1 Region of Male Rats	-	-	X	-
Mittler et al. (1984)	Changes in Testosterone Hydroxylase Activity in Rat Testis Following Administration of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	X	-
Mizuyachi et al. (2002)	Alteration in Ovarian Gene Expression in Response to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: Reduction of Cyclooxygenase-2 in the Blockage of Ovulation	-	-	X	-
Mocarelli (2001)	Seveso a Teaching Story	-	-	X	-
Moennikes et al. (2004)	A Constitutively Active Dioxin/Aryl Hydrocarbon Receptor Promotes Hepatocarcinogenesis in Mice	-	-	X	-
Moolgavkar et al. (1996)	Quantitative Analysis of Enzyme-altered Liver Foci in Rats Initiated with Diethylnitrosamine and Promoted with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin or 1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin	-	-	-	X
Moon et al. (2004)	Effect of TCDD on Corpus Cavernosum Histology and Smooth Muscle Physiology-IP Injection	-	-	X	-
Moon et al. (2008)	A Single Administration of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin that Produces Reduced Food and Water Intake Induces Long-lasting Expression of Corticotropin-releasing Factor, Arginine Vasopressin, and Proopiomelanocortin in Rat Brain	-	X	-	-
Moore and Peterson (1985)	Enhanced Catabolism and Elimination of Androgens do Not Cause the Androgenic Deficiency in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-treated Rats	-	-	X	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
		Reason for excluding study			
Moore et al. (1973)	Postnatal Effects of Maternal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Moore et al. (1976)	Tissue Distribution of [14C] Tetrachlorodibenzo-*p*-dioxin in Pregnant and Neonatal Rats	X	-	-	-
Moore et al. (1979)	Comparative Toxicity of Three Halogenated Dibenzofurans in Guinea Pigs, Mice, and Rhesus Monkeys	-	-	X	-
Moore et al. (1985)	Enhanced Catabolism and Elimination of Androgens do Not Cause the Androgenic Deficiency in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-treated Rats	-	-	X	-
Moore et al. (1989)	Plasma Concentrations of Pituitary Hormones in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-treated Male Rats	-	-	X	-
Moore et al. (1991)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Inhibits Steroidogenesis in the Rat Testis by Inhibiting the Mobilization of Cholesterol to Cytochrome P450_scc 1	-	X	-	-
Moore et al. (1985)	Androgenic Deficiency in Male Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Moore et al. (1992)	In Utero and Lactational 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Exposure Decreases Androgenic Responsiveness of Male Sex Organs and Permanently Inhibits Spermatogenesis and Demasculinizes Sexual Behavior in Rats	-	X	-	-
Moos et al. (1994)	Acute Inflammatory Response to Sheep Red Blood Cells in Mice Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: the Role of Proinflammatory Cytokines, IL-1 and TNF	-	-	X	-
Moran et al. (2001)	Effect of Dioxin on Ovarian Function in the Cynomolgus Macaque (*M. fascicularis*)	X	X	-	-
Moriguchi et al. (2003)	Distinct Response to Dioxin in an Arylhydrocarbon Receptor (AHR)-humanized Mouse-IP Injection	-	-	X	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Morris et al. (1992)	Enhanced Suppression of Humoral Immunity in DBA/2 Mice Following Subchronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Morrissey et al. (1992)	Limited PCB Antagonism of TCDD-induced Malformations in Mice	-	X	-	-
Morse et al. (1993)	Interference of polychlorinated biphenyls in hepatic and brain thyroid hormone metabolism in fetal and neonatal rats	-	-	X	-
Morse et al. (1996)	Alterations in rat brain thyroid hormone status following pre- and postnatal exposure to polychlorinated biphenyls (Aroclor 1254)	-	-	X	-
Moshammer and Neuberger (2000)	Sex ratio in the children of the Austrian chloracne cohort	-	X	-	-
Mukai et al. (2008)	Behavioral Rhythmicity of Mice Lacking AhR and Attenuation of Light-Induced Phase Shift by 2,3,7,8-Tetrachlorodibenzo- *p*-Dioxin	-	X	X	-
Murante and Gasiewicz (2000)	Hemopoietic Progenitor Cells Are Sensitive Targets of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in C57BL/6J Mice	-	X	-	-
Mustafa et al. (2008)	An Enhanced Postnatal Autoimmune Profile in 24 Week-old C57BL/6 Mice Developmentally Exposed to TCDD	-	X	-	-
Myllymaki et al. (2005)	In Utero and Lactational Exposure to TCDD; Steroidogenic Outcomes Differ in Male and Female Rat Pups	-	X	-	-
Nagarkatti et al. (1984)	Sensitivity of Suppression of Cytotoxic T Cell Generation by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is Dependent on the Ah Genotype of the Murine Host	X	-	-	-
Nayyar et al. (2007)	Developmental Exposure of Mice to TCDD Elicits a Similar Uterine Phenotype in Adult Animals as Observed in Women with Endometriosis	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Neff-LaFord et al. (2003)	Fewer CTL, Not Enhanced NK Cells, are Sufficient for Viral Clearance From the Lungs of Immunocompromised Mice	-	X	-	-
Negish et al. (2006)	Gestational and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Affects Social Behaviors Between Developing Rhesus Monkeys (*Macaca mulatta*)	-	X	-	-
Ness et al. (1993)	Effects of Perinatal Exposure to Specific PCB Congeners on Thyroid Hormone Concentrations and Thyroid Histology in the Rat	-	-	X	-
Neubert et al. (1990)	Polyhalogenated Dibenzo-*p*-dioxins and Dibenzofurans and the Immune System 1. Effects on Peripheral Lymphocyte Subpopulations of a Non-human Primate (*Callithrix jacchus*) After Treatment with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	-	-	X
Nienstedt et al. (1979)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Hepatic Metabolism Of Testosterone in the Rat	-	X	-	-
Niittynen et al. (2003)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-Induced Accumulation of Biliverdin and Hepatic Peliosis in Rats	-	X	-	-
Niittynen et al. (2007)	Differences in Acute Toxicity Syndromes of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and 1,2,3,4,7,8-Hexachlorodibenzo-*p*-dioxin in Rats	-	X	-	-
Niittynen et al. (2008)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Heme Oxygenase-1, Biliverdin IXα Reductase and δ-aminolevulinic Acid Synthetase 1 in Rats with Wild-type or Variant AH Receptor	X	X	-	-
Nikolaidis et al. (1990)	TCDD Inhibits the Support of B-cell Development by the Bursa of Fabricius	X	-	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Nilsson et al. (2000)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Increases Serum and Kidney Retinoic Acid Levels and Kidney Retinol Esterification in the Rat	-	X	-	-
Nishijo et al. (2007)	Effects of Maternal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Fetal Brain Growth and Motor and Behavioural Development in Offspring Rats	-	X	-	-
Nishimura et al. (2001)	Induction of Metallothionein in the Livers of Female Sprague-Dawley Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Nishimura et al. (2002)	Immunohistochemical Localization of Thyroid Stimulating Hormone Induced by a Low Oral Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Female Sprague-Dawley Rats	-	X	-	-
Nishimura et al. (2003)	Rat Thyroid Hyperplasia Induced by Gestational and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin	-	X	-	-
Nishimura et al. (2005a)	Altered Thyroxin and Retinoid Metabolic Response to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Aryl Hydrocarbon Receptor-null Mice	-	X	-	-
Nishimura et al. (2005b)	Disruption of Thyroid Hormone Homeostasis at Weaning of Holtzman Rats by Lactational but Not In Utero Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin	-	X	-	-
Nishimura et al. (2006)	Localization of Cytochrome P450 1A1 in a Specific Region of Hydronephrotic Kidney of Rat Neonates Lactationally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Nishimura et al. (2008)	Critical Role of Cyclooxygenase-2 Activation in Pathogenesis of Hydronephrosis Caused by Lactational Exposure of Mice to Dioxin	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Nishiumi et al. (2008)	Involvement of SREBPs in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-induced Disruption of Lipid Metabolism in Male Guinea Pig-IP Injection	-	-	-	X
Nohara et al. (2000a)	Alterations of Thymocyte Development, Thymic Emigrants and Peripheral T Cell Population in Rats Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Nohara et al. (2002b)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on T Cell-derived Cytokine Production in Ovalbumin (OVA)-Immunized C57Bl/6 Mice	-	X	-	-
Nohara et al. (2008)	Arsenite-Induced Thymus Atrophy is Mediated by Cell Cycle Arrest: A Characteristic Downregulation of E2F-Related Genes Revealed by a Microarray Approach-IP injection	X	-	-	X
Nottebrock et al. (2006)	Effects of 2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin on the Extracellular Matrix of the Thymus in Juvenile Marmosets (*Callithrix jacchus*)-Subcutaneous Exposure	-	-	-	X
Novelli et al. (2005)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-induced Impairment of Glucose-stimulated Insulin Secretion in Isolated Rat Pancreatic Islets-IP Injection	-	-	-	X
Ohbayashi et al. (2008)	Occurrence of Two Different Types of Glutathione S-Transferase Placental Form-Positive Hepatocytes after a Single Administration of 2,3,7,8-Tetrabromodibenzo-pdioxin in Rats	-	X	-	-
Ohsako et al. (2002)	Developmental Stage-Specific Effects of Perinatal 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exposure on Reproductive Organs of Male Rat Offspring	-	X	-	-
Ohyama (2006)	Disorders of Sex Differentiation Caused by Exogenous Hormones	-	-	X	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Ohyama et al. (2007)	Maternal Exposure of Low Dose of TCDD Modulates the Expression of Estrogen Receptor Subunits of Male Gonads in Offspring-subcutaneous Exposure	-	-	-	X
Okey et al. (1989)	Detection and Characterization of a Low-affinity Form of Cytosolic Ah Receptor in Livers of Mice Nonresponsive to Induction of Cytochrome P1-450 by 3-Methylcholanthrene	X	-	-	-
Olson (1980)	Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Golden Syrian Hamster	-	X	-	-
Olson and McGarrigle (1990)	Characterization of the Developmental Toxicity of 2,3,7,8-TCDD in the Golden Syrian Hamster	-	X	-	-
Olson and McGarrigle (1992)	Comparative Developmental Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Olson et al. (1990)	Developmental Toxicity of 2,3,7,8-TCDD in the Rat and Hamster	-	X	-	-
Operana et al. (2007)	Human CYP1A1^GFP Expression in Transgenic Mice Serves as a Biomarker for Environmental Toxicant Exposure-IP Injection	-	-	-	X
Paajarvi et al. (2005)	TCDD Activates Mdm2 and Attenuates the P53 Response to DNA Damaging Agents	-	X	-	-
Pan et al. (2004)	Evaluation of Relative Potencies of PCB126 and PCB169 for the Immunotoxicities in Ovalbumin (OVA)-immunized Mice	-	X	-	-
Pande et al. (2005)	Aspects of Dioxin Toxicity Are Mediated by Interleukin 1-Like Cytokines-IP injection	-	-	-	X
Park et al. (2006)	The Therapeutic Effect of Tissue Cultured Root of Wild Panax ginseng C.A. Mayer on Spermatogenetic Disorder-IP injection	-	-	X	-
Parkinson et al. (1983)	Differential Time Course of Induction of Rat Liver Microsomal Cytochrome P450 Isozymes and Epoxide Hydrolase by Arochlor 1254	-	-	X	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Partanen et al. (1998)	Epidermal Growth Factor Receptor as a Mediator of Developmental Toxicity of Dioxin in Mouse Embryonic Teeth	-	-	-	X
Patterson et al. (2003)	Induction of Apoptosis by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Following Endotoxin Exposure	-	X	-	-
Peraino et al. (1981)	Early Appearance of Histochemically Altered Hepatocyte Foci and Liver Tumors in Female Rats Treated with Carcinogens 1 Day After Birth	-	-	X	-
Perucatti et al. (2006)	Increased Frequencies of Both Chromosome Abnormalities and SCEs in Two Sheep Flocks Exposed to High Dioxin Levels During Pasturage	X	-	-	-
Pesonen et al. (2006)	Effects of In Utero and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Rat Follicular Steroidogenesis	-	X	-	-
Peters and Wiley (1995)	Evidence that Murine Preimplantation Embryos Express Aryl Hydrocarbon Receptor	-	-	X	-
Peters et al. (1999)	Amelioration of TCDD-induced Teratogenesis in Aryl Hydrocarbon Receptor (AhR)-null Mice	X	X	-	-
Petroff et al. (2000)	Interaction of Estradiol and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in an Ovulation Model: Evidence for Systemic Potentiation and Local Ovarian Effects	-	X	-	-
Petroff et al. (2001)	The Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Weight Gain and Hepatic Ethoxyresorufin-*o*-deethylase (EROD) Induction Vary with Ovarian Hormonal Status in the Immature Gonadotropin-primed Rat Model	-	X	-	-
Petroff et al. (2002)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Serum Inhibin Concentrations and Inhibin Immunostaining During Follicular Development in Female Sprague-Dawley Rats	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Pitt et al. (2000)	Adrenocoricotropin (ACTH) and Corticosterone Secretion by Perifused Pituitary and Adrenal Glands From Rodents Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Plüess et al. (1988)	Subchronic Toxicity of Some Chlorinated Dibenzofurans (PCDFs) and a Mixture of PCDFs and Chlorinated Dibenzodioxins (PCDDs) in rats	-	X	-	-
Pohjanvirta et al. (1988)	Hepatic Ah-receptor Levels and the Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Hepatic Microsomal Monooxygenase Activity in a TCDD-susceptible and -resistant Rat Strain	X	-	-	-
Pohjanvirta et al. (1989)	The Central Nervous System May be Involved in TCDD Toxicity	-	-	-	X
Pohjanvirta et al. (1990)	Effects of TCDD on Vitamin A Status and Liver Microsomal Enzyme Activities in a TCDD-susceptible and a TCDD-resistant Rat Strain	-	-	-	X
Pohjanvirta et al. (1993)	Comparative Acute Lethality of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), 1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin and 1,2,3,4,7,8- Hexachlorodibenzo-*p*-dioxin in the most TCDD-susceptible and the Most TCDD-resistant Rat Strain	X	-	-	-
Pohjanvirta et al. (1998)	Point Mutation in Intron Sequence Causes Altered Carboxyl-terminal Structure in the Aryl Hydrocarbon Receptor of the most 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-resistant Rat Strain	X	-	-	-
Pohjanvirta et al. (2006)	Evaluation of Various Housekeeping Genes for Their Applicability for Normalization of mRNA Expression in Dioxin-treated Rats	-	X	-	-
Poland and Glover (1990)	Characterization and Strain Distribution Pattern of the Murine Ah Receptor Specified by the Ahd and Ahb-3 Alleles	-	-	X	-
Poland et al. (1982)	Tumor Promotion by TCDD in Skin of HRS/J Mice	-	-	-	X

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Pollenz et al. (1998)	Female Sprague-Dawley Rats Exposed to a Single Oral Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Exhibit Sustained Depletion of Aryl Hydrocarbon Receptor Protein in Liver, Spleen, Thymus, and Lung	-	X	-	-
Porterfield et al. (2000)	Thyroidal Dysfunction and Environmental Chemicals -- Potential Impact on Brain Development	-	-	X	-
Potter et al. (1983)	Hypothyroxinemia and Hypothermia in Rats in Response to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Administration	-	X	-	-
Potter et al. (1986a)	Relationship of Alterations in Energy Metabolism to Hypophagia in Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Potter et al. (1986b)	Thyroid Status and Thermogenesis in Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Powers et al. (2005)	Tetrachlorodibenzo-*p*-dioxin Exposure Alters Radial Arm Maze Performance and Hippocampal Morphology in Female AhR+/- Mice	X	X	-	-
Prell et al. (2000)	CTL Hyporesponsiveness Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: Role of Cytokines and Apoptosis	-	X	-	-
Puhvel and Sakamoto (1988)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Murine Skin	-	-	-	X
Puhvel et al. (1982)	Hairless Mice as Models for Chloracne: a Study of Cutaneous Changes Induced by Topical Application of Established Chloracnegens	X	-	-	X
Puhvel et al. (1991)	Vitamin A Deficiency and the Induction of Cutaneous Toxicity in Murine Skin by TCDD	-	-	-	X

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
		Reason for excluding study			
Ramakrishna et al. (2002)	Decrease in K-ras p21 and Increase in Raf1 and Activated Erk1 and 2 in Murine Lung Tumors Initiated by N-nitrosodimethylamine and Promoted by 2,3,7,8-TCDD-IP Injection	-	-	-	X
Randerath et al. (1988)	Organ-specific Effects of Long-term Feeding of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and 1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin on I-compounds in Hepatic and Renal DNA of Female Sprague-Dawley Rats	-	X	-	-
Render et al. (2000)	Proliferation of Periodontal Squamous Epithelium in Mink Fed 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Render et al. (2001)	Squamous Epithelial Proliferation in the Jaws of Mink Fed Diets Containing 3,3',4,4',5-Pentachlorobiphenyl (PCB 126) or 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Rhile et al. (1996)	Role of Fas Apoptosis and MHC Genes in 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-induced Immunotoxicity of T Cells	-	X	-	-
Rice (1997)	Effect of Postnatal Exposure to a PCB Mixture in Monkeys on Multiple Fixed Internal-fixed Ratio Performance	-	-	X	-
Rice (1999)	Effect of Exposure to 3,3',4,4',5-Pentachlorobiphenyl (PCB 126) Throughout Gestation and Lactation on Development and Spatial Delayed Alternation Performance in Rats	-	-	X	-
Rice and Hayward (1998)	Lack of Effect of 3,3'4,4',5-Pentachlorobiphenyl (PCB 126) Throughout Gestation and Lactation on Multiple Fixed Interval-fixed Ratio and DRL Performance in Rats	-	-	X	-
Rice and Hayward (1999)	Effects of Exposure to 3,3',4,4',5-Pentachlorobiphenyl (PCB 126) Throughout Gestation and Lactation on Behavior (Concurrent Random Interval-random Interval and Progressive Ratio Performance) in Rats	-	-	X	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Riecke et al. (2002)	Low Doses of 2,3,7,8-Tetrachlorodibenzo-p-dioxin Increase Transforming Growth Factor [TGF] β and Cause Myocardial Fibrosis In Marmosets (*Callithrix jacchus*)-Subcutaneous Exposure	-	-	-	X
Rier et al. (1993)	Endometriosis in Rhesus Monkeys (*Macaca mulata*) Following Chronic Exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin	-	-	X	-
Rier et al. (1995)	Immunoresponsiveness in Endometriosis: Implications of Estrogenic Toxicants	-	-	X	-
Rier et al. (2001a)	Increased Tumor Necrosis Factor-α Production by Peripheral Blood Leukocytes from TCDD-exposed Rhesus Monkeys	-	X	-	-
Rifkind and Muschick (1983)	Benoxaprofen Suppression of Polychlorinated Biphenyl Toxicity Without Alteration of Mixed Function Oxidase Function	-	-	X	-
Roby (2001)	Alterations in Follicle Development, Steroidogenesis, and Gonadotropin Receptor Binding in a Model of Ovulatory Blockade	-	X	-	-
Roman and Peterson (1998)	In Utero and Lactational Exposure of the Male Rat to 2,3,7,8-Tetrachlorodibenzo-p-dioxin Impairs Prostate Development	-	X	-	-
Roman et al. (1995)	In Utero and Lactational Exposure of the Male Rat to 2,3,7,8-Tetrachlorodibenzo-p-dioxin: Impaired Prostate Growth and Development Without Inhibited Androgen Production	-	X	-	-
Roman et al. (1998)	In Utero and Lactational Exposure of the Male Rat to 2,3,7,8-Tetrachlorodibenzo-p-dioxin Impairs Prostate Development. 1. Effects on Gene Expression	-	X	-	-
Roman et al. (1998)	In Utero and Lactational Exposure of the Male Rat to 2,3,7,8-Tetrachlorodibenzo-p-dioxin Impairs Prostate Development. 2. Effects on Growth and Cytodifferentiation	-	X	-	-

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Romkes and Safe (1988)	Comparative Activities of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Progesterone as Antiestrogens in the Female Rat Uterus	-	-	-	X
Rosenthal et al. (1989)	Characteristics of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Induced Endotoxin Hypersensitivity: Association with Hepatotoxicity	-	X	-	-
Rozman et al. (1984)	Effect of Thyroidectomy and Thyroxine on 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-induced Toxicity	-	-	X	-
Russell et al. (1988)	Hypothalamic Site of Action of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	-	-	X
Russo and Russo (1978)	Developmental Stage of the Rat Mammary Gland as Determinant of its Susceptibility to 7,12-Dimethylbenz[a]anthracene	-	-	X	-
Ryo et al. (2006)	Germ-line Mutations at a Mouse ESTR (Pc-3) Locus and Human Microsatellite Loci-IP Injection	-	-	-	X
Salisbury and Marcinkiewicz (2002)	In Utero and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and 2,3,4,7,8-Pentachlorodibenzofuran Reduces Growth and Disrupts Reproductive Parameters in Female Rats	-	X	-	-
Sanders et al. (1988)	Thyroid and Liver Trophic Changes in Rats Secondary to Liver Microsomal Enzyme Induction Caused by an Experimental Leukotriene Antagonist (L-649,923)	-	-	X	-
Santostefano et al. (1998)	A Pharmacodynamic Analysis of TCDD-induced Cytochrome P450 Gene Expression in Multiple Tissues: Dose- and Time-dependent Effects	-	X	-	-
Schantz et al. (1979)	Toxicological Effects Produced in Nonhuman Primates Chronically Exposed to Fifty Parts per Trillion 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
		Reason for excluding study			
Schantz et al. (1991)	Effects of Perinatal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Spatial Learning and Memory and Locomotor Activity in Rats	-	X	-	-
Schantz et al. (1995)	Spatial Learning Deficits in Adult Rats Exposed to Ortho-substituted PCB Congeners During Gestation and Lactation	-	-	X	-
Schantz et al. (1997)	Long-term Effects of Developmental Exposure to 2,2',3,5',6-Pentachlorobiphenyl (PCB 95) on Locomotor Activity, Spatial Learning and Memory and Brain Ryanodine Binding	-	-	X	-
Schrenk et al. (1994)	Promotion of Preneoplastic Foci in Rat Liver with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, 1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin and a Defined Mixture of 49 Polychlorinated Dibenzo-*p*-dioxins	-	-	-	X
Schulz et al. (2000)	Identification of Theta-class Glutathione S-transferase in Liver Cytosol of the Marmoset Monkey	-	-	X	-
Schuur et al. (1997)	Extrathyroidal Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Thyroid Hormone Turnover in Male Sprague-Dawley Rats	-	-	-	X
Scott et al. (2001)	Exposure to the Dioxin 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Induces Squamous Metaplasia in the Endocervix of *Cynomolgus Macaques*	-	X	-	-
Seefeld and Peterson (1984)	Digestible Energy and Efficiency of Feed Utilization in Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Seefeld et al. (1979)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Indocyanine Green Blood Clearance in Rhesus Monkeys	-	X	-	-
Seefeld et al. (1984a)	Body Weight Regulation in Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Seefeld et al. (1984b)	Characterization of the Wasting Syndrome in Rats Treated with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Seegal et al. (1990)	Lightly Chlorinated Ortho-substituted PCB Congeners Decrease Dopamine in Nonhuman Primate Brain and in Tissue Culture	-	-	X	-
Seegal et al. (1997)	Effects of In Utero and Lactational Exposure of the Laboratory Rat to 2,4,2',4'- and 3,4,3',4'-Tetrachlorobiphenyl on Dopamine Function	-	-	X	-
Senft et al. (2002)	Mitochondrial Reactive Oxygen Production is Dependent on the Aromatic Hydrocarbon Receptor-IP Injection	-	-	-	X
Seo and Meserve (1995)	Effects of Maternal Ingestion of Aroclor 1254 (PCB) on the Developmental Pattern of Oxygen Consumption and Body Temperature in Neonatal Rats	-	-	X	-
Seo et al. (1999)	Learning and Memory in Rats Gestationally and Lactationally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Seo et al. (2000)	Radial Arm Maze Performance in Rats Following Gestational and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Sewall et al. (1995b)	TCDD Reduces Rat Hepatic Epidermal Growth Factor Receptor: Comparison of Binding, Immunodetection, and Autophosphorylation	-	X	-	-
Shepherd et al. (2000)	The Effects of TCDD on the Activation of Ovalbumin (OVA)-Specific DO11.10 Transgenic CD4+ T-cells in Adoptively Transferred Mice	-	X	-	-
Shepherd et al. (2001)	Anti-CD40 Treatment of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)-Exposed C57Bl/6 Mice Induces Activation of Antigen Presenting Cells Yet Fails to Overcome TCDD-Induced	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
		Reason for excluding study			
Shirota et al. (2007)	Internal Dose-effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Gonadotropin-primed Weanling Rat Model	-	X	-	-
Shiverick and Muther (1982)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Serum Concentrations and the Uterotrophic Action of Exogenous Estrone in Rats	-	X	-	-
Shiverick and Muther (1983)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Effects on Hepatic Microsomal Steroid Metabolism and Serum Estradiol of Pregnant Rats	-	X	-	-
Shon et al. (2002)	Effect of Chitosan Oligosaccharide on 2,3,7,8-Tetrachlorodibenzop-dioxin-Induced Oxidative Stress in Mice	-	X	-	-
Silkworth and Antrim (1985)	Relationship Between Ah Receptor-mediated Polychlorinated Biphenyl (PCB)-induced Humoral Immunosuppression and Thymic Atrophy	-	-	X	-
Silkworth et al. (1984)	Correlations Between Polychlorinated Biphenyl Immunotoxicity, the Aromatic Hydrocarbon Locus, and Liver Microsomal Enzyme Induction in C57Bl/6 and DBA/2 Mice	-	-	X	-
Silkworth et al. (1989)	Teratology of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in a Complex Environmental Mixture From the Love Canal	-	-	X	-
Silkworth et al. (1997)	Tumor responses, PCB Tissue Concentrations and PCB Hepatic Binding in S-D Rats Fed Aroclors 1016, 1242, 1254 or 1260	-	-	X	-
Sills et al. (1994)	Tumor-Promoting Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin and Phenobarbital in Initiated Weanling Sprague-Dawley Rats: A Quantitative, Phenotypic, and ras p21 Protein Study	-	-	X	-
Simanainen et al. (2004a)	Adult 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) Exposure and Effects on Male Reproductive Organs in Three Differentially TCDD-Susceptible Rat Lines	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
		Reason for excluding study			
Slezak et al. (1999)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-Mediated Oxidative Stress in CYP1A2 Knockout (CYP1A2-/-) Mice	-	X	-	-
Slezak et al. (2002)	TCDD-Mediated Oxidative Stress in Male Rat Pups Following Perinatal Exposure	-	X	-	-
Sloop and Lucier (1987)	Dose-dependent Elevation of Ah Receptor Binding by TCDD in Rat Liver	-	X	-	-
Smialowicz et al. (1997)	Opposite Effects of 2,2',4,4',5,5'-Hexachlorobiphenyl and 2,3,7,8-TCDD on the Antibody Response to Sheep Erythrocytes in Mice	-	-	X	-
Smith et al. (1981)	Hepatic Toxicity and Uroporphyrinogen Decarboxylase Activity Following a Single Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin to Mice	-	X	-	-
Smith et al. (1998)	Interaction Between Iron Metabolism and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Mice with Variants of the AhR Gene: a Hepatic Oxidative Mechanism	-	-	X	-
Sommer et al. (2005)	Early Developmental 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin Exposure Decreases Chick Embryo Heart Chronotropic Response to Isoproterenol but Not to Agents Affecting Signals Downstream of the Beta-Adrenergic Receptor	X	-	-	-
Staples et al. (1998)	Thymic Alterations Induced by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin are Strictly Dependent on Aryl Hydrocarbon Receptor Activation in Hematopoietic Cells	-	-	-	X
Stohs et al. (1983)	Lipid Peroxidation as a Possible Cause of TCDD Toxicity	-	X	-	-
Sugihara et al. (2001)	Aryl Hydrocarbon Receptor (AhR)-Mediated Induction of Xanthine Oxidase/Xanthine Dehydrogenase Activity by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
		Reason for excluding study			
Sweeney et al. (1979)	Iron Deficiency Prevents Liver Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	X	-	-	-
Takagi et al. (2000)	Pathogenesis of Cleft Palate in Mouse Embryos Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Tani et al. (2004)	Follicular Epithelial Cell Hypertrophy Induced by Chronic Oral Administration of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Female Harlan Sprague-Dawley Rats	-	X	-	-
Teske et al. (2005)	Activation of the Aryl Hydrocarbon Receptor Increases Pulmonary Neutrophilia and Diminishes Host Resistance to Influenza A Virus	-	X	-	-
Thackaberry et al. (2005a)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin on Murine Heart Development: Alteration in Fetal and Postnatal Cardiac Growth, and Postnatal Cardiac Chronotropy	-	X	-	-
Thackaberry et al. (2005b)	Toxicogenomic Profile of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in the Murine Fetal Heart: Modulation of Cell Cycle and Extracellular Matrix Genes	-	X	-	-
Theobald and Peterson (1997)	In Utero and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-rho-dioxin: Effects on Development of the Male and Female Reproductive System of the Mouse	-	X	-	-
Theobald et al. (2000)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Inhibits Lumen Cell Differentiation and Androgen Responsiveness of the Ventral Prostate Without Inhibiting Prostatic 5α-Dihrdrotestosterone or Testicular Androgen Production in Rat Offspring	-	X	-	-
Thigpen et al. (1975)	Increased Susceptibility to Bacterial Infection as a Sequela of Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Thomas and Hinsdill (1979)	The Effect of Perinatal Exposure to Tetrachlorodibenzo-*p*-dioxin on the Immune Response of Young Mice	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	**Low dose too high**	**Doses not TCDD only; unspecified TCDD dose**	**Nonoral dose**
Thornton et al. (2001)	Mutagenicity of TCDD in Big Blue® Transgenic Rats	-	X	-	-
Thornton et al. (2004)	The Dioxin TCDD Protects Against Aflatoxin-induced Mutation in Female Rats, but Not in Male Rats	-	X	-	-
Thunberg (1984)	Effects of TCDD on Vitamin A and its Relation to TCDD Toxicity	-	X	-	-
Thunberg and Hakansson (1983)	Vitamin A (retinol) Status in the Gunn Rat: the Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	X	-	-	-
Thunberg et al. (1979)	Vitamin A (Retinol) Status in the Rat After a Single Oral Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Tilson et al. (1979)	The Effects of Polychlorinated Biphenyls Given Prenatally on the Neurobehavioral Development of Mice	-	-	X	-
Timms et al. (2002)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Interacts with Endogenous Estradiol to Disrupt Prostate Gland Morphogenesis in Male Rat Fetuses	-	X	-	-
Tomar and Kerkvliet (1991)	Reduced T helper Cell Function in Mice Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Tritscher et al. (1995)	Persistence of TCDD-induced Hepatic Cell Proliferation and Growth of Enzyme Altered Foci After Chronic Exposure Followed by Cessation of Treatment in DEN Initiated Female Rats	-	X	-	-
Tritscher et al. (1996)	Increased Oxidative DNA Damage in Livers of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Treated Intact but Not Ovariectomized Rats	-	X	-	-
Tritscher et al. (1999)	TCDD-induced Lesions in Rat Lung After Chronic Oral Exposure. Dioxin '99: 19th International Symposium on Halogenated Environmental Organic Pollutants and POPs	-	X	-	-

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	**Low dose too high**	**Doses not TCDD only; unspecified TCDD dose**	**Nonoral dose**
Tritscher et al. (2000)	Induction of Lung Lesions in Female Rats following Chronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Truelove et al. (1982)	Polychlorinated Biphenyl Toxicity in the Pregnant Cynomolgus Monkey: A Pilot Study	-	-	X	-
Tsutsumi (2000)	Effects of Endocrine Disruptors on Preimplantation Embryo Development	X	-	-	-
Tucker et al. (1986)	Suppression of B Cell Differentiation by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Tuner and Collins (1983)	Liver Morphology in Guinea Pigs Administered Either Pyrolysis Products of a Polychlorinated Biphenyl Transformer Fluid or 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	X	-
Unkila et al. (1994a)	Characterization of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Induced Brain Serotonin Metabolism in Rat	-	X	-	-
Unkila et al. (1994b)	Dose Response and Time Course of Alterations in Tryptophan Metabolism by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in the Most TCDD- susceptible and the Most TCDD-resistant Rat Strain: Relationship with TCDD Lethality	-	X	-	-
Unkila et al. (1995)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Tryptophan and Glucose Homeostasis in the Most TCDD-susceptible and the Most TCDD-resistant Species, Guinea Pigs and Hamsters	-	X	-	-
Unkila et al. (1998)	Body Weight Loss and Changes in Tryptophan Homeostasis by Chlorinated Dibenzo-*p*-dioxin Congeners in the Most TCDD-Susceptible and the Most TCDD-resistant Rat Strain	X	-	-	-
Ushinohama et al. (2001)	Impaired Ovulation by 2,3,7,8 Tetrachlorodibenzo-*p*-dioxin (TCDD) in Immature Rats Treated with Equine Chorionic Gonadotropin	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Van Birgelen et al. (1996)	Synergistic Effect of 2,2',4,5,5'-Hexachlorobiphenyl and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on Hepatic Porphyrin Levels in the Rat	-	X	-	-
Van Birgelen et al. (1999b)	Dose and Time-response of TCDD in Tg.AC Mice After Dermal and Oral Exposure. Dioxin '99: 19th International Symposium on Halogenated Environmental Organic Pollutants and POPs	-	X	-	-
Van Birgelen et al. (1999a)	Toxicity of 3,3',4,4'-Tetrachloroazobenzene in Rats and Mice	-	X	-	-
Van den Berg et al. (1987)	Transfer of Polychlorinated Dibenzo-*p*-dioxins and Dibenzofurans to Fetal and Neonatal Rats	-	-	X	-
Vanden Heuvel (1994)	Accumulation of Polychlorinated Dibenzo-*p*-dioxins and Dibenzofurans in Liver of Control Laboratory Rats	-	-	X	-
Van der Kolk (1992)	Interactions of 2,2',4,4',5,5'- Hexachlorobiphenyl and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in a Subchronic Feeding Study in the Rat	-	-	X	-
Van Logten et al. (1980)	Role of the Endocrine System in the Action of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on the Thymus	-	X	-	-
Van Miller et al. (1977)	Increased Incidence of Neoplasms in Rats Exposed to Low Levels of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Vecchi et al. (1983)	Immunosuppressive Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Strains of Mice with Different Susceptibility	-	X	-	X
Vezina et al. (2008)	Dioxin Causes Ventral Prostate Agenesis by Disrupting Dorsoventral Patterning in Developing Mouse Prostate	-	X	-	-
Viluksela et al. (1995)	Tissue-specific Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on the Activity of Phosphoeno/Pyruvate Carboxykinase (PEPCK) in Rats	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Viluksela et al. (1997b)	Subchronic/Chronic Toxicity of 1,2,3,4,6,7,8-Heptachlorodibenzop-dioxin (HpCDD) in Rats: Part I. Design, General Observations, Hematology, and Liver Concentrations	-	X	-	-
Viluksela et al. (1997a)	Subchronic/Chronic Toxicity of 1,2,3,4,6,7,8-Heptachlorodibenzop-dioxin (HpCDD) in Rats: Part II. Biochemical Effects	-	X	-	-
Viluksela et al. (1998)	Subchronic/Chronic Toxicity of Four Chlorinated Dibenzo-*p*-dioxins in Rats. Part I. Design, General Observations, Hematology, and Liver Concentrations	-	-	X	-
Viluksela et al. (1999)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Liver Phosphoenolpyruvate Carboxylase (PEPCK) Activity, Glucose Homeostasis and Plasma Amino Acid Concentrations in the Most TCDD-susceptible and the Most TCDD-resistant Rat Strains	-	X	-	-
Viluksela et al. (2000)	Liver Tumor-promoting Activity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in TCDD-sensitive and TCDD-resistant Rat Strains	X	X	-	-
Vogel et al. (2003)	The Use of c-src Knockout Mice for the Identification of the Main Toxic Signaling Pathway of TCDD to Induce Wasting Syndrome	-	-	-	X
Vogel et al. (2007)	Modulation of the Chemokines KC and MCP-1 by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Mice	-	-	-	X
Vorderstrasse and Kerkvliet (2001)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Affects the Number and Function of Murine Splenic Dendritic Cells and Their Expression of Accessory Molecules	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Vorderstrasse and Lawrence (2006)	Protection Against Lethal Challenge with Streptococcus Pneumoniae is Conferred by Aryl Hydrocarbon Receptor Activation but is Not Associated with an Enhanced Inflammatory Response	X	-	-	-
Vorderstrasse et al. (2001)	Aryl Hydrocarbon Receptor-deficient Mice Generate Normal Immune Responses to Model Antigens and are Resistant to TCDD-induced Immune Suppression	X	X	X	-
Vorderstrasse et al. (2003)	Examining the Relationship Between Impaired Host Resistance and Altered Immune Function in Mice Treated with TCDD	X	-	-	-
Vorderstrasse et al. (2004)	Developmental Exposure to the Potent Aryl Hydrocarbon Receptor Agonist 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin Impairs the Cell-Mediated Immune Response to Infection with Influenza A Virus, but Enhances Elements of Innate Immunity	-	X	-	-
Vorderstrasse et al. (2006)	A Dose-response Study of the Effects of Prenatal and Lactational Exposure to TCDD on the Immune Response to Influenza A Virus	-	X	-	-
Vos and Moore (1974)	Suppression of Cellular Immunity in Rats and Mice by Maternal Treatment with 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	X	-	-
Vos et al. (1974)	Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in C57B1/6 Mice	-	X	-	-
Vos et al. (1978)	Studies on 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-induced Immune Suppression and Decreased Resistance to Infection: Endotoxin Hypersensitivity, Serum Zinc Concentrations and Effect of Thymosin Treatment	-	X	-	-
Waern et al. (1991)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in the Lactating Rat on Maternal and Neonatal Vitamin A Status and Hepatic Enzyme Induction: A Dose-Response Study	-	-	-	X

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Wagner et al. (2001)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Natural Immunity: Lack of an Effect on the Complement System in a Guinea Pig Model	-	-	-	X
Wahba et al. (1988)	Induction of Hepatic DNA Single Strand Breaks in Rats by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Wahba et al. (1989)	Factors Influencing the Induction of DNA Single Strand Breaks in Rats by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Wahba et al. (1990a)	Altered Hepatic Iron Distribution and Release in Rats After Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Wahba et al. (1990b)	Desferrioxamine-induced Alterations in Hepatic Iron Distribution, DNA Damage, and Lipid Peroxidation in Control and 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-treated Rats	-	-	X	-
Walisser et al. (2004)	Patent Ductus Venosus and Dioxin Resistance in Mice Harboring a Hypomorphic ARNT Allele	-	X	-	-
Walker et al. (1995)	Rat CYP1B1: an Adrenal Cytochrome P450 that Exhibits Sex-dependent Expression in Livers and Kidneys of TCDD-treated Animals	-	X	-	-
Walker et al. (1997)	Hepatocarcinogenesis in a Sprague-Dawley Rat Initiation/Promotion Model Following Discontinuous Exposure to TCDD	-	X	-	-
Walker et al. (1998a)	Differences in Kinetics of Induction and Reversibility of TCDD-Induced Changes in Cell Proliferation and CYP1A1 Expression in Female Sprague-Dawley Rat Liver	-	X	-	-
Walker et al. (1998b)	Induction and Localization of Cytochrome P450 1B1 (CYP1B1) Protein in the Livers of TCDD-treated Rats: Detection Using Polyclonal Antibodies Raised to Histidine-tagged Fusion Proteins Produced and Purified From Bacteria	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Walker et al. (1999)	Characterization of the Dose-response of CYP1B1, CYP1A1, and CYP1A2 in the Liver of Female Sprague-Dawley Rats Following Chronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	-	X
Walker et al. (2004)	Persistent Suppression of Contact Hypersensitivity, and Altered T-cell Parameters in F344 Rats Exposed Perinatally to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	-	X	-	-
Warren et al. (2000)	Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Suppresses the Humoral and Cell-mediated Immune Responses to Influenza A Virus Without Affecting Cytolytic Activity in the Lung	X	-	-	-
Weber and Birnbaum (1985)	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and 2,3,7,8-Tetrachlorodibenzofuran (TCDF) in Pregnant C57BL/6 Mice: Distribution to the Embryo and Excretion	-	X	-	X
Weber et al. (1985)	Teratogenic Potency of TCDD, TCDF and TCDD-TCDF Combinations in C57BL/6N Mice	-	X	-	X
Weber et al. (1994)	Reduced Activity of Tryptophan 2,3,-Dioxygenase in the Liver of Rats Treated with Chlorinated Dibenzo-*p*-dioxins (CDDs): Dose-responses and Structure-activity Relationship	-	X	-	-
Weinand-Harer et al. (1997)	Behavioral Effects of Maternal Exposure to an Ortho-chlorinated or a Coplanar PCB Congener in Rats	-	-	X	-
Weinstein et al. (2008)	Mid-gestation Exposure of C57BL/6 Mice to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Causes Postnatal Morphologic Changes in the Spleen and Liver	-	X	-	-
Weissberg and Zinkl (1973)	Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Upon Hemostasis and Hematologic Function in the Rat	-	X	-	-

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Wheatley (1968)	Enhancement and Inhibition of the Induction by 7,12-Dimethylbenz(a)anthracene of Mammary Tumors in Female Sprague-Dawley Rats	-	-	X	-
Widholm et al. (2003)	Effects of Perinatal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin on Spatial and Visual Reversal Learning in Rats	-	X	-	-
Wolf et al. (1999a)	Administration of Potentially Antiandrogenic Pesticides (Procymidone, Linuron, Iprodione, Chlozolinate, *p,p*'-DDE, and Ketoconazole) and Toxic Substances (Dibutyl- and Diethylhexyl Phthalate, PCB 169, and Ethane Dimethane Sulphonate) During Sexual Differentiation Produces Diverse Profiles of Reproductive Malformations in the Male Rat	-	-	X	-
Wolf et al. (1999b)	Gestational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Severely Alters Reproductive Function of Female Hamster Offspring [In Process Citation]	-	X	-	-
Wu et al. (2004)	Exposure of Mouse Preimplantation Embryos to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Alters the Methylation Status of Imprinted Genes H19 and Igf2	X	-	-	-
Wyde et al. (1999)	Influence of Ovariectomy and 17 ß-Estradiol on the Promotion of Altered Hepatocellular Foci by TCDD. Dioxin '99: 19th International Symposium on Halogenated Environmental Organic Pollutants and POPs	X	-	-	-
Wyde et al. (2000)	Toxicity of Chronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Diethylnitrosamine-initiated Ovariectomized Rats Implanted with Subcutaneous 17 Beta-estradiol Pellets	X	-	-	-
Wyde et al. (2001a)	Induction of Hepatic 8-Oxo-deoxyguanosine adducts by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Sprague-Dawley Rats is Female-specific and Estrogen-dependent	X	-	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Wyde et al. (2001b)	Regulation of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-induced Tumor Promotion by 17 Beta-estradiol in Female Sprague-Dawley Rats	X	-	-	-
Wyde et al. (2002)	Promotion of Altered Hepatic Foci by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and 17Beta-estradiol in Male Sprague-Dawley Rats	-	-	X	-
Wyde et al. (2004)	Oral and Dermal Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Induces Cutaneous Papillomas and Squamous Cell Carcinomas in Female Hemizygous Tg.AC Transgenic Mice	-	X	-	-
Yang and Foster (1997)	Continuous Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Inhibits the Growth of Surgically Induced Endometriosis in the Ovariectomized Mouse Treated with High Dose Estradiol	X	-	-	X
Yang et al. (1983)	Effects of Halogenated Dibenzo-*p*-dioxins on Plasma Disappearance and Biliary Excretion of Ouabain in Rats	-	X	-	-
Yang et al. (1994)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) on Pulmonary Influenza Virus Titer and Natural Killer (NK) Activity in Rats	-	X	-	-
Yang et al. (2005)	Inhibitory Effects of vitamin A on TCDD-induced Cytochrome P-450 1A1 Enzyme Activity and Expression	-	X	-	-
Yasuda et al. (1999)	Palatal rugae Anomalies Induced by Dioxins in Mice	-	X	-	-
Ye and Leung (2008)	Effect of Dioxin Exposure on Aromatase Expression in Ovariectomized Rats	-	X	-	-
Yoon et al. (2000)	Teratological Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD): Induction of Cleft Palate in the DDY and C57BL/6 Mouse	-	X	-	-

Table D-2. Summary of studies excluded from the dioxin reanalysis and reasons for exclusion (continued)

Author (year)	Title of study	Reason for excluding study			
		Genetically altered animals	Low dose too high	Doses not TCDD only; unspecified TCDD dose	Nonoral dose
Yoon et al. (2001a)	Hemopoietic Cell Kinetics After Intraperitoneal Single Injection of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in Mice-IP Injection	-	-	-	X
Yoon et al. (2001b)	Transgene Expression of Thioredoxin (TRX/ADF) Protects Against 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD)-Induced Hematotoxicity-IP injection	-	-	-	X
Yoon et al. (2006)	Gene Expression Profile by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in the Liver of Wild-type (Ahr +/+) and Aryl Hydrocarbon Receptor Deficient (Ahr -/-) Mice-IP Injection	-	-	-	X
Zhu et al. (2008)	Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Administration and High-fat Diet on the Body Weight and Hepatic Estrogen Metabolism in Female C3H/HeN Mice-IP Injection	-	-	-	X
Zingeser (1979)	Anomalous Development of the Soft Palate in Rhesus Macaques (*Macaca mulatta*) Prenatally Exposed to 3,4,7,8-Tetrachlorodibenzo-*p*-dioxin	-	-	X	-
Zinkl et al. (1973)	Hematologic and Clinical Chemistry Effects of 2,3,7,8-Tetrachlorodi-benzo-*p*-dioxin in Laboratory Animals	-	X	-	-
	Totals	66	370	140	135

Table D-3. Cross-species concordance of male reproductive effects

Study	Species	Specific endpoint	Endpoint category	Administered dose (ng/kg-day)		Human-equivalent dose (HED)[a] (ng/kg-day)	
				NOAEL	LOAEL	NOAEL	LOAEL
(1) Bell et al. (2007c)	Rat	Delayed balanopreputial separation	Altered sexual development	2.40E+00	8.00E+00	8.85E-02	3.23E-01
		Increased ventral prostate weight	Organ weight changes	2.40E+00	8.00E+00	8.85E-02	3.23E-01
		Higher proportion of abnormal sperm	Sperm effects	8.00E+00	4.60E+01	3.23E-01	2.05E+00
(2) Ishihara et al. (2007)	Mouse	Altered sex ratio (decreased percentage of males)	Altered sex ratio	1.00E-01	1.00E+02	4.91E-05	4.96E-01
(3) Ikeda et al. (2005b)	Rat	Decreased ventral prostate weight	Organ weight changes	−	1.65E+01	−	2.75E+00
		Altered sex ratio (decreased percentage of males)	Altered sex ratio	−	1.65E+01	−	2.75E+00
(4) Kociba et al. (1976)	Rat	Increased testes weight	Organ weight changes	7.14E+01	7.14E+02	3.03E+00	3.19E+01
(5) Latchoumycandane and Mathur (2002)	Rat	Decreased daily sperm production	Sperm effects	−	1.00E+00	−	1.62E-02
		Decreased testis, epididymis, seminal vesicle, and ventral prostate weights	Organ weight changes	−	1.00E+00	−	1.62E-02
(6) Mocarelli et al. (2008)	Human	Decreased sperm count, progressive sperm motility, and total number of motile sperm	Sperm effects	−	−	−	2.01E-02
(7) Ohsako et al. (2001)	Rat	Decreased anogenital distance	Altered sexual development	1.25E+01	5.00E+01	2.74E-02	1.78E-01
		Decreased urogenital complex and ventral prostate weights	Organ weight changes	5.00E+01	2.00E+02	1.78E-01	1.04E+00
(8) Simanainen et al. (2004b)	Rat	Decreased daily sperm production	Sperm effects	1.00E+02	3.00E+02	4.33E-01	1.70E+00
		Decreased ventral prostate weight	Organ weight changes	3.00E+02	1.00E+03	1.70E+00	6.92E+00
		Epididymal degeneration	Organ toxicity	3.00E+02	1.00E+03	1.70E+00	6.92E+00

[a] HED for rat and mouse studies based on Emond rodent and human PBPK models described in Section 3.3.6.

Table D-4. Cross-species concordance of female reproductive effects

Study	Species	Specific Endpoint	Endpoint Category	Administered Dose (ng/kg-day)		Human-Equivalent Dose (HED)[a] (ng/kg-day)	
				NOAEL	LOAEL	NOAEL	LOAEL
(1) Bowman et al.(1989a; 1989b)	Monkey	Reduced reproductive rate	Reduced fertility	1.20E-01	6.70E-01	8.22E-03[b]	4.59E-02 [b]
		Decreased days of offspring survival	Decreased offspring survival	1.20E-01	6.70E-01	8.22E-03[b]	4.59E-02 [b]
(2) Eskenazi et al. (2002).	Human	Increased length of menstrual period	Altered menstrual cycle	−	−	−	3.11E+02
(3) Franczak et al. (2006)	Rat	Altered estrus cyclicity	Altered menstrual cycle	−	7.14E+00	−	3.18E-01
(4) Hutt et al. (2008)	Rat	Lower proportion of morphologically normal preimplantation embryos	Early embryo loss	−	7.14E+00	−	2.52E-01
(5) Li et al. (1997)	Rat	Increased serum FSH	Altered hormone levels	3.00E+00	1.00E+01	2.90E-03	1.67E-02
		Increased serum LH	Altered hormone levels	1.00E+02	3.00E+02	3.78E-01	1.48E+00
(6) Li et al. (2006)	Mouse	Increased serum estradiol, decreased serum progesterone	Altered hormone levels	−	2.00E+00	−	1.58E-03
		Early embryo loss	Early embryo loss	2.00E+00	5.00E+01	1.58E-03	1.31E-01
		Decreased uterine weight	Organ weight changes	2.00E+00	5.00E+01	1.58E-03	1.31E-01
(7) Murray et al. (1979)	Rat	Reduced fertility	Reduced fertility	1.00E+00	1.00E+01	2.89E-02	3.79E-01
		Reduced neonatal survival	Decreased offspring survival	1.00E+00	1.00E+01	2.89E-02	3.79E-01
(8) Shi et al. (2007)	Rat	Decreased serum estradiol	Altered hormone levels	1.43E-01	7.14E-01	4.47E-03	2.69E-02
		Accelerated reproductive senescence with normal cyclicity	Altered menstrual cycle	7.14E-01	7.14E+00	2.69E-02	3.18E-01
		Delayed vaginal opening	Altered sexual development	7.14E+00	2.86E+01	3.18E-01	1.34E+00
(9) Smith et al. (1976)	Mouse	Increased percentage of resorptions per implantations	Late embryo loss	1.00E+02	1.00E+03	5.24E-01	7.61E+00
(10) Sparschu et al. (2008; 1971)	Rat	Decreased mean number of viable fetuses per litter	Late embryo loss	1.25E+02	5.00E+02	1.73E+00	8.03E+00

[a] HED for rat and mouse studies based on Emond rodent and human PBPK models described in Section 3.3.6.
[b] HED based on 1st order body burden model described in Section 3.2.4.4.

Table D-5. Cross-species concordance of thyroid effects

Study	Species	Specific Endpoint	Endpoint Category	Administered Dose (ng/kg-day)		Human-Equivalent Dose (HED)[a] (ng/kg-day)	
				NOAEL	LOAEL	NOAEL	LOAEL
(1) Baccarelli et al. (2008)	Human	Elevated blood TSH in male and female neonates	Altered hormone levels	−	−	−	2.00E-02
(2) Chu et al. (2007)	Rat	Reduced follicles, reduced colloid density, and increased epithelial height in females	Histopathological lesions	2.50E+02	1.00E+03	7.03E+00	2.96E+01
(3) Crofton et al. (2005)	Rat	Reduced serum T4 levels in females	Altered hormone levels	3.00E+01	1.00E+02	1.69E-01	7.43E-01
(4) NTP (2006)	Rat	Reduced serum free and total T4 levels at 14 and 31 weeks	Altered hormone levels	7.14E+00	1.57E+01	4.09E-01	9.14E-01
		Increased serum total T3 levels at 53 weeks	Altered hormone levels	7.14E+00	1.57E+01	4.34E-01	9.63E-01
		Follicular cell hypertrophy at 2 years	Histopathological lesions	7.14E+00	1.57E+01	4.53E-01	9.98E-01
		Increased serum TSH levels in females	Altered hormone levels	1.57E+01	3.29E+01	9.98E-01	2.09E+00
(5) Seo et al. (1995)	Rat	Decreased serum T4 and thymus weight	Altered hormone levels	2.50E+01	1.00E+02	1.67E-01	9.15E-01
(6) Sewall et al. (1995a)	Rat	Decreased serum T4	Altered hormone levels	5.16E+00 [b]	3.57E+01	1.80E-01 [b]	1.71E+00
		Increased serum TSH levels in females	Altered hormone levels	3.57E+01	1.25E+02	1.71E+00	6.30E+00
(7) Simanainen et al. (2002)	Rat	Decreased serum T4	Altered hormone levels	1.00E+02	3.00E+02	4.26E-01	1.67E+00
(8) VanBirgelen et al. (1995a)	Rat	Reduced serum free and total T4 levels in females	Altered hormone levels	2.64E+01	4.69E+01	1.05E+00	1.93E+00

[a] HED for rat and mouse studies based on Emond rodent and human PBPK models described in Section 3.3.6.
[b] BMDL used instead of NOAEL.

Table D-6. Cross-species concordance of developmental dental effects

Study	Species	Specific Endpoints	Endpoints Category	Administered Dose (ng/kg-day)		Human-Equivalent Dose (HED)[a] (ng/kg-day)	
				NOAEL	LOAEL	NOAEL	LOAEL
(1) Alaluusua et al. (2004)	Human	Developmental dental defects	Enamel defects	−	−	4.06E-02	9.00E-01
(2) Kattainen et al. (2001)	Rat	Reduced mesiodistal length of the lower third molar in males and females	Altered tooth morphology	−	3.00E+01	−	9.01E-02
(3) Keller et al. (2008a; 2008b; 2007c)	Mouse	Variation in molar morphology and shape, decreased mandible shape and size in males and females	Altered tooth morphology	−	1.00E+01	−	9.88E-03

[a] HED for rat and mouse studies based on Emond rodent and human PBPK models described in Section 3.3.6.

Table D-7. Cross-species concordance of immune system effects

Study	Species	Specific Endpoint	Endpoint Category	Administered Dose (ng/kg-day)		Human-Equivalent Dose (HED)[a] (ng/kg-day)	
				NOAEL	LOAEL	NOAEL	LOAEL
(1) Chu et al. (2001)	Rat	Decreased relative thymus weight in females	Organ weight changes	2.50E+02	1.00E+03	7.03E+00	2.96E+01
(2) Chu et al. (2007)	Rat	Reduced thymic cortex and increased medullar volume in females	Histopathological lesions	2.50E+01	2.50E+02	5.63E-01	7.03E+00
		Decreased thymus weight in females	Organ weight changes	2.50E+02	1.00E+03	7.03E+00	2.96E+01
(3) DeCaprio et al. (1986)	Guinea pig	Decreased relative thymus weight in males	Organ weight changes	6.10E-01	4.90E+00	4.11E-03 [b]	3.30E-02 [b]
(4) Franc et al. (2001)	Rat	Decreased relative thymus weight in females	Organ weight changes	1.00E+01	3.00E+01	4.49E-01	1.41E+00
(5) Kociba et al. (1976)	Rat	Increased relative spleen and thymus weights in males and females	Organ weight changes	7.14E+01	7.14E+02	3.03E+00	3.19E+01
(6) Kociba et al. (1978)	Rat	Decreased relative thymus weight	Organ weight changes	1.00E+01	1.00E+02	6.34E-01	6.35E+00
		Thymic and splenic atrophy in females	Organ weight changes	1.00E+01	1.00E+02	6.34E-01	6.35E+00
(7) Simanainen et al. (2002)	Rat	Decreased relative thymus weight in females	Organ weight changes	3.00E+02	1.00E+03	1.67E+00	6.80E+00
(8) Simanainen et al. (2003)	Rat	Decreased relative thymus weight	Organ weight changes	1.00E+02	3.00E+02	4.26E-01	1.67E+00
(9) Smialowicz et al. (2004)	Mouse	Decreased antibody response to SRBCs in females	Immunosuppressive effects	3.00E+02	1.00E+03	7.23E-01	3.28E+00
(9) Smialowicz et al. (2004)	Mouse	Decreased thymus weight in females	Organ weight changes	3.00E+03	1.00E+04	1.18E+01	4.35E+01
(10) Smialowicz et al. (2008)	Mouse	Decreased antibody response to SRBCs in females	Immunosuppressive effects	−	1.07E+00	−	6.26E-03
		Decreased relative spleen weight in females	Organ weight changes	1.07E+01	1.07E+02	9.96E-02	1.27E+00
(11) VanBirgelen et al. (1995a)	Rat	Decreased absolute and relative thymus weight in females	Organ weight changes	−	1.35E+01	−	5.14E-01

Table D-7. Cross-species concordance of immune system effects (continued)

Study	Species	Specific Endpoint	Endpoint Category	Administered Dose (ng/kg-day)		Human-Equivalent Dose (HED)[a] (ng/kg-day)	
				NOAEL	LOAEL	NOAEL	LOAEL
(12) Vos et al. (1973)7	Guinea pig	Decreased delayed-type hypersensitivity response to tuberculin	Immunosuppressive effects	1.14E+00	5.71E+00	6.43E-03	3.22E-02
		Decreased relative thymus weight, relative cervical lymph node weight	Organ weight changes	5.71E+00	2.86E+01	3.22E-02	1.61E-01
		Cortical atrophy of the thymus, lymphopenia and thymic degeneration	Histopathological lesions	5.71E+00	2.86E+01	3.22E-02	1.61E-01
(13) White et al. (1986)	Mouse	Decreased serum complement activity in females	Altered immune system components	−	1.00E+01	−	2.77E-02 [b]
		Decreased component hemolytic activity and C3 levels in females	Altered immune system components	1.00E+02	5.00E+02	5.07E-01 [b]	3.27E+00 [b]

[a] HED for rat and mouse studies based on Emond rodent and human PBPK models described in Section 3.3.6.
[b] HED based on 1st order body burden model described in Section 3.2.4.4.

Table D-8. Cross-species concordance of neurological effects

Study	Species	Specific Endpoint	Endpoint Category	Administered Dose (ng/kg-day)		Human-Equivalent Dose (HED)[a] (ng/kg-day)	
				NOAEL	LOAEL	NOAEL	LOAEL
(1) Schantz et al. (1992)	Monkey	Altered social behavior	Neurobehavioral effects	−	1.20E-01	−	8.22E-03 [b]
(2) Hojo et al. (2002)	Rat	Food-reinforced operant behavior in pups	Neurobehavioral effects	−	2.00E+01	−	5.51E-02
(3) Kuchiiwa et al. (2002)	Mouse	Decreased number of serotonin-immunoreactive neurons in the raphe nuclei of males	Histopathological lesions	−	7.00E-01	−	2.75E-03
(4) Markowski et al. (2001)	Rat	Neurobehavioral effects in pups (running, lever press, wheel spinning)	Neurobehavioral effects	−	2.00E+01	−	5.15E-02
(5) Schantz et al. (1996)	Rat	Maze errors	Neurobehavioral effects	−	2.50E+01	−	1.71E-01
(6) Zareba et al. (2002)	Rat	Reduced cortical thickness and altered brain morphometry in males and females	Brain structural alterations	6.00E+01	1.80E+02	2.35E-01	9.54E-01

[a] HED for rat and mouse studies based on Emond rodent and human PBPK models described in Section 3.3.6.
[b] HED based on 1st order body burden model described in Section 3.2.4.4.
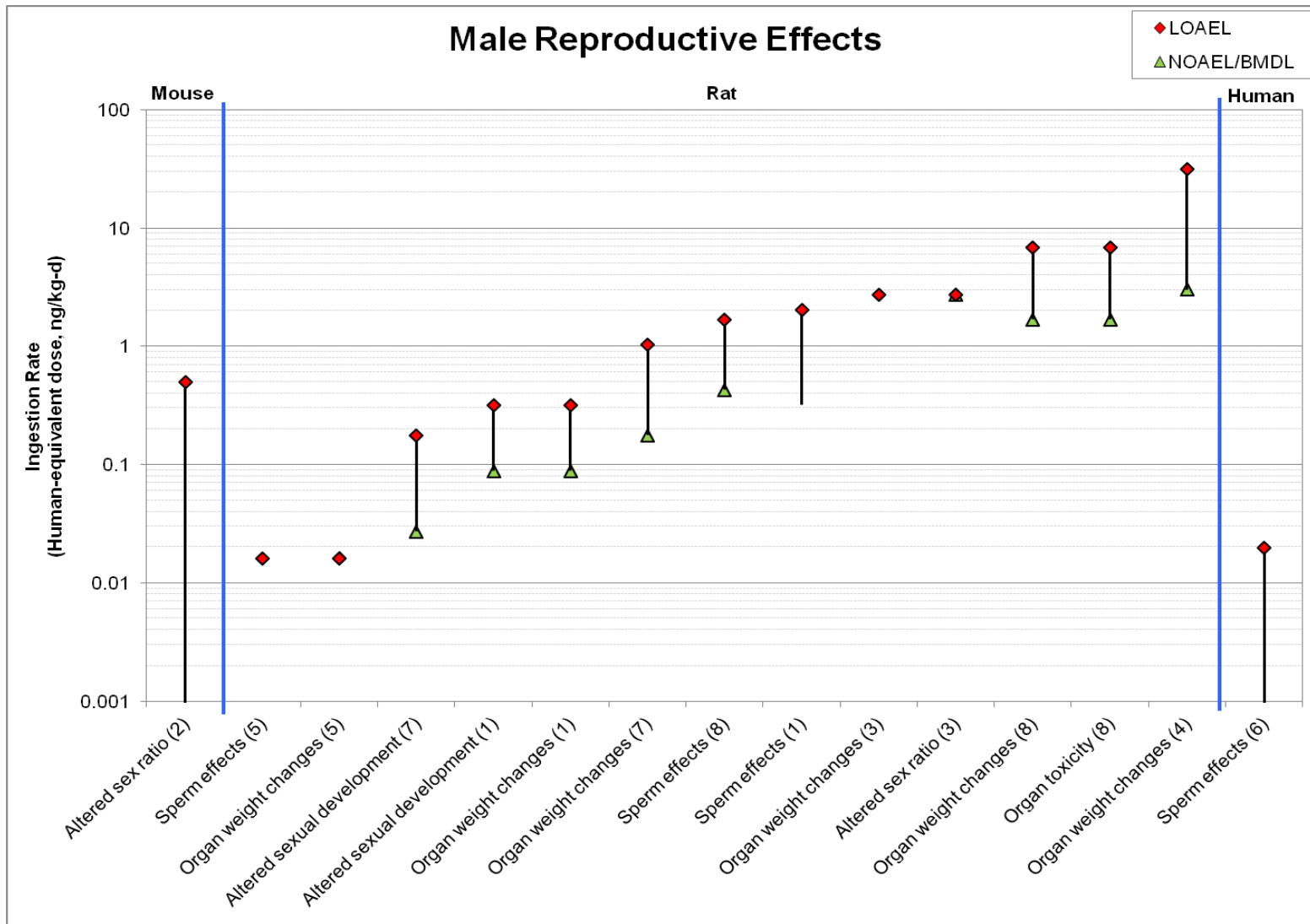
Figure D-1. Male reproductive effects across species.
The corresponding data are in Table D-3. The numbers following the effect designations indicate the corresponding study in Table D-3. Vertical solid black lines indicate the range of exposures tested below the LOAEL.
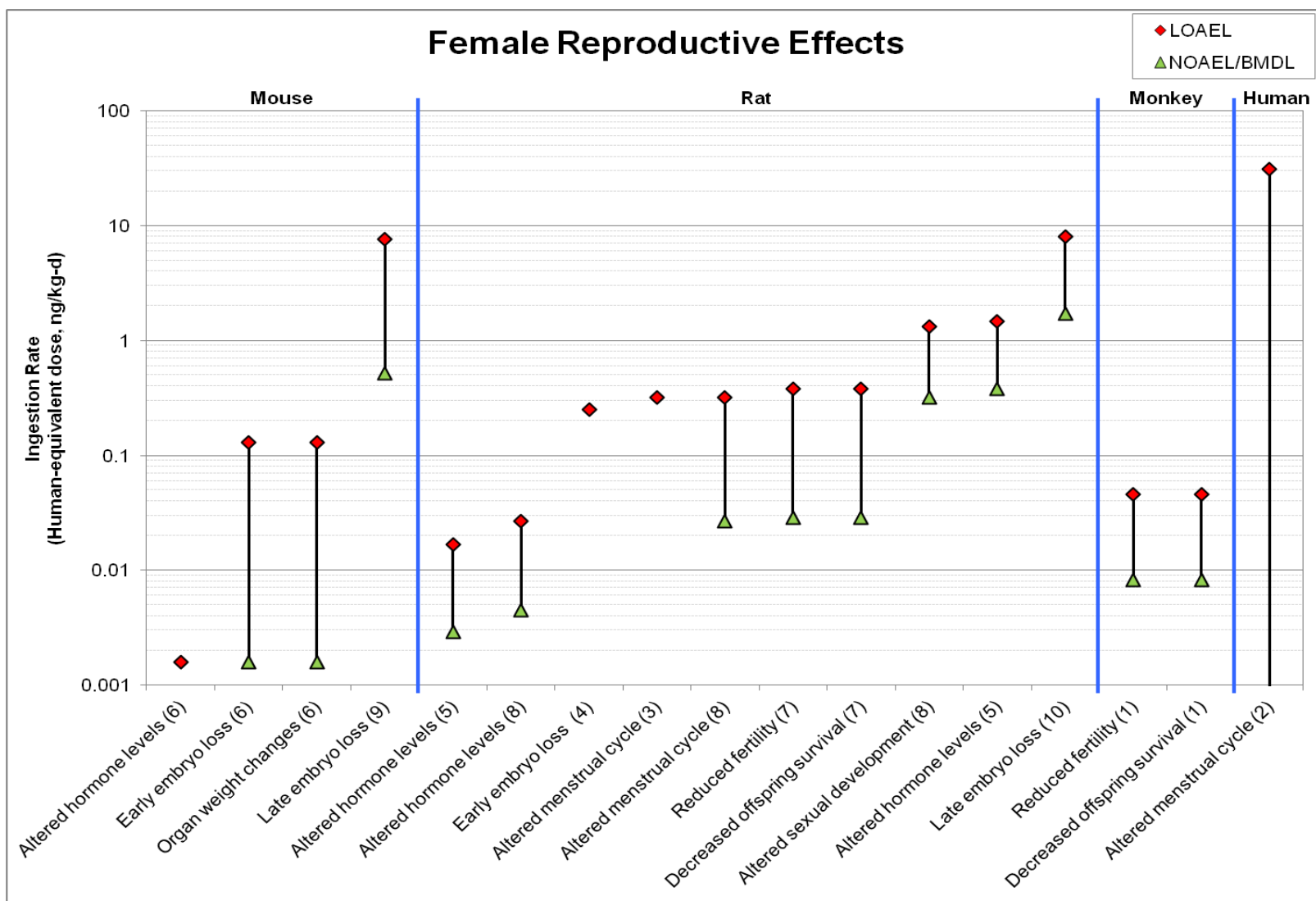
Figure D-2. Female reproductive effects across species.
The corresponding data are in Table D-4. The numbers following the effect designations indicate the corresponding study in Table D-4. Vertical solid black lines indicate the range of exposures tested below the LOAEL.
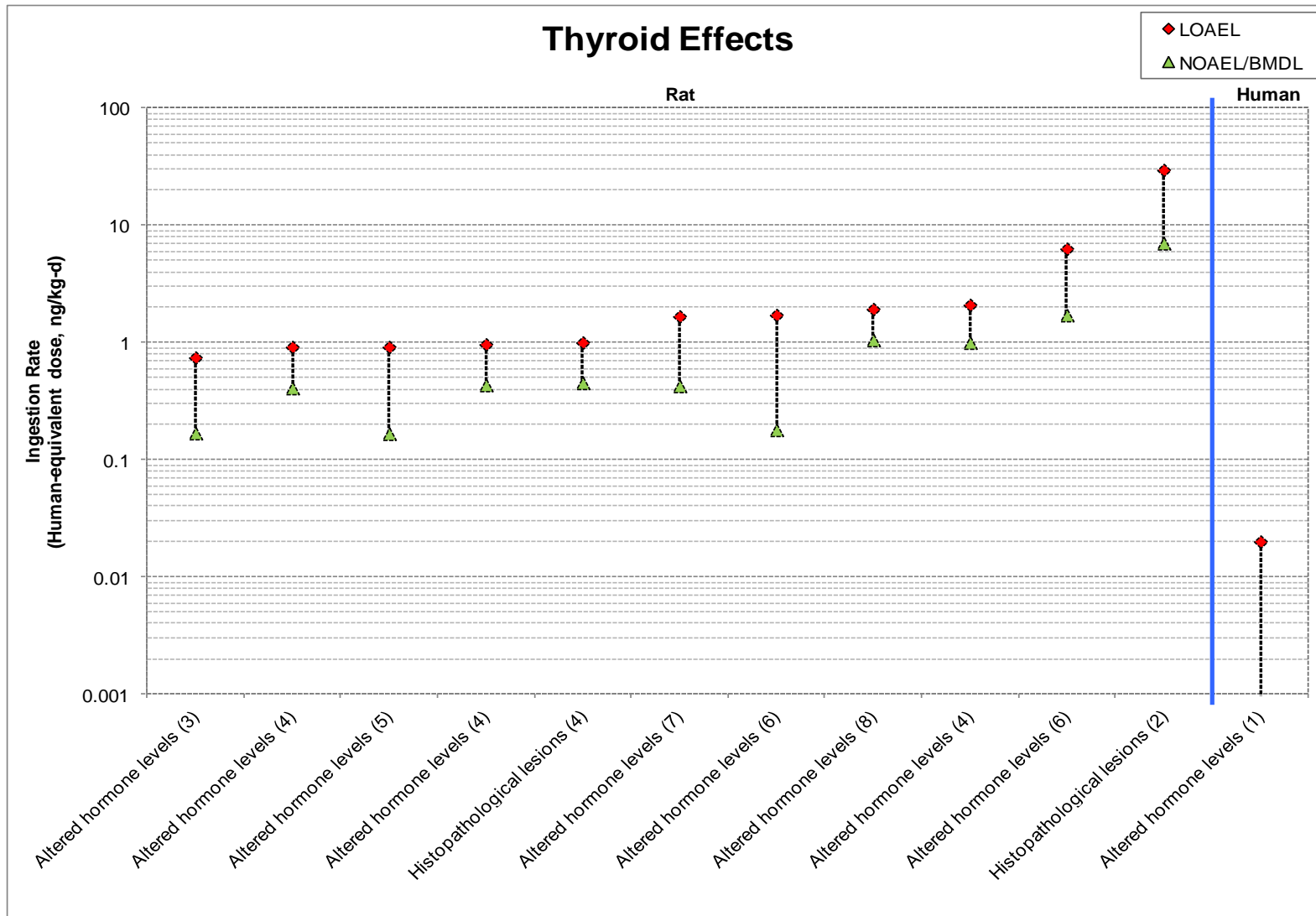
Figure D-3. Thyroid effects across species.
The corresponding data are in Table D-5. The numbers following the effect designations indicate the corresponding study in Table D-5. Vertical solid black lines indicate the range of exposures tested below the LOAEL.
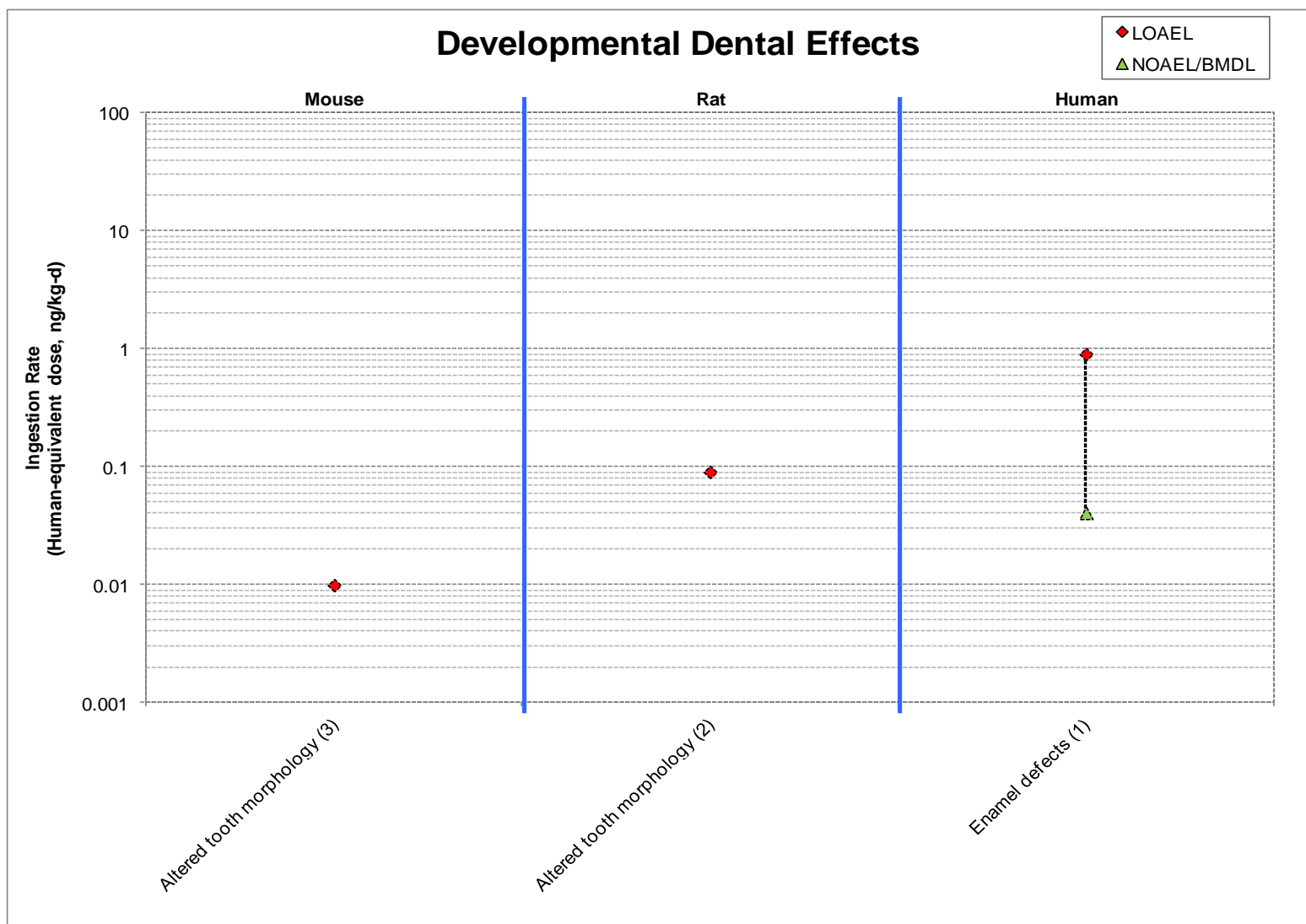
Figure D-4. Developmental dental effects across species.

The corresponding data are in Table D-6. The numbers following the effect designations indicate the corresponding study in Table D-6. Vertical solid black lines indicate the range of exposures tested below the LOAEL.
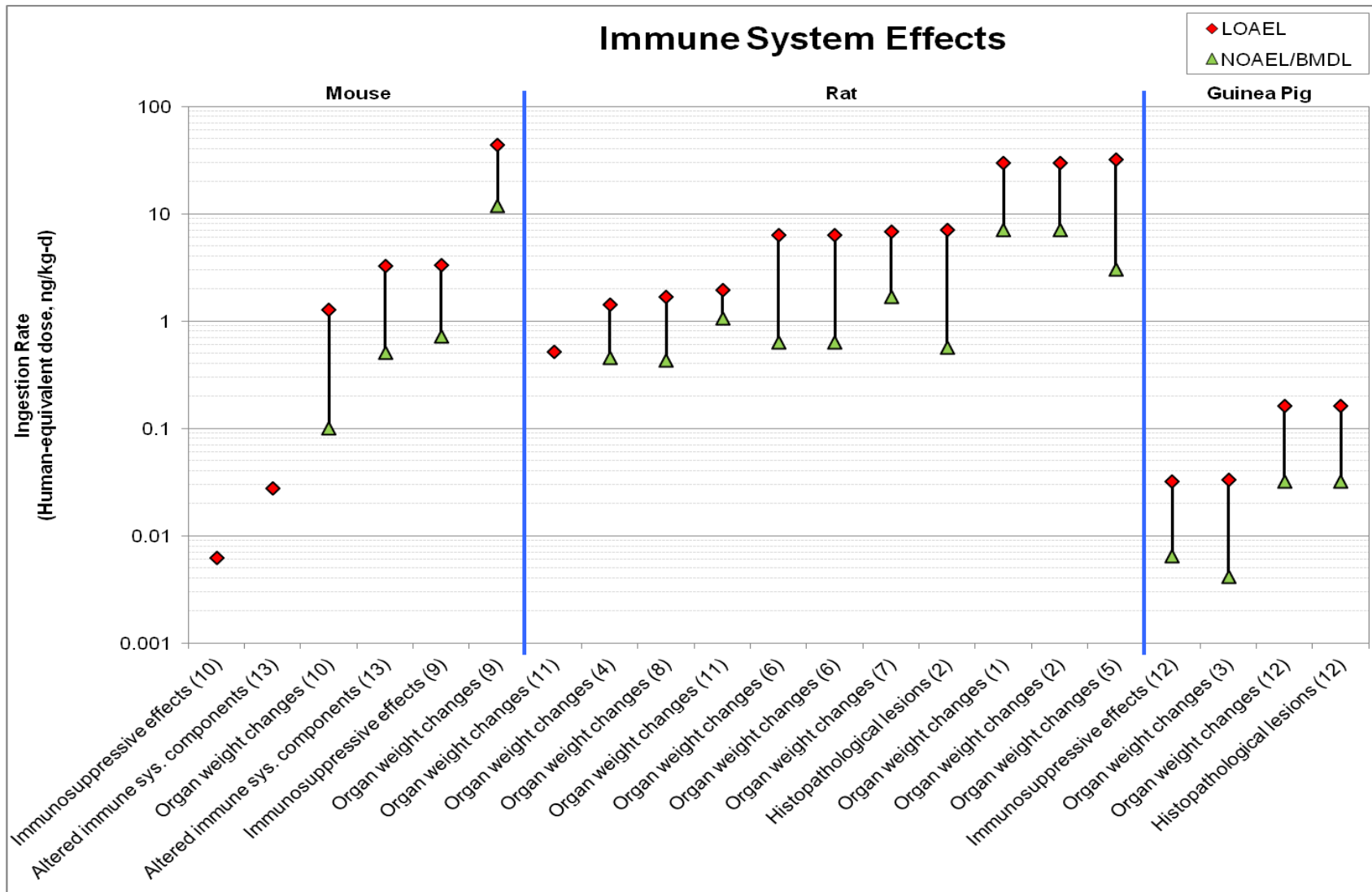
Figure D-5. Immune system effects across species.
The corresponding data are in Table D-7. The numbers following the effect designations indicate the corresponding study in Table D-7. Vertical solid black lines indicate the range of exposures tested below the LOAEL.
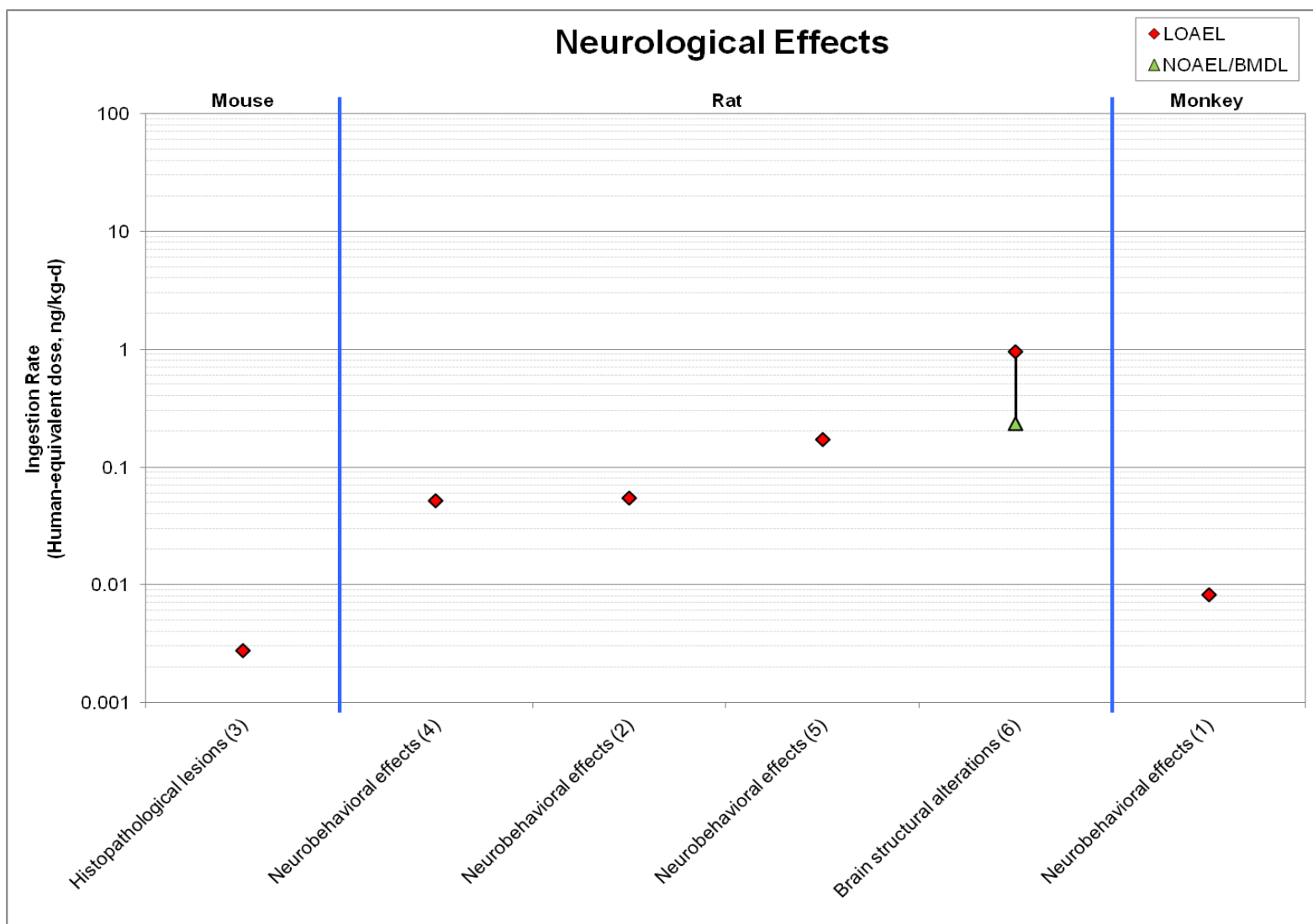
Figure D-6. Neurological effects across species.
The corresponding data are in Table D-8. The numbers following the effect designations indicate the corresponding study in Table D-8. Vertical solid black lines indicate the range of exposures tested below the LOAEL.

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APPENDIX E

Rodent Bioassay Kinetic Modeling

November 2011

NOTICE

THIS DOCUMENT IS AN AGENCY/INTERAGENCY REVIEW DRAFT. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

CONTENTS—APPENDIX E: Rodent Bioassay Kinetic Modeling

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APPENDIX E.   RODENT BIOASSAY KINETIC MODELING

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E.1. LITERATURE SEARCH STRATEGY AND RESULTS—IDENTIFYING RECENT PUBLICATIONS FOR UPDATING 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD) TOXICOKINETIC MODEL INPUT PARAMETERS

The purpose of this literature search was to identify recent publications that address the input parameters for the physiologically based pharmacokinetic (PBPK) models Aylward and colleagues (described in articles published in 2005 and 2009) and Emond and colleagues (described in articles published in 2004, 2005, and 2006). This literature search was part of the U.S. Environmental Protection Agency (EPA)'s preparation of a response to the National Academy of Sciences' review (*Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment*, (NAS, 2006) of EPA *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (U.S. EPA, 2003), herein called the "2003 Reassessment." English-only references from 2003 to May 2009 were searched using bibliographic data bases relevant to health effects and toxicology of TCDD. The search focused on toxicokinetic data that could be used to update the dynamic disposition of 2,3,7,8-TCDD in mice, rats, guinea pigs, monkeys, and humans.

In the primary search, EPA identified 775 distinct citations based on the literature search criteria described below. EPA also performed an independent supplemental search to avoid missing key studies. EPA identified 28 papers for further analysis that appeared on first review to report data to update the input parameters of the Aylward and Emond PBPK models; considerations for selection are described in Section E.1.3.

E.1.1.   Data Bases Searched

EPA used the following DIALOG bibliographic data bases in the primary search. Brief descriptions of the DIALOG data bases searched are provided in Section E.1.5.

1. File 6: NTIS
2. File 41: Pollution Abstracts
3. File 55: Biosis
4. File 153: IPA Toxicology
5. File 155: MedLine
6. File 156: ToxFile
7. File 157: Biosis Toxicology

8. File 159: CancerLit
9. File 336: RTECS

NTIS = National Technical Information Service; IPA = International Pharmaceutical Abstracts;
RTECS = Registry of Toxic Effects of Chemical Substances.

The PUBMED data base was used for the supplemental search.

E.1.2.   Literature Search Strategy and Approach

The primary search used a tiered key-word approach, as documented below. The

principal search term was the Chemical Abstract Service Registry Number (CASRN) or specific

chemical name, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin or 2,3,7,8-TCDD. The next tier of search

terms was species, and finally toxicokinetic keywords, as listed below. The period of the search

was 2003 through May 2009, and articles were limited to English language.

The supplemental PUBMED search was limited to the most recent five years (2004 to

present) and used four combinations of key words:

- TCDD + pharmacokinetic + humans,
- TCDD + toxicokinetic + humans,
- TCDD + pharmacokinetic + animals, and
- TCDD + toxicokinetic + animals.

E.1.2.1. *Chemical Search Terms—DIALOG Search*

- CASRN: 1746-01-6
- 2,3,7,8-tetrachlorodibenzo-*p*-dioxin
- 2,3,7,8-TCDD

E.1.2.2. *Primary Search Terms (Species)—DIALOG Search*

- Guinea pig(s)
- Human(s)
- Monkey(s)
- Mouse
- Mice
- Rodent(s)
- Rat(s)

1 **E.1.2.3.** *Secondary Search Terms (Toxicology)—DIALOG Search*

1. Absor*	16. Elimin*	32. Mechanism (1w)
2. ADME	17. Excret*	action
3. Aryl hydrocarbon	18. Epidemiolog*	33. Metabo*
receptor	19. Feces	34. Oral*
4. AhR	20. Feed*	35. P450
5. Bioavail*	21. First order kinetics	36. Partition coefficient
6. Biliar*	22. Food*	37. PBPK
7. Biotransform*	23. Gastro*	38. Pharmacodynamic*
8. Cytochrome	24. Gavage*	39. Pharmacokinetic*
9. CYP*	25. Half-life	40. Physiologically
10. CYP1A1	26. Induct*	based
11. CYP1A2	27. Ingest*	41. Pharmacokinetic
12. Diet, dietary, diets	28. In silico	42. Protein bind*
13. Disposit*	29. Kinetic*	43. Toxicokinetic*
14. Distrib*	30. Liver	44. Uri
15. Drink*	31. Lymph*	

2 * = truncated.
3 1w = terms are within one word of each other and in the order specified (see search term 32).
4
5 ADME = absorption, distribution, metabolism, elimination; AhR = aryl hydrocarbon receptor;
6 CYP = cytochrome P450.
7
8
9 **E.1.3. Citation Screening Procedures and Results**

10   Initial DIALOG searches resulted in a very large number of citation hits. Therefore,

11 some title and key word restrictions were applied iteratively to screen out less relevant citations

12 (e.g., requiring some search terms in title, requiring 2,3,7,8-TCDD rather than just TCDD).

13 Then, using reference management software, pooled information obtained from the various

14 DIALOG data bases was screened to remove duplicates. Citations then were numbered

15 sequentially (as a unique identifier). Information retrieved included the following (when

16 available): author(s), publication year, title, source document name, volume, and page numbers.

17   The DIALOG search and duplicate removal procedure produced 775 unique citations. In

18 the next step, all 775 citations were screened for potential applicability to updating parameters in

19 the Aylward and Emond PBPK models. Of these 775 citations, 26 were selected for more

20 detailed review to determine their potential applicability, and full publications were retrieved.

21 Two citations were added from the supplemental search, giving a total of 28 articles identified

22 for further review.

1   Bibliographic information for the 28 articles selected for full review is provided in the

2   reference list at the end of this section. Table E-1 summarizes the model input parameters

3   potentially addressed by the selected articles.

4   During 2003 to May 2009, the authors of the two kinetic models under consideration

5   published several articles. For the Emond model, which was first published in 2004 (Emond et

6   al., 2004), two subsequent papers have been published (Emond et al., 2006; 2005). The Aylward

7   model, which originated from the 1995 papers by Carrier et al. (1995a, b), was later updated by

8   the same group (Aylward et al., 2005a; 2005b). The major change implemented in the last two

9   papers was the description of a desorption process in the digestive tract. The transfer rate

10   described is slow, but for a low body burden of TCDD, this process remains significant. This

11   concept was reported in 2002 by Moser and McLachlan (2002). The major modifications

12   expected to update the Emond model are (1) consideration of the desorption process in the

13   gastrointestinal tract and (2) rearrangement of the elimination constant, which will have a

14   negligible impact on the simulation. These changes are motivated by plausible observations

15   reported in the literature.

16   Because of the body burden found in humans and the importance of selecting an

17   appropriate dose metric in human risk assessment, the physiological model is an important tool

18   for assessing the kinetics following exposure to TCDD (Kim et al., 2003). Based on the

19   literature identified in this search, the major contributions that should be reviewed with respect to

20   the Aylward and Emond kinetic models are not modes of action or pharmacokinetic mechanisms,

21   but rather information for verifying or improving the accuracy of some model parameters.

22   Pharmacokinetics typically refers to four distinct steps including absorption, distribution,

23   metabolism, and excretion. Physiologically-based models consider each step. In the model each

24   step is parameterized to reflect better predictions of the real observations. Occasionally,

25   reviewing these models is essential to determine if any key processes or parameters might be

26   described with better accuracy. This perspective underlies the review of the literature described

27   here. The review indicates TCDD disposition has become recognized as relatively significant

28   since the publication of the Emond and Aylward models. The literature that provides

29   information related to improving these models, however, is limited. For the benefit of this

30   exercise, EPA selected the literature that would likely contribute significantly to model response,

31   or to clarify or confirm different key issues driving the model results. Regarding the two TCDD

1   models, the two major issues that should be evaluated with respect to the recent literature

2   identified are the elimination profile and the induction of CYP1A2.

3   Reviewing the elimination variation in different species and testing variable elimination

4   with a data set appears to be appropriate. The literature reports that various factors might

5   influence elimination rate. Recent publications report the influence of diverse predictors such

6   age, body fat, or smoking habit on the elimination half-life (Milbrath et al., 2009; Kerger et al.,

7   2007; 2006). Determining whether using the Milbrath et al. information would help account for

8   intraspecies variability in elimination rate in the Emond and Aylward kinetic models would be

9   useful. In 2006, Emond et al. (2006) reviewed the influence of body fat mass and CYP1A2

10   induction on the pharmacokinetics of TCDD. These two factors appear to contribute

11   significantly to elimination and their influences seem to be driven by TCDD body burden.

12   Mullerova and Kopecky (2007) discussed the influence of adipose tissue and the "yo-yo" effects

13   on various diseases that might be influenced by persistent organic pollutant distribution. One

14   group explored the importance of variable elimination and compared these predictions to first-

15   order elimination using the Aylward and Emond models and supported these approaches for risk

16   assessment (Heinzl et al., 2007). Two groups of authors considered a one-compartment model to

17   derive the elimination half-life (Aylward et al., 2009; Nadal et al., 2008). Comparing the

18   half-life they obtained using this approach for a range of body burden to the variable elimination

19   half-life would be interesting.

20   The second important mechanism driving the distribution and elimination of TCDD is the

21   induction of CYP1A2, identified as the major ligand protein in liver (Diliberto et al., 1997). For

22   that process, authors suggested different aspects that should be investigated, including the

23   importance of the dose metrics in the target tissue and the inducible level of CYP1A2 (Wilkes et

24   al., 2008; Staskal et al., 2005). Other papers address the intraspecies variability of lethal potency

25   in mature species versus the developing fetus (Kransler et al., 2007; Korkalainen et al., 2004).

26   Still others point out pronounced differences among species (namely, guinea pigs, hamsters,

27   mice, and rats) (Bohonowych and Denison, 2007), as observed in studies of long-term effects of

28   low TCDD dose in liver and in studies comparing hepatic accumulation and clearance of TCDD

29   (Korenaga et al., 2007; Boverhoff et al., 2005). The interspecies variation of the binding affinity

30   constant of aryl hydrocarbon receptor (AhR) also has been reported (Connor and Aylward, 2006;

31   Nohara et al., 2006).

1   The articles identified in this literature review should be adequate to update the Aylward

2   and Emond models, which need to be evaluated according to the same structure of compartments

3   described in the literature by the two model authors.

4

5   **E.1.4.   References Selected for More Detailed Review for Updating the PBPK Models**

6   Aylward, LL; Brunet, RC; Carrier, G; et al. (2004). Concentration-dependent TCDD elimination
7   kinetics in humans: toxicokinetic modeling for moderately to highly exposed adults from Seveso,
8   Italy, and Vienna, Austria, and impact on dose estimates for the NIOSH cohort. J Expo Anal
9   Environ Epidemiol 15(1):51−65.

10   Aylward, LL; Brunet, RC; Starr, TB; et al. (2005). Exposure reconstruction for the
11   TCDD-exposed NIOSH cohort using a concentration- and age-dependent model of elimination.
12   Risk Anal 25(4):945−956.

13   Aylward, LL; Bodner, KM; Collins, JJ; et al. (2009). TCDD exposure estimation for workers at
14   a New Zealand 2,4,5-T manufacturing facility based on serum sampling data. J Expo Sci
15   Environ Epidemiol. doi: 10.1038/jes.2009.31.

16   Bohonowych, JE; Denison, MS. (2007). Persistent binding of ligands to the aryl hydrocarbon
17   receptor. Toxicol Sci 98(1):99-109.

18   Boverhof, DR; Burgoon, LD; Tashiro, C; et al. (2005). Temporal and dose-dependent hepatic
19   gene expression patterns in mice provide new insights into TCDD-mediated hepatotoxicity.
20   Toxicol Sci 85(2):1048−1063.

21   Connor, KT; Aylward, LL. (2006). Human response to dioxin: aryl hydrocarbon receptor (AhR)
22   molecular structure, function, and dose-response data for enzyme induction indicate an impaired
23   human AhR. J Toxicol Environ Health B 9(2):147−171.

24   Heinzl, H; Mittlback, M; Edler, L. (2007). On the translation of uncertainty from toxicokinetic
25   to toxicodynamic models - the TCDD example. Chemosphere 67(9):S365−S374.

26   Irigaray, P; Mejean, L; Laurent, F. (2005). Behaviour of dioxin in pig adipocytes. Food Chem
27   Toxicol 43(3):457−460.

28   Kerger, BD; Leung, HW; Scott, P; et al. (2006). Age- and concentration-dependent elimination
29   half-life of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in Seveso children. Environ Health Perspect
30   114(10):1596−1602.

31   Kerger, BD; Leung, HW; Scott, PK; et al. (2007). Refinements on the age-dependent half-life
32   model for estimating child body burdens of polychlorodibenzodioxins and dibenzofurans.
33   Chemosphere 67(9):S272−S278.

Kim, AH; Kohn, MC; Nyska, A; et al. (2003). Area under the curve as a dose metric for promotional responses following 2,3,7,8-tetrachlorodibenzo-*p*-dioxin exposure. Toxicol Appl Pharmacol 191(1):12−21.

Korenaga, T; Fukusato, T; Ohta, M; et al. (2007). Long-term effects of subcutaneously injected 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on the liver of rhesus monkeys. Chemosphere 67(9):S399−S404.

Korkalainen, M; Tuomisto, J; Pohjanvirta, R. (2004). Primary structure and inducibility by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) of aryl hydrocarbon receptor repressor in a TCDD-sensitive and a TCDD-resistant rat strain. Biochem Biophys Res Communications 315(1):123−131.

Kransler, KM; McGarrigle, BP; Olson, JR. (2007). Comparative developmental toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the hamster, rat and guinea pig. Toxicology 229(3):214−225.

Maruyama, W; Yoshida, K; Tanaka, T; et al. (2002). Determination of tissue-blood partition coefficients for a physiological model for humans, and estimation of dioxin concentration in tissues. Chemosphere 46(7):975−985.

Maruyama, W; Yoshida, K; Tanaka, T; et al. (2003). Simulation of dioxin accumulation in human tissues and analysis of reproductive risk. Chemosphere 53(4):301-313.

Maruyama, W; Aoki, Y. (2006). Estimated cancer risk of dioxins to humans using a bioassay and physiologically based pharmacokinetic model. Toxicol Appl Pharmacol 214(2):188−198.

Milbrath, MO; Wenger, Y; Chang, C-W; et al. (2009). Apparent Half-Lives of Dioxins, Furans, and Polychlorinated Biphenyls as a Function of Age, Body Fat, Smoking Status, and Breast-Feeding. Environ Health Perspect 117(3):417−425.

Moser, GA; McLachlan, MS. (2002). Modeling digestive tract absorption and desorption of lipophilic organic contaminants in humans. Environ Sci Technol 36(15):3318−25.

Mullerova, D; Kopecky, J. (2007). White adipose tissue: storage and effector site for environmental pollutants. Physiol Res 56(4):375−381.

Nadal, M; Perello, G; Schuhmacher, M; et al. (2008). Concentrations of PCDD/PCDFs in plasma of subjects living in the vicinity of a hazardous waste incinerator: Follow-up and modeling validation. Chemosphere 73(6):901−906.

Nohara, K; Ao, K; Miyamoto, Y; et al. (2006). Comparison of the 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)-induced CYP1A1 gene expression profile in lymphocytes from mice, rats, and humans: Most potent induction in humans. Toxicology 225(2-3):204−213.

Olsman, H; Engwall, M; Kammann, U; et al. (2007). Relative differences in aryl hydrocarbon receptor-mediated response for 18 polybrominated and mixed halogenated dibenzo-*p*-dioxins and -furans in cell lines from four different species. Environ Toxicol Chem 26(11):2448−2454.

Saghir, SA; Lebofsky, M; Pinson, DM; et al. (2005). Validation of Haber's Rule (doseX time=constant) in rats and mice for monochloroacetic acid and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin under conditions of kinetic steady state. Toxicology 215(1−2):48−56.

Schecter, A; Pavuk, M; Popke, O; et al. (2003). Dioxin, dibenzofuran, and coplanar PCB Levels in Laotian blood and milk from Agent Orange-sprayed and nonsprayed areas, 2001. J Toxicol Environ Health A 66(21):2067−2075.

Staskal, DF; Diliberto, JJ; Devito, MJ; et al. (2005). Inhibition of human and rat CYP1A2 by TCDD and dioxin-like chemicals. Toxicol Sci 84(2):225−231.

Toyoshiba, H; Walker, NJ; Bailer, AJ; et al. (2004). Evaluation of toxic equivalency factors for induction of cytochromes P450 CYP1A1 and CYP1A2 enzyme activity by dioxin-like compounds. Toxicol Appl Pharmacol 194(2):156−168.

Wilkes, JG; Hass, BS; Buzatu, DA; et al. (2008) Modeling and assaying dioxin-like biological effects for both dioxin-like and certain non-dioxin-like compounds. Toxicol Sci 102(1):187−195.

E.1.5.   Brief Descriptions of DIALOG Bibliographic Data Bases Searched

The NTIS database comprises summaries of U.S. government-sponsored research, development, and engineering, plus analyses prepared by federal agencies, their contractors, or grantees. It is the means through which unclassified, publicly available, unlimited distribution reports are made available for sale from 240 agencies. Additionally, some state and local government agencies contribute summaries of their reports to the database. NTIS also provides access to the results of government-sponsored research and development from countries outside the United States. Organizations that currently contribute to the NTIS database include but are not limited to the following: the Japan Ministry of International Trade and Industry; laboratories administered by the United Kingdom Department of Industry; the German Federal Ministry of Research and Technology; and the French National Center for Scientific Research.

Pollution Abstracts provides access to environmental information that combines information on scientific research and government policies in a single resource. Topics of growing concern are extensively covered from the standpoints of atmosphere, emissions, mathematical models, effects on people and animals, and environmental action in response to global pollution issues. This database also contains material from conference proceedings and hard-to-find summarized documents along with information from primary journals in the field of pollution.

1   BIOSIS Previews® contains citations from Biological Abstracts® (BA) and Biological

2   Abstracts/Reports, Reviews, and Meetings® (BA/RRM) (formerly BioResearch Index®), the

3   major publications of BIOSIS®. These publications constitute the major English-language

4   service providing comprehensive worldwide coverage of research in the biological and

5   biomedical sciences. Biological Abstracts includes approximately 350,000 accounts of original

6   research yearly from nearly 5,000 primary journal and monograph titles. BA/RRM includes an

7   additional 200,000+ citations a year from meeting abstracts, reviews, books, book chapters,

8   notes, letters, and selected reports.

9   IPA Toxicology provides focused toxicology information on all phases of the

10   development and use of drugs and on professional pharmaceutical practice. The scope of the

11   database ranges from the clinical and practical to the theoretical aspects of toxicology literature.

12   A unique feature of abstracts reporting clinical studies is the inclusion of the study design,

13   number of patients, dosage, dosage forms, and dosage schedule.

14   Medical Literature, Analysis, and Retrieval System Online (MEDLINE®), produced by

15   the U.S. National Library of Medicine (NLM), is NLM's premier bibliographic database. It

16   contains more than 15 million references to journal articles in life sciences with a concentration

17   on biomedicine. The broad coverage of the database includes basic biomedical research and the

18   clinical sciences since 1950, including nursing, dentistry, veterinary medicine, pharmacy, allied

19   health, and preclinical sciences. MEDLINE® also covers life sciences that are vital to

20   biomedical practitioners, researchers, and educators, including some aspects of biology,

21   environmental science, marine biology, and plant and animal science, as well as biophysics and

22   chemistry. MEDLINE® is indexed using NLM's controlled vocabulary, Medical Subject

23   Headings. Approximately 400,000 records are added per year, of which more than 76% are in

24   English. MEDLINE® contains AIDSLINE, HealthSTAR, Toxline, In Process (formerly known

25   as Pre-MEDLINE®), In Data Review, and POPLINE.

26   ToxFile covers the toxicological, pharmacological, biochemical, and physiological

27   effects of drugs and other chemicals. Adverse drug reactions, chemically induced diseases,

28   carcinogenesis, mutagenesis, teratogenesis, environmental pollution, waste disposal, radiation,

29   and food contamination are typical areas of coverage. The databases Environmental Mutagen

30   Information Center, Developmental and Reproductive Toxicology, and Toxic Substances

31   Control Act Test Submissions are included in ToxFile. It is not clearly stated whether the

1   Chemical Carcinogenesis Research Information System, Hazardous Substances Data Bank, or

2   Genetic Toxicology Data Bank are included in ToxFile. Consequently, a separate, online search

3   was conducted to ensure that these databases were searched.

4   BIOSIS® Toxicology contains citations from BA and BA/RRM (formerly BioResearch

5   Index®), the major publications of BIOSIS®, that focus on toxicology and related topics.

6   Records are drawn from journal articles, conference papers, monographs and book chapters,

7   notes, letters, and reports, as well as original research. U.S. patent records are also included.

8   CANCERLIT® is produced by the International Cancer Research DataBank Branch of

9   the U.S. National Cancer Institute. The database consists of bibliographic records referencing

10   cancer research publications dating from 1963 to 2002. Most records contain abstracts, and all

11   records contain citation information and additional descriptive fields such as document type and

12   language. Beginning with the June 1983 CANCERLIT update, records from the MEDLINE®

13   database dealing with cancer topics have been added to CANCERLIT.

14   The RTECS® is a comprehensive database of basic toxicity information for over 150,000

15   chemical substances including prescription and nonprescription drugs, food additives, pesticides,

16   fungicides, herbicides, solvents, diluents, chemical wastes, reaction products of chemical waste,

17   and substances used in both industrial and household situations. Reports of the toxic effects of

18   each compound are cited. In addition to toxic effects and general toxicology reviews, data on

19   skin and/or eye irritation, mutation, reproductive consequences and tumorigenicity are provided.

20   Federal standards and regulations, National Institute for Occupational Safety and Health

21   (NIOSH) recommended exposure limits and information on the activities of EPA, NIOSH,

22   National Toxicology Program (NTP), and Occupational Safety and Health Administration

23   regarding the substance are also included. The toxic effects are linked to literature citations from

24   both published and unpublished governmental reports, and published articles from the scientific

25   literature. The database corresponds to the print version of the RTECS®, formerly known as the

26   Toxic Substances List, which was started in 1971. Originally prepared by the NIOSH, the

27   RTECS® database is now produced and distributed by Symyx Technologies, Inc.

28

E.2. TOXICOKINETIC MODELING CODE ([Emond et al., 2005](#))

E.2.1. Human Standard Model

E.2.1.1. *Model Code*

PROGRAM: 'Three Compartment PBPK Model for TCDD in Human: Standard Model (Nongestation)'

```
INITIAL  !INITIALIZATION OF PARAMETERS

    !SIMULATION PARAMETERS ====
CONSTANT EXP_TIME_ON       =     0.         ! TIME AT WHICH EXPOSURE BEGINS
(HOUR)
CONSTANT EXP_TIME_OFF      =     6.132e5  ! TIME AT WHICH EXPOSURE ENDS
(HOUR)
CONSTANT DAY_CYCLE         =     24.0     ! NUMBER OF HOURS BETWEEN DOSES
(HOUR)
CONSTANT BCK_TIME_ON       =     6.132e5    ! TIME AT WHICH BACKGROUND
EXPOSURE BEGINS (HOUR)
CONSTANT BCK_TIME_OFF      =     6.132e5    ! TIME AT WHICH BACKGROUND
EXPOSURE ENDS (HOUR)

    !EXPOSURE DOSES
CONSTANT  MSTOTBCKGR       =     0.0   ! ORAL BACKGROUND EXPOSURE DOSE
(NG/KG)
CONSTANT  MSTOT            =     1.0E-7     ! ORAL EXPOSURE DOSE (NG/KG)
CONSTANT  DOSEIV           =     0.0          ! INJECTED DOSE (NG/KG)
CONSTANT  MW               =     322.0     ! MOLECULAR WEIGHT (G/MOL)
 MSTOT_NM = MSTOT/MW                         ! CONVERTS THE DOSE TO NMOL/KG
 MSTOT_NMBCKGR = MSTOTBCKGR/MW  !CONVERTS THE BACKGROUND DOSE TO NMOL/KG
   DOSEIV_NM = DOSEIV/MW                      ! CONVERTS THE INJECTED DOSE TO
NMOL/KG

    !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
INDICATED BELOW) ====
CONSTANT CFLLI0        =    0.0                  ! LIVER  (NMOL/L)

    !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
BELOW) ===
CONSTANT LIBMAX        =    0.35            ! LIVER  (NMOL/L)

    ! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
===
CONSTANT KDLI          =    0.1                ! LIVER (AhR) (NMOL/L) WANG
ET AL.. 1997
CONSTANT KDLI2         =    40.0           ! LIVER (1A2) (NMOL/L) EMOND ET
AL. 2004

    !EXCRETION AND ABSORPTION CONSTANTS
CONSTANT KST           =    0.01              ! GASTRIC RATE CONSTANT (HR-
1), EMOND ET AL., 2005
CONSTANT KABS          =    0.06           ! INTESTINAL ABSORPTION CONSTANT
(HR-1), EMOND ET AL. 2005

    !ELIMINATION CONSTANTS
```

```
CONSTANT CLURI            =        4.17D-8        ! URINARY CLEARANCE (L/HR), EMOND
ET AL., 2005
CONSTANT KELV             =        1.1e-3            ! INTERSPECIES VARIABLE
ELIMINATION CONSTANT (1/HOUR)

        !CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
CONSTANT A                =        0.7                          ! LYMPHATIC FRACTION,
WANG ET AL. (1997)

        !PARTITION COEFFICIENTS
CONSTANT PF               =        1.0e2                  ! ADIPOSE TISSUE/BLOOD,
WANG ET AL. 1997
CONSTANT PRE              =        1.5                    ! REST OF THE BODY/BLOOD,
WANG ET AL. 1997
CONSTANT PLI              =        6.0                      ! LIVER/BLOOD, WANG ET
AL. 1997

        !PARAMETERS FOR INDUCTION OF CYP1A2
CONSTANT IND_ACTIVE       =        1.0              ! INCLUDE INDUCTION? (1 = YES,
0 = NO)
CONSTANT CYP1A2_1OUTZ     =    1.6e3        ! DEGRADATION CONCENTRATION CONSTANT
OF 1A2 (NMOL/L)
CONSTANT CYP1A2_1A1       =        1.6e3        ! BASAL CONCENTRATION OF 1A1
(NMOL/L)
CONSTANT CYP1A2_1EC50     =        1.3e2        ! DISSOCIATION CONSTANT TCDD-CYP1A2
(NMOL/L)
CONSTANT CYP1A2_1A2       =        1.6e3        ! BASAL CONCENTRATION OF 1A2
(NMOL/L)
CONSTANT CYP1A2_1KOUT     =        0.1          ! FIRST ORDER RATE OF DEGRADATION
(H-1)
CONSTANT CYP1A2_1TAU      =        0.25         ! HOLDING TIME (H)
CONSTANT CYP1A2_1EMAX     =        9.3e3    ! MAXIMUM INDUCTION OVER BASAL EFFECT
(UNITLESS)
CONSTANT HILL             =        0.6          !HILL CONSTANT; COOPERATIVE LIGAND
BINDING EFFECT CONSTANT (UNITLESS)
        ! DIFFUSIONAL PERMEABILITY FRACTION
CONSTANT PAFF             =        0.12                    ! ADIPOSE (UNITLESS)
CONSTANT PAREF            =        0.03                    ! REST OF BODY (UNITLESS)
CONSTANT PALIF            =        0.35                    ! LIVER (UNITLESS)

        !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT  =========
CONSTANT QFF              =        0.05        ! ADIPOSE TISSUE BLOOD FLOW FRACTION
(UNITLESS), KRISHNAN 2008
CONSTANT QLIF             =        0.26        ! LIVER (UNITLESS), KRISHNAN 2008

        !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL
COMPARTMENT VOLUME =========
CONSTANT WFB0             =        0.050    ! ADIPOSE TISSUE, WANG ET AL. 1997
CONSTANT WREB0            =        0.030    ! REST OF THE BODY, WANG ET AL. 1997
CONSTANT WLIB0            =        0.266    ! LIVER, WANG ET AL. 1997

        !EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
        !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG         =        0.0          ! TIME ELAPSED BEFORE EXPOSURE
BEGINS (WEEK)
CONSTANT WEEK_PERIOD      =        168.0     ! NUMBER OF HOURS IN THE WEEK
(HOURS)
```

```
1    CONSTANT WEEK_FINISH   =        168.0       ! TIME EXPOSURE ENDS (HOURS)
2        !NUMBER OF EXPOSURES PER MONTH
3    CONSTANT MONTH_LAG     =        0.0         ! TIME ELAPSED BEFORE EXPOSURE
4    BEGINS (MONTH)
5
6        !SET FOR BACKGROUND EXPOSURE===========
7        !TIME CONSTANT FOR BACKGROUND EXPOSURE===========
8    CONSTANT Day_LAG_BG      =     0.0          ! TIME ELAPSED BEFORE EXPOSURE
9    BEGINS (HOUR)
10   CONSTANT Day_PERIOD_BG   =     24.0         ! LENGTH OF EXPOSURE (HOUR)
11
12       !TIME CONSTANT FOR WEEKLY EXPOSURE
13   CONSTANT WEEK_LAG_BG     =     0.0          ! TIME ELAPSED BEFORE BACKGROUND
14   EXPOSURE BEGINS (WEEK)
15   CONSTANT WEEK_PERIOD_BG  =     168.0        !  NUMBER OF HOURS IN THE WEEK
16   (HOURS)
17   CONSTANT WEEK_FINISH_BG  =     168.0        ! TIME EXPOSURE ENDS (HOURS)
18
19       ! CONSTANT USED IN CARDIAC OUTPUT EQUATION
20   CONSTANT QCC            =     15.36                     ! (L/KG-H),  EMOND ET AL.
21   2004
22
23       ! COMPARTMENT TOTAL LIPID FRACTION
24       !Data from Emonds Thesis 2001
25   CONSTANT F_TOTLIP       =     0.8000                ! ADIPOSE TISSUE
26   (UNITLESS)
27   CONSTANT B_TOTLIP       =     0.0057               ! BLOOD (UNITLESS)
28   CONSTANT RE_TOTLIP      =     0.0190               ! REST OF THE BODY
29   (UNITLESS)
30   CONSTANT LI_TOTLIP      =     0.0670                ! LIVER (UNITLESS)
31   CONSTANT MEANLIPID      =     974.0
32
33   END  ! END OF THE INITIAL SECTION
34
35
36   DYNAMIC ! DYNAMIC SIMULATION SECTION
37      !
38   ALGORITHM  IALG          =       2         ! GEAR METHOD
39   CINTERVAL  CINT          =       10.0       ! COMMUNICATION INTERVAL
40   MAXTERVAL  MAXT          =     1.0e+10    !MAXIMUM INTERVAL CALCULATION
41   MINTERVAL  MINT          =     1.0E-10    !MINIMUM INTERVAL CALCULATION
42   VARIABLE   T             =       0.0
43   CONSTANT   TIMELIMIT     =     1.752e5   !SIMULATION LIMIT TIME (HOUR)
44   CONSTANT    Y0            =       0.0        ! AGE (YEARS) AT BEGINNING OF
45   SIMULATION
46   CONSTANT   GROWON        =       1.0    ! INCLUDE BODY WEIGHT AND HEIGHT
47   GROWTH? (1 = YES, 0 = NO)
48     CINTXY  = CINT
49     PFUNC   = CINT
50
51     DAY=T/24.0                                  ! TIME IN DAYS
52     WEEK =T/168.0                               ! TIME IN WEEKS
53     MONTH =T/730.0                             ! TIME IN MONTHS
54     YEAR=Y0+T/8760.0                          ! TIME IN YEARS
55     GYR =Y0 + growon*T/8760.0        ! TIME FOR USE IN GROWTH EQUATION (YEARS)
56
57   DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS
```

```
     ! CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
       ! NUMBER OF EXPOSURES PER DAY
 DAY_LAG     = EXP_TIME_ON        ! TIME ELAPSED BEFORE EXPOSURE BEGINS
 (HOURS)
 DAY_PERIOD  = DAY_CYCLE          ! EXPOSURE PERIOD (HOURS)
 DAY_FINISH  = CINTXY             ! LENGTH OF EXPOSURE (HOURS)
 MONTH_PERIOD = TIMELIMIT         ! EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH = EXP_TIME_OFF      ! LENGTH OF EXPOSURE (MONTHS)


       ! NUMBER OF EXPOSURES PER DAY AND MONTH
 DAY_FINISH_BG   = CINTXY
 MONTH_LAG_BG    = BCK_TIME_ON    !TIME ELAPSED BEFORE BACKGROUND EXPOSURE
 BEGINS (MONTHS)
 MONTH_PERIOD_BG = TIMELIMIT      ! BACKGROUND EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH_BG = BCK_TIME_OFF   ! LENGTH OF BACKGROUND EXPOSURE (MONTHS)

 B = 1.0-A ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER

      !HUMAN BODY WEIGHT GROWTH EQUATION========
       ! POLYNOMIAL REGRESSION EXPRESSION WRITTEN
!APRIL 10 2008, OPTIMIZED WITH DATA OF PELEKIS ET AL. 2001
! POLYNOMIAL REGRESSION EXPRESSION WRITTEN WITH
!HUH AND BOLCH 2003 FOR BMI CALCULATION

  ! BODY WEIGHT CALCULATION
  WT0 = (0.0006*GYR**3 - 0.0912*GYR**2 + 4.32*GYR + 3.652)! BODY WEIGHT IN KG

   ! BODY MASS INDEX CALCULATION
     BH =  -2D-5*GYR**4+4.2D-3*GYR**3.0-0.315*GYR**2.0+9.7465*GYR+72.098

   !HEIGHT EQUATION FORMULATED FOR USE FROM 0 TO 70 YEARS
     BHM= (BH/100.0)                 !HUMAN HEIGHT IN METERS (BHM)
     HBMI= WT0/(BHM**2.0) ! HUMAN BODY MASS INDEX (BMI)

    ! ADIPOSE TISSUE FRACTION
    WT0GR= WT0*1.0e3     ! BODY WEIGHT IN GRAMS
    WF0= -6.36D-20*WT0GR**4.0 +1.12D-14*WT0GR**3.0 -5.8D-10*WT0GR**2.0 +1.2D-
 5*WT0GR+5.91D-2

    ! LIVER,VOLUME FRACTION
    ! APPROACH BASED ON LUECKE (2007)
    WLI0= (3.59D-2 -(4.76D-7*WT0GR)+(8.50D-12*WT0GR**2.0)-(5.45D-
 17*WT0GR**3.0))

 WRE0 = (0.91 -(WLIB0*WLI0+WFB0*WF0+WLI0+WF0))/(1.0+WREB0)
                                    !REST OF THE BODY FRACTION; UPDATED FOR
 EPA ASSESSMENT
 QREF = 1.0-(QFF+QLIF)              !REST OF BODY BLOOD FLOW
 QTTQF = QFF+QREF+QLIF              ! SUM MUST EQUAL 1

    !COMPARTMENT VOLUME (L OR KG) =========
 WF  =  WF0  * WT0                 ! ADIPOSE
 WRE =  WRE0 * WT0                 ! REST OF THE BODY
 WLI =  WLI0 * WT0                 ! LIVER
 WB=0.075*WT0                       ! BLOOD
```

```
     !COMPARTMENT TISSUE BLOOD (L OR KG) =========
 WFB  =   WFB0  * WF                        ! ADIPOSE
 WREB =   WREB0 * WRE                       ! REST OF THE BODY
 WLIB =   WLIB0 * WLI                       ! LIVER
    !CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT
QC= QCC*(WT0**0.75)                         ! [L BLOOD/HOUR]

QF  = QFF*QC                                ! ADIPOSE TISSUE BLOOD FLOW RATE
[L/HR]
QLI = QLIF*QC                               ! LIVER TISSUE BLOOD FLOW RATE [L/HR]
QRE = QREF*QC                               !REST OF THE BODY BLOOD FLOW RATE [L/HR]

QTTQ = QF+QRE+QLI                  ! TOTAL FLOW RATE [L/HR]

    !PERMEABILITY ORGAN FLOW [L/HR]=======
PAF  = PAFF*QF                              ! ADIPOSE
PARE = PAREF*QRE                            ! REST OF THE BODY
PALI = PALIF*QLI                            ! LIVER TISSUE

   ! ABSORPTION SECTION
   ! INTRAVENOUS
 IV         =     DOSEIV_NM * WT0           !AMOUNT IN NMOL
 MSTTBCKGR  =     MSTOT_NMBCKGR *WT0        !AMOUNT IN NMOL
 MSTT       =     MSTOT_NM * WT0            !AMOUNT IN NMOL

      !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIOS
DAY_EXPOSURE_BG   = PULSE(DAY_LAG_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
WEEK_EXPOSURE_BG  = PULSE(WEEK_LAG_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
MONTH_EXPOSURE_BG = PULSE(MONTH_LAG_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
MSTTFR_BG = MSTTBCKGR/CINT

CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG


    ! CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
    ABSMSTT_GB= MSTTFR_BG
ELSE
    ABSMSTT_GB = 0.0
END IF


    !REPETITIVE ORAL MAIN EXPOSURE SCENARIO
DAY_EXPOSURE   = PULSE(DAY_LAG,DAY_PERIOD,DAY_FINISH)
WEEK_EXPOSURE  = PULSE(WEEK_LAG,WEEK_PERIOD,WEEK_FINISH)
MONTH_EXPOSURE = PULSE(MONTH_LAG,MONTH_PERIOD,MONTH_FINISH)

MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
MSTTFR=MSTT/CINT

    !CONDITIONAL ORAL EXPOSURE
IF (MSTTCH.EQ.MSTT) THEN
   ABSMSTT= MSTTFR
```

```
1    ELSE
2       ABSMSTT = 0.
3    END IF
4
5     CYCLETOT=INTEG(CYCLE,0.0)
6
7          ! MASS Balance CHANGE IN THE LUMEN
8    RMSTT= -(KST+KABS)*MST+ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
9     MST = INTEG(RMSTT,0.)                      !AMOUNT REMAINING IN GI TRACT
10   (NMOL)
11
12         ! ABSORPTION IN LYMPH CIRCULATION
13   LYRMLUM = KABS*MST*A
14    LYMLUM = INTEG(LYRMLUM,0.0)
15
16         ! ABSORPTION IN PORTAL CIRCULATION
17   LIRMLUM = KABS*MST*B
18     LIMLUM = INTEG(LIRMLUM,0.0)
19
20
21         !IV ABSORTPION SCENARIO ---------
22    IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
23    EXPIV= IVR * (1.0-STEP(PFUNC))
24    IVDOSE = integ(EXPIV,0.0)
25
26         !SYSTEMIC BLOOD COMPARTMENT
27         ! MODIFICATION OCT 8 2009
28   CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM)/(QC+CLURI) !
29    CA = CB                                      !CONCENTRATION (NMOL/L)
30
31      !CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM-RAURI)/QC !
32      ! CA = CB                                ! CONCENTRATION (NMOL/L)
33
34          !URINARY EXCRETION BY KIDNEY
35          ! MODIFICATION OCT 8 2009
36   RAURI = CLURI *CB
37     AURI = INTEG(RAURI,0.0)
38
39
40          !CONCENTRATION UNIT
41
42     CBSNGKGLIADJ = CB*MW/(0.55*B_TOTLIP) !serum concentration in lipid adjust
43   (PG/G LIPID=PPT)
44         CBPPT = CBSNGKGLIADJ
45     CBNGKG = CB*MW
46
47   CBpptRH = CB*MW*10000/(0.55*MEANLIPID) !SERUM CONCENTRATION IN LIPID ADJUST
48   (PG/G LIPID=PPT)
49
50      AUC_CBSNGKGLIADJ=INTEG(CBSNGKGLIADJ,0.0)
51
52         !ADIPOSE TISSUE COMPARTMENT
53   RAFB= QF*(CA-CFB)-PAF*(CFB-CF/PF)        !(NMOL/HR)
54    AFB = INTEG(RAFB,0.0)                   !(NMOL)
55    CFB = AFB/WFB                           !(NMOL/KG)
56         !TISSUE SUBCOMPARTMENT
57   RAF = PAF*(CFB-CF/PF)                    !(NMOL/HR)
```

```
1    AF = INTEG(RAF,0.0)                              !(NMOL)
2    CF  = AF/WF                                      !(NMOL/KG)
3
4         !POST SIMULATION UNIT CONVERSION
5    CFTOTAL = (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION NMOL/L
6    CFNGKG =CFTOTAL*MW
7
8         !REST OF THE BODY COMPARTMENT========
9    RAREB= QRE*(CA-CREB)-PARE*(CREB-CRE/PRE) !(NMOL/HR)
10    AREB = INTEG(RAREB,0.0)                   !(NMOL)
11    CREB = AREB/WREB                          !(NMOL/KG)
12         !TISSUE SUBCOMPARTMENT
13   RARE = PARE*(CREB-CRE/PRE)               !(NMOL/HR)
14    ARE = INTEG(RARE,0.0)                  !(NMOL)
15    CRE  = ARE/WRE                           !(NMOL/KG)
16
17         !POST SIMULATION UNIT CONVERSION
18   CRETOTAL = (ARE + AREB)/(WRE + WREB) ! TOTAL CONCENTRATION IN NMOL/L
19
20         !LIVER COMPARTMENT
21         !TISSUE BLOOD SUBCOMPARTMENT
22   RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM          !(NMOL/HR)
23     ALIB = INTEG(RALIB,0.0)                                 !(NMOL)
24    CLIB = ALIB/WLIB
25         !TISSUE SUBCOMPARTMENT
26    RALI =  PALI*(CLIB-CFLLIR)-REXCLI                        !(NMOL/HR)
27     ALI = INTEG(RALI,0.0)                   !(NMOL)
28     CLI  = ALI/WLI                 !(NMOL/KG)
29
30
31         !FREE TCDD IN LIVER
32         ! MODIFICATION OCTOBER 8 2009
33   CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR)) &
34         +((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR)*IND_ACTIVE)))-CFLLI,CFLLI0) !
35   CONCENTRATION OF FREE TCDD IN LIVER
36      CFLLIR=DIM(CFLLI,0.0)
37
38   !MODIFIED FROM:
39       !PARAMETER (LIVER_1RMN = 1.0E-30)
40       ! CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &          !
41   +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR &
42       !          +LIVER_1RMN)*IND_ACTIVE)))-CFLLI,CFLLI0)
43       !     CFLLIR=DIM(CFLLI,0.0)
44
45
46   CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR) !CONC OF TCDD BOUDN TO AhR
47
48   !CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !CONC BIND
49
50         !POST SIMULATION UNIT CONVERSION
51   CLITOTAL = (ALI + ALIB)/(WLI + WLIB)        ! TOTAL CONCENTRATION IN NMOL/L
52   rec_occ_AHR= 100.0*CFLLIR/(KDLI+CFLLIR+1.0)   ! PERCENT  BOUND TO AhR
53   OCCUPANCY
54   PROT_occ_1A2= 100.0*CFLLIR/(KDLI2+CFLLIR)     ! PERCENT  BOUND TO 1A2
55   OCCUPANCY
56   CLINGKG= CLITOTAL*MW                         ![NG TCDD/KG]
57   CBNDLINGKG = CBNDLI*MW
```

```
 1
 2        !FRACTION INCREASE OF INDUCTION OF CYP1A2
 3    fold_ind=CYP1A2_1OUT/CYP1A2_1A2
 4    VARIATIONOFAC =(CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2
 5
 6        !VARIABLE ELIMINATION BASED ON THE CYP1A2
 7    KBILE_LI_T = Kelv*VARIATIONOFAC!
 8
 9     REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT RATE OF BILLIARY EXCRETION
10    OF DIOXIN
11        EXCLI = INTEG(REXCLI,0.0)   !TOTAL AMOUNT OF DIOXIN EXCRETED
12
13        !CHEMICAL IN CYP450 (1A2) COMPARTMENT
14        !PARAMETER FOR INDUCTION OF CYP1A2
15
16    CYP1A2_1KINP = CYP1A2_1KOUT*CYP1A2_1OUTZ ! BASAL RATE OF CYP1A2 PRODUCTION
17    SET EQUAL TO BASAL RATE OF DEGRDATION AT STEADY STATE
18
19        ! MODIFICATION OCTOBER 8 2009
20    CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-30)**HILL
21    &
22        /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
23         - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ) ! LEVELS OF CYP1A2
24    ! MODEIFIED FROM:
25    !PARAMETER (CYP1A2_1RMN = 1e-30)
26    !CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1 + CYP1A2_1EMAX *(CBNDLI &
27    !      +CYP1A2_1RMN)**HILL/(CYP1A2_1EC50 + (CBNDLI + CYP1A2_1RMN)**HILL) &
28    !      +CYP1A2_1RMN) - CYP1A2_1KOUT*CYP1A2_1&
29    !       OUT, CYP1A2_1OUTZ)
30
31    ! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
32    SIMULATIONS)
33    CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
34        CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)
35     CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
36        CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)
37
38        !CHECK MASS BALANCE
39      BDOSE= LYMLUM+LIMLUM+IVDOSE
40      BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI
41         BDIFF = BDOSE-BMASSE
42        ! BODY BURDEN IN TERMS OF CONCENTRATION (NG/KG)
43      BBNGKG = (AFB+AF+AREB+ARE+ALIB+ALI)*MW/WT0          !
44
45        !COMMAND END OF THE SIMULATION
46    TERMT (T.GE. TIMELIMIT, 'Time limit has been reached.')
47
48    END   ! END OF THE DERIVATIVE SECTION
49    END   ! END OF THE DYTNAMIC SECTION
50    END   ! END OF THE PROGRAM
51
```

52   **E.2.1.2. *Input File***

```
53    output @clear
54    prepare @clear year T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG  CBNDLINGKG CBNGKG
55    % PARAMETERS FOR SIMULATION
```

```
1    CINT = 1 %0.5
2    EXP_TIME_ON  =   0.       % TIME AT WHICH EXPOSURE BEGINS (HOUR)
3    EXP_TIME_OFF = 613200    %324120     % HOUR/YEAR !TIME AT WHICH EXPOSURE
4    ENDS (HOUR)
5    DAY_CYCLE   = 24        % NUMBER OF HOURS BETWEEN DOSES (HOUR)
6    BCK_TIME_ON  = 613200    %324120     % TIME AT WHICH BACKGROUND EXPOSURE
7    BEGINS (HOUR)
8    BCK_TIME_OFF = 613200    %324120     % TIME AT WHICH BACKGROUND EXPOSURE
9    ENDS (HOUR)
10   TIMELIMIT   = 613200    %324120      %324120    % SIMULATION TIME LIMIT
11   (HOUR)
12   MSTOTBCKGR  =   0.       % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)
13
14   % oral dose oral dose oral dose
15   MSTOT       = 9.97339283634997E-07     % ORAL DAILY EXPOSURE DOSE (NG/KG)
16   DOSEIV     =   0          %NG/KG
17   % oral dose oral dose oral dose
18
19   MEANLIPID   = 730        %
20   IND_ACTIVE= 1          % INDUCTION INCLUDED? (1=YES, 0=NO)
21
```

22 **E.2.2.   Human Gestational Model**

23 **E.2.2.1.** *Model Code*

24 PROGRAM: 'Three Compartment PBPK Model for TCDD in Human (Gestation)'

```
25
26   INITIAL  !
27
28       !SIMULATION PARAMETERS
29   CONSTANT PARA_ZERO          = 1e-30
30   CONSTANT EXP_TIME_ON     = 0.0        !TIME AT WHICH EXPOSURE BEGINS (HOURS)
31   CONSTANT EXP_TIME_OFF    = 530.0       !TIME AT WHICH EXPOSURE ENDS (HOURS)
32   CONSTANT DAY_CYCLE       =  24.0       !NUMBER OF HOURS BETWEEN DOSES (HOURS)
33   CONSTANT BCK_TIME_ON     = 0.0        !TIME AT WHICH BACKGROUND EXPOSURE
34   BEGINS (HOURS)
35   CONSTANT BCK_TIME_OFF    = 0.0        !TIME AT WHICH BACKGROUND EXPOSURE ENDS
36   (HOURS)
37   CONSTANT TRANSTIME_ON    = 0.0         !CONTROL TRANSFER FROM MOTHER TO FETUS
38   AT 9 WEEKS OR 1512 HOURS OF GESTATION
39
40       ! INTRAVENOUS SEQUENCY
41   CONSTANT IV_LAG        = 0.0
42   CONSTANT IV_PERIOD       = 0.0
43
44       !PREGNANCY PARAMETER
45   CONSTANT CONCEPTION_T        = 0.0       !TIME OF CONCEPTION  (HOUR)
46   CONSTANT PFETUS         = 4.0       !PARTITION COEFFICIENT
47   CONSTANT CLPLA_FET      = 1.0e-3    !CLEARANCE TRANSFER FOR MOTHER TO FETUS
48   (L/HR)
49
50       !CONSTANT EXPOSURE CONTROL
51       !ACUTE, SUBCHRONIC, CHRONIC EXPOSURE =====
52       !OR BACKGROUND EXPOSURE (IN THIS CASE 3 TIMES A DAY)===
53   CONSTANT MSTOTBCKGR      = 0.0       ! ORAL BACKGROUND EXPOSURE DOSE (NG/KG)
54   CONSTANT MSTOT          = 0.0       ! ORAL EXPOSURE DOSE (NG/KG)
```

```
      !ORAL ABSORPTION
      ! MSTT= MSTOT/1000 *WT0 *1/322*1000 !AMOUNT IN NMOL
   MSTOT_NM = MSTOT/MW                  !CONVERTS THE DOSE TO NMOL/KG

      !INTRAVENOUS ABSORPTION
CONSTANT  DOSEIV         = 0.0        ! INJECTED DOSE (NG/KG)
   DOSEIV_NM = DOSEIV/MW                ! CONVERTS THE INJECTED DOSE TO NMOL/KG
CONSTANT DOSEIVLATE = 0.0               !INJECTED DOSE LATE (NG/KG)
   DOSEIVNMlate = DOSEIVLATE/MW      !AMOUNT IN NMOL/G

      !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
INDICATED BELOW)====
CONSTANT CFLLI0           =  0.0     !LIVER    (NMOL/L)
CONSTANT CFLPLA0          =  0.0     !PLACENTA (NMOL/L)

      !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
BELOW) (NMOL/L) ===
CONSTANT LIBMAX           = 0.35    ! LIVER  (NMOL/L)
CONSTANT PLABMAX          = 0.2       !TEMPORARY PARAMETER

      !PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
(NMOL/ML)===
CONSTANT KDLI             = 0.1     !LIVER (AhR) (NMOL/L), WANG ET AL. 1997
CONSTANT KDLI2            = 40.0      !LIVER (1A2) (NMOL/L), EMOND ET AL.
2004
CONSTANT KDPLA            = 0.1       !ASSUME IDENTICAL TO KDLI (AhR)

      !EXCRETION AND ABSORPTION CONSTANT
CONSTANT KST              = 0.01     ! GASTRIC RATE CONSTANT (HR-1), EMOND ET
AL. 2005
CONSTANT KABS             = 0.06     ! INTESTINAL ABSORPTION CONSTANT (HR-1),
EMOND ET AL. (2005)

      !INTERSPECIES ELIMINATION CONSTANT
      !TEST ELIMINATION VARIABLE, EMOND ET AL. 2005
CONSTANT KELV           =     1.1e-3 !4.0D-3         ! INTERSPECIES VARIABLE
ELIMINATION CONSTANT (1/HOUR)

      ! ELIMINATION CONSTANTS
CONSTANT CLURI           =  4.17e-8 ! URINARY CLEARANCE (L/HR), EMOND ET AL.
2005

      ! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
CONSTANT A               = 0.7         ! LYMPHATIC FRACTION, WANG ET AL. 1997

      !PARTITION COEFFICIENTS
CONSTANT PF              = 1.0e2     ! ADIPOSE TISSUE/BLOOD, WANG ET AL. 1997
CONSTANT PRE             = 1.5      ! REST OF THE BODY/BLOOD, WANG ET AL.
1997
CONSTANT PLI             = 6.0       ! LIVER/BLOOD, WANG ET AL. 1997
CONSTANT PPLA            = 1.5       ! TEMPORARY PARAMETER NOT CONFIGURED,
WANG ET AL. 1997

      !PARAMETER FOR INDUCTION OF CYP 1A2, WANG ET AL. 1997
CONSTANT IND_ACTIVE       = 1.0          ! INCLUDE INDUCTION? (1 = YES, 0 = NO)
```

```
1   CONSTANT CYP1A2_1OUTZ   = 1.6e3    ! DEGRADATION CONCENTRATION CONSTANT OF
2   1A2 (NMOL/L)
3   CONSTANT CYP1A2_1A1      = 1.6e3    ! BASAL CONCENTRATION OF 1A1 (NMOL/L)
4   CONSTANT CYP1A2_1EC50    = 1.3e2    ! DISSOCIATION CONSTANT TCDD-CYP1A2
5   (NMOL/L)
6   CONSTANT CYP1A2_1A2      = 1.6e3     !BASAL CONCENTRATION OF 1A2 (NMOL/L)
7   CONSTANT CYP1A2_1KOUT    = 0.1      ! FIRST ORDER RATE OF DEGRADATION (H-1)
8   CONSTANT CYP1A2_1TAU     = 0.25     !HOLDING TIME (H)
9   CONSTANT CYP1A2_1EMAX    = 9.3e3     ! MAXIMUM INDUCTION OVER BASAL EFFECT
10  (UNITLESS)
11  CONSTANT HILL            = 0.6      !HILL CONSTANT; COOPERATIVE LIGAND
12  BINDING EFFECT CONSTANT (UNITLESS)
13
14     !DIFFUSIONAL PERMEABILITY FRACTION, WANG ET AL (1997)
15  CONSTANT PAFF            = 0.12     ! ADIPOSE (UNITLESS)
16  CONSTANT PAREF           = 0.03     ! REST OF THE BODY (UNITLESS)
17  CONSTANT PALIF           = 0.35     ! LIVER (UNITLESS)
18  CONSTANT PAPLAF          = 0.3      ! OPTIMIZED PARAMETER
19
20  !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT, KRISHNAN 2007
21  CONSTANT QFF             = 0.05     ! ADIPOSE TISSUE BLOOD FLOW FRACTION
22  (UNITLESS), KRISHNAN 2008
23  CONSTANT QLIF            = 0.26     ! LIVER (UNITLESS), KRISHNAN 2008
24
25  !===FRACTION OF TISSUE BLOOD WEIGHT Wang et al . (1997)
26  CONSTANT WFB0            = 0.050    !ADIPOSE TISSUE, WANG ET AL. 1997
27  CONSTANT WREB0           = 0.030    !REST OF THE BODY, WANG ET AL. 1997
28  CONSTANT WLIB0           = 0.266    !LIVER, WANG ET AL. 1997
29  CONSTANT WPLAB0          = 0.500    !ASSUME HIGHLY VASCULARIZED
30
31  ! EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
32  ! NUMBER OF EXPOSURES PER WEEK
33  CONSTANT WEEK_LAG        = 0.0      !TIME ELAPSED BEFORE EXPOSURE BEGINS
34  (WEEK)
35  CONSTANT WEEK_PERIOD     = 168.0     ! NUMBER OF HOURS IN THE WEEK (HOURS)
36  CONSTANT WEEK_FINISH     = 168.0     ! TIME EXPOSURE ENDS (HOURS)
37
38  ! NUMBER OF EXPOSURES PER MONTH
39  CONSTANT MONTH_LAG       = 0.0       !TIME ELAPSED BEFORE EXPOSURE BEGINS
40  (MONTHS)
41
42  !======= CONSTANT FOR BACKGROUND EXPOSURE==========
43  CONSTANT Day_LAG_BG      = 0.0       ! TIME ELAPSED BEFORE EXPOSURE BEGINS
44  (HOURS)
45  CONSTANT Day_PERIOD_BG   = 24.0      !LENGTH OF EXPOSURE (HOURS)
46
47  ! NUMBER OF EXPOSURES PER WEEK
48  CONSTANT WEEK_LAG_BG     = 0.0       !TIME ELAPSED BEFORE BACKGROUND EXPOSURE
49  BEGINS (WEEK)
50  CONSTANT WEEK_PERIOD_BG  = 168.0     ! NUMBER OF HOURS IN THE WEEK (HOURS)
51  CONSTANT WEEK_FINISH_BG  = 168.0      !TIME EXPOSURE ENDS (HOURS)
52
53
54  ! CONSTANT USED IN CARDIAC OUTPUT EQUATION
55  CONSTANT QCC             = 15.36     ![L/KG-H], EMOND ET AL. 2004
56
57  ! COMPARTMENT LIPID EXPRESSED AS THE FRACTION OF TOTAL LIPID
```

```
1    !Data from Emonds Thesis 2001
2    CONSTANT F_TOTLIP        =     0.8000        ! ADIPOSE TISSUE (UNITLESS)
3    CONSTANT B_TOTLIP        =     0.0057        ! BLOOD (UNITLESS)
4    CONSTANT RE_TOTLIP       =     0.0190        ! REST OF THE BODY (UNITLESS)
5    CONSTANT LI_TOTLIP       =     0.0670        ! LIVER (UNITLESS)
6    CONSTANT PLA_TOTLIP      =     0.019         ! PLACENTA (UNITLESS)
7    CONSTANT FETUS_TOTLIP    =     0.019       ! FETUS (UNITLESS)
8
9    CONSTANT MEANLIPID       =     974
10
11   END  ! END OF THE INITIAL SECTION
12
13   DYNAMIC ! DYNAMIC SIMULATION SECTION
14
15   ALGORITHM  IALG          =             2       ! GEAR METHOD
16   CINTERVAL  CINT          =           0.1       ! COMMUNICATION INTERVAL
17   MAXTERVAL  MAXT          =        1.0e+10      ! MAXIMUM CALCULATION INTERVAL
18   MINTERVAL  MINT          =        1.0E-10      ! MINIMUM CALCULATION INTERVAL
19   VARIABLE   T             =           0.0
20   CONSTANT   TIMELIMIT     =           100        !SIMULATION LIMIT TIME (HOUR)
21   CONSTANT      Y0         =           0.0       ! AGE (YEARS) AT BEGINNING OF
22   SIMULATION
23   CONSTANT   GROWON        =           1.0      ! INCLUDE BODY WEIGHT AND HEIGHT
24   GROWTH? (1=YES, 0=NO)
25
26    CINTXY  = CINT
27    PFUNC   = CINT
28
29      !TIME TRANSFORMATION
30    DAY= T/24.0
31    WEEK  =T/168.0
32    YEAR=Y0+T/8760.0                              ! TIME IN YEARS
33     GYR =Y0 + growon*T/8760.0                    ! TIME FOR USE IN GROWTH
34   EQUATION
35
36   DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS
37
38   !====== CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
39   ! NUMBER OF EXPOSURES PER DAY
40
41    DAY_LAG        = EXP_TIME_ON    ! TIME ELAPSED BEFORE EXPOSURE BEGINS
42   (HOURS)
43    DAY_PERIOD      = DAY_CYCLE      ! EXPOSURE PERIOD (HOURS)
44    DAY_FINISH      = CINTXY         ! LENGTH OF EXPOSURE (HOURS)
45    MONTH_PERIOD    = TIMELIMIT      ! EXPOSURE PERIOD (MONTHS)
46    MONTH_FINISH    = EXP_TIME_OFF   ! LENGTH OF EXPOSURE (MONTHS)
47
48
49   ! NUMBER OF EXPOSURES PER DAY AND MONTH
50    DAY_FINISH_BG   = CINTXY
51    MONTH_LAG_BG    = BCK_TIME_ON    !TIME ELAPSED BEFORE BACKGROUND EXPOSURE
52   BEGINS (MONTHS)
53    MONTH_PERIOD_BG = TIMELIMIT      !BACKGROUND EXPOSURE PERIOD (MONTHS)
54    MONTH_FINISH_BG = BCK_TIME_OFF   !LENGTH OF BACKGROUND EXPOSURE (MONTHS)
55
56   ! INTRAVENOUS LATE
57    IV_FINISH = CINTXY
```

```
1    B = 1-A ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER
2
3    ! MOTHER BODY WEIGHT GROWTH EQUATION
4    ! MODIFICATION TO ADAPT THIS MODEL AT HUMAN MODEL
5    ! BECAUSE LINEAR DESCRIPTION IS NOT GOOD ENOUGH FOR MOTHER GROWTH
6    ! MOTHER BODY WEIGHT GROWTH
7    ! HUMAN BODY WEIGHT (0 TO 45 YEARS)
8    ! POLYNOMIAL REGRESSION EXPRESSION WRITTEN
9    !APRIL 10 2008, OPTIMIZED WITH DATA OF PELEKIS ET AL. 2001
10   ! POLYNOMIAL REGRESSION EXPRESSION WRITTEN WITH
11   !HUH AND BOLCH 2003 FOR BMI CALCULATION
12
13   ! BODY WEIGHT CALCULATION.  UNIT IN KG FOR GESTATIONAL PORTION
14
15       WT0 = (0.0006*GYR**3 - 0.0912*GYR**2 + 4.32*GYR + 3.652)
16
17    !BODY MASS INDEX CALCULATION
18
19       BH =  -2D-5*GYR**4+4.2D-3*GYR**3.0-0.315*GYR**2.0+9.7465*GYR+72.098
20   !HEIGHT EQUATION FORMULATED FOR USE FROM 0 TO 70 YEARS
21       BHM= (BH/100.0)!HUMAN HEIGHT IN METER (BHM)
22       HBMI= WT0/(BHM**2.0) ! HUMAN BODY MASS INDEX (BMI)
23
24
25   !MODIFICATION IN KG
26   RTESTGEST= T-CONCEPTION_T ! TIME FOR FETAL GROWTH
27   TESTGEST=DIM(RTESTGEST,0.0)
28   ! GROWTH OF FETAL TISSUE
29   GESTATTION_FE=((4d-15*TESTGEST**4 -3d-11*TESTGEST**3 +1d-7*TESTGEST**2 -8d-
30   5*TESTGEST +0.0608))
31      WTFER= DIM(GESTATTION_FE,0.0) ! FETAL COMPARTMENT WEIGHT
32    WTFE= WTFER
33
34   !///////////////////////////////////////////////////////////////////
35   ! FAT GROWTH EXPRESSION LINEAR DURING PREGNANCY
36   ! FROM O'FLAHERTY_1992
37   !///////////////////////////////////////////////////////////////////
38
39   WT0GR= WT0*1.0e3    ! MOTHER BODY WEIGHT IN G
40
41   WF0 =(-6.36D-20*WT0GR**4.0 +1.12D-14*WT0GR**3.0 &
42            -5.8D-10*WT0GR**2.0+1.2D-5*WT0GR+5.91D-2) ! MOTHER FAT COMPARTMENT
43   GROWTH
44
45   !///////////////////////////////////////////////////////////////////
46   ! WPLA PLACENTA GROWTH EXPRESSION, SINGLE EXPONENTIAL WITH OFFSET
47   ! FROM O'FLAHERTY_1992  ! FOR EACH PUP
48   !///////////////////////////////////////////////////////////////////
49   !SAME EQUATION THEN THE FORST MODEL. BODY WEIGHT KEPT IN G
50   !A CORRECTION FOR THE BODY WEIGHT (WTO(KG)*1000 = WTOGR)
51
52   WPLA0N_HUMAN= (850*exp(-9.434*(exp(-5.23d-4*(TESTGEST)))))
53    WPLA0R = WPLA0N_HUMAN/WT0GR
54    WPLA0W = DIM(WPLA0R,0.0) ! PLACENTA WEIGHT
55      WPLA0=WPLA0W
56
57   !///////////////////////////////////////////////////////////////////
```

```
1   ! QPLA PLACENTA GROWTH EXPRESSION, DOUBLE EXPONENTIAL WITH OFFSET
2   ! FROM O'FLAHERTY_1992
3   !///////////////////////////////////////////////////////////////
4
5   QPLAF_HUMAN= SWITCH_trans*((1d-10*TESTGEST**3.0 -5D-7*TESTGEST**2.0
6   +0.0017*TESTGEST+1.1937)/QC)
7     GEST_QPLAF=DIM(QPLAF_HUMAN,0.0) ! PLACENTA BLOOD FLOW RATE
8     QPLAF =GEST_QPLAF
9
10  ! LIVER,VOLUME FRACTION  (HUMAN 0 TO 70 YEARS)
11  ! APPROACH BASED ON LUECKE (2007)
12   WLI0= (3.59D-2 -(4.76D-7*WT0GR)+(8.50D-12*WT0GR**2.0)-(5.45D-17*WT0GR**3.0))
13  ! LIVER VOLUME IN GROWING HUMAN
14
15  ! VARIABILITY OF REST OF THE BODY DEPENDS ON OTHER ORGAN
16   WRE0 = (0.91-(WLIB0*WLI0+WFB0*WF0+ WPLAB0*WPLA0 + WLI0 + WF0 +
17  WPLA0))/(1+WREB0)
18   QREF = 1-(QFF+QLIF+QPLAF)              !REST BODY BLOOD FLOW (ML/HR)
19   QTTQF = QFF+QREF+QLIF+QPLAF            ! SUM MUST EQUAL 1
20
21  ! COMPARTMENT TISSUE BLOOD VOLUME (L) =========
22   WF  =  WF0  * WT0                     ! ADIPOSE TISSUE
23   WRE =  WRE0 * WT0                     ! REST OF THE BODY
24   WLI =  WLI0 * WT0                     ! LIVER
25   WPLA=  WPLA0* WT0                     ! PLACENTA
26
27  ! COMPARTMENT TISSUE VOLUME (L) =========
28   WFB  =  WFB0  * WF                    ! ADIPOSE TISSUE
29   WREB =  WREB0 * WRE                   ! REST OF THE BODY
30   WLIB =  WLIB0 * WLI                   ! LIVER
31   WPLAB = WPLAB0* WPLA                  ! PLACANTA
32
33  ! TOTAL VOLUME OF COMPARTMENT (L)======
34  WFT =   WF                            ! TOTAL ADIPOSE TISSUE
35  WRET =  WRE                           ! TOTAL REST OF THE BODY
36  WLIT =  WLI                           ! TOTAL LIVER TISSUE
37  WPLAT=  WPLAB                         ! TOTAL PLACENTA TISSUE
38
39  ! CONSTANT USED IN CARDIAC OUTPUT EQUATION
40
41  ! UNIT CHANGED ON JULY 14 2009  (L/HR)
42  QC= QCC*(WT0)**0.75
43
44  QF  = QFF*QC                          ! ADIPOSE TISSUE BLOOD FLOW RATE (L/HR)
45  QLI = QLIF*QC                         ! LIVER TISSUE BLOOD FLOW RATE (L/HR)
46  QRE = QREF*QC                         !REST OF THE BODY BLOOD FLOW RATE (L/HR)
47  QPLA = QPLAF*QC                       !PLACENTA TISSUE BLOOD FLOW RATE (L/HR)
48  QTTQ = QF+QRE+QLI+QPLA     !TOTAL FLOW RATE (L/HR)
49
50  ! ========= DIFFUSIONAL PERMEABILITY FACTORS FRACTION ORGAN FLOW =========
51  PAF  = PAFF*QF                        ! ADIPOSE TISSUE BLOOD FLOW RATE (L/HR)
52  PARE = PAREF*QRE                      ! REST OF THE BODY BLOOD FLOW RATE
53  (L/HR)
54  PALI = PALIF*QLI                      ! LIVER TISSUE BLOOD FLOW RATE (L/HR)
55  PAPLA = PAPLAF*QPLA                   ! PLACENTA TISSUE BLOOD FLOW RATE (L/HR)
56
57  !***********************************
```

```
1    ! ABSORPTION SECTION
2    ! ORAL
3    ! INTRAPERITONEAL
4    ! SUBCUTANEOUS
5    ! INTRAVENOUS
6    !************************************
7
8    !BACKGROUND EXPOSURE
9    !EXPOSURE FOR STEADY STATE CONSIDERATION
10   !REPETITIVE EXPOSURE SCENARIO
11
12   MSTOT_NMBCKGR = MSTOTBCKGR/322        !AMOUNT IN NMOL/G
13   MSTTBCKGR =MSTOT_NMBCKGR *WT0
14
15   DAY_EXPOSURE_BG   = PULSE(DAY_LAG_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
16   WEEK_EXPOSURE_BG  = PULSE(WEEK_LAG_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
17   MONTH_EXPOSURE_BG = PULSE(MONTH_LAG_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)
18
19   MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
20   MSTTFR_BG = MSTTBCKGR/CINT
21
22   CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG
23
24   ! CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
25
26   IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
27       ABSMSTT_GB= MSTTFR_BG
28   ELSE
29       ABSMSTT_GB = 0.0
30   END IF
31
32   CYCLETOTBG=INTEG(CYCLE_BG,0.0)
33
34   !************************************
35   !MULTIROUTE  EXPOSURE
36   !REPETITIVE EXPOSURE SCENARIO
37   !************************************
38   MSTT= MSTOT_NM * WT0                     !AMOUNT IN NMOL
39   DAY_EXPOSURE   = PULSE(DAY_LAG,DAY_PERIOD,DAY_FINISH)
40   WEEK_EXPOSURE  = PULSE(WEEK_LAG,WEEK_PERIOD,WEEK_FINISH)
41   MONTH_EXPOSURE = PULSE(MONTH_LAG,MONTH_PERIOD,MONTH_FINISH)
42
43   MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
44
45   MSTTFR = MSTT/CINT
46
47   CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
48
49   SUMEXPEVENT= INTEG (CYCLE,0.0) !NUMBER OF CYCLES GENERATED DURING SIMULATION
50
51   ! CONDITIONAL ORAL EXPOSURE
52   IF (MSTTCH.EQ.MSTT) THEN
53      ABSMSTT= MSTTFR
54   ELSE
55      ABSMSTT = 0.0
56   END IF
57
```

```
CYCLETOT=INTEG(CYCLE,0.0)

! MASS CHANGE IN THE LUMEN
 RMSTT= -(KST+KABS)*MST +ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
  MST = INTEG(RMSTT,0.0)                        !AMOUNT REMAINING IN DUODENUM
(NMOL)

! ABSORPTION IN LYMPH CIRCULATION
 LYRMLUM = KABS*MST*A
  LYMLUM = INTEG(LYRMLUM,0.0)

! ABSORPTION IN PORTAL CIRCULATION
 LIRMLUM = KABS*MST*B
  LIMLUM = INTEG(LIRMLUM,0.0)


    !IV ABSORPTION SCENARIO---------
 IV= DOSEIV_NM * WT0 !AMOUNT IN NMOL
 IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
 EXPIV= IVR * (1-STEP(PFUNC))
 IVDOSE = integ(EXPIV,0.0)

   !IV LATE IN THE CYCLE
   !MODIFICATION JANUARY 13 2004
 IV_RlateR = DOSEIVNMlate*WT0
 IV_EXPOSURE=PULSE(IV_LAG,IV_PERIOD,IV_FINISH)

 IV_lateT = IV_EXPOSURE *IV_RlateR
 IV_late = IV_lateT/CINT

SUMEXPEVENTIV= integ(IV_EXPOSURE,0.0) !NUMBER OF CYCLES GENERATED DURING
SIMULATION

     !SYSTEMIC BLOOD COMPARTMENT
     ! MODIFICATION OCT 8 2009
CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late)/(QC+CLURI) !
 CA = CB                                     ! CONCENTRATION (NMOL/L)

     !CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late-RAURI)/QC
!(NMOL/L)

    !URINARY EXCRETION BY KIDNEY
    ! MODIFICATION OCT 8 2009
RAURI = CLURI *CB
  AURI = INTEG(RAURI,0.0)

    !RAURI = CLURI * CRE
    !AURI = INTEG(RAURI,0.0)

    !UNIT CONVERSION POST SIMULATION
CONSTANT MW=322 !MOLECULAR WEIGHT (NG/NMOL)
CONSTANT SERBLO = 0.55
CONSTANT UNITCORR = 1.0e3

 CBSNGKGLIADJ = CB*MW/(0.55*B_TOTLIP) !NG SERUM LIPID ADJUSTED/KG
   AUCBS_NGKGLIADJ=integ(CBSNGKGLIADJ,0.)
```

```
1    CBNGKG= CB*MW    !NG/KG
2
3
4        !ADIPOSE COMPARMTENT
5        !TISSUE BLOOD SUBCOMPARTMENT
6    RAFB= QF*(CA-CFB)-PAF*(CFB-CF/PF)       !(NMOL/H)
7     AFB = INTEG(RAFB,0.0)                      !(NMOL)
8     CFB = AFB/WFB                      !(NMOL/L)
9        !TISSUE SUBCOMPARTMENT
10   RAF = PAF*(CFB-CF/PF)                   !(NMOL/H)
11    AF = INTEG(RAF,0.0)                !(NMOL)
12    CF  = AF/WF                        !(NMOL/L)
13
14       !UNIT CONVERSION POST SIMULATION
15   CFTOTAL= (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION IN NMOL/ML
16   CFNGKG=CFTOTAL*MW ! FAT CONCENTRATION IN NG/KG
17   AUCF_NGKGH=integ(CFNGKG,0.)
18
19
20       !REST OF THE BODY COMPARTMENT
21       !TISSUE BLOOD SUBCOMPARTMENT
22   RAREB= QRE *(CA-CREB)-PARE*(CREB-CRE/PRE)       !(NMOL/H)
23    AREB = INTEG(RAREB,0.0)                     !(NMOL)
24    CREB = AREB/WREB                      !(NMOL/L)
25       !TISSUE SUBCOMPARTMENT
26   RARE = PARE*(CREB - CRE/PRE)               !(NMOL/H)
27    ARE = INTEG(RARE,0.0)                !(NMOL)
28    CRE  = ARE/WRE                          !(NMOL/L)
29   ARETOT = ARE +AREB
30
31       !POST SIMULATION UNIT CONVERSION
32   CRETOTAL= (ARE + AREB)/(WRE + WREB)             ! TOTAL CONCENTRATION (NMOL/L)
33   CRENGKG=CRETOTAL*MW                             ! REST OF THE BODY
34   CONCENTRATION (NG/KG)
35
36
37       !LIVER COMPARTMENT
38       !TISSUE BLOOD SUBCOMPARTMENT
39    RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM ! (NMOL/HR)
40     ALIB = INTEG(RALIB,0.0)                        !(NMOL)
41    CLIB = ALIB/WLIB                       !(NMOL/L)
42       !TISSUE SUBCOMPARMTENT
43    RALI = PALI*(CLIB - CFLLIR)-REXCLI         ! (NMOL/HR)
44     ALI = INTEG(RALI,0.0)                        !(NMOL)
45    CLI  = ALI/WLI                         !(NMOL/L)
46
47       !FREE TCDD CONCENTRATION IN LIVER
48         ! MODIFICATION OCTOBER 8 2009
49    CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR)) &
50         +((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR)*IND_ACTIVE)))-CFLLI,CFLLI0)
51      CFLLIR=DIM(CFLLI,0.0) ! FREE TCDD CONCENTRATION IN LIVER
52   !MODIFIED FROM:
53   !PARAMETER (LIVER_1RMN = 1.0E-30)
54   ! CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
55   !+LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2 + CFLLIR &
56   !+LIVER_1RMN)*IND_ACTIVE)))-CFLLI,CFLLI0)
57   !CFLLIR=DIM(CFLLI,0.0)
```

```
1
2    ! MODIFICATION OCTOBER 8 2009
3    CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR) !BOUND CONCENTRATION (NMOL/L)
4
5        !POST SIMULATION UNIT CONVERSION
6    CLITOTAL= (ALI + ALIB)/(WLI + WLIB) ! TOTAL CONCENTRATION (NMOL/L)
7    Rec_occ= CFLLIR/(KDLI+CFLLIR)
8    CLINGKG=CLITOTAL*MW ! LIVER CONCENTRATION IN NG/KG
9      AUCLI_NGKGH=integ(CLINGKG,0.0)
10   CBNDLINGKG = CBNDLI*MW ! BOUND CONCENTRATION IN NG/KG
11     AUCBNDLI_NGKGH =INTEG(CBNDLINGKG,0.0)
12
13       !FRACTION INCREASE OF INDUCTION OF CYP1A2
14   fold_ind=CYP1A2_1OUT/CYP1A2_1A2
15   VARIATIONOFAC =(CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2
16
17   !VARIABLE ELIMINATION BASED ON THE CYP1A2
18   ! MODIFICATION OCTOBER 8 2009
19   KBILE_LI_T = Kelv*VARIATIONOFAC! ! DOSE-DEPENDENT EXCRETION RATE CONSTANT
20
21    REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT BILLIARY EXCRETION RATE
22       EXCLI = INTEG(REXCLI,0.0)
23
24   !KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv !
25
26
27   !CHEMICAL IN CYP450 (1A2) COMPARTMENT
28
29   CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ ! BASAL PRODCUTION RATE OF CYP1A2
30   SET EQUAL TO BASAL DEGREDATION RATE
31
32       ! MODIFICATION OCTOBER 8 2009
33   CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-30)**HILL
34   &
35       /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
36        - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)
37   !MODIFIED FROM:
38   !PARAMETER (CYP1A2_1RMN = 1E-30)
39   !CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1 + CYP1A2_1EMAX *(CBND&
40   !LI +CYP1A2_1RMN)**HILL/(CYP1A2_1EC50 + (CBNDLI + CYP1A2_1&
41   !RMN)**HILL) +CYP1A2_1RMN) - CYP1A2_1KOUT*CYP1A2_1&
42   !OUT, CYP1A2_1OUTZ)
43
44   ! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
45   SIMULATIONS)
46   CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
47     CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)
48
49   CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
50     CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)
51
52       !PLACENTA COMPARTMENT
53       !TISSUE BLOOD SUBCOMPARTMENT
54   RAPLAB= QPLA*(CA - CPLAB)-PAPLA*(CPLAB -CFLPLAR)    ! NMOL/HR)
55    APLAB = INTEG(RAPLAB,0.0)                          ! (NMOL)
56    CPLAB = APLAB/(WPLAB+1E-30)                        ! (NMOL/ML)
57       !TISSUE SUBCOMPARTMENT
```

```
1    RAPLA = PAPLA*(CPLAB-CFLPLAR)-RAMPF + RAFPM          ! (NMOL/HR)
2     APLA = INTEG(RAPLA,0.0)                              ! (NMOL)
3     CPLA  = APLA/(WPLA+1e-30)                            ! (NMOL/ML)
4
5        ! NEW EQUATION AUGUST 28  2009
6    PARAMETER (PARA_ZERO = 1.0E-30)
7    CFLPLA= IMPLC(CPLA-(CFLPLAR*PPLA +(PLABMAX*CFLPLAR/(KDPLA&
8        +CFLPLAR+PARA_ZERO)))-CFLPLA,CFLPLA0)
9    CFLPLAR=DIM(CFLPLA,0.0)
10
11       !POST SIMULATION UNIT CONVERSION
12   CPLATOTAL = ((APLAB+APLA)/(WPLAB+WPLA))
13
14       !FETUS COMPARTMENT
15   RAFETUS= RAMPF-RAFPM
16    AFETUS=INTEG(RAFETUS,0.0)
17   CFETUS=AFETUS/(WTFE+1.0e-30)
18   CFETOTAL= CFETUS
19   CFETUS_v = CFETUS/PFETUS
20
21       !POST SIMULATION UNIT CONVERSION
22    CFETUSNGKG = CFETUS*MW                        !(NG/KG)
23
24
25       !TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
26       !FETAL EXPOSURE ONLY DURING EXPOSURE
27
28   IF (T.LT.TRANSTIME_ON) THEN
29    SWITCH_trans = 0.0
30   ELSE
31    SWITCH_trans = 1
32   END IF
33
34       !TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
35       ! MODIFICATION 26 SEPTEMBER 2003
36
37   RAMPF = (CLPLA_FET*CPLA)*SWITCH_trans
38     AMPF=INTEG(RAMPF,0.0)
39
40       !TRANSFER OF DIOXIN FROM FETUS TO PLACENTA
41   RAFPM = (CLPLA_FET*CFETUS_v)*SWITCH_trans!
42    AFPM = INTEG(RAFPM,0.0)
43
44       !CHECK MASS BALANCE ----------
45   BDOSE= IVDOSE +LYMLUM+LIMLUM
46   BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB+AFETUS !
47   BDIFF = BDOSE-BMASSE
48
49       !BODY BURDEN (NMOL)
50   BODY_BURDEN = AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB
51
52       !BODY BURDEN CONCENTRATION (NG/KG)
53    BBNGKG =(AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB)*MW/WT0
54
55   ! END SIMULATION COMMAND
56
57   TERMT (T.GE. TimeLimit, 'Time limit has been reached.')
```

```
1
2   END   ! END OF THE DERIVATIVE SECTION
3   END   ! END OF THE DYNAMIC SECTION
4   END   ! END OF THE PROGRAM
5
```

6   ### E.2.2.2. *Input File*

```
7   output @clear
8   prepare @clear T  year CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG  CBNDLINGKG CBNGKG
9
10  CINT = 1
11     %EXPOSURE SCENARIO
12  EXP_TIME_ON      = 0          %TIME EXPOSURE BEGINS (HOUR)
13  EXP_TIME_OFF     = 401190     %TIME EXPOSURE ENDS (HOUR)
14  DAY_CYCLE        = 24         %HOURS BETWEEN DOSES (HOUR)
15  BCK_TIME_ON      = 401190     %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
16  BCK_TIME_OFF     = 401190     %TIME BACKGROUND EXPOSURE ENDS (HOUR)
17  IV_LAG           = 401190
18  IV_PERIOD        = 401190
19     %GESTATION CONTROL
20  CONCEPTION_T     = 393120     %TIME OF CONCEPTION AT 45 YEARS OLD
21  TIMELIMIT        = 399840     %SIMULATION DURATION (HOUR)
22  TRANSTIME_ON     = 394632     %TRANSFER FROM MOTHER TO FETUS AT 1512 HOURS
23  GESTATION
24     %EXPOSURE DOSE
25  MSTOT            = 9.977E-07  %NG OF TCDD PER KG OF BW
26  MSTOTBCKGR       = 0.         %ORAL BACKGROUND EXPOSURE DOSE (NG/KG)
27  DOSEIV           = 0.
28  DOSEIVLATE       = 0.
29
30     % TRANFER MOTHER TO FETUS CLEARANCE
31  CLPLA_FET        = 0.001      %MOTHER TO FETUS TRANFER CLEARANCE (L/HR)
32
```

33 ### E.2.3. **Rat Standard Model**

34 ### E.2.3.1. *Model Code*

35 PROGRAM: 'Three Compartment PBPK Model in Rat: Standard Model (Nongestation)'

```
36
37
38  INITIAL  ! INITIALIZATION OF PARAMETERS
39
40      !SIMULATION PARAMETERS
41  CONSTANT PARA_ZERO       =       1d-30
42  CONSTANT EXP_TIME_ON     =       0.0          ! TIME AT WHICH EXPOSURE BEGINS
43  (HOURS)
44  CONSTANT EXP_TIME_OFF    =       900.0        ! TIME AT WHICH EXPOSURE ENDS
45  (HOURS)
46  CONSTANT DAY_CYCLE       =       900.0        ! NUMBER OF HOURS BETWEEN
47  DOSES (HOURS)
48  CONSTANT BCK_TIME_ON     =       0.0          ! TIME AT WHICH BACKGROUND
49  EXPOSURE BEGINS (HOURS)
50  CONSTANT BCK_TIME_OFF    =       0.0          ! TIME AT WHICH BACKGROUND
51  EXPOSURE ENDS (HOURS)
52
```

```
1   CONSTANT MW=322 !MOLECULAR WEIGHT (NG/NMOL)
2   CONSTANT SERBLO = 0.55
3   CONSTANT UNITCORR = 1000
4
5
6       !EXPOSURE DOSES
7   CONSTANT MSTOTBCKGR       =       0.0              !ORAL BACKGROUND EXPOSURE DOSE
8   (UG/KG)
9   CONSTANT MSTOT           =       10        !ORAL EXPOSURE DOSE (UG/KG)
10  CONSTANT MSTOTsc         =       0.0              !SUBCUTANEOUS EXPOSURE DOSE
11  (UG/KG)
12  CONSTANT DOSEIV          =       0.0              ! INJECTED DOSE (UG/KG)
13
14      !ORAL DOSE
15    MSTOT_NM               =    MSTOT/MW        !AMOUNT IN NMOL/G
16    MSTOT_NMBCKGR          =    MSTOTBCKGR/MW   !AMOUNT IN NMOL/G
17
18      !INTRAVENOUS DOSE
19    DOSEIV_NM              =    DOSEIV/MW       !AMOUNT IN NMOL/G
20
21      !INITIAL GUESS OF THE FREE CONCENTRATION  IN THE LIGAND (COMPARTMENT
22  INDICATED BELOW)====
23  CONSTANT CFLLI0          =     0.0             !LIVER (NMOL/ML)
24
25      !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
26  BELOW) (NMOL/ML) ===
27  CONSTANT LIBMAX          =     3.5e-4          ! LIVER (NMOL/ML), WANG ET AL.
28  1997
29
30      ! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
31  (NMOL/ML)===
32  CONSTANT KDLI            =     1.0e-4          ! LIVER (AhR) (NMOL/ML), WANG
33  ET AL. 1997
34  CONSTANT KDLI2           =     4.0e-2          !LIVER (1A2) (NMOL/ML), EMOND
35  ET AL. 2004
36
37      !EXCRETION AND ABSORPTION CONSTANT [RAT]
38  CONSTANT KST             =     0.36            ! GASTRIC RATE CONSTANT (HR-1),
39  WANG ET AL. (1997)
40  CONSTANT KABS            =     0.48            !INTESTINAL ABSORPTION CONSTANT
41  (HR-1), WANG ET AL. 1997
42
43      !URINARY ELIMINATION CLEARANCE (ML/HR)
44  CONSTANT CLURI           =     0.01            !URINARY CLEARANCE (ML/HR),
45  EMOND ET AL. 2004
46
47      !INTERSPECIES VARIABLE ELIMINATION
48  CONSTANT KELV            =     0.15            ! INTERSPECIES VARIABLE
49  ELIMINATION CONSTANT (1/HOUR) (OPTIMIZED), EMOND ET AL. 2004
50
51      ! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
52  CONSTANT A               =     0.7             ! LYMPHATIC FRACTION, WANG ET
53  AL. 1997
54
55      !PARTITION COEFFICIENTS
56  CONSTANT PF              =     100             ! ADIPOSE TISSUE/BLOOD, WANG ET
57  AL. 1997
```

```
CONSTANT PRE              =      1.5              ! REST OF THE BODY/BLOOD, WANG
ET AL. 1997
CONSTANT PLI              =      6.0                ! LIVER/BLOOD, WANG ET AL.
1997


     !PARAMETER FOR INDUCTION OF CYP 1A2 [MOUSE] ===
CONSTANT IND_ACTIVE       =      1.0              ! INCLUDE INDUCTION? (1 = YES,
0 = NO)
CONSTANT CYP1A2_1OUTZ     =      1.6              ! DEGRADATION CONCENTRATION
CONSTANT OF 1A2 (NMOL/ML), WANG ET AL. 1997
CONSTANT CYP1A2_1A1       =      1.6              ! BASAL CONCENTRATION OF 1A1
(NMOL/ML), WANG ET AL. 1997
CONSTANT CYP1A2_1EC50     =      0.13             ! DISSOCIATION CONSTANT TCDD-
CYP1A2 (NMOL/ML) , WANG ET AL. 1997
CONSTANT CYP1A2_1A2       =      1.6              ! BASAL CONCENTRATION OF 1A2
(NMOL/ML) Wang et al (1997)
CONSTANT CYP1A2_1KOUT     =      0.1              ! FIRST ORDER RATE OF
DEGRADATION (H-1), WANG ET AL. 1997
CONSTANT CYP1A2_1TAU      =      0.25             ! HOLDING TIME (H), WANG ET AL.
1997
CONSTANT CYP1A2_1EMAX     =      600              ! MAXIMUM INDUCTION OVER BASAL
EFFECT (UNITLESS), WANG ET AL. 1997
CONSTANT HILL             =      0.6       !HILL CONSTANT; COOPERATIVE LIGAND
BINDING EFFECT CONSTANT (UNITLESS)

   !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT
CONSTANT QFF  = 0.069                             ! ADIPOSE TISSUE BLOOD FLOW
FRACTION (UNITLESS), WANG ET AL. 1997
CONSTANT QLIF = 0.183                             ! LIVER (UNITLESS), WANG ET AL.
1997


     !DIFFUSIONAL PERMEABILITY FRACTION
CONSTANT PAFF            = 0.0910                 ! ADIPOSE (UNITLESS), WANG ET
AL. 1997
CONSTANT PAREF           = 0.0298                 ! REST OF THE BODY (UNITLESS),
WANG ET AL. 1997
CONSTANT PALIF           = 0.35                   ! LIVER (UNITLESS), WANG ET AL.
1997


     !FRACTION OF TISSUE VOLUME (UNITLESS)
CONSTANT WLI0            =  0.0360                ! LIVER, WANG ET AL. 1997
CONSTANT WF0             =  0.069                 ! BLOOD, WANG ET AL. 1997


     !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL
COMPARTMENT VOLUME =========
CONSTANT WFB0            =  0.050                 ! ADIPOSE TISSUE, WANG ET AL.
1997
CONSTANT WREB0           =  0.030                 ! REST OF THE BODY, WANG ET AL.
1997
CONSTANT WLIB0           =  0.266                 ! LIVER , WANG ET AL. 1997


     !EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
     ! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG        = 0.0                    ! TIME ELAPSED BEFORE EXPOSURE
BEGINS (WEEK)
CONSTANT WEEK_PERIOD     = 168.0                  ! NUMBER OF HOURS IN THE WEEK
(HOURS)
```

```
CONSTANT WEEK_FINISH      = 168.0                        ! TIME EXPOSURE ENDS (HOURS)

     !NUMBER OF EXPOSURES PER MONTH
CONSTANT MONTH_LAG      = 0.0                            ! TIME ELAPSED BEFORE EXPOSURE
BEGINS (MONTH)

     !SET FOR BACKGROUND EXPOSURE===========
     !CONSTANT FOR BACKGROUND EXPOSURE===========
CONSTANT Day_LAG_BG     = 0.0                            ! TIME ELAPSED BEFORE EXPOSURE
BEGINS (HOURS)
CONSTANT Day_PERIOD_BG  = 24.0                           ! LENGTH OF EXPOSURE (HOURS)

     !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG_BG    = 0.0                            ! DELAY BEFORE BACKGROUND
EXPOSURE (WEEK)
CONSTANT WEEK_PERIOD_BG = 168.0                          !NUMBER OF HOURS IN THE WEEK
(HOURS)
CONSTANT WEEK_FINISH_BG = 168.0                          ! TIME EXPOSURE ENDS (HOURS)

     !GROWTH CONSTANT FOR RAT
     !CONSTANT FOR MOTHER BODY WEIGHT GROWTH ======
CONSTANT BW_T0 = 250.0                                   !(IN G) CHANGED FOR
SIMULATION

     ! CONSTANT USED IN CARDIAC OUTPUT EQUATION
CONSTANT QCCAR =311.4                                    !CONSTANT (ML/MIN/KG), WANG ET
AL.

     ! COMPARTMENT TOTAL LIPID FRACTION
CONSTANT F_TOTLIP       = 0.855                  !ADIPOSE TISSUE (UNITLESS)
CONSTANT B_TOTLIP       = 0.0033                 !BLOOD (UNITLESS)
CONSTANT RE_TOTLIP      = 0.019                  !REST OF THE BODY (UNITLESS)
CONSTANT LI_TOTLIP      = 0.06                   !LIVER (UNITLESS)

END      !END OF THE INITIAL SECTION

DYNAMIC  !DYNAMIC SIMULATION SECTION

ALGORITHM  IALG          =             2        ! GEAR METHOD
CINTERVAL  CINT          =           0.1        ! COMMUNICATION INTERVAL
MAXTERVAL  MAXT          =        1.0e+10        ! MAXIMUM CALCULATION INTERVAL
MINTERVAL  MINT          =        1.0E-10        ! MINIMUM CALCULATION INTERVAL
VARIABLE   T             =           0.0
CONSTANT   TIMELIMIT     =         900.0         !SIMULATION TIME LIMIT
(HOURS)
 CINTXY  = CINT
 PFUNC   = CINT

        !TIME CONVERSION
  DAY=T/24.0                                             ! TIME IN DAYS
  WEEK =T/168.0                                          ! TIME IN WEEKS
  MONTH =T/730.0                                         ! TIME IN MONTHS
  YEAR=T/8760.0                                          ! TIME IN YEARS


DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS
```

```
          !CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
          !NUMBER OF EXPOSURES PER DAY
 DAY_LAG      = EXP_TIME_ON                      ! TIME ELAPSED BEFORE EXPOSURE
BEGINS (HOURS)
 DAY_PERIOD   = DAY_CYCLE                         ! EXPOSURE PERIOD (HOURS)
 DAY_FINISH   = CINTXY                            ! LENGTH OF EXPOSURE (HOURS)
 MONTH_PERIOD = TIMELIMIT                         ! EXPOSURE PERIOD (MONTHS)
 MONTH_FINISH = EXP_TIME_OFF                      ! LENGTH OF EXPOSURE (MONTHS)

          !NUMBER OF EXPOSURES PER DAY AND MONTH
 DAY_FINISH_BG   = CINTXY                         ! LENGTH OF EXPOSURE (HOURS)
 MONTH_LAG_BG    = BCK_TIME_ON                    ! TIME ELAPSED BEFORE BACKGROUND
EXPOSURE BEGINS (MONTHS)
 MONTH_PERIOD_BG = TIMELIMIT                      ! BACKGROUND EXPOSURE PERIOD
(MONTHS)
 MONTH_FINISH_BG = BCK_TIME_OFF                   ! LENGTH OF BACKGROUND EXPOSURE
(MONTHS)


   B = 1-A                                        ! FRACTION OF DIOXIN ABSORBED IN
THE PORTAL FRACTION OF THE LIVER

          ! BODY WEIGHT GROWTH EQUATION========
  PARAMETER (BW_RMN = 1.0E-30)
  WT0= (BW_T0 *(1.0+(0.41*T)/(1402.5+T+BW_RMN))) ! IN GRAMS

          !VARIABILITY OF REST OF THE BODY DEPEND OTHERS ORGAN
  WRE0 = (0.91 - (WLIB0*WLI0 + WFB0*WF0 + WLI0 + WF0))/(1.0+WREB0) !REST OF
THE BODY FRACTION; UPDATED FOR EPA ASSESSMENT
  QREF = 1.0-(QFF+QLIF)                           !REST OF BODY BLOOD FLOW
  QTTQF = QFF+QREF+QLIF                           ! SUM MUST EQUAL 1

          !COMPARTMENT VOLUME (G OR ML) =========
  WF  =  WF0  * WT0                               ! ADIPOSE
  WRE =  WRE0 * WT0                               ! REST OF THE BODY
  WLI =  WLI0 * WT0                               ! LIVER

          !COMPARTMENT TISSUE BLOOD VOLUME (G OR ML) =========
  WFB  =  WFB0  * WF                              ! ADIPOSE
  WREB =  WREB0 * WRE                             ! REST OF THE BODY
  WLIB =  WLIB0 * WLI                             ! LIVER

     !CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT
   QC= QCCAR*60.0*(WT0/UNITCORR)**0.75

          ! COMPARTMENT BLOOD FLOW (ML/HR)
   QF  = QFF*QC                                   ! ADIPOSE TISSUE BLOOD FLOW RATE
   QLI = QLIF*QC                                  ! LIVER TISSUE BLOOD FLOW RATE
   QRE = QREF*QC                                  ! REST OF THE BODY BLOOD FLOW
RATE
   QTTQ = QF+QRE+QLI                              ! TOTAL FLOW RATE

          !PERMEABILITY ORGAN FLOW (ML/HR)
  PAF  = PAFF*QF                                  ! ADIPOSE
  PARE = PAREF*QRE                                ! REST OF THE BODY
  PALI = PALIF*QLI                                ! LIVER TISSUE
```

```
           !CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
           !EXPOSURE + !REPETITIVE EXPOSURE SCENARIO
   IV= DOSEIV_NM * WT0   !AMOUNT IN NMOL
   MSTT= MSTOT_NM * WT0  !AMOUNT IN NMOL
   MSTTBCKGR =MSTOT_NMBCKGR *WT0


          !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIOS
   DAY_EXPOSURE_BG   = PULSE(DAY_LAG_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
   WEEK_EXPOSURE_BG  = PULSE(WEEK_LAG_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
   MONTH_EXPOSURE_BG = PULSE(MONTH_LAG_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

   MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
   MSTTFR_BG = MSTTBCKGR/CINT

   CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG

IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
    ABSMSTT_GB= MSTTFR_BG
ELSE
    ABSMSTT_GB = 0.0
END IF



          !REPETITIVE ORAL MAIN EXPOSURE SCENARIO
   DAY_EXPOSURE   = PULSE(DAY_LAG,DAY_PERIOD,DAY_FINISH)
   WEEK_EXPOSURE  = PULSE(WEEK_LAG,WEEK_PERIOD,WEEK_FINISH)
   MONTH_EXPOSURE = PULSE(MONTH_LAG,MONTH_PERIOD,MONTH_FINISH)

   MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
   CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
   MSTTFR = MSTT/CINT

   SUMEXPEVENT= integ (CYCLE,0.0) !NUMBER OF CYCLES GENERATED DURING
SIMULATION



          !CONDITIONAL ORAL EXPOSURE
IF (MSTTCH.EQ.MSTT) THEN
    ABSMSTT= MSTTFR
ELSE
    ABSMSTT = 0.0
END IF

 CYCLETOT=INTEG(CYCLE,0.0)

          !MASS CHANGE IN THE LUMEN
 RMSTT = -(KST+KABS)*MST+ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
   MST = INTEG(RMSTT,0.0)   !AMOUNT REMAINING IN DUODENUM (NMOL)

          !ABSORPTION IN LYMPH CIRCULATION
 LYRMLUM = KABS*MST*A
   LYMLUM = INTEG(LYRMLUM,0.0)

          !ABSORPTION IN PORTAL CIRCULATION
 LIRMLUM = KABS*MST*B
   LIMLUM = INTEG(LIRMLUM,0.0)
```

```
         !PERCENT OF DOSE REMAINING IN THE GI TRACT


         !ABSORPTION of Dioxin by IV route---------
 IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
 EXPIV= IVR * (1.0-STEP(PFUNC))
   IVDOSE = integ(EXPIV,0.0)

         !SYSTEMIC BLOOD COMPARTMENT
         ! MODIFICATION ON OCTOBER 6, 2009
CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM)/(QC+CLURI) !
   CA = CB

         !URINARY EXCRETION BY KIDNEY
         ! MODIFICATION ON OCTOBER 6, 2009
RAURI = CLURI *CB
  AURI = INTEG(RAURI,0.0)

         !CONVERSION EQUATION POST SIMULATION

 CBNGKG = CB*MW*UNITCORR ![NG/KG]


CBSNGKGLIADJ= (CB*MW*UNITCORR*(1.0/B_TOTLIP)*(1.0/SERBLO))![NG of TCDD
Serum/Kg OF LIPID]

         !ADIPOSE TISSUE COMPARTMENT
         !TISSUE BLOOD SUBCOMPARTMENT
 RAFB = QF*(CA-CFB)-PAF*(CFB-CF/PF)                 !(NMOL/HR)
   AFB = INTEG(RAFB,0.0)                             !(NMOL)
   CFB = AFB/WFB                                     !(NMOL/ML)
         !TISSUE SUBCOMPARTMENT
 RAF  = PAF*(CFB-CF/PF)                              !(NMOL/HR)
   AF  = INTEG(RAF,0.0)                              !(NMOL)
   CF  = AF/WF                                       !(NMOL/ML)

     !CONVERSION EQUATION POST SIMULATION
   CFTOTAL     = (AF + AFB)/(WF + WFB)          !TOTAL CONCENTRATION IN NMOL/ML

   CFNGKG   = CFTOTAL*MW*UNITCORR               ! CONCENTRATION [NG/KG]

         !REST OF THE BODY COMPARTMENT
         ! TISSUE BLOOD SUBCOMPARTMENT
 RAREB= QRE*(CA-CREB)-PARE*(CREB-CRE/PRE)           !(NMOL/HR)
   AREB = INTEG(RAREB,0.0)                           !(NMOL)
   CREB = AREB/WREB                                  !(NMOL/ML)
     ! TISSUE COMPARTMENT
 RARE = PARE*(CREB - CRE/PRE)                        !(NMOL/HR)
   ARE = INTEG(RARE,0.0)                             !(NMOL)
   CRE  = ARE/WRE                                    !(NMOL/ML)

   !CONVERSION EQUATION POST SIMULATION
   CRETOTAL= (ARE + AREB)/(WRE + WREB)               ! TOTAL CONCENTRATION IN
NMOL/ML

   CTREPGG= CRETOTAL*MW*UNITCORR !(PG/ML)
    AUC_REPGG = integ(CTREPGG,0.0)
```

```
1
2        !LIVER COMPARTMENT
3        !TISSUE BLOOD COMPARTMENT
4     RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM    !(NMOL/HR)
5        ALIB = INTeg(RALIB,0.0)                          !(NMOL)
6        CLIB = ALIB/WLIB
7        !TISSUE COMPARTMENT
8     RALI =  PALI*(CLIB-CFLLIR)-REXCLI                   !(NMOL/HR)
9        ALI = integ(RALI,0.0)                            !(NMOL)
10       CLI  = ALI/WLI                                   !(NMOL/ML)
11
12
13    PARAMETER (LIVER_1RMN = 1.0E-30)
14    CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
15    +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR &
16    +LIVER_1RMN)*IND_ACTIVE)))-CFLLIR,CFLLI0) ! FREE TCDD CONCENTRATION IN LIVER
17    CFLLIR=DIM(CFLLI,0.0)
18
19      CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND CONCENTRATION
20
21          !CONVERSION EQUATION POST SIMULATION
22      CLITOTAL= (ALI + ALIB)/(WLI + WLIB)              ! TOTAL CONCENTRATION IN
23    NMOL/ML
24
25      rec_occ_AHR= (CFLLIR/(KDLI+CFLLIR+1))*100.0      ! PERCENT OF AhR
26    OCCUPANCY
27      PROT_occ_1A2= (CFLLIR/(KDLI2+CFLLIR))*100.0      ! PERCENT OF 1A2
28    OCCUPANCY
29      CLINGKG =(CLITOTAL*MW*UNITCORR)
30      CBNDLINGKG = CBNDLI*MW*UNITCORR
31        AUCLI_NGKGH=INTEG(CLINGKG,0.0)
32      CLINGG=CLITOTAL*MW
33
34          !VARIABLE ELIMINATION HALF-LIFE BASED ON THE CONCENTRATION OF CYP1A2
35       KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv ! INDUCED BILIARY
36    EXCRETION RATE CONSTANT
37
38     REXCLI= (KBILE_LI_T*CFLLIR*WLI) ! DOSE-DEPENDENT BILIARY EXCRETION RATE
39       EXCLI = INTEG(REXCLI,0.0)
40
41          !CHEMICAL IN CYP450 (1A2) COMPARTMENT
42       !===PARAMETER FOR INDUCTION OF CYP1A2
43
44     CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ ! BASAL RATE OF CYP1A2 PRODUCTION
45    SET EQUAL TO BASAL RATE OF DEGREDATION
46
47
48          ! MODIFICATION ON OCTOBER 6, 2009
49     CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-
50    30)**HILL &
51        /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &-
52         - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)
53
54    ! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
55    SIMULATIONS)
56
57     CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
```

```
    CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)
 CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
    CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)

! -----------CHECK MASS BALANCE ----------
  BDOSE= LYMLUM+LIMLUM+IVDOSE
  BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI
     BDIFF = BDOSE-BMASSE

!--------------BODY BURDEN-----------------------
  BBNGKG =(((AFB+AF+AREB+ARE+ALIB+ALI)*MW)/(WT0/UNITCORR)) !
! ----------- END OF THE SIMULATION COMMAND ----------

TERMT (T.GE. TimeLimit, 'Time limit has been reached.')

END  ! END OF THE DERIVATIVE SECTION
END  ! END OF THE DYNAMIC SIMULATION SECTION
END  ! END OF THE PROGRAM.
```

E.2.3.2. *Input Files*

E.2.3.2.1. *Cantoni et al. ([1981](#))*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

%Cantoni et al. 1981
%protocol:  oral exposure 1 dose/week for 45 weeks; female CD-COBS rats
%dose levels: 0.01, 0.1, 1  ug/kg 1 dose/week for 45 weeks
%dose levels: 10, 100, 1000 ng/kg 1 dose/week for 45 weeks
%dose levels equivalent to: 1.43, 14.3 143 ng/kg 7 days/week for 45 weeks

MAXT            = 0.01
CINT            = 0.1
EXP_TIME_ON     = 0.        %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    = 7560      %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       = 168       %HOURS BETWEEN DOSES
BCK_TIME_ON     = 0.        %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF    = 0.        %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT       = 7560      %SIMULATION DURATION (HOUR)
BW_T0           = 125       %BODY WEIGHT AT THE BEGINNING OF THE SIMULATION
(G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT         = 0.01     %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT       = 0.1      %ORAL EXPOSURE DOSE (UG/KG)
   MSTOT        = 1        %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.2. *Chu et al. ([2007](#)) and Chu et al. ([2001](#))*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Chu et al. 2007
```

```
1   %protocol:  oral exposure daily for 28 days
2   %dose levels: 0.0025, 0.025, 0.250, 1.0 ug/kg every day for 28 days
3   %dose levels = 2.5, 25, 250, 1000 ng/kg every day for 28 days
4   MAXT            =  0.01
5   CINT            =  0.1
6   EXP_TIME_ON     =  0.            %TIME EXPOSURE BEGINS (HOUR)
7   EXP_TIME_OFF    =  672.          %TIME EXPOSURE ENDS (HOUR)
8   DAY_CYCLE       =  24.           %HOURS BETWEEN DOSES
9   BCK_TIME_ON     =  0.            %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
10  BCK_TIME_OFF    =  0.            %TIME BACKGROUND EXPOSURE ENDS (HOUR)
11  TIMELIMIT       =  672.          %SIMULATION DURATIOHN (HOUR)
12  BW_T0           =  200.          %BODY WEIGHT AT THE BEGINNING OF THE
13  SIMULATION (G)
14
15  %EXPOSURE DOSE SCENARIOS (UG/KG)
16    %MSTOT        = 0.0025         %ORAL EXPOSURE DOSE (UG/KG)
17    %MSTOT        = 0.025          %ORAL EXPOSURE DOSE (UG/KG)
18    %MSTOT        = 0.250          %ORAL EXPOSURE DOSE (UG/KG)
19    MSTOT         = 1.0            %ORAL EXPOSURE DOSE (UG/KG)
```

20 ### E.2.3.2.3.   *Crofton et al. ([2005](#))*

```
21  output @clear
22  prepare @clear
23  prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG
24
25  % Crofton et al. 2005
26  %protocol:  oral exposure daily for 4 days
27  %dose levels: 0.0001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, and 10 ug/kg every
28  day for four days
29  %dose levels: 0.1, 3, 10, 30, 100, 300, 1000, 3000, and 10000 ng/kg every day
30  for four days
31
32  MAXT            =  0.001
33  CINT            =  0.1
34  EXP_TIME_ON     =  0.            %TIME EXPOSURE BEGINS (HOUR)
35  EXP_TIME_OFF    =  96.           %TIME EXPOSURE ENDS (HOUR)
36  DAY_CYCLE       =  24.           %HOURS BETWEEN DOSES
37  BCK_TIME_ON     =  0.            %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
38  BCK_TIME_OFF    =  0.            %TIME BACKGROUND EXPOSURE ENDS (HOUR)
39  TIMELIMIT       =  96.           %SIMULATION DURATION (HOUR)
40  BW_T0           =  250           %BODY WEIGHT AT THE BEGINNING OF THE
41  SIMULATION (G)
42
43  %EXPOSURE DOSE SCENARIOS (UG/KG)
44    MSTOT         = 0.0001         %ORAL EXPOSURE DOSE (UG/KG)
45    %MSTOT        = 0.003          %ORAL EXPOSURE DOSE (UG/KG)
46    %MSTOT        = 0.01           %ORAL EXPOSURE DOSE (UG/KG)
47    %MSTOT        = 0.03           %ORAL EXPOSURE DOSE (UG/KG)
48    %MSTOT        = 0.1            %ORAL EXPOSURE DOSE (UG/KG)
49    %MSTOT        = 0.3            %ORAL EXPOSURE DOSE (UG/KG)
50    %MSTOT        = 1.             %ORAL EXPOSURE DOSE (UG/KG)
51    %MSTOT        = 3.             %ORAL EXPOSURE DOSE (UG/KG)
52    MSTOT         = 10.            %ORAL EXPOSURE DOSE (UG/KG)
53
54
```

E.2.3.2.4. *Croutch et al. ([2005](#))*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Croutch et al., 2005

 MAXT              = 0.001
 CINT              = 0.1
 TIMELIMIT         = 672         %SIMULATION DURATION (HOUR)
 EXP_TIME_ON       = 72          %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF      = 672         %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE         = 72          %HOURS BETWEEN DOSES
 WEEK_FINISH       = 672         %LENGTH OF EXPOSURE (HOUR)
 BCK_TIME_ON       = 0.          %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
 BCK_TIME_OFF      = 0.02        %TIME BACKGROUND EXPOSURE ENDS (HOUR)
  BW_T0            = 250         %BODY WEIGHT AT THE BEGINNING OF THE SIMULATION
(G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOTBCKGR      = 0.0125   %INITIAL LOADING DOSE [UG/KG]
   %MSTOT           = 0.00125 %EXPOSURE DOSE [UG/KG]
   %MSTOTBCKGR   = 0.05        %INITIAL LOADING DOSE [UG/KG]
   %MSTOT        = 0.005       %EXPOSURE DOSE [UG/KG]
   %MSTOTBCKGR   = 0.2         %INITIAL LOADING DOSE [UG/KG]
   %MSTOT        = 0.02        %EXPOSURE DOSE [UG/KG]
   %MSTOTBCKGR   = 0.8         %INITIAL LOADING DOSE [UG/KG]
   %MSTOT        = 0.08        %EXPOSURE DOSE [UG/KG]
   MSTOTBCKGR   = 3.2          %INITIAL LOADING DOSE [UG/KG]
   MSTOT        = 0.32         %EXPOSURE DOSE [UG/KG]
```

E.2.3.2.5. *Fattore et al. ([2000](#))*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Fattore et al. 2000
%protocol:  oral exposure in diet for 13 weeks; SD rats
%dose levels:  0.02, 0.1, 0.2, 2 ug/kg 7 days/week for 13 weeks
%dose levels equivalent to: 20, 100, 200, 2000 ng/kg 7 days/week for 13 weeks

MAXT = 0.01
CINT  = 0.1
EXP_TIME_ON       = 0.         %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 2184       %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE         = 24         %HOURS BETWEEN DOSES
BCK_TIME_ON       = 0.         %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF      = 0.         %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT         = 2184       %SIMULATION DURATION (HOUR)
BW_T0             = 150        %BODY WEIGHT AT THE BEGINNING OF THE SIMULATION
 (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT              = 0.02       %EXPOSURE DOSE IN UG/KG
```

```
%MSTOT            = 0.1       %EXPOSURE DOSE IN UG/KG
%MSTOT            = 0.2       %EXPOSURE DOSE IN UG/KG
 MSTOT            = 2         %EXPOSURE DOSE IN UG/KG
```

E.2.3.2.6. *Fox et al. (1993)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Fox 1993

 MAXT             = 0.001
 CINT             = 0.1
 TIMELIMIT        = 336       %SIMULATION DURATION (HOUR)
 EXP_TIME_ON      = 96        %TIME EXPOSURE BEGINS(HOUR)
 EXP_TIME_OFF     = 336       %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE        = 96        %HOURS BETWEEN DOSES
 BCK_TIME_ON      = 0.        %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
 BCK_TIME_OFF     = 0.02      %TIME BACKGROUND EXPOSURE ENDS (HOUR)
  BW_T0           = 200       %BODY WEIGHT AT THE BEGINNING OF THE SIMULATION
(G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
   MSTOTBCKGR      = 0.005     %INITIAL LOADING DOSE [UG/KG]
   MSTOT           = 0.0009    %EXPOSURE DOSE [UG/KG]
   %MSTOTBCKGR   = 2.5       %INITIAL LOADING DOSE [UG/KG]
   %MSTOT        = 0.6       %EXPOSURE DOSE [UG/KG]
   %MSTOTBCKGR   = 12.       %INITIAL LOADING DOSE [UG/KG]
   %MSTOT        = 3.5       %EXPOSURE DOSE [UG/KG]
```

E.2.3.2.7. *Franc et al. (2001) Sprague-Dawley rats*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Franc et al. 2001
% dose levels: 0.140, 0.420, and 1.400 ug/kg every 2 weeks for 22 weeks
% dose levels: 140, 420, and 1400 ng/kg every 2 weeks for 22 weeks
% dose levels equivalent to 10, 30, and 100 ng/kg-day

MAXT            =  0.01
CINT            =  0.1
EXP_TIME_ON     =  0.          %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  3696.       %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  336.
BCK_TIME_ON     =  0.          %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF    =  0.          %TIME OF BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT       =  3696.       %SIMULATION DURATION (HOUR)
BW_T0           =  200.        %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
```

```
%MSTOT              = 0.14           %ORAL EXPOSURE DOSE (UG/KG)
%MSTOT              = 0.42           %ORAL EXPOSURE DOSE (UG/KG)
 MSTOT              = 1.4            %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.8.   *Franc et al. ([2001](#)) Long-Evans rats*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Franc et al. 2001
% dose levels: 0.140, 0.420, and 1.400 ug/kg every 2 weeks for 22 weeks
% dose levels: 140, 420, and 1400 ng/kg every 2 weeks for 22 weeks
% dose levels equivalent to 10, 30, and 100 ng/kg-day

MAXT              =  0.01
CINT              =  0.1
EXP_TIME_ON       =  0.             %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      =  3696.          %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE         =  336.           %HOURS BETWEEN DOSES
BCK_TIME_ON       =  0.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF      =  0.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT         =  3696.          %SIMULATION DURATION (HOUR)
BW_T0             =  190.           %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT              = 0.14           %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT              = 0.42           %ORAL EXPOSURE DOSE (UG/KG)
    MSTOT              = 1.4            %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.9.   *Franc et al. ([2001](#)) Hans Wistar rats*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Franc et al. 2001
% dose levels: 0.140, 0.420, and 1.400 ug/kg every 2 weeks for 22 weeks
% dose levels: 140, 420, and 1400 ng/kg every 2 weeks for 22 weeks
% dose levels equivalent to 10, 30, and 100 ng/kg-day

MAXT              =  0.01
CINT              =  0.1
EXP_TIME_ON       =  0.             %TIME EXPOSURE BEGINS(HOUR)
EXP_TIME_OFF      =  3696.          %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE         =  336.           %HOURS BETWEEN DOSES
BCK_TIME_ON       =  0.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF      =  0.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT         =  3696.          %SIMULATION DURATION (HOUR)
BW_T0             =  205.           %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT              = 0.14           %ORAL EXPOSURE DOSE (UG/KG)
```

```
%MSTOT          = 0.42           %ORAL EXPOSURE DOSE (UG/KG)
 MSTOT          = 1.4            %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.10. *Hassoun et al. (2000)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Hassoun et al. 2000
%protocol:  oral exposure for 13 weeks; SD rats
%dose levels:  0.003, 0.010, 0.022, 0.046 0.1 ug/kg 5 days/week for 13 weeks
%dose levels equivalent to: 3, 10, 22, 46 100 ng/kg 5 days/week for 13 weeks
%dose levels equivalent to: 2.14, 7.14, 15.7, 32.9 71.4 ng/kg 7 days/week for
13 weeks

MAXT           = 0.01
CINT           = 0.1
EXP_TIME_ON    = 0.             %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF   = 2184.          %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE      = 24.            %HOURS BETWEEN DOSES
WEEK_PERIOD    = 168.           %HOURS IN A WEEK
WEEK_FINISH    = 119.           %LAST HOUR IN WEEK WHEN DOSE OCCURS
BCK_TIME_ON    = 0.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF   = 0.             %TIME EXPOSURE ENDS (HOUR)
TIMELIMIT      = 2184.          %SIMULATION DURATION (HOUR)
BW_T0          = 215.           %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
     %MSTOT          = 0.003        %EXPOSURE DOSE UG/KG
     %MSTOT          = 0.010        %EXPOSURE DOSE UG/KG
     %MSTOT          = 0.022        %EXPOSURE DOSE UG/KG
     %MSTOT          = 0.046        %EXPOSURE DOSE UG/KG
      MSTOT          = 0.1          %EXPOSURE DOSE UG/KG
```

E.2.3.2.11. *Hutt et al. (2008)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Hutt et al. 2008
% dose levels: 0.050 ug/kg every week for 13 weeks
% dose levels: 50 ng/kg every week for 13 weeks
% dose levels equivalent to 7.14 ng/kg-day

MAXT           =  0.01
CINT           =  0.1
EXP_TIME_ON    =  0.            %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF   =  2184.         %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE      =  168.          %HOURS BETWEEN DOSES
BCK_TIME_ON    =  0.            %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
BCK_TIME_OFF   =  0.            %TIME BACKGROUND EXPOSURE ENDS(HOUR)
TIMELIMIT      =  2184.         %SIMULATION DURATION (HOUR)
```

```
BW_T0              = 4.5            %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
    MSTOT          = 0.05           %ORAL EXPOSURE DOSE (UG/KG)

```

E.2.3.2.12. *Kitchin and Woods ([1979](#))*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Kitchen and Woods 1979
%protocol: single oral gavage
%dose levels:  0.0006, 0.002, 0.004, 0.020, 0.060, 0.200, 0.600, 2.000,
5.000, 20.000 ug/kg single oral gavage
% dose levels = 0.6, 2, 4, 20, 60, 200, 600, 2000, 5000, 20000 ng/kg single
oral gavage
MAXT              = 0.001
CINT              = 0.1
EXP_TIME_ON       = 0.             %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 24.            %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE         = 24.            %HOURS BETWEEN DOSES
BCK_TIME_ON       = 0.             %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
BCK_TIME_OFF      = 0.             %TIME OF BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT         = 24.            %SIMULATION DURATION (HOUR)
BW_T0             = 225.           %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
    %MSTOT         = 0.0006         %ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 0.002          %ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 0.004          %ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 0.020          %ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 0.060          %ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 0.200          %ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 0.600          %ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 2.000          %ORAL EXPOSURE DOSE (UG/KG)
    %MSTOT         = 5.000          %ORAL EXPOSURE DOSE (UG/KG)
    MSTOT          = 20.000         %ORAL EXPOSURE DOSE (UG/KG)

```

E.2.3.2.13. *Kociba et al. ([1976](#)) 13 weeks*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Kociba et al. 1976.
%dose levels:  0.001, 0.01, 0.1, 1 ug/kg 5 days/week for 13 weeks
%dose levels: 1, 10, 100, 1000 ng/kg 5 days/week for 13 weeks
%dose levels equivalent to: 0.714, 7.14, 71.4, 714 ng/kg-d (adj) 7 days/week
for 13 weeks

MAXT              = 0.001
CINT              = 0.1
```

```
EXP_TIME_ON        = 0.          %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF       = 2184        %TIME EXPOSURE ENDS (HOUR)
WEEK_PERIOD        = 168         %HOURS IN A WEEK
WEEK_FINISH        = 119         %LAST HOUR IN WEEK WHEN DOSE OCCURS
DAY_CYCLE          =  24         %HOURS BETWEEN DOSES
BCK_TIME_ON        = 0.          %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
BCK_TIME_OFF       = 0.          %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT          = 2184        %SIMULATION DURATION (HOUR)
BW_T0              = 180         %BODY WEIGHT AT THE BEGINNING OF THE SIMULATION
(G)
%EXPOSURE DOSE SCENARIOS (UG/KG)
%MSTOT            = 0.001        %ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT           = 0.01         %ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT           = 0.1          %ORAL EXPOSURE DOSE (UG/KG)
 MSTOT            = 1            %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.3.2.14. *Kociba et al. ([1978](#)) female, 104 weeks*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Kociba et al, 1978.
%protocol:  daily dietary exposure for 104 weeks; SD rats
%dose levels:  0.001, 0.01, 0.1 ug/kg 7 days/week for 104 weeks
%dose levels: 1, 10, 100 ng/kg 7 days/week for 104 weeks

MAXT              =  0.01
CINT              =  0.1
EXP_TIME_ON       = 0.           %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 17472        %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE         = 24           %HOURS BETWEEN DOSES
BCK_TIME_ON       = 0.           %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF      = 0.           %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT         = 17472        %SIMULATION DURATION (HOUR)
BW_T0             = 180          %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT           = 0.001        %EXPOSURE DOSE IN UG/KG
 %MSTOT           = 0.01         %EXPOSURE DOSE IN UG/KG
 MSTOT           = 0.1          %EXPOSURE DOSE IN UG/KG
```

E.2.3.2.15. *Kociba et al. ([1978](#)) male, 104 weeks*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Kociba et al, 1978.
%dose levels:  0.001, 0.01, 0.1 ug/kg 7 days/week for 104 weeks
%dose levels: 1, 10, 100 ng/kg 7 days/week for 104 weeks

MAXT              =  0.01
CINT              =  0.1
```

```
1   EXP_TIME_ON     = 0.              %TIME EXPOSURE BEGINS (HOUR)
2   EXP_TIME_OFF    = 17472          %TIME EXPOSURE ENDS (HOUR)
3   DAY_CYCLE       = 24             %HOURS BETWEEN DOSES
4   BCK_TIME_ON     = 0.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
5   BCK_TIME_OFF    = 0.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
6   TIMELIMIT       = 17472          %SIMULATION DURATION (HOUR)
7   BW_T0           = 250            %BODY WEIGHT AT THE BEGINNING OF THE
8   SIMULATION (G)
9
10  %EXPOSURE DOSE SCENARIOS (UG/KG)
11   %MSTOT         = 0.001          %EXPOSURE DOSE IN UG/KG
12   %MSTOT         = 0.01           %EXPOSURE DOSE IN UG/KG
13   MSTOT          = 0.1            %EXPOSURE DOSE IN UG/KG
14
```

15 **E.2.3.2.16.** *Latchoumycandane and Mathur (2002)*

```
16  output @clear
17  prepare @clear
18  prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG
19
20  % Latchoumycandane and Mathur 2002.
21  %protocol:  1 time per day for 45 days oral gavage
22  %dose levels:  0.001, 0.01, 0.1 ug/kg daily for 45 days
23  %dose levels:  1, 10, 100 ng/kg daily for 45 days
24
25  MAXT            = 0.01
26  CINT            = 0.1
27  EXP_TIME_ON     = 0.             %TIME EXPOSURE BEGINS (HOUR)
28  EXP_TIME_OFF    = 1080           %TIME EXPOSURE ENDS (HOUR)
29  DAY_CYCLE       = 24             %HOURS BETWEEN DOSES
30  BCK_TIME_ON     = 0.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
31  BCK_TIME_OFF    = 0.             %TIME OF BACKGROUND EXPOSURE ENDS (HOUR)
32  TIMELIMIT       = 1080           %SIMULATION DURATION (HOUR)
33  BW_T0           = 200            %BODY WEIGHT AT THE BEGINNING OF THE
34  SIMULATION (G)
35
36  %EXPOSURE DOSE SCENARIOS (UG/KG)
37    %MSTOT        = 0.001          %EXPOSURE DOSE UG/KG
38    %MSTOT        = 0.01           %EXPOSURE DOSE UG/KG
39    MSTOT         = 0.1            %EXPOSURE DOSE UG/KG
40
41
```

42 **E.2.3.2.17.** *Li et al. (1997)*

```
43  output @clear
44  prepare @clear
45  prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG
46
47  % Li et al 1997
48  % dose levels: 3, 10, 30, 100, 300, 1000, 3000, 10000, 30000 nkd one dose via
49  gavage, sacrificed 24 hrs later
50
51  MAXT            =  0.1
52  CINT            =  0.1
53  EXP_TIME_ON     =  0.            %TIME EXPOSURE BEGINS (HOUR)
```

```
1    EXP_TIME_OFF     =  24.              %TIME EXPOSURE ENDS(HOUR)
2    DAY_CYCLE        =  24.              %HOURS BETWEEN DOSES
3    BCK_TIME_ON      =  0.               %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
4    BCK_TIME_OFF     =  0.               %TIME BACKGROUND EXPOSURE ENDS (HOUR)
5    TIMELIMIT        =  24.              %SIMULATION DURATION (HOUR)
6    BW_T0            =  56.5             %BODY WEIGHT AT THE BEGINNING OF THE
7    SIMULATION (G)
8
9    %EXPOSURE DOSE SCENARIOS (UG/KG)
10      MSTOT          = 0.003            %ORAL EXPOSURE DOSE (UG/KG)
11      %MSTOT         = 0.01             %ORAL EXPOSURE DOSE (UG/KG)
12      %MSTOT         = 0.03             %ORAL EXPOSURE DOSE (UG/KG)
13      %MSTOT         = 0.1              %ORAL EXPOSURE DOSE (UG/KG)
14      %MSTOT         = 0.3              %ORAL EXPOSURE DOSE (UG/KG)
15      %MSTOT         = 1.               %ORAL EXPOSURE DOSE (UG/KG)
16      %MSTOT         = 3.               %ORAL EXPOSURE DOSE (UG/KG)
17      %MSTOT         = 10.              %ORAL EXPOSURE DOSE (UG/KG)
18      %MSTOT         = 30.              %ORAL EXPOSURE DOSE (UG/KG)
19
```

20 **E.2.3.2.18.** *Murray et al. ([1979](#))*

```
21   output @clear
22   prepare @clear
23   prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG
24
25   % Murray et al 1979
26   %built and check in August 7 2009
27   %protocol:  dietary exposure for 3 generations (assume 120 day exposure for
28   each)
29   %dose levels: 0.001 0.01, 0.1 ug/kg-d
30   %dose levels: 1, 10, 100  ng/kg-d
31
32   MAXT             =  0.01
33   CINT             =  0.1
34   EXP_TIME_ON      =  0.               %TIME EXPOSURE BEGINS (HOUR)
35   EXP_TIME_OFF     =  2880             %TIME EXPOSURE ENDS (HOUR)
36   DAY_CYCLE        =  24.              %HOURS BETWEEN DOSES
37   BCK_TIME_ON      =  0.               %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
38   BCK_TIME_OFF     =  0.               %TIME BACKGROUND EXPOSURE ENDS (HOUR)
39   TIMELIMIT        =  2880             %SIMULATION DURATION (HOUR)
40   BW_T0            =  4.5              % BODY WEIGHT AT THE BEGINNING OF THE
41   SIMULATION (G)
42
43   %EXPOSURE DOSE SCENARIOS (UG/KG)
44     %MSTOT          = 0.001            %ORAL EXPOSURE DOSE IN UG/KG
45     %MSTOT          = 0.01             %ORAL EXPOSURE DOSE IN UG/KG
46     MSTOT           = 0.1              %ORAL EXPOSURE DOSE IN UG/KG
47
```

48 **E.2.3.2.19.** *National Toxicoloty Program ([NTP, 1982](#)) female, chronic*

```
49   output @clear
50   prepare @clear
51   prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG
52
53   %NTP 1982
```

```
%dose levels:  0.005, 0.025, 0.25 ug/kg twice weekly for 104 weeks
%dose levels:  5, 25, 250 ng/kg twice weekly for 104 weeks
%dose levels equivalent to: 1.43, 7.14, 71.4 ng/kg-day (adj)

MAXT              = 0.01
CINT              = 0.1
EXP_TIME_ON       = 0.              %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 17472           %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE         = 84              %HOURS BETWEEN DOSES
BCK_TIME_ON       = 0.              %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF      = 0.              %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT         = 17472           %SIMULATION DURATION (HOUR)
BW_T0             = 250             %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)

  %MSTOT          = 0.005           %EXPOSURE DOSE UG/KG
  %MSTOT          = 0.025           %EXPOSURE DOSE UG/KG
  MSTOT           = 0.25            %EXPOSURE DOSE UG/KG
```

E.2.3.2.20. *NTP (1982) male,chronic*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

%NTP 1982
%dose levels:  0.005, 0.025, 0.25 ug/kg twice weekly for 104 weeks
%dose levels:  5, 25, 250 ng/kg twice weekly for 104 weeks
%dose levels equivalent to: 1.43, 7.14, 71.4 ng/kg-day (adj)

MAXT              = 0.01
CINT              = 0.1
EXP_TIME_ON       = 0.              %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF      = 17472           %TIME EXPOSURE ENDS(HOUR)
DAY_CYCLE         = 84              %HOURS BETWEEN DOSES
BCK_TIME_ON       = 0.              %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF      = 0.              %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT         = 17472           %SIMULATION DURATION (HOUR)
BW_T0             = 350             %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
%EXPOSURE DOSE SCENARIOS (UG/KG)

%MSTOT            = 0.005           %EXPOSURE DOSE UG/KG
%MSTOT            = 0.025           %EXPOSURE DOSE UG/KG
MSTOT             = 0.25            %EXPOSURE DOSE UG/KG
```

E.2.3.2.21. *NTP (2006)14 weeks*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% NTP 2006
```

```
1    %dose levels:  0.003, 0.010, 0.022, 0.046 0.1 ug/kg 5 days/week for 14 weeks
2    %dose levels equivalent to: 3, 10, 22, 46 100 ng/kg 5 days/week for 14 weeks
3    %dose levels equivalent to: 2.14, 7.14, 15.7, 32.9 71.4 ng/kg-day days/week
4
5    MAXT            = 0.01
6    CINT            = 0.1
7    EXP_TIME_ON     = 0.            %TIME EXPOSURE BEGINS (HOUR)
8    EXP_TIME_OFF    = 2352          %TIME EXPOSURE ENDS (HOUR)
9    DAY_CYCLE       =  24           %HOURS BETWEEN DOSES
10   WEEK_PERIOD     = 168           %HOURS IN A WEEK
11   WEEK_FINISH     = 119           %LAST HOUR IN WEEK WHEN DOSE OCCURS
12   BCK_TIME_ON     = 0.            %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
13   BCK_TIME_OFF    = 0.            %TIME BACKGROUND EXPOSURE ENDS (HOUR)
14   TIMELIMIT       = 2352          %SIMULATION DURATION (HOUR)
15   BW_T0           = 215           %BODY WEIGHT AT THE BEGINNING OF THE
16   SIMULATION (G)
17   %EXPOSURE DOSE SCENARIOS (UG/KG)
18       %MSTOT       = 0.003         %EXPOSURE DOSE UG/KG
19       %MSTOT       = 0.010         %EXPOSURE DOSE UG/KG
20       %MSTOT       = 0.022         %EXPOSURE DOSE UG/KG
21       %MSTOT       = 0.046         %EXPOSURE DOSE UG/KG
22        MSTOT       = 0.1           %EXPOSURE DOSE UG/KG
23
```

24 **E.2.3.2.22. *NTP ([2006](#)) 31 weeks***

```
25   output @clear
26   prepare @clear
27   prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG
28
29   % NTP 2006
30   %dose levels:  0.003, 0.010, 0.022, 0.046 0.1 ug/kg 5 days/week for 31 weeks
31   %dose levels equivalent to: 3, 10, 22, 46 100 ng/kg 5 days/week for 31 weeks
32   %dose levels equivalent to: 2.14, 7.14, 15.7, 32.9 71.4 ng/kg 7 days/week for
33   31 weeks
34
35   MAXT            = 0.01
36   CINT            = 0.1
37   EXP_TIME_ON     = 0.            %TIME EXPOSURE BEGINS (HOUR)
38   EXP_TIME_OFF    = 5208          %TIME EXPOSURE ENDS (HOUR)
39   DAY_CYCLE       =  24           %HOURS BETWEEN DOSES
40   WEEK_PERIOD     = 168           %HOURS IN A WEEK
41   WEEK_FINISH     = 119           %LAST HOUR IN WEEK WHEN DOSE OCCURS
42   BCK_TIME_ON     = 0.            %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
43   BCK_TIME_OFF    = 0.            %TIME BACKGROUND EXPOSURE ENDS (HOUR)
44   TIMELIMIT       = 5208          %SIMULATION DURATION (HOUR)
45   BW_T0           = 215           %BODY WEIGHT AT THE BEGINNING OF THE
46   SIMULATION (G)
47
48   %EXPOSURE DOSE SCENARIOS (UG/KG)
49       %MSTOT       = 0.003         %EXPOSURE DOSE UG/KG
50       %MSTOT       = 0.010         %EXPOSURE DOSE UG/KG
51       %MSTOT       = 0.022         %EXPOSURE DOSE UG/KG
52       %MSTOT       = 0.046         %EXPOSURE DOSE UG/KG
53        MSTOT       = 0.1           %EXPOSURE DOSE UG/KG
54
```

E.2.3.2.23. *NTP (2006) 53 weeks*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% NTP 2006
%protocol:  oral exposure for 53 weeks; SD rats
%dose levels:  0.003, 0.010, 0.022, 0.046 0.1 ug/kg 5 days/week for 53 weeks
%dose levels equivalent to: 3, 10, 22, 46 100 ng/kg 5 days/week for 53 weeks
%dose levels equivalent to: 2.14, 7.14, 15.7, 32.9 71.4 ng/kg 7 days/week for
53 weeks

MAXT            = 0.01
CINT            = 0.1
EXP_TIME_ON     = 0.           %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    = 8904         %TIME EXPOSURE ENDS(HOUR)
DAY_CYCLE       =  24          %HOURS BETWEEN DOSES
WEEK_PERIOD     = 168          %HOURS IN A WEEK
WEEK_FINISH     = 119          %LAST HOUR IN WEEK WHEN DOSE OCCURS
BCK_TIME_ON     = 0.           %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
BCK_TIME_OFF    = 0.           %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT       = 8904         %SIMULATION DURATION (HOUR)
BW_T0           = 215          %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
     %MSTOT       = 0.003      %EXPOSURE DOSE UG/KG
     %MSTOT       = 0.010      %EXPOSURE DOSE UG/KG
     %MSTOT       = 0.022      %EXPOSURE DOSE UG/KG
     %MSTOT       = 0.046      %EXPOSURE DOSE UG/KG
     MSTOT       = 0.1         %EXPOSURE DOSE UG/KG
```

E.2.3.2.24. *NTP (2006) 2 year*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% NTP 2006
%protocol:  oral exposure for 105 weeks; SD rats
%dose levels:  0.003, 0.010, 0.022, 0.046, 0.1 ug/kg 5 days/week for 105
weeks
%dose levels equivalent to: 3, 10, 22, 46, 100 ng/kg 5 days/week for 105
weeks
%dose levels equivalent to: 2.14, 7.14, 15.7, 32.9, 71.4 ng/kg 7 days/week
for 105 weeks

MAXT            = 0.01
CINT            = 0.1
EXP_TIME_ON     = 0.           %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    = 17640        %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  24          %HOURS BETWEEN DOSES
WEEK_PERIOD     = 168          %HOURS IN A WEEK
WEEK_FINISH     = 119          %LAST HOUR IN WEEK WHEN DOSE OCCURS
BCK_TIME_ON     = 0.           %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
```

```
1    BCK_TIME_OFF    = 0.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
2    TIMELIMIT       = 17640          %SIMULATION DURATION (HOUR)
3    BW_T0           = 215            %BODY WEIGHT AT THE BEGINNING OF THE
4    SIMULATION (G)
5
6    %EXPOSURE DOSE SCENARIOS (UG/KG)
7        %MSTOT       = 0.003          %EXPOSURE DOSE IN UG/KG
8        %MSTOT       = 0.010          %EXPOSURE DOSE IN UG/KG
9        %MSTOT       = 0.022          %EXPOSURE DOSE IN UG/KG
10       %MSTOT       = 0.046          %EXPOSURE DOSE IN UG/KG
11       MSTOT        = 0.1            %EXPOSURE DOSE IN UG/KG
12
```

E.2.3.2.25. *Sewall et al. (1995) and Maronpot et al. (1993)*

```
14   output @clear
15   prepare @clear
16   prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG
17   % Sewall et al. 1995
18   %protocol: gavage every 2 weeks for 30 weeks
19   %dose levels: 0.049, 0.1498, 0.49, and 1.75 ug/kg every 2 weeks
20   %dose levels: 3.5, 10.7, 35, and 125 ng/kg-d or 49, 149.8, 490, and 1750
21   ng/kg every 2 weeks
22
23   MAXT            = 0.01
24   CINT            = 0.1
25   EXP_TIME_ON     = 0.             %TIME EXPOSURE BEGINS (HOUR)
26   EXP_TIME_OFF    = 5040           %TIME EXPOSURE ENDS(HOUR)
27   DAY_CYCLE       = 336.           %HOURS BETWEEN DOSES
28   BCK_TIME_ON     = 0.             %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
29   BCK_TIME_OFF    = 0.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
30   TIMELIMIT       = 5040           %SIMULATION DURATION (HOUR)
31   BW_T0           = 250            %BODY WEIGHT AT THE BEGINNING OF THE
32   SIMULATION (G)
33
34   %EXPOSURE DOSE SCENARIOS (UG/KG)
35     %MSTOT         = 0.049          %ORAL EXPOSURE DOSE (UG/KG)
36     %MSTOT         = 0.1498         %ORAL EXPOSURE DOSE (UG/KG)
37     %MSTOT         = 0.49           %ORAL EXPOSURE DOSE (UG/KG)
38     MSTOT          = 1.75           %ORAL EXPOSURE DOSE (UG/KG)
39
```

E.2.3.2.26. *Shi et al. (2007) adult portion*

```
41   output @clear
42   prepare @clear
43   prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG
44
45   % Shi et al 2007
46   %protocol:  gavage once per week for 322 days
47   %dose levels: 0.001, 0.005, 0.05 and 0.2 ug TCDD:kg body weight by gavage
48   once per week
49   %dose levels: 1, 5, 50 and 200 ng/kg ng TCDD:kg body weight by gavage once
50   per week
51   % dose equivalent adjusted 0.143, 0.714, 7.14 and 28.6 ng/kg-d
52
53   MAXT            = 0.0001
```

```
1   CINT              =  0.1
2   EXP_TIME_ON       =  504.           %TIME EXPOSURE BEGINS (HOUR)
3   EXP_TIME_OFF      =  7728           %TIME EXPOSURE ENDS (HOUR)
4   DAY_CYCLE         =  168.           %HOURS BETWEEN DOSES
5   BCK_TIME_ON       =  0.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
6   BCK_TIME_OFF      =  0.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
7   TIMELIMIT         =  7728           %SIMULATION DURATION (HOUR)
8   BW_T0             =  4.5            %BODY WEIGHT AT THE BEGINNING OF THE
9   SIMULATION (G)
10
11  %EXPOSURE DOSE SCENARIOS (UG/KG)
12    %MSTOT          = 0.001          %ORAL EXPOSURE DOSE IN UG/KG
13    %MSTOT          = 0.005          %ORAL EXPOSURE DOSE IN UG/KG
14    %MSTOT          = 0.05           %ORAL EXPOSURE DOSE IN UG/KG
15     MSTOT          = 0.2            %ORAL EXPOSURE DOSE IN UG/KG
16
```

17 ### E.2.3.2.27. *Van Birgelen et al. ([1995](#))*

```
18  output @clear
19  prepare @clear
20  prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG
21
22  % Van Birgelen et al. (1995)
23  %protocol:  daily dietary exposure for 13 weeks
24  %dose levels: 0.0135, 0.0264, 0.0469, 0.320, 1.024 ug/kg every day for 13
25  weeks
26  % dose levels = 13.5, 26.4, 46.9, 320, 1024 ng/kg every day for 13 weeks
27  MAXT              =  0.001
28  CINT              =  0.1
29  EXP_TIME_ON       =  0.             %TIME EXPOSURE BEGINS (HOUR)
30  EXP_TIME_OFF      =  2184.          %TIME EXPOSURE ENDS (HOUR)
31  DAY_CYCLE         =  24.            %HOURS BETWEEN DOSES
32  BCK_TIME_ON       =  0.             %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
33  BCK_TIME_OFF      =  0.             %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
34  TIMELIMIT         =  2184.          %SIMULATION LIMIT TIME (HOUR)
35  BW_T0             =  150.           %BODY WEIGHT AT THE BEGINNING OF THE
36  SIMULATION (G)
37
38  %EXPOSURE DOSE SCENARIOS (UG/KG)
39    %MSTOT          = 0.0135          %ORAL EXPOSURE DOSE (UG/KG)
40    %MSTOT          = 0.0264          %ORAL EXPOSURE DOSE (UG/KG)
41    %MSTOT          = 0.0469          %ORAL EXPOSURE DOSE (UG/KG)
42    %MSTOT          = 0.320           %ORAL EXPOSURE DOSE (UG/KG)
43     MSTOT          = 1.024           %ORAL EXPOSURE DOSE (UG/KG)
44
```

45 ### E.2.3.2.28. *Simanainen et al. ([2002](#)) and Simanainen et al. ([2003](#))*

```
46  output @clear
47  prepare @clear
48  prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG
49
50  % Simanainen et al., 2002 and Simanainen et al., 2003
51
52   MAXT             =  0.01
53   CINT             =  0.1
```

```
 1    TIMELIMIT          = 24              %SIMULATION DURATION (HOUR)
 2    EXP_TIME_ON        = 0               %TIME EXPOSURE BEGINS (HOUR)
 3    EXP_TIME_OFF       = 24              %TIME EXPOSURE ENDS (HOUR)
 4    DAY_CYCLE          = 24              %HOURS BETWEEN DOSES
 5    BCK_TIME_ON        = 0.              %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 6    BCK_TIME_OFF       = 0.              %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 7    BW_T0              = 200             %BODY WEIGHT AT THE BEGINNING OF THE
 8    SIMULATION (G)
 9
10    %EXPOSURE DOSE SCENARIOS (UG/KG)
11       %MSTOT         = 0.1             %EXPOSURE DOSE [UG/KG]
12        MSTOT         = 0.3             %EXPOSURE DOSE [UG/KG]
13
```

14 **E.2.3.2.29.** *Vanden Heuvel et al. ([1994](#))*

```
15    output @clear
16    prepare @clear
17    prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG
18
19    % Vanden Heuvel et al. 1994.
20    %protocol: single gavage
21    %dose levels:0.00005, 0.0001, 0.001, 0.010, 0.1, 1, 10 ug/kg-d
22    %dose levels equivalent to: 0.05, 0.1, 1, 10, 100, 1000, 10000 ng/kg-d
23
24    MAXT               = 0.001
25    CINT               = 0.1
26    EXP_TIME_ON        = 0.              %TIME EXPOSURE BEGINS (HOUR)
27    EXP_TIME_OFF       = 24              %TIME EXPOSURE ENDS (HOUR)
28    DAY_CYCLE          = 24              %HOURS BETWEEN DOSES
29    BCK_TIME_ON        = 0.              %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
30    BCK_TIME_OFF       = 0.              %TIME BACKGROUND EXPOSURE ENDS (HOUR)
31    TIMELIMIT          = 24              %SIMULATION DURATION (HOUR)
32    BW_T0              = 250             %BODY WEIGHT AT THE BEGINNING OF THE
33    SIMULATION (G)
34
35    %EXPOSURE DOSE SCENARIOS (UG/KG)
36
37      %MSTOT            = 0.00005       %EXPOSURE DOSE UG/KG
38      %MSTOT           = 0.0001        %EXPOSURE DOSE UG/KG
39      %MSTOT           = 0.001         %EXPOSURE DOSE UG/KG
40      %MSTOT           = 0.01          %EXPOSURE DOSE UG/KG
41      %MSTOT           = 0.1           %EXPOSURE DOSE UG/KG
42      %MSTOT           = 1             %EXPOSURE DOSE UG/KG
43       MSTOT           = 10            %EXPOSURE DOSE UG/KG
44
```

45 **E.2.4.   Rat Gestational Model**

46 **E.2.4.1.** *Model Code*

47 PROGRAM: 'Three Compartment PBPK Model for TCDD in Rat (Gestation)'

```
48
49
50    INITIAL  ! INITIALIZATION OF PARAMETERS
51
52        !SIMULATION PARAMETERS ====
```

```
1    CONSTANT PARA_ZERO           = 1E-30
2    CONSTANT EXP_TIME_ON      = 0.0        ! TIME AT WHICH EXPOSURE BEGINS (HOURS)
3    CONSTANT EXP_TIME_OFF     = 530        ! TIME AT WHICH EXPOSURE ENDS (HOURS)
4    CONSTANT DAY_CYCLE        = 24.0       ! NUMBER OF HOURS BETWEEN DOSES (HOURS)
5    CONSTANT BCK_TIME_ON      = 0.0        ! TIME AT WHICH BACKGROUND EXPOSURE
6    BEGINS (HOURS)
7    CONSTANT BCK_TIME_OFF     = 0.0        ! TIME AT WHICH BACKGROUND EXPOSURE ENDS
8    (HOURS)
9    CONSTANT TRANSTIME_ON     = 144.0      !CONTROL TRANSFER FROM MOTHER TO FETUS
10   AT GESTATIONAL DAY 6
11
12    !UNIT CONVERSION
13   CONSTANT MW=322 ! MOLECULAR WEIGHT (NG/NMOL)
14   CONSTANT SERBLO = 0.55
15   CONSTANT UNITCORR = 1000
16
17
18       !INTRAVENOUS SEQUENCE
19   constant IV_LAG        = 0.0
20   constant IV_PERIOD     = 0.0
21
22       !PREGNANCY PARAMETER ====
23   CONSTANT CONCEPTION_T        = 0.0        !TIME OF CONCEPTION(HOUR)
24   CONSTANT N_FETUS         = 10.0       !NUMBER OF FETUS PRESENT
25
26       !CONSTANT EXPOSURE CONTROL ===========
27       !ACUTE, SUBCHRONIC, CHRONIC EXPOSURE =====
28       !OR BACKGROUND EXPOSURE (IN THIS CASE 3 TIMES A DAY)===
29   CONSTANT MSTOTBCKGR      = 0.0        ! ORAL BACKGROUND EXPOSURE DOSE (UG/KG)
30   CONSTANT MSTOT           = 0.0        ! ORAL EXPOSURE DOSE (UG/KG)
31
32       !ORAL ABSORPTION
33     MSTOT_NM = MSTOT/MW                ! CONVERTS THE DOSE TO NMOL/G
34
35       !INTRAVENOUS ABSORPTION
36   CONSTANT  DOSEIV         = 0.0        ! INJECTED DOSE (UG/KG)
37     DOSEIV_NM = DOSEIV/MW              ! CONVERTS THE INJECTED DOSE TO NMOL/G
38   CONSTANT DOSEIVLATE = 0.0            ! INJECTED DOSE LATE (UG/KG)
39     DOSEIVNMlate = DOSEIVLATE/MW      !AMOUNT IN NMOL/G
40
41       !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
42   INDICATED BELOW)====
43   CONSTANT CFLLI0          = 0.0  !LIVER    (NMOL/ML)
44   CONSTANT CFLPLA0         = 0.0  !PLACENTA (NMOL/ML)
45
46       !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
47   BELOW) (NMOL/ML) ===
48   CONSTANT LIBMAX          = 3.5E-4    ! LIVER  (NMOL/ML), WANG ET AL. 1997
49   CONSTANT PLABMAX         = 2.0E-4    !TEMPORARY PARAMETER
50
51       ! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
52   (NMOL/ML)===
53   CONSTANT KDLI            = 1.0E-4    !LIVER (AhR) (NMOL/ML), WANG ET AL. 1997
54   CONSTANT KDLI2           = 4.0E-2    !LIVER (1A2) (NMOL/ML), EMOND ET AL. 2004
55   CONSTANT KDPLA           = 1.0E-4    !TEMPORARY PARAMETER; ASSUME IDENTICAL TO
56   KDLI (AhR)
57
```

```
 1      !EXCRETION AND ABSORPTION CONSTANT
 2   CONSTANT KST            = 0.36     ! GASTRIC RATE CONSTANT (HR-1), WANG ET
 3   AL. 1997
 4   CONSTANT KABS           = 0.48     !INTESTINAL ABSORPTION CONSTANT (HR-1) ),
 5   WANG ET AL. 1997
 6
 7      ! ELIMINATION CONSTANTS
 8   CONSTANT CLURI          = 0.01     ! URINARY CLEARANCE (ML/HR), EMOND ET
 9   AL. 2004
10
11      !INTERSPECIES ELIMINATION VARIABLE
12   CONSTANT kelv           = 0.15     ! INTERSPECIES VARIABLE ELIMINATION
13   CONSTANT (1/HOUR)
14
15      ! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
16   CONSTANT A              = 0.7       ! LYMPHATIC FRACTION, WANG ET AL. 1997
17
18      !PARTITION COEFFICIENTS
19   CONSTANT PF             = 100     ! ADIPOSE TISSUE/BLOOD, WANG ET AL. 1997
20   CONSTANT PRE            = 1.5      ! REST OF THE BODY/BLOOD, WANG ET AL.
21   1997
22   CONSTANT PLI            = 6.0       ! LIVER/BLOOD, WANG ET AL. 1997
23   CONSTANT PPLA           = 1.5      ! TEMPORARY PARAMETER NOT CONFIGURED,
24   WANG ET AL. 1997
25
26      !PARAMETER FOR INDUCTION OF CYP 1A2, WANG ET AL. 1997
27   CONSTANT IND_ACTIVE      = 1.0         ! INCLUDE INDUCTION? (1 = YES, 0 = NO)
28   CONSTANT CYP1A2_1OUTZ    = 1.6      ! DEGRADATION CONCENTRATION CONSTANT OF
29   1A2 (NMOL/ML)
30   CONSTANT CYP1A2_1A1      = 1.6      ! BASAL CONCENTRATION OF 1A1 (NMOL/ML)
31   CONSTANT CYP1A2_1EC50    = 0.13      ! DISSOCIATION CONSTANT TCDD-CYP1A2
32   (NMOL/ML)
33   CONSTANT CYP1A2_1A2      = 1.6      !BASAL CONCENTRATION OF 1A2 (NMOL/ML)
34   CONSTANT CYP1A2_1KOUT    = 0.1      ! FIRST ORDER RATE OF DEGRADATION (H-1)
35   CONSTANT CYP1A2_1TAU     = 0.25     !HOLDING TIME (H)
36   CONSTANT CYP1A2_1EMAX    = 600      ! MAXIMUM INDUCTION OVER BASAL EFFECT
37   (UNITLESS)
38   CONSTANT HILL           = 0.6       !HILL CONSTANT; COOPERATIVE LIGAND
39   BINDING EFFECT CONSTANT (UNITLESS)
40
41      !DIFFUSIONAL PERMEABILITY FRACTION
42   CONSTANT PAFF           = 0.0910    !ADIPOSE (UNITLESS), WANG ET AL. 1997
43   CONSTANT PAREF          = 0.0298    !REST OF THE BODY  (UNITLESS), WANG ET
44   AL. 1997
45   CONSTANT PALIF          = 0.3500    !LIVER (UNITLESS), WANG ET AL. 1997
46   CONSTANT PAPLAF         = 0.3       !TEMPORARY PARAMETER NOT CONFIGURED
47
48      !FRACTION OF TISSUE WEIGHT =========
49   CONSTANT WLI0           = 0.0360    !LIVER, WANG ET AL. 1997
50
51      !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT
52   CONSTANT QFF            = 0.069     ! ADIPOSE TISSUE BLOOD FLOW FRACTION
53   (UNITLESS), WANG ET AL. 1997
54   CONSTANT QLIF           = 0.183     !LIVER (UNITLESS), WANG ET AL. 1997
55
56      !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL COMPARTMENT
57   VOLUME
```

```
1    CONSTANT WFB0             = 0.050     !ADIPOSE TISSUE, WANG ET AL. 1997
2    CONSTANT WREB0            = 0.030     !REST OF THE BODY, WANG ET AL. 1997
3    CONSTANT WLIB0            = 0.266     !LIVER, WANG ET AL. 1997
4    CONSTANT WPLAB0           = 0.500     !TEMPORARY PARAMETER NOT CONFIGURED
5
6       !EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
7       !NUMBER OF EXPOSURES PER WEEK
8    CONSTANT WEEK_LAG        = 0.0       !TIME ELAPSED BEFORE EXPOSURE BEGINS
9    (WEEK)
10   CONSTANT WEEK_PERIOD     = 168       ! NUMBER OF HOURS IN THE WEEK (HOURS)
11   CONSTANT WEEK_FINISH     = 168       ! TIME EXPOSURE ENDS (HOURS)
12
13      !NUMBER OF EXPOSURES PER MONTH
14   CONSTANT MONTH_LAG       = 0.0       !TIME ELAPSED BEFORE EXPOSURE BEGINS
15   (MONTHS)
16
17      !CONSTANT FOR BACKGROUND EXPOSURE==========
18   CONSTANT Day_LAG_BG      = 0.0       !TIME ELAPSED BEFORE EXPOSURE BEGINS
19   (HOURS)
20   CONSTANT Day_PERIOD_BG   = 24        !LENGTH OF EXPOSURE (HOURS)
21
22      !NUMBER OF EXPOSURES PER WEEK
23   CONSTANT WEEK_LAG_BG      = 0.0       !TIME ELAPSED BEFORE BACKGROUND EXPOSURE
24   BEGINS (WEEKS)
25   CONSTANT WEEK_PERIOD_BG   = 168       !NUMBER OF HOURS IN THE WEEK (HOURS)
26   CONSTANT WEEK_FINISH_BG   = 168       !TIME EXPOSURE ENDS (HOURS)
27
28      !INITIAL BODY WEIGHT
29   CONSTANT BW_T0           = 250       ! (IN G) WANG ET AL. 1997
30   CONSTANT RATIO_RATF_MOUSEF = 1.0        !RATIO OF FETUS MOUSE/RAT AT
31   GESTATIONAL DAY 22
32
33      ! COMPARTMENT TOTAL LIPID FRACTION , POULIN ET AL 2000
34   CONSTANT F_TOTLIP         = 0.855               ! ADIPOSE TISSUE (UNITLESS)
35   CONSTANT B_TOTLIP         = 0.0023               ! BLOOD (UNITLESS)
36   CONSTANT RE_TOTLIP        = 0.019               ! REST OF THE BODY
37   (UNITLESS)
38   CONSTANT LI_TOTLIP        = 0.060               ! LIVER (UNITLESS)
39   CONSTANT PLA_TOTLIP       = 0.019
40   CONSTANT FETUS_TOTLIP     = 0.019
41
42   END     ! END OF THE INITIAL SECTION
43
44   DYNAMIC ! DYNAMIC SIMULATION SECTION
45   ALGORITHM  IALG         =              2         ! GEAR METHOD
46   CINTERVAL  CINT         =              0.1       ! COMMUNICATION INTERVAL
47   MAXTERVAL  MAXT         =              1.0e+10   ! MAXIMUM CALCULATION INTERVAL
48   MINTERVAL  MINT         =              1.0E-10   ! MINIMUM CALCULATION INTERVAL
49   VARIABLE   T            =              0.0
50   CONSTANT   TIMELIMIT    =              100       !SIMULATION LIMIT TIME (HOURS)
51    CINTXY  = CINT
52    PFUNC   = CINT
53
54      !TIME CONVERSION
55    DAY          = T/24         ! TIME IN DAYS
56    WEEK         = T/168        ! TIME IN WEEKS
57    MONTH        = T/730        ! TIME IN MONTHS
```

```
 1     YEAR        = T/8760            ! TIME IN YEARS
 2
 3   DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS
 4
 5      !CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
 6      !NUMBER OF EXPOSURES PER DAY
 7    DAY_LAG          = EXP_TIME_ON    ! TIME ELAPSED BEFORE EXPOSURE BEGINS
 8   (HOURS)
 9    DAY_PERIOD       = DAY_CYCLE       ! EXPOSURE PERIOD (HOURS)
10    DAY_FINISH       = CINTXY          ! LENGTH OF EXPOSURE (HOURS)
11    MONTH_PERIOD     = TIMELIMIT       ! EXPOSURE PERIOD (MONTHS)
12    MONTH_FINISH     = EXP_TIME_OFF    ! LENGTH OF EXPOSURE (MONTHS)
13
14      !NUMBER OF EXPOSURES PER DAY AND MONTH
15    DAY_FINISH_BG    = CINTXY
16    MONTH_LAG_BG     = BCK_TIME_ON     !TIME ELAPSED BEFORE BACKGROUND EXPOSURE
17   BEGINS (MONTHS)
18    MONTH_PERIOD_BG  = TIMELIMIT       !BACKGROUND EXPOSURE (MONTHS)
19    MONTH_FINISH_BG  = BCK_TIME_OFF    !LENGTH OF BACKGROUND EXPOSURE (MONTHS)
20
21      !INTRAVENOUS LATE
22    IV_FINISH = CINTXY
23    B = 1-A ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER
24
25
26   !FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUM
27   E
28     ! FROM OFLAHERTY_1992
29
30   RTESTGEST= T-CONCEPTION_T
31   TESTGEST=DIM(RTESTGEST,0.0)
32
33   WTFER_RODENT= (2.3d-3*EXP(1.49d-2*(TESTGEST))+1.3d-2)*Gest_on
34   WTFER = (WTFER_RODENT*RATIO_RATF_MOUSEF*N_FETUS)
35   WTFE = DIM(WTFER,0.0)
36
37     !
38   FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME
39     ! FAT GROWTH EXPRESSION LINEAR DURING PREGNANCY
40     ! FROM O'FLAHERTY_1992
41
42   WF0= (((9.66d-5*(TESTGEST))*gest_on)+0.069)
43
44     ! PLACENTA,VOLUME, PLACENTA,VOLUME, PLACENTA,VOLUME, PLACENTA,VOLUME
45     ! WPLA PLACENTA GROWTH  EXPRESSION, SINGLE EXPONENTIAL WITH OFFSET
46     ! FROM O'FLAHERTY_1992  ! FOR EACH PUP
47
48   WPLA0N_RODENT = (0.6/(1+(5d+3*EXP(-0.0225*(TESTGEST)))))*N_FETUS
49   WPLA0R = (WPLA0N_RODENT/WT0)*Gest_on
50   WPLA0 = DIM(WPLA0R,0.0)
51
52     ! PLACENTA,FLOW RATE, PLACENTA,FLOW RATE, PLACENTA,FLOW RATE, PLACENTA,FLOW
53   RATE
54     ! QPLA PLACENTA GROWTH EXPRESSION, DOUBLE EXPONENTIAL WITH OFFSET
55     ! FROM O'FLAHERTY_1992
56
57    QPLARF = (1.67d-7 *exp(9.6d-3*(TESTGEST)) &
```

```
        +1.6d-3*exp(7.9d-3*(TESTGEST))+0.0)*Gest_on*SWITCH_trans
    QPLAF=DIM(QPLARF,0.0)                        !FRACTION OF FLOW RATE IN PLACENTA

    ! GESTATION CONTROL
IF (T.LT.CONCEPTION_T) THEN
    Gest_off = 1.0
    Gest_on=   0.0
ELSE
    Gest_off = 0.0
    Gest_on  = 1.0
END IF

    ! MOTHER BODY WEIGHT GROWTH EQUATION========
    ! MODIFICATION TO ADAPT THIS MODEL AT HUMAN MODEL
    ! BECAUSE LINEAR DESCRIPTION IS NOT GOOD ENOUGH FOR MOTHER GROWTH
    ! MOTHER BODY WEIGHT GROWTH

    PARAMETER (BW_RMN = 1.0E-30)
    WT0= BW_T0 *(1+(0.41*T)/(1402.5+T+BW_RMN)) ! IN GRAMS

    ! VARIABILITY OF REST OF THE BODY DEPENDS ON OTHER ORGANS
    WRE0 = (0.91 - (WLIB0*WLI0 + WFB0*WF0 +WPLAB0*WPLA0 + WLI0 + WF0 +
WPLA0))/(1+WREB0)  ! REST OF THE BODY FRACTION; UPDATED FOR EPA ASSESSMENT
    QREF = 1-(QFF+QLIF+QPLAF)                !REST OF BODY BLOOD FLOW RATE (ML/HR)
    QTTQF = QFF+QREF+QLIF+QPLAF          ! SUM MUST EQUAL 1

    ! COMPARTMENT VOLUME (ML OR G) =========
  WF  =  WF0  * WT0                         ! ADIPOSE TISSUE
  WRE =  WRE0 * WT0                         ! REST OF THE BODY
  WLI =  WLI0 * WT0                         ! LIVER
  WPLA=  WPLA0* WT0                         ! PLACENTA

    ! COMPARTMENT TISSUE BLOOD (ML OR G) =========
  WFB  =  WFB0  * WF                        ! ADIPOSE TISSUE
  WREB =  WREB0 * WRE                       ! REST OF THE BODY
  WLIB =  WLIB0 * WLI                       ! LIVER
  WPLAB = WPLAB0* WPLA                      ! PLACANTA

    ! CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT (ML/H) =========
    !QC= QCCAR*60*(WT0/1000.0)**0.75
CONSTANT QCC=18684.0                        ! EQUIVALENT TO 311.4 * 60
QC= QCC*(WT0/UNITCORR)**0.75

    !COMPARTMENT BLOOD FLOW RATE (ML/HR)
QF  = QFF*QC                               !ADIPOSE TISSUE BLOOD FLOW RATE
QLI = QLIF*QC                              !LIVER TISSUE BLOOD FLOW RATE
QRE = QREF*QC                              !REST OF THE BODY BLOOD FLOW RATE
QPLA = QPLAF*QC                            !PLACENTA TISSUE BLOOD FLOW RATE
QTTQ = QF+QRE+QLI+QPLA    !TOTAL FLOW RATE

    !PERMEABILITY ORGAN FLOW (ML/HR)=========
PAF  = PAFF*QF                            ! ADIPOSE TISSUE
PARE = PAREF*QRE                          ! REST OF THE BODY
PALI = PALIF*QLI                          ! LIVER TISSUE
PAPLA = PAPLAF*QPLA                       ! PLACENTA

    !*********************************
```

```
1      ! ABSORPTION SECTION
2      ! ORAL
3      ! INTRAPERITONEAL
4      ! INTRAVENOUS
5      !**************************************
6
7      !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIO
8
9   MSTOT_NMBCKGR = MSTOTBCKGR/MW        ! CONVERTS THE BACKGROUND DOSE TO NMOL/G
10  MSTTBCKGR =MSTOT_NMBCKGR *WT0
11
12  DAY_EXPOSURE_BG   = PULSE(DAY_LAG_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
13  WEEK_EXPOSURE_BG  = PULSE(WEEK_LAG_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
14  MONTH_EXPOSURE_BG = PULSE(MONTH_LAG_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)
15
16  MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
17  MSTTFR_BG = MSTTBCKGR/CINT
18
19  CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG
20
21      ! CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
22
23  IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
24      ABSMSTT_GB= MSTTFR_BG
25  ELSE
26      ABSMSTT_GB = 0.0
27  END IF
28
29  CYCLETOTBG=INTEG(CYCLE_BG,0.0)
30
31     !REPETITIVE ORAL EXPOSURE SCENARIO
32
33  MSTT= MSTOT_NM * WT0                    !AMOUNT IN NMOL
34
35  DAY_EXPOSURE   = PULSE(DAY_LAG,DAY_PERIOD,DAY_FINISH)
36  WEEK_EXPOSURE  = PULSE(WEEK_LAG,WEEK_PERIOD,WEEK_FINISH)
37  MONTH_EXPOSURE = PULSE(MONTH_LAG,MONTH_PERIOD,MONTH_FINISH)
38
39  MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
40  MSTTFR = MSTT/CINT
41
42  CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
43  SUMEXPEVENT= INTEG (CYCLE,0.0) !NUMBER OF CYCLES GENERATED DURING SIMULATION
44
45      ! CONDITIONAL ORAL EXPOSURE
46  IF (MSTTCH.EQ.MSTT) THEN
47      ABSMSTT= MSTTFR
48  ELSE
49      ABSMSTT = 0.0
50  END IF
51
52
53   CYCLETOT=INTEG(CYCLE,0.0)
54
55      ! MASS CHANGE IN THE LUMEN
56   RMSTT= -(KST+KABS)*MST +ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
```

```
1     MST = INTEG(RMSTT,0.0)                        !AMOUNT REMAINING IN DUODENUM
2    (NMOL)
3
4       ! ABSORPTION IN LYMPH CIRCULATION
5     LYRMLUM = KABS*MST*A
6      LYMLUM = INTEG(LYRMLUM,0.0)
7
8       ! ABSORPTION IN PORTAL CIRCULATION
9     LIRMLUM = KABS*MST*B
10     LIMLUM = INTEG(LIRMLUM,0.0)
11
12
13   ! -----IV EXPOSURE ---------
14
15    IV= DOSEIV_NM * WT0 !AMOUNT IN NMOL
16    IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
17    EXPIV= IVR * (1.0-STEP(PFUNC))
18    IVDOSE = integ(EXPIV,0.0)
19
20       !------IV LATE IN THE CYCLE
21       ! MODIFICATION ON January 13 2004
22    IV_RlateR = DOSEIVNMlate*WT0
23    IV_EXPOSURE=PULSE(IV_LAG,IV_PERIOD,IV_FINISH)
24
25    IV_lateT = IV_EXPOSURE *IV_RlateR
26    IV_late = IV_lateT/CINT
27
28   SUMEXPEVENTIV= integ (IV_EXPOSURE,0.0) !NUMBER OF CYCLES GENERATED DURING
29   SIMULATION
30
31       !SYSTEMIC CONCENTRATION OF TCDD
32
33       ! MODIFICATION ON OCTOBER 6, 2009
34    CB= (QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late)/(QC+CLURI) !
35     CA = CB ! CONCENTRATION (NMOL/ML)
36
37
38       !URINARY EXCRETION BY KIDNEY
39       ! MODIFICATION ON OCTOBER 6, 2009
40   RAURI = CLURI *CB
41     AURI = INTEG(RAURI,0.0)
42
43
44
45    !UNIT CONVERSION POST SIMULATION
46    CBSNGKGLIADJ=(CB*MW*UNITCORR*(1.0/B_TOTLIP)*(1.0/SERBLO))!(NG of TCDD
47   Serum/Kg OF LIPID]
48     AUCBS_NGKGLIADJ=integ(CBSNGKGLIADJ,0.0)
49
50
51     CBNGKG= CB*MW*UNITCORR
52
53
54     !ADIPOSE COMPARTMENT
55     !TISSUE BLOOD COMPARTMENT
56   RAFB= QF*(CA-CFB)-PAF*(CFB-CF/PF)      !(NMOL/H)
57    AFB = INTEG(RAFB,0.0)                 !(NMOL)
```

```
  1      CFB = AFB/WFB                        !(NMOL/ML)
  2        !TISSUE COMPARTMENT
  3    RAF = PAF*(CFB-CF/PF)                   !(NMOL/H)
  4     AF = INTEG(RAF,0.0)                    !(NMOL)
  5      CF  = AF/WF                           !(NM/ML)
  6
  7       !UNIT CONVERSION POST SIMULATION
  8      CFTOTAL= (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION IN NMOL/ML
  9      CFTFREE = CFB + CF !TOTAL FREE CONCENTRATION IN FAT   (NM/ML)
 10
 11      CFNGKG=CFTOTAL*MW*UNITCORR ! FAT CONCENTRATION NG/KG
 12        AUCF_NGKGH=integ(CFNGKG,0.0)
 13
 14       !REST OF THE BODY COMPARTMENT
 15    RAREB= QRE *(CA-CREB)-PARE*(CREB-CRE/PRE)   !(NMOL/H)
 16     AREB = INTEG(RAREB,0.0)                        !(NMOL)
 17      CREB = AREB/WREB                              !(NMOL/H)
 18        !TISSUE COMPARTMENT
 19    RARE = PARE*(CREB - CRE/PRE)             !(NMOL/H)
 20     ARE = INTEG(RARE,0.0)                   !(NMOL)
 21      CRE  = ARE/WRE                         !(NMOL/ML)
 22
 23       !UNIT CONVERSION POST SIMULATION
 24      CRETOTAL= (ARE + AREB)/(WRE + WREB)           ! TOTAL CONCENTRATION IN
 25    NMOL/ML
 26
 27      CRENGKG=CRETOTAL*MW*UNITCORR ! REST OF THE BODY CONCENTRATION IN NG/KG
 28
 29
 30       !LIVER COMPARTMENT
 31       !TISSUE BLOOD COMPARTMENT
 32     RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM !
 33      ALIB = INTEG(RALIB,0.0)                         !(NMOL)
 34       CLIB = ALIB/WLIB                               !(NMOL/ML)
 35       !TISSUE COMPARTMENT
 36     RALI = PALI*(CLIB - CFLLIR)-REXCLI              !  (NMOL/HR)
 37      ALI = INTEG(RALI,0.0)                          !(NMOL)
 38       CLI  = ALI/WLI                                !(NMOL/ML)
 39
 40       !FREE TCDD CONCENTRATION IN LIVER COMPARTMENT
 41    PARAMETER (LIVER_1RMN = 1.0E-30)
 42     CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
 43          +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2 + CFLLIR &
 44          +LIVER_1RMN)*IND_ACTIVE)))-CFLLI,CFLLI0)
 45        CFLLIR=DIM(CFLLI,0.0) ! FREE CONCENTRATION IN LIVER
 46
 47      CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND CONCENTRATION
 48
 49       !VARIABLE ELIMINATION BASED ON THE CYP1A2
 50     KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv ! INDUCED BILIARY
 51    EXCRETION RATE CONSTANT IN LIVER
 52      REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT BILIARY EXCRETION RATE
 53        EXCLI = INTEG(REXCLI,0.0)
 54
 55       !UNIT CONVERSION POST SIMULATION
 56      CLITOTAL= (ALI + ALIB)/(WLI + WLIB) ! TOTAL CONCENTRATION IN NMOL/ML
 57      Rec_occ= CFLLIR/(KDLI+CFLLIR)
```

```
1    CLINGKG=CLITOTAL*MW*UNITCORR ! LIVER CONCENTRATION NG/KG
2        AUCLI_NGKGH=INTEG(CLINGKG,0.0)
3    CBNDLINGKG = CBNDLI*MW*UNITCORR
4        AUCBNDLI_NGKGH =INTEG(CBNDLINGKG,0.0)
5
6
7      !CHEMICAL IN CYP450 (1A2) COMPARTMENT
8    CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ
9
10
11       ! MODIFICATION ON OCTOBER 6, 2009
12   CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-30)**HILL
13   &
14       /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
15        - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)
16
17   ! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
18   SIMULATIONS)
19
20   CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
21     CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)
22
23   CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
24     CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)
25
26   ! TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
27   ! FETAL EXPOSURE ONLY DURING EXPOSURE
28
29   IF (T.LT.TRANSTIME_ON) THEN
30    SWITCH_trans = 0.0
31   ELSE
32    SWITCH_trans = 1.0
33   END IF
34
35   !TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
36   ! MODIFICATION 26 SEPTEMBER 2003
37
38   CONSTANT PFETUS= 4.0 !
39   CONSTANT CLPLA_FET = 0.17 !
40
41   RAMPF = (CLPLA_FET*CPLA) *SWITCH_trans
42     AMPF=INTEG(RAMPF,0.0)
43
44   !TRANSFER OF DIOXIN FROM FETUS TO PLACENTA
45   RAFPM = (CLPLA_FET*CFETUS_v)*SWITCH_trans !
46     AFPM = INTEG(RAFPM,0.0)
47
48   ! TCDD IN PLACENTA (MOTHER) COMPARTMENT
49   RAPLAB= QPLA*(CA - CPLAB)-PAPLA*(CPLAB -CFLPLAR)    ! NMOL/H)
50    APLAB = INTEG(RAPLAB,0.0)                          ! (NMOL)
51    CPLAB = APLAB/(WPLAB+1E-30)                        ! (NMOL/ML)
52   RAPLA = PAPLA*(CPLAB-CFLPLAR)-RAMPF + RAFPM         ! (NMOL/H)
53    APLA = INTEG(RAPLA,0.0)                            ! (NMOL)
54    CPLA  = APLA/(WPLA+1e-30)                          ! (NMOL/ML)
55
56
57   PARAMETER (PARA_ZERO = 1.0E-30)
```

```
1    CFLPLA= IMPLC(CPLA-(CFLPLAR*PPLA +(PLABMAX*CFLPLAR/(KDPLA&
2        +CFLPLAR+PARA_ZERO)))-CFLPLA,CFLPLA0)
3    CFLPLAR=DIM(CFLPLA,0.0)
4
5       !UNIT CONVERSION POST SIMULATION
6      CPLATOTAL= (APLA + APLAB)/((WPLA + WPLAB)+1e-30)! TOTAL CONCENTRATION IN
7    NMOL/ML
8
9
10
11      !FETUS COMPARTMENT
12   RAFETUS= RAMPF-RAFPM
13    AFETUS=INTEG(RAFETUS,0.0)
14   CFETUS=AFETUS/(WTFE+1E-30)
15   CFETOTAL= CFETUS
16   CFETUS_v = CFETUS/PFETUS
17
18     ! UNIT CONVERSION POST SIMULATION
19   CFETUSNGKG = CFETUS*MW*UNITCORR                       !(NG/KG)
20   AUC_FENGKGH = INTEG(CFETUSNGKG,0.0)
21
22
23   ! ------------CONTROL MASS BALANCE ----------
24   BDOSE= IVDOSE +LYMLUM+LIMLUM
25   BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB+AFETUS
26   BDIFF = BDOSE-BMASSE
27
28        !BODY BURDEN (NG)
29   BODY_BURDEN = AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB !
30   BBFETUSNG     = AFETUS*MW*UNITCORR    ! UNIT (NG)
31        ! BODY BURDEN IN TERMS OF CONCENTRATION (NG/KG)
32    BBNGKG =(((AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB)/WT0)*MW*UNITCORR) !
33     AUC_BBNGKGH=INTEG(BBNGKG,0.0)
34
35
36   ! ------------COMMAND OF THE END OF SIMULATION ----------
37   TERMT (T.GE. TimeLimit, 'Time limit has been reached.')
38   END   ! END OF THE DERIVATIVE SECTION
39   END   ! END OF THE DYNAMIC SECTION
40   END   ! END OF THE PROGRAM
41
```

E.2.4.2. *Input Files*

E.2.4.2.1. *Bell et al. ([2007](#))*

```
44   output @clear
45   prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
46   AUCF_NGKG AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
47   CBNGKG AUC_CBNGKGH
48
49   %Bell et al. 2007 (rat species)
50   %protocol:  daily dietary dose for 12 weeks followed by a two-week mating
51   time and 21-day gestation period
52   %dose levels: 0.0024, 0.008, 0.046 ug/kg-d with 0.00003 ug/kg-d background
53   %dose levels: 2.4, 8, 46 ng/kg-d with 0.03 ng/kg-day background
54
```

```
  %EXPOSURES SCENARIOS
 MAXT             = 0.01
 CINT             = 0.1  %
 EXP_TIME_ON      = 0                 %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF     = 2856              %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE        = 24                %HOURS BETWEEN DOSES
 BCK_TIME_ON      = 0.                %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF     = 2856.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT        = 2856              %SIMULATION DURATION(HOUR)
 BW_T0            = 85                %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
 CONCEPTION_T     = 2352              %HOUR OF CONCEPTION (HOUR)
 TRANSTIME_ON     = 2496              %HOUR OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS          = 10                %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)
   MSTOT           = 0.00243          %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT          = 0.008            %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT = 0.0461                    %ORAL EXPOSURE DOSE (UG/KG)

```

E.2.4.2.2. *Hojo et al. (2002)*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH
%Hojo et al. 2002
%protocol:  single oral dose at GD8
%dose levels: 0.02 0.06, 0.18 ug/kg  at GD8
%dose levels: 20, 60, 180  ng/kg at GD8
% author provided the body weight for each group at the beginning of
gestation (g)
    %20 ng/kg BW = 271g
    %60 ng/kg BW = 275g
    %180 ng/kg BW = 262g

%EXPOSURES SCENARIOS
 MAXT= 0.001
 CINT =0.1
 EXP_TIME_ON     = 192                %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 216                %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 24                 %HOURS BETWEEN DOSES
 BCK_TIME_ON     = 0.                 %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
 BCK_TIME_OFF    = 0.                 %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT       = 216                %SIMULATION DURATION (HOUR)
 CONCEPTION_T    = 0.                 %TIME OF CONCEPTION_(HOUR)
 TRANSTIME_ON    = 144.               %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS         = 10                 %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)

   %MSTOT          = 0.02             %ORAL EXPOSURE DOSE (UG/KG)
   %BW_T0          = 275              %20 ng/kg BW = 271g

   %MSTOT          = 0.06             %ORAL EXPOSURE DOSE (UG/KG)
```

```
%BW_T0          = 262                    %60 ng/kg BW = 275g

MSTOT           = 0.18                    %ORAL EXPOSURE DOSE (UG/KG)
BW_T0           = 278                     %180 ng/kg BW = 262g
```

E.2.4.2.3. *Ikeda et al. ([2005](#))*

```
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH

%Ikeda et al. 2005
%protocol:  loading dose of 400 ng/kg followed by weekly maintenance doses of
80 ng/kg for 6 weeks,
%dose levels: 0.4 ug/kg-day followed by weekly 0.08 ug/kg-day
%dose levels: 400 ng/kg-day followed by weekly 80 ng/kg-day

   %EXPOSURES SCENARIOS
 MAXT            =.1
 CINT            = 0.1
 EXP_TIME_ON     = 0                      %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 1008                   %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 168                    %HOURS IN A WEEK
 BCK_TIME_ON     = 0.                     %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF    = 167.                   %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT       = 1008                   %SIMULATION DURATION (HOUR)
 BW_T0           = 250                    %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
 CONCEPTION_T        = 504                %TIME OF CONCEPTION (HOUR)
 TRANSTIME_ON    = 648                    %TIME OF CONCEPTION + 6 DAYS (144 HOURS)
 N_FETUS         = 10                     %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)
   MSTOT           = 0.08                 %ORAL EXPOSURE DOSE IN UG/KG
   MSTOTBCKGR      = 0.32                 %BACKGROUND EXPOSURE IN UG/KG
```

E.2.4.2.4. *Kattainen et al. ([2001](#))) and Simanainen et al. ([2004](#))*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Kattainen et al. 2001
%protocol:  single gavage at GD15
%dose levels: 0.03 0.1, 0.3, 1 ug/kg  at GD15
%dose levels: 30, 100 300, 1000 ng/kg at GD15

 MAXT=0.001
 CINT =0.1

   %EXPOSURES SCENARIOS
 EXP_TIME_ON         = 336                %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF        = 360                %TIME EXPOSURE ENDS (HOUR)
```

```
 1    DAY_CYCLE              = 24              %HOURS BETWEEN DOSES
 2    BCK_TIME_ON            = 0.              %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 3    BCK_TIME_OFF           = 0.              %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 4    TIMELIMIT              = 360             %SIMULATION DURATION (HOUR)
 5    BW_T0                  = 190             %BODY WEIGHT AT THE BEGINNING OF THE
 6    SIMULATION
 7    CONCEPTION_T             = 0.            %TIME OF CONCEPTION (HOUR)
 8    TRANSTIME_ON           = 144.            %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
 9    N_FETUS                = 10             %NUMBER OF FETUSES
10
11    %EXPOSURE DOSE SCENARIOS (UG/KG)
12    %MSTOT                 = 0.03            %ORAL EXPOSURE DOSE (UG/KG)
13    %MSTOT                 = 0.1             %ORAL EXPOSURE DOSE (UG/KG)
14    %MSTOT                 = 0.3             %ORAL EXPOSURE DOSE (UG/KG)
15     MSTOT                 = 1               %ORAL EXPOSURE DOSE (UG/KG
16
```

17   **E.2.4.2.5. *Markowski et al. (2001)***

```
18    %clear variable
19    output @clear
20    prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
21    AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
22    CBNGKG AUC_CBNGKGH
23
24    %Markowski et al. 2001
25    %protocol:  single gavage at GD18
26    %dose levels: 0.02 0.06, 0.18 ug/kg at GD18
27    %dose levels: 20, 60, 180 ng/kg at GD18
28
29    %EXPOSURES SCENARIOS
30     MAXT=0.0001
31     CINT =0.1
32     EXP_TIME_ON    = 408            %TIME EXPOSURE BEGINS(HOUR)
33     EXP_TIME_OFF   = 432            %TIME EXPOSURE ENDS (HOUR)
34     DAY_CYCLE      = 24             %HOURS BETWEEN DOSES
35     BCK_TIME_ON    = 0.             %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
36     BCK_TIME_OFF   = 0.             %TIME BACKGROUND EXPOSURE ENDS (HOUR)
37     TIMELIMIT      = 432            %SIMULATION DURATION (HOUR)
38     BW_T0          = 190            %BODY WEIGHT AT THE BEGINNING OF THE
39    SIMULATION
40     CONCEPTION_T     = 0.           %TIME OF CONCEPTION (HOUR)
41     TRANSTIME_ON   = 144.           %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
42     N_FETUS        = 10             %NUMBER OF FETUSES
43
44    %EXPOSURE DOSE SCENARIOS (UG/KG)
45       %MSTOT          = 0.02          %ORAL EXPOSURE DOSE (UG/KG)
46       %MSTOT         = 0.06           %ORAL EXPOSURE DOSE (UG/KG)
47       MSTOT          = 0.18           %ORAL EXPOSURE DOSE (UG/KG)
48
```

49   **E.2.4.2.6. *Miettinen et al. (2006)***

```
50    %clear variable
51    output @clear
```

```
1   prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
2   AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
3   CBNGKG AUC_CBNGKGH
4
5   %Miettinen et al. 2006
6   %protocol:  single oral dose at GD15
7   %dose levels: 0.03 0.1, 0.3, 1 ug/kg at GD15
8   %dose levels: 30, 100, 300, 1000 ng/kg at GD15
9
10   MAXT=0.01
11   CINT =0.1
12
13  EXP_TIME_ON   = 336                    %TIME EXPOSURE BEGINS(HOUR)
14   EXP_TIME_OFF  = 360                   %TIME EXPOSURE ENDS (HOUR)
15   DAY_CYCLE     = 24                    %HOURS BETWEEN DOSES
16   BCK_TIME_ON   = 0.                    %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
17   BCK_TIME_OFF  = 0.                    %TIME BACKGROUND EXPOSURE ENDS (HOUR)
18   TIMELIMIT     = 360                   %SIMULATION DURATION (HOUR)
19   BW_T0         = 180                   %BODY WEIGHT AT THE BEGINNING OF THE
20  SIMULATION (G)
21   CONCEPTION_T      = 0.                %TIME OF CONCEPTION (HOUR)
22   TRANSTIME_ON  = 144.                  %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
23   N_FETUS       = 10                    %NUMBER OF FETUSES
24
25  %EXPOSURE DOSE SCENARIOS (UG/KG)
26     %MSTOT       = 0.03                 %ORAL EXPOSURE DOSE (UG/KG)
27     %MSTOT      = 0.1                   %ORAL EXPOSURE DOSE (UG/KG)
28     %MSTOT      = 0.3                   %ORAL EXPOSURE DOSE (UG/KG)
29     MSTOT       = 1                     %ORAL EXPOSURE DOSE (UG/KG)
30
```

31 **E.2.4.2.7.** *Nohara et al. ([2000](#))*

```
32  %clear variable
33  output @clear
34  prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
35  AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
36  CBNGKG AUC_CBNGKGH
37
38  %Nohara et al. 2000
39  %protocol:  single gavage at GD15
40  %dose levels: 0.0125, 0.050, 0.2, or 0.8 ug TCDD:kg body weight by gavage on
41  GD15.
42  %dose levels: 12.5, 50, 200, or 800 ng TCDD:kg body weight by gavage on GD15.
43
44   MAXT=0.01
45   CINT =0.1
46   EXP_TIME_ON   = 336                   %TIME EXPOSURE BEGINS (HOUR)
47   EXP_TIME_OFF  = 360                   %TIME EXPOSURE ENDS (HOUR)
48   DAY_CYCLE     = 24                    %HOURS BETWEEN DOSES
49   BCK_TIME_ON   = 0.                    %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
50   BCK_TIME_OFF  = 0.                    %TIME BACKGROUND EXPOSURE ENDS (HOUR)
51   TIMELIMIT     = 360                   %SIMULATION DURATION (HOUR)
52   BW_T0         = 180                   %BODY WEIGHT AT THE BEGINNING OF THE
53  SIMULATION (G)
54   CONCEPTION_T  = 0.                    %TIME OF CONCEPTION (HOUR)
55   TRANSTIME_ON  = 144.                  %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
```

```
1    N_FETUS        = 10                    %NUMBER OF FETUSES
2
3   %EXPOSURE DOSE SCENARIOS (UG/KG)
4     %MSTOT         = 0.0125               %ORAL EXPOSURE DOSE (UG/KG)
5     %MSTOT         = 0.050                %ORAL EXPOSURE DOSE (UG/KG)
6     %MSTOT         = 0.2                  %ORAL EXPOSURE DOSE (UG/KG)
7      MSTOT         = 0.8                  %ORAL EXPOSURE DOSE (UG/KG)
8
```

E.2.4.2.8. *Ohsako et al. ([2001](#))*

```
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Ohsako et al. 2001
%protocol:  single oral dose at GD15
%dose levels: 0.0125, 0.05, 0.2, 0.8 ug/kg at GD15
%dose levels: 12.5, 50, 200, 800 ng/kg at GD15

 MAXT=0.01
 CINT =0.1
 EXP_TIME_ON    = 360                    %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF   = 384                    %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE      = 24                     %HOURS BETWEEN DOSES
 BCK_TIME_ON    = 0.                     %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF   = 0.                     %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT      = 384                    %SIMULATION DURATION (HOUR)
 BW_T0          = 200                    %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
 CONCEPTION_T        = 0.               %TIME OF CONCEPTION_(HOUR)
 TRANSTIME_ON   = 144.                   %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS        = 10                     %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)

 %MSTOT         = 0.0125                 %ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT         = 0.05                   %ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT         = 0.20                   %ORAL EXPOSURE DOSE (UG/KG)
  MSTOT         = 0.80                   %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.4.2.9. *Schantz et al. ([1996](#)) and Amin et al. ([2000](#))*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Amin et al. 2000 (rat species) and Schantz et al. 1996
%protocol:  daily doses on GDs 10 to 16
%dose levels: 25 and 100 ng/kg-day
%dose levels: 0.025 and 0.100 ug/kg-day

 MAXT           = 0.001
```

```
CINT                = 0.1
EXP_TIME_ON         = 240.           %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF        = 384.           %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE           = 24             %HOURS BETWEEN DOSES
BCK_TIME_ON         = 1000.          %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF        = 1000.          %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT           = 384.           %SIMULATION DURATION (HOUR)
BW_T0               = 250.           %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
CONCEPTION_T            = 0          %TIME OF CONCEPTION_ (HOUR)
TRANSTIME_ON        = 144.           %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
N_FETUS             = 10             %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT            = .025          %ORAL EXPOSURE DOSE (UG/KG)
   MSTOT            = .100          %ORAL EXPOSURE DOSE (UG/KG)

```

E.2.4.2.10. *Seo et al. (1995)*

```
%clear variable
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Seo et al. 1995
%protocol:  daily doses on GDs 10-16
%dose levels: 0.025 and 0.1 ug/kg on GDs 10-16
%dose levels: 25 and 100 ng/kg on GDs 10-16

 MAXT = 0.01
 CINT = 0.1

 EXP_TIME_ON         = 240           %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF        = 384           %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE           = 24
 BCK_TIME_ON         = 0.            %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF        = 0.            %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT           = 384           %SIMULATION DURATION (HOUR)
 BW_T0               = 190           %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
 CONCEPTION_T           = 0.         %TIME OF CONCEPTION (HOUR)
 TRANSTIME_ON        = 144.          %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS             = 10            %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT             = 0.025         %ORAL EXPOSURE DOSE (UG/KG)
 MSTOT             = 0.1           %ORAL EXPOSURE DOSE (UG/KG)

```

E.2.4.2.11. *Sparschu et al. (1971)*

```
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH
```

```
1
2   %protocol:  daily oral dose from GD6 to GD15
3
4   %EXPOSURES SCENARIOS
5    MAXT=0.01
6    CINT =0.1
7    EXP_TIME_ON     = 120.                    %TIME EXPOSURE BEGINS (HOUR)
8    EXP_TIME_OFF    = 337.                    %TIME EXPOSURE ENDS (HOUR)
9    DAY_CYCLE       = 24                      %HOURS BETWEEN DOSES
10   BCK_TIME_ON     = 0.                      %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
11   BCK_TIME_OFF    = 0.                      %TIME BACKGROUND EXPOSURE ENDS (HOUR)
12
13   TIMELIMIT       = 360.                    %SIMULATION DURATION (HOUR)
14   BW_T0           = 295                     %BODY WEIGHT AT THE BEGINNING OF THE
15   SIMULATION (G)
16   T_CONCEPTION        = 0.                  %TIME OF CONCEPTION (HOUR)
17   TRANSTIME_ON    = 144.                    %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
18   N_FETUS         = 10                      %NUMBER OF FETUSES
19
20   %EXPOSURE DOSE SCENARIOS (UG/KG)
21
22      %MSTOT          = 0.03                 %ORAL EXPOSURE DOSE (UG/KG)
23      %MSTOT        = 0.125                  %ORAL EXPOSURE DOSE (UG/KG)
24      %MSTOT        = 0.5                    %ORAL EXPOSURE DOSE (UG/KG)
25      %MSTOT         = 2.                    %ORAL EXPOSURE DOSE (UG/KG)
26       MSTOT        = 8.                     %ORAL EXPOSURE DOSE (UG/KG)
27
```

28 ### E.2.5.   Mouse Standard Model

29 ### E.2.5.1. *Model Code*

30 PROGRAM: 'Three Compartment PBPK Model for TCDD in Mice: Standard Model
31 (Nongestation)'

```
32
33   !****************************************************
34
35   INITIAL   ! INITIALIZATION OF PARAMETERS
36
37      !SIMULATION PARAMETERS ====
38   CONSTANT PARA_ZERO      =    1D-30
39   CONSTANT EXP_TIME_ON     =     0.0        ! TIME AT WHICH EXPOSURE BEGINS
40   (HOURS)
41   CONSTANT EXP_TIME_OFF    =    2832        ! TIME AT WHICH EXPOSURE ENDS
42   (HOURS)
43   CONSTANT DAY_CYCLE       =     24         ! NUMBER OF HOURS BETWEEN DOSES
44   (HOURS)
45   CONSTANT BCK_TIME_ON     =     0.0        ! TIME AT WHICH BACKGROUND EXPOSURE
46   BEGINS (HOURS)
47   CONSTANT BCK_TIME_OFF    =     0.0        ! TIME AT WHICH BACKGROUND EXPOSURE
48   ENDS (HOURS)
49
50   CONSTANT MW=322 ! MOLECULAR WEIGHT (NG/NMOL)
51   CONSTANT SERBLO = 0.55
52   CONSTANT UNITCORR = 1000
53
54      !CONSTANT EXPOSURE CONTROL ===========
```

```
     !ACUTE, SUBCHRONIC, CHRONIC EXPOSURE =====
     !OR BACKGROUND EXPOSURE (IN THIS CASE 3 TIMES A DAY)===
CONSTANT MSTOTBCKGR      =        0.0         !ORAL BACKGROUND EXPOSURE DOSE
(UG/KG)
CONSTANT MSTOT           =        0.15      !ORAL EXPOSURE DOSE (UG/KG)
CONSTANT MSTOTsc         =        0.0        ! SUBCUTANEOUS EXPOSURE DOSE
(UG/KG)

   !ORAL ABSORPTION
  MSTOT_NM               =     MSTOT/MW    !AMOUNT IN NMOL/G

   ! INTRAVENOUS ABSORPTION
CONSTANT  DOSEIV  = 0.0                          !INJECTED DOSE (UG/KG)
  DOSEIV_NM = DOSEIV/MW   ! CONVERTS THE INJECTED DOSE TO NMOL/G

  !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
INDICATED BELOW)====
CONSTANT CFLLI0          =        0.0        !LIVER (NMOL/ML)

   !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
BELOW) (NMOL/ML)
CONSTANT LIBMAX          =      3.5e-4     ! LIVER  (NMOL/ML), WANG ET AL.
1997

! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
(NMOL/ML)===
CONSTANT KDLI            =      1.0e-4     !LIVER (AhR)(NMOL/ML), WANG ET AL.
1997
CONSTANT KDLI2           =      2.0e-2     !LIVER (1A2)(NMOL/ML), EMOND ET AL.
2004

!===EXCRETION AND ABSORPTION CONSTANT (OPTIMIZED)
CONSTANT KST             =     0.3   ! GASTRIC RATE CONSTANT (HR-1),
CONSTANT KABS            =     0.48  !INTESTINAL ABSORPTION CONSTANT (HR-1) ),
WANG ET AL. 1997

! ELIMINATION CONSTANTS
CONSTANT CLURI           =       0.09 ! URINARY CLEARANCE (ML/HR)

! ==test elimination variable
constant kelv            =      0.4       ! INTERSPECIES VARIABLE ELIMINATION
CONSTANT (1/HOUR)

! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
CONSTANT A               =      0.7       ! LYMPHATIC FRACTION, WANG ET AL.
1997

!PARTITION COEFFICIENTS OPTIMIZED
CONSTANT PF              =    400          ! ADIPOSE TISSUE/BLOOD
CONSTANT PRE             =    3            ! REST OF THE BODY/BLOOD, WANG ET
AL. 2000
CONSTANT PLI             =    6            ! LIVER/BLOOD, WANG ET AL. 1997

!===PARAMETER FOR INDUCTION OF CYP 1A2
CONSTANT IND_ACTIVE=     1.0     ! INCLUDE INDUCTION? (1 = YES, 0 = NO)
CONSTANT CYP1A2_1OUTZ = 1.6   ! DEGRADATION CONCENTRATION CONSTANT OF 1A2
(NMOL/ML)
```

```
CONSTANT CYP1A2_1A1 =   1.5   ! BASAL CONCENTRATION OF 1A1 (NMOL/ML)
CONSTANT CYP1A2_1EC50 = 0.13    ! DISSOCIATION CONSTANT TCDD-CYP1A2 (NMOL/ML)
CONSTANT CYP1A2_1A2 =   1.5   ! BASAL CONCENTRATION OF 1A2 (NMOL/ML)
CONSTANT CYP1A2_1KOUT = 0.1    ! FIRST ORDER RATE OF DEGRADATION (H-1)
CONSTANT CYP1A2_1TAU  = 1.5   ! HOLDING TIME (H)
CONSTANT CYP1A2_1EMAX = 600    ! MAXIMUM INDUCTION OVER BASAL EFFECT
(UNITLESS)
CONSTANT HILL        = 0.6      !HILL CONSTANT; COOPERATIVE LIGAND BINDING
EFFECT CONSTANT (UNITLESS)
     !DIFFUSIONAL PERMEABILITY FRACTION
CONSTANT PAFF     = 0.12      ! ADIPOSE (UNITLESS), WANG ET AL. 2000
CONSTANT PAREF    = 0.03      ! REST OF THE BODY (UNITLESS)
CONSTANT PALIF    = 0.35      ! LIVER (UNITLESS)

     !COMPARTMENT TISSUE BLOOD VOLUME  =========
CONSTANT WLI0     =  0.0549   ! LIVER, ILSI 1994
CONSTANT WF0      =  0.069    ! ADIPOSE

     !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT
CONSTANT QFF  = 0.070          ! ADIPOSE TISSUE BLOOD FLOW FRACTION
(UNITLESS), LEUNG ET AL. 1990
CONSTANT QLIF = 0.161          ! LIVER (UNITLESS)  ILSI ET AL. 1994

     !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL
COMPARTMENT VOLUME
CONSTANT WFB0 =    0.050      ! ADIPOSE TISSUE, WANG ET AL. 1997
CONSTANT WREB0 =    0.030     ! REST OF THE BODY, WANG ET AL. 1997
CONSTANT WLIB0 =    0.266     ! LIVER, WANG ET AL. 1997

     ! EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
     ! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG   = 0.0     ! TIME ELAPSED BEFORE EXPOSURE BEGINS (WEEK)
CONSTANT WEEK_PERIOD = 168    ! NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH = 120    ! TIME EXPOSURE ENDS (HOURS)

     ! NUMBER OF EXPOSURES PER MONTH
CONSTANT MONTH_LAG   = 0.0    ! DELAY BEFORE EXPOSURE (MONTH)

     !SET FOR BACKGROUND EXPOSURE===========
     !CONSTANT FOR BACKGROUND EXPOSURE===========
CONSTANT Day_LAG_BG = 0.0     ! TIME ELAPSED BEFORE EXPOSURE BEGINS (HOURS)
CONSTANT Day_PERIOD_BG = 24   ! LENGTH OF EXPOSURE (HOURS)

     ! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG_BG   = 0.0 ! TIME ELAPSED BEFORE BACKGROUND EXPOSURE (WEEK)
CONSTANT WEEK_PERIOD_BG = 168 !NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH_BG = 168 ! TIME EXPOSURE ENDS (HOURS)

     !GROWTH CONSTANT FOR RAT AND MOUSE
     !CONSTANT FOR MOTHER BODY WEIGHT GROWTH ======
CONSTANT BW_T0 = 20           !CHANGED FOR SIMULATION (IN G)

     !CONSTANT USED IN CARDIAC OUTPUT EQUATION, HADDAD 2001
CONSTANT QCCAR =275          !CONSTANT (ML/MIN/KG)

     ! COMPARTMENT TOTAL LIPID FRACTION
CONSTANT F_TOTLIP =  0.855    !ADIPOSE TISSUE (UNITLESS)
```

```
1    CONSTANT B_TOTLIP =  0.0033    !BLOOD (UNITLESS)
2    CONSTANT RE_TOTLIP = 0.019     !REST OF THE BODY (UNITLESS)
3    CONSTANT LI_TOTLIP = 0.06      !LIVER (UNITLESS)
4
5    END  ! END OF THE INITIAL SECTION
6
7    DYNAMIC ! DYNAMIC SIMULATION SECTION
8
9    ALGORITHM  IALG          =            2         !GEAR METHOD
10   CINTERVAL  CINT          =           1.0        !COMMUNICATION INTERVAL
11   MAXTERVAL  MAXT          =         1.0e+10      !MAXIMUM CALCULATION INTERVAL
12   MINTERVAL  MINT          =         1.0E-10      !MINIMUM CALCULATION INTERVAL
13   VARIABLE   T             =           0.0        !HOUR
14   CONSTANT   TIMELIMIT     =         2904.0         !SIMULATION TIME LIMIT
15   (HOURS)
16    CINTXY  = CINT
17    PFUNC   = CINT
18
19        !TIME CONVERSION
20    DAY         = T/24.0          ! TIME IN DAYS
21    WEEK        = T/168.0         ! TIME IN WEEKS
22    MONTH       = T/730.0         ! TIME IN MONTHS
23    YEAR        = T/8760.0        ! TIME IN YEARS
24
25        !NMAX =MAX(T,CTFNGKG)
26   nmax =max(T,CFNGKG)
27
28   DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS
29
30        !CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
31        !NUMBER OF EXPOSURES PER DAY
32    DAY_LAG      = EXP_TIME_ON        ! TIME ELAPSED BEFORE EXPOSURE BEGINS
33   (HOURS)
34    DAY_PERIOD   = DAY_CYCLE          ! EXPOSURE PERIOD (HOURS)
35    DAY_FINISH   = CINTXY             ! LENGTH OF EXPOSURE (HOURS)
36    MONTH_PERIOD = TIMELIMIT          ! EXPOSURE PERIOD (MONTHS)
37    MONTH_FINISH = EXP_TIME_OFF       ! LENGTH OF EXPOSURE (MONTHS)
38
39        !NUMBER OF EXPOSURES PER DAY AND MONTH
40    DAY_FINISH_BG   = CINTXY
41    MONTH_LAG_BG    = BCK_TIME_ON     ! TIME ELAPSED BEFORE BACKGROUND EXPOSURE
42   BEGINS (MONTHS)
43    MONTH_PERIOD_BG = TIMELIMIT       ! BACKGROUND EXPOSURE PERIOD (MONTHS)
44    MONTH_FINISH_BG = BCK_TIME_OFF    ! LENGTH OF BACKGROUND EXPOSURE (MONTHS)
45
46        ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER
47    B = 1.0-A
48
49
50        !GROWTH UP EQUATION (G)
51
52   PARAMETER (BW_RMN = 1.0E-30)
53   WT0= (BW_T0 *(1.0+(0.41*T)/(1402.5+T+BW_RMN))) ! IN GRAMS
54
55        ! VARIABILITY OF REST OF THE BODY DEPENDS ON OTHER ORGANS
56        !REST OF THE BODY FRACTION; UPDATED FOR EPA ASSESSMENT
57    WRE0 = (0.91 - (WLIB0*WLI0 + WFB0*WF0 + WLI0 + WF0))/(1+WREB0)
```

```
 1
 2        ! REST OF THE BODY BLOOD FLOW FRACTION
 3    QREF = 1.0-(QFF+QLIF)              !REST OF BODY BLOOD FLOW (ML/HR)
 4        !SUMMATION OF BLOOD FLOW FRACTION (SHOULD BE EQUAL TO 1)
 5    QTTQF = QFF+QREF+QLIF          ! SUM MUST EQUAL 1
 6
 7        !COMPARTMENT VOLUME (ML OR G)
 8    WF  =  WF0  * WT0                ! ADIPOSE
 9    WRE =  WRE0 * WT0                ! REST OF THE BODY
10    WLI =  WLI0 * WT0                ! LIVER
11
12        !COMPARTMENT TISSUE BLOOD (NL OR G )
13    WFB  =  WFB0  * WF              ! ADIPOSE
14    WREB =  WREB0 * WRE             ! REST OF THE BODY
15    WLIB =  WLIB0 * WLI             ! LIVER
16
17       !CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT
18      QC= QCCAR*60*(WT0/1000.0)**0.75
19
20    QF  = QFF*QC          ! ADIPOSE TISSUE BLOOD FLOW RATE (ML/HR)
21    QLI = QLIF*QC         ! LIVER TISSUE BLOOD FLOW RATE (ML/HR)
22    QRE = QREF*QC         ! REST OF THE BODY BLOOD FLOW RATE (ML/HR)
23
24    QTTQ = QF+QRE+QLI    !TOTAL FLOW RATE (ML/HR)
25
26       !PERMEABILITY ORGAN FLOW (ML/HR) =======
27    PAF  = PAFF*QF        ! ADIPOSE TISSUE
28    PARE = PAREF*QRE      ! REST OF THE BODY
29    PALI = PALIF*QLI      ! LIVER TISSUE
30
31        !ABSORPTION SECTION
32        !ORAL
33        !BACKGROUND EXPOSURE
34        !EXPOSURE FOR STEADY STATE CONSIDERATION
35        !REPETITIVE EXPOSURE SCENARIO
36
37    MSTOT_NMBCKGR = MSTOTBCKGR/322 !AMOUNT IN NMOL/G
38    MSTTBCKGR =MSTOT_NMBCKGR *WT0
39
40        !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIOS
41    DAY_EXPOSURE_BG   = PULSE(DAY_LAG_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
42    WEEK_EXPOSURE_BG  = PULSE(WEEK_LAG_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
43    MONTH_EXPOSURE_BG = PULSE(MONTH_LAG_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)
44
45    MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
46    MSTTFR_BG = MSTTBCKGR/CINT
47
48    totalBG= integ (MSTTCH_BG,0.0)
49    CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG
50
51
52        !CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
53    IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
54        ABSMSTT_GB= MSTTFR_BG
55    ELSE
56        ABSMSTT_GB = 0.0
57    END IF
```

```
 1
 2        !EXPOSURE + !REPETITIVE EXPOSURE SCENARIO
 3   IV= DOSEIV_NM * WT0  !AMOUNT IN NMOL
 4   MSTT= MSTOT_NM * WT0 !AMOUNT IN NMOL
 5
 6   DAY_EXPOSURE   = PULSE(DAY_LAG,DAY_PERIOD,DAY_FINISH)
 7   WEEK_EXPOSURE  = PULSE(WEEK_LAG,WEEK_PERIOD,WEEK_FINISH)
 8   MONTH_EXPOSURE = PULSE(MONTH_LAG,MONTH_PERIOD,MONTH_FINISH)
 9
10   MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
11   CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
12
13   SUMEXPEVENT= integ (CYCLE,0.0)*cint !NUMBER OF CYCLES GENERATED DURING
14   SIMULATION
15
16   MSTTFR = MSTT/CINT
17
18       ! CONDITIONAL ORAL EXPOSURE
19   IF (MSTTCH.EQ.MSTT) THEN
20      ABSMSTT= MSTTFR
21   ELSE
22      ABSMSTT = 0.0
23   END IF
24
25    CYCLETOT=INTEG(CYCLE,0.0)
26
27
28       !MASS CHANGE IN THE LUMEN
29   RMSTT= -(KST+KABS)*MST+ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
30    MST = INTEG(RMSTT,0.0)   !AMOUNT REMAINING IN DUODENUM (NMOL)
31
32       !ABSORPTION IN LYMPH CIRCULATION
33   LYRMLUM = KABS*MST*A
34    LYMLUM = INTEG(LYRMLUM,0.0)
35
36       !ABSORPTION IN PORTAL CIRCULATION
37   LIRMLUM = KABS*MST*B
38     LIMLUM = INTEG(LIRMLUM,0.0)
39
40       !PERCENT OF DOSE REMAINING IN THE GI TRACT
41   RFECES = KST*MST + REXCLI
42     FECES = INTEG(RFECES,0.0)
43   prctFECES = (FECES/(BDOSE_TOTAL+1E-30))*100
44
45
46       !ABSORPTION OF DIOXIN BY IV ROUTE---------
47    IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
48    EXPIV= IVR * (1.0-STEP(PFUNC))
49    IVDOSE = integ(EXPIV,0.0)
50
51       !SYSTEMIC BLOOD CONCENTRATION (NMOL/ML)
52       ! MODIFICATION ON OCTOBER 6, 2009
53   CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM)/(QC+CLURI) !
54    CA = CB
55
56       !URINARY EXCRETION BY KIDNEY
57       ! MODIFICATION ON OCTOBER 6, 2009
```

```
1   RAURI = CLURI *CB
2    AURI = INTEG(RAURI,0.0)
3
4   prctAURI = (AURI/(BDOSE_TOTAL+1E-30))*100
5
6
7       !UNIT CONVERSION POST SIMULATION
8   CBNGKG=CB*MW*UNITCORR
9   CBSNGKGLIADJ= (CB*MW*UNITCORR*(1.0/B_TOTLIP)*(1.0/SERBLO))![NG of TCDD
10  Serum/Kg OF LIPID]
11  CBPMOL_KG= CB*UNITCORR*UNITCORR        !CONCENTRATION IN PMOL/KG
12  CBNGG = CB*MW
13      !ADIPOSE TISSUE COMPARTMENT
14      !TISSUE BLOOD SUBCOMPARTMENT
15  RAFB = QF*(CA-CFB)-PAF*(CFB-CF/PF)        !(NMOL/HR)
16   AFB = INTEG(RAFB,0.0)                    !(NMOL)
17   CFB = AFB/WFB                            !(NMOL/ML)
18      !TISSUE SUBCOMPARTMENT
19  RAF  = PAF*(CFB-CF/PF)                    !(NMOL/HR)
20   AF  = INTEG(RAF,0.0)                     !(NMOL)
21   CF  = AF/WF                              !(NMOL/ML)
22
23      !POST SIMULATION UNIT CONVERSION
24  CFTOTAL    = (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION IN FAT(NM/ML)
25  CFNGKG  = CFTOTAL*MW*UNITCORR
26  CFUGG=(CFTOTAL*MW)/UNITCORR
27  CFPMOL_KG= CFTOTAL*UNITCORR*UNITCORR      !CONCENTRATION IN PMOL/KG
28  CFNGG = CFTOTAL*MW
29
30      !REST OF THE BODY COMPARTMENT
31      !TISSUE BLOOD SUBCOMPARTMENT
32  RAREB= QRE*(CA-CREB)-PARE*(CREB-CRE/PRE)        !(NMOL/HR)
33   AREB = INTEG(RAREB,0.0)                        !(NMOL)
34   CREB = AREB/WREB                               !(NMOL/ML)
35      !TISSUE SUBCOMPARTMENT
36  RARE = PARE*(CREB - CRE/PRE)                    !(NMOL/HR)
37   ARE = INTEG(RARE,0.0)                          !(NMOL)
38   CRE  = ARE/WRE                                 !(NMOL/ML)
39
40      !POST SIMULATION UNIT CONVERSION
41  CRETOTAL= (ARE + AREB)/(WRE + WREB)             ! CONCENTRATION AT STEADY
42  STATE
43
44
45      !LIVER COMPARTMENT
46      !TISSUE BLOOD SUBCOMPARTMENT
47  RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM    !(NMOL/HR)
48   ALIB = INTeg(RALIB,0.0)                           !(NMOL)
49   CLIB = ALIB/WLIB
50      !TISSUE SUBCOMPARTMENT
51   RALI =  PALI*(CLIB-CFLLIR)-REXCLI                 !(NMOL/HR)
52   ALI = integ(RALI,0.0)                             !(NMOL)
53   CLI  = ALI/WLI                                    !(NMOL/ML)
54
55      !FREE TCCD CONCENTRATION IN LIVER (NMOL/ML)
56  PARAMETER (LIVER_1RMN = 1.0E-30)
57   CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLI &
```

```
 1          +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR &
 2          +LIVER_1RMN)*IND_ACTIVE)))-CFLLI,CFLLI0)
 3        CFLLIR=DIM(CFLLI,0.0) ! FREE CONCENTRATION IN LIVER
 4
 5    CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND CONCENTRATION
 6
 7       !POST SIMULATION UNIT CONVERSION
 8    CLITOTAL= (ALI + ALIB)/(WLI + WLIB)!
 9    rec_occ_AHR= (CFLLIR/(KDLI+CFLLIR+1E-30))*100.0  ! PERCENT OF AhR OCCUPANCY
10    PROT_occ_1A2= (CFLLIR/(KDLI2+CFLLIR))*100.0  ! PERCENT OF 1A2 OCCUPANCY
11    CLINGKG =(CLITOTAL*MW*UNITCORR)
12    CBNDLINGKG = CBNDLI*MW*UNITCORR
13    CLIUGG=(CLITOTAL*MW)/UNITCORR
14    CLIPMOL_KG= CLITOTAL*UNITCORR*UNITCORR        !CONCENTRATION IN PMOL/KG
15    CLINGG = CLITOTAL*MW
16
17       !Fraction increase of induction of CYP1A2
18    fold_ind=(CYP1A2_1OUT/CYP1A2_1A2)
19    VARIATIONofAC =(CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2
20
21       !VARIABLE ELIMINATION BASED ON THE CYP1A2
22    KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv !INDUCED BILIARY
23    EXCRETION RATE CONSTANT
24
25    REXCLI= (KBILE_LI_T*CFLLIR*WLI) !DOSE-DEPENDENT EXCRETION RATE
26     EXCLI = INTEG(REXCLI,0.0)
27
28       !CHEMICAL IN CYP450 (1A2) COMPARTMENT
29       !EQUATION FOR INDUCTION OF CYP1A2
30
31    CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ
32
33       ! MODIFICATION ON OCTOBER 6, 2009
34    CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-30)**HILL
35    &
36        /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
37         - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)
38    ! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
39    SIMULATIONS)
40
41    CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
42      CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)
43    CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
44      CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)
45
46          ! MASS BALANCE CONTROL
47     BDOSE= LYMLUM+LIMLUM+IVDOSE
48     BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI
49     BDIFF = BDOSE-BMASSE
50          ! AMOUNT TOTAL PRESENT IN THE GI TRACT
51    BDOSE_TOTAL =LYMLUM+LIMLUM+FECES
52
53          !BODY BURDEN IN NG
54     Body_burden =(AFB+AF+AREB+ARE+ALIB+ALI)*MW
55
56          !BODY BURDEN CONCENTRATION (NG/KG)
57     BBNGKG =(((AFB+AF+AREB+ARE+ALIB+ALI)*MW)/(WT0/UNITCORR)) !
```

```
      !COMMAND FOR END OF SIMULATION
TERMT (T.GE. TimeLimit, 'Time limit has been reached.')

END   ! END OF THE DERIVATIVE SECTION
END   ! END OF THE DYNAMIC SECTION
END   ! END OF PROGRAM
```

E.2.5.2. *Input Files*

E.2.5.2.1. *Della Porta (1987) female*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Della Porta 1987 for female mice.
%dose levels:  2.5 and 5 ug/kg/week for 52 weeks
%dose levels:  2500 and 5000 ng/kg/week for 52 weeks
%dose levels equivalent to: 357 and 714 ng/kg-d

MAXT =  0.01
CINT  = 0.1
EXP_TIME_ON      = 0.            %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     = 8736         %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE        = 168          %HOURS BETWEEN DOSES
BCK_TIME_ON      = 0.           %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF     = 0.           %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT        = 8736         %SIMULATION DURATION (HOUR)
BW_T0            = 20           %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
    %MSTOT         = 2.5          %EXPOSURE DOSE UG/KG
    MSTOT          = 5.0          %EXPOSURE DOSE UG/KG
```

E.2.5.2.2. *Della Porta (1987) male*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Della Porta 1987 for male mice.
%dose levels:  2.5 and 5 ug/kg/week for 52 weeks
%dose levels:  2500 and 5000 ng/kg/week for 52 weeks
%dose levels equivalent to: 357 and 714 ng/kg-d

MAXT =  0.01
CINT  = 0.1
EXP_TIME_ON      = 0.            %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     = 8736         %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE        = 168          %HOURS BETWEEN DOSES
BCK_TIME_ON      = 0.           %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF     = 0.           %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT        = 8736         %SIMULATION DURATION (HOUR)
```

```
BW_T0              = 26                  %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
    %MSTOT          = 2.5                %EXPOSURE DOSE UG/KG
    MSTOT           = 5.0                %EXPOSURE DOSE UG/KG
```

E.2.5.2.3. *Ishihara et al. ([2007](#))*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Ishihara 2007
%dose levels:  1) 2 ng/kg loading; 0.4 ng/kg weekly
              %2) 2,000 ng/kg loading; 400 ng/kg weekly

 MAXT              = 0.01
 CINT              = 0.1
 TIMELIMIT         = 840                 %SIMULATION DURATION (HOUR)
 EXP_TIME_ON       = 168                 %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF      = 840                 %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE         = 168                 %HOURS BETWEEN DOSES
 BCK_TIME_ON       = 0.                  %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF      = 0.02                %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 BW_T0             = 23                  %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOTBCKGR     = 0.002               %INITIAL LOADING EXPOSURE DOSE [UG/KG]
   %MSTOT          = 0.0004              %EXPOSURE DOSE [UG/KG]
   MSTOTBCKGR   = 2                      %INITIAL LOADING EXPOSURE DOSE [UG/KG]
   MSTOT        = 0.4                    %EXPOSURE DOSE [UG/KG]
```

E.2.5.2.4. *Kuchiiwa et al. ([2002](#))*

```
% Kuchiiwa 2002
%protocol:  oral exposure once weekly for 8 weeks
%dose levels:  0.0049, 0.490  ug/kg once weekly for 8 weeks

 MAXT = 0.01
 CINT  = 0.1
 TIMELIMIT        = 1344                 %SIMULATION DURATION (HOUR)
 EXP_TIME_ON      = 0.                   %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF     = 1344                 %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE        = 168                  %HOURS BETWEEN DOSES
 BCK_TIME_ON      = 0.                   %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF     = 0.0                  %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 BW_T0            = 25                   %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (g)


%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT          = 0.0049              %EXPOSURE DOSE [UG/KG]
   MSTOT        = 0.490                  %EXPOSURE DOSE [UG/KG]
```

E.2.5.2.5. *NTP (1982) female, chronic*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% NTP 1982.
%protocol: twice weekly gavage for 104 weeks
%dose levels:  0.02, 0.1, 1 ug/kg twice weekly for 104 weeks
%dose levels:  20, 100, 1000 ng/kg twice weekly for 104 weeks
%dose levels equivalent to: 5.71, 28.57, 285.1 ng/kg-d

MAXT =  0.01
CINT  = 0.1
EXP_TIME_ON        = 0.              %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF       = 17472           %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE          = 84              %HOURS BETWEEN DOSES
BCK_TIME_ON        = 0.              %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF       = 0.              %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT          = 17472           %SIMULATION DURATION (HOUR)
BW_T0              = 23              %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
    %MSTOT          = 0.02           %EXPOSURE DOSE UG/KG
    %MSTOT          = 0.1            %EXPOSURE DOSE UG/KG
    MSTOT           = 1.0            %EXPOSURE DOSE UG/KG
```

E.2.5.2.6. *NTP (1982) male, chronic*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% NTP 1982.
%protocol: twice weekly gavage for 104 weeks
%dose levels:  0.005, 0.025, 0.25 ug/kg twice weekly for 104 weeks
%dose levels:  5, 25, 250 ng/kg twice weekly for 104 weeks
%dose levels equivalent to: 1.4, 7.1, 71 ng/kg-d

MAXT =  0.01
CINT  = 0.1
EXP_TIME_ON        = 0.              %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF       = 17472           %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE          = 84              %HOURS BETWEEN DOSES
BCK_TIME_ON        = 0.              %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF       = 0.              %TIME BACKGROUND EXPOSURE ENDS (HOUR)
TIMELIMIT          = 17472           %SIMULATION DURATION (HOUR)
BW_T0              = 25              %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
    %MSTOT          = 0.005          %EXPOSURE DOSE UG/KG
    %MSTOT          = 0.025          %EXPOSURE DOSE UG/KG
```

```
MSTOT           = 0.25                  %EXPOSURE DOSE UG/KG
```

E.2.5.2.7. *Nohara et al. (2002)*

```
%Nohara 2002
%protocol:  single oral exposure dose
%dose levels:  0.005, 0.020, 0.100 and 0.500 ug/kg single dose
%dose levels equivalent 5, 20, 100 and 500 ng/kg single dose

MAXT = 0.01
CINT  = 0.1
TIMELIMIT       = 24                  %SIMULATION DURATION (HOUR)
EXP_TIME_ON     = 0.                  %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    = 24                  %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE       = 24                  %HOURS BETWEEN DOSES
WEEK_FINISH     = 193                 %LAST HOUR WHEN DOSE OCCURS (HOUR)
BCK_TIME_ON     = 0.                  %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF    = 0.                  %TIME BACKGROUND EXPOSURE ENDS (HOUR)
BW_T0           = 23                  %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
     %MSTOT        = 0.005            %EXPOSURE DOSE UG/KG
     %MSTOT       = 0.020            %EXPOSURE DOSE UG/KG
     %MSTOT       = 0.100            %EXPOSURE DOSE UG/KG
     MSTOT        = 0.500            %EXPOSURE DOSE UG/KG
```

E.2.5.2.8. *Smialowicz et al. (2004)*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Smialowicz et al. 2004.

MAXT           = 0.01
CINT           = 0.1
TIMELIMIT      = 24.                  %SIMULATION DURATION (HOUR)
EXP_TIME_ON    = 0.                   %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF   = 24.                  %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE      =  24.                 %HOURS BETWEEN DOSES
BCK_TIME_ON    = 0.                   %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF   = 0.                   %TIME BACKGROUND EXPOSURE ENDS (HOUR)
BW_T0          = 25                   %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT       = 0.03               %EXPOSURE DOSE (UG/KG)
   %MSTOT    = 0.1                %EXPOSURE DOSE (UG/KG)
   %MSTOT    = 0.3                %EXPOSURE DOSE (UG/KG)
   %MSTOT    = 1.0                %EXPOSURE DOSE (UG/KG)
   %MSTOT    = 3.0                %EXPOSURE DOSE (UG/KG)
   MSTOT    = 10.0               %EXPOSURE DOSE (UG/KG)
```

E.2.5.2.9. *Smialowicz et al. ([2008](#))*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Smialowicz et al. 2008.
%protocol:  oral gavage 5 days/week for 13 weeks
%dose levels:  0, 0.0015, 0.015, 0.15, 0.45 ug/kg
%dose levels:  0, 1.5, 15, 150, 450 nkd (0, 1.07, 10.7, 107, 321 nkd adj)

MAXT          = 0.01
CINT          = 0.1
TIMELIMIT     = 2184                %SIMULATION DURATION (HOUR)
EXP_TIME_ON   = 0.                  %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF  = 2184                %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE     =  24                 %HOURS BETWEEN DOSES
WEEK_PERIOD   = 168                 %HOURS IN A WEEK
WEEK_FINISH   = 119                 %LAST HOUR IN WEEK WHERE DOSE OCCURS
BCK_TIME_ON   = 0.                  %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF  = 0.                  %TIME BACKGROUND EXPOSURE ENDS (HOUR)
BW_T0         = 28                  %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT      = 0.0015             %EXPOSURE DOSE (UG/KG)
   %MSTOT   = 0.015                 %EXPOSURE DOSE (UG/KG)
   %MSTOT   = 0.150                 %EXPOSURE DOSE (UG/KG)
    MSTOT   = 0.450                 %EXPOSURE DOSE (UG/KG)
```

E.2.5.2.10. *Toth et al. ([1979](#)) 1 year*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

% Toth et al. 1979
%protocol:  weekly gavage for 1 year
%dose levels:  7, 700, 7000 ng/kg once weekly for 52 weeks (1 year)
%dose levels:  0.007, 0.7, 7 ug/kg once weekly for 52 weeks (1 year)
%dose equivalent: 1, 100, 1000 ng/kg-day

MAXT          = 0.01
CINT          = 0.1
TIMELIMIT     = 8760                %SIMULATION DURATION (HOUR)
EXP_TIME_ON   = 0.                  %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF  = 8760                %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE     =  168                %HOURS BETWEEN DOSES
BCK_TIME_ON   = 0.                  %TIME BACKGROUND EXPOSURE BEGINS(HOUR)
BCK_TIME_OFF  = 0.                  %TIME BACKGROUND EXPOSURE ENDS (HOUR)
BW_T0         = 27                  %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT    = 0.007                %EXPOSURE DOSE (UG/KG)
```

```
    %MSTOT = 0.7                         %EXPOSURE DOSE (UG/KG)
    MSTOT = 7                            %EXPOSURE DOSE (UG/KG)
```

E.2.5.2.11. *Weber et al. ([1995](#))*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG CBNGKG

%Weber et al. 1995 C57 strain
%protocol:  single oral exposure dose

MAXT = 0.01
CINT  = 0.1
TIMELIMIT        = 24                 %SIMULATION DURATION (HOUR)
EXP_TIME_ON      = 0.                 %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     = 24                 %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE        = 24                 %HOURS BETWEEN DOSES
BCK_TIME_ON      = 0.                 %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF     = 0.                 %TIME BACKGROUND EXPOSURE ENDS (HOUR)
BW_T0            = 24.1               %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
       %MSTOT        = 0.03          %EXPOSURE DOSE UG/KG
       %MSTOT        = 0.1           %EXPOSURE DOSE UG/KG
       %MSTOT        = 0.3           %EXPOSURE DOSE UG/KG
       %MSTOT        = 1.0           %EXPOSURE DOSE UG/KG
       %MSTOT        = 3.0           %EXPOSURE DOSE UG/KG
       %MSTOT        = 9.4           %EXPOSURE DOSE UG/KG
       %MSTOT        = 37.5          %EXPOSURE DOSE UG/KG
       %MSTOT        = 75.0          %EXPOSURE DOSE UG/KG
       %MSTOT        = 100.0         %EXPOSURE DOSE UG/KG
       %MSTOT        = 133.0         %EXPOSURE DOSE UG/KG
       %MSTOT        = 150.0         %EXPOSURE DOSE UG/KG
       MSTOT      = 235.0            %EXPOSURE DOSE UG/KG
```

E.2.5.2.12. *White et al. ([1986](#))*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% White et al 1986
%protocol:  oral exposure single dose
%dose levels: 10, 50, 100, 500, 1000, 2000 ng /kg-d ug/kg 1/day for 14
consecutive days
%dose levels: 0.010, 0.050, 0.100, 0.500, 1.0, 2.0 ug /kg-d ug/kg 1/day for
14 consecutive days

MAXT        = 0.01
CINT        = 0.1
TIMELIMIT   = 336                    %SIMULATION DURATION (HOUR)
EXP_TIME_ON = 0.                     %TIME EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF = 336                   %TIME EXPOSURE ENDS (HOUR)
DAY_CYCLE   =  24                    %HOURS BETWEEN DOSES
```

```
1    BCK_TIME_ON  = 0.                          %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
2    BCK_TIME_OFF = 0.                          %TIME BACKGROUND EXPOSURE ENDS (HOUR)
3    BW_T0     = 23                             %BODY WEIGHT AT THE BEGINNING OF THE
4    SIMULATION (G)
5
6    %EXPOSURE DOSE SCENARIOS (UG/KG)
7       %MSTOT = 0.010                          %EXPOSURE DOSE IN UG/KG
8       %MSTOT = 0.050                          %EXPOSURE DOSE IN UG/KG
9       %MSTOT = 0.100                          %EXPOSURE DOSE IN UG/KG
10      %MSTOT = 0.500                          %EXPOSURE DOSE IN UG/KG
11      %MSTOT =  1                             %EXPOSURE DOSE IN UG/KG
12      MSTOT =  2                              %EXPOSURE DOSE IN UG/KG
13
```

14 **E.2.6.   Mouse Gestational Model**

15 **E.2.6.1.** *Model Code*

16 PROGRAM: 'Three Compartment PBPK Model for TCDD in Mice (Gestation)'

```
17
18   INITIAL  !
19
20       !SIMULATION PARAMETERS ====
21   CONSTANT PARA_ZERO        = 1E-30
22   CONSTANT EXP_TIME_ON    = 288.       ! TIME AT WHICH EXPOSURE BEGINS (HOURS)
23   CONSTANT EXP_TIME_OFF   = 504        ! TIME AT WHICH EXPOSURE ENDS (HOURS)
24   CONSTANT DAY_CYCLE      =  504.      ! NUMBER OF HOURS BETWEEN DOSES (HOURS)
25   CONSTANT BCK_TIME_ON     = 0.0       ! TIME AT WHICH BACKGROUND EXPOSURE
26   BEGINS (HOURS)
27   CONSTANT BCK_TIME_OFF    = 0.0       ! TIME AT WHICH BACKGROUND EXPOSURE ENDS
28   (HOURS)
29   CONSTANT TRANSTIME_ON    = 144       !CONTROL TRANSFER FROM MOTHER TO FETUS
30   AT GESTATIONAL DAY 6
31
32      !UNIT CONVERSION
33   CONSTANT MW=322 ! MOLECULAR WEIGHT (NG/NMOL)
34   CONSTANT SERBLO = 0.55
35   CONSTANT UNITCORR = 1000
36
37      !INTRAVENOUS SEQUENCY
38   constant IV_LAG       = 0.0
39   constant IV_PERIOD    = 0.0
40
41      !PREGNANCY PARAMETER ====
42   CONSTANT CONCEPTION_T        = 0.0       !TIME OF CONCEPTION (HOUR)
43   CONSTANT N_FETUS        = 10        !NUMBER OF FETUS PRESENT
44
45      !CONSTANT EXPOSURE CONTROL ===========
46      !ACUTE, SUBCHRONIC, CHRONIC EXPOSURE =====
47      !OR BACKGROUND EXPOSURE (IN THIS CASE 3 TIMES A DAY)===
48   CONSTANT MSTOTBCKGR     = 0.0       ! ORAL BACKGROUND EXPOSURE DOSE (UG/KG)
49   CONSTANT MSTOT          = 0.0       ! ORAL EXPOSURE DOSE (UG/KG)
50
51      !ORAL ABSORPTION
52    MSTOT_NM = MSTOT/MW                  !CONVERTS THE DOSE TO NMOL/G
53
54      ! INTRAVENOUS ABSORPTION
```

```
CONSTANT  DOSEIV         = 0.0        ! INJECTED DOSE (UG/KG)
   DOSEIV_NM = DOSEIV/MW              ! CONVERTS THE INJECTED DOSE TO NMOL/G
CONSTANT DOSEIVLATE = 0.0             ! INJECTED DOSE LATE (UG/KG)
   DOSEIVNMlate = DOSEIVLATE/MW       !AMOUNT IN NMOL/G

    !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND (COMPARTMENT
INDICATED BELOW)====
CONSTANT CFLLI0          = 0.0  !LIVER    (NMOL/ML)
CONSTANT CFLPLA0         = 0.0  !PLACENTA (NMOL/ML)

    !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT INDICATED
BELOW) (NMOL/ML) ===
CONSTANT LIBMAX          = 3.5E-4   ! LIVER  (NMOL/ML), WANG ET AL. 1997
CONSTANT PLABMAX         = 2.0E-4   !TEMPORARY PARAMETER

    ! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED BELOW)
(NMOL/ML)===
CONSTANT KDLI            = 1.0E-4   !LIVER (AhR) (NMOL/ML), WANG ET AL. 1997
CONSTANT KDLI2           = 4.0E-2   !LIVER (1A2) (NMOL/ML), EMOND ET AL. 2004
CONSTANT KDPLA           = 1.0E-4   !TEMPORARY PARAMETER (AhR)

    !EXCRETION AND ABSORPTION CONSTANT
CONSTANT KST             =    0.3   ! GASTRIC RATE CONSTANT (HR-1)
CONSTANT KABS            =    0.48  !INTESTINAL ABSORPTION CONSTANT (HR-1) ),
WANG ET AL. 1997

! ELIMINATION CONSTANTS
CONSTANT CLURI           =       0.09 ! URINARY CLEARANCE (ML/HR)

   !TEST ELIMINATION VARIABLE
constant kelv            =      0.4       ! INTERSPECIES VARIABLE ELIMINATION
CONSTANT (1/HOUR)

    ! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL FRACTIONS
CONSTANT A               = 0.7           ! LYMPHATIC FRACTION, WANG ET AL. 1997

    !PARTITION COEFFICIENTS
CONSTANT PF              = 400    ! ADIPOSE TISSUE/BLOOD
CONSTANT PRE             = 3      ! REST OF THE BODY/BLOOD, WANG ET AL. 2000
CONSTANT PLI             = 6      ! LIVER/BLOOD, WANG ET AL. 1997
CONSTANT PPLA            = 3      ! TEMPORARY PARAMETER NOT CONFIGURED

    !PARAMETER FOR INDUCTION OF CYP 1A2, WANG ET AL. 1997 OR OPTIMIZED
CONSTANT IND_ACTIVE      = 1          ! INCLUDE INDUCTION? (1 = YES, 0 = NO)
CONSTANT CYP1A2_1OUTZ    = 1.6        ! DEGRADATION CONCENTRATION CONSTANT OF
1A2 (NMOL/ML) (OPTIMIZED)
CONSTANT CYP1A2_1A1      = 1.5        ! BASAL CONCENTRATION OF 1A1 (NMOL/ML),
WANG ET AL . (2000)
CONSTANT CYP1A2_1EC50    = 0.13       ! DISSOCIATION CONSTANT TCDD-CYP1A2
(NMOL/ML)
CONSTANT CYP1A2_1A2      = 1.5        !BASAL CONCENTRATION OF 1A2
(NMOL/ML),WANG ET AL. (2000)
CONSTANT CYP1A2_1KOUT    = 0.1        ! FIRST ORDER RATE OF DEGRADATION (H-1)
CONSTANT CYP1A2_1TAU     = 1.5        !HOLDING TIME (H) (OPTIMIZED), WANG ET AL
. (2000)
CONSTANT CYP1A2_1EMAX    = 600        ! MAXIMUM INDUCTION OVER BASAL EFFECT
(UNITLESS)
```

```
CONSTANT HILL              = 0.6        !HILL CONSTANT; COOPERATIVELY LIGAND
BINDING EFFECT CONSTANT (UNITLESS)

    !DIFFUSIONAL PERMEABILITY FRACTION, WANG ET AL. 1997
CONSTANT PAFF              = 0.12   !ADIPOSE (UNITLESS) OPTIMIZED, WANG ET AL.
2000
CONSTANT PAREF             = 0.03   !REST OF THE BODY (UNITLESS)
CONSTANT PALIF             = 0.35   !LIVER (UNITLESS)
CONSTANT PAPLAF            = 0.03   !TEMPORARY PARAMETER NOT CONFIGURED

    !FRACTION OF TISSUE WEIGHT =========
CONSTANT WLI0              = 0.0549   !LIVER  ILSI (1994)

    !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT CONSTANT QFF
= 0.070    ! ADIPOSE TISSUE BLOOD FLOW FRACTION (UNITLESS), LEUNG ET AL. 1990
CONSTANT QLIF             = 0.161    !LIVER (UNITLESS), ILSI 1994

    !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL COMPARTMENT
VOLUME
CONSTANT WFB0             = 0.050    !ADIPOSE TISSUE, WANG ET AL. 1997
CONSTANT WREB0            = 0.030    !REST OF THE BODY, WANG ET AL. 1997
CONSTANT WLIB0            = 0.266    !LIVER, WANG ET AL. 1997
CONSTANT WPLAB0           = 0.500    !TEMPORARY PARAMETER NOT CONFIGURED

    !EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY EXPOSURE
    !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG       = 0.0        !TIME ELAPSED BEFORE EXPOSURE BEGINS
(WEEK)
CONSTANT WEEK_PERIOD    = 168        ! NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH    = 168        ! TIME EXPOSURE ENDS (HOURS)

    !NUMBER OF EXPOSURES PER MONTH
CONSTANT MONTH_LAG      = 0.0        !TIME ELAPSED BEFORE EXPOSURE BEGINS
(MONTH)

    !CONSTANT FOR BACKGROUND EXPOSURE==========
CONSTANT Day_LAG_BG     = 0.0        ! TIME ELAPSED BEFORE EXPOSURE BEGINS
(HOUR)
CONSTANT Day_PERIOD_BG  = 24         !LENGTH OF EXPOSURE (HOUR)

    !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LAG_BG      = 0.0        !TIME ELAPSED BEFORE BACKGROUND EXPOSURE
(WEEK)
CONSTANT WEEK_PERIOD_BG   = 168        ! NUMBER OF HOURS IN THE WEEK (HOURS)
CONSTANT WEEK_FINISH_BG   = 168        !TIME EXPOSURE ENDS (HOURS)

    !INITIAL BODY WEIGHT
CONSTANT BW_T0             = 30       ! WANG ET AL. 1997 (IN G)
CONSTANT RATIO_RATF_MOUSEF = 0.2       !RATIO OF FETUS MOUSE/RAT AT
GESTATIONAL DAY 22
                                       ! FOR RAT (1) AND FOR MOUSE (0.2)

    !COMPARTMENT TOTAL LIPID FRACTION , POULIN ET AL. 2000
CONSTANT F_TOTLIP          = 0.855               ! ADIPOSE TISSUE (UNITLESS)
CONSTANT B_TOTLIP          = 0.0033              ! BLOOD (UNITLESS)
CONSTANT RE_TOTLIP         = 0.019               ! REST OF THE BODY
(UNITLESS)
```

```
1    CONSTANT LI_TOTLIP         = 0.060                    ! LIVER (UNITLESS)
2    CONSTANT PLA_TOTLIP        = 0.019                    ! PLACENTA (UNITLESS)
3    CONSTANT FETUS_TOTLIP      = 0.019                ! FETUS (UNITLESS)
4
5    END     ! END OF THE INITIAL SECTION
6
7    DYNAMIC ! DYNAMIC SIMULATION SECTION
8    ALGORITHM   IALG          =              2        ! GEAR METHOD
9    CINTERVAL   CINT          =            0.1        ! COMMUNICATION INTERVAL
10   MAXTERVAL   MAXT          =         1.0e+10       ! MAXIMUM CALCULATION INTERVAL
11   MINTERVAL   MINT          =         1.0E-10       ! MINIMUM CALCULATION INTERVAL
12   VARIABLE    T             =           0.0
13   CONSTANT    TIMELIMIT     =            313        !SIMULATION LIMIT TIME (HOUR)
14    CINTXY  = CINT
15    PFUNC   = CINT
16
17      !TIME CONVERSION
18    DAY          = T/24          ! TIME IN DAYS
19    WEEK         = T/168         ! TIME IN WEEKS
20    MONTH        = T/730         ! TIME IN MONTHS
21    YEAR         = T/8760        ! TIME IN YEARS
22
23   DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS
24
25      !CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
26      !NUMBER OF EXPOSURES PER DAY
27    DAY_LAG           = EXP_TIME_ON    ! TIME ELAPSED BEFORE EXPOSURE BEGINS
28   (HOURS)
29    DAY_PERIOD        = DAY_CYCLE       ! EXPOSURE PERIOD (HOURS)
30    DAY_FINISH        = CINTXY          ! LENGTH OF EXPOSURE (HOURS)
31    MONTH_PERIOD      = TIMELIMIT       ! EXPOSURE PERIOD (MONTHS)
32    MONTH_FINISH      = EXP_TIME_OFF    ! LENGTH OF EXPOSURE (MONTHS)
33
34      !NUMBER OF EXPOSURES PER DAY AND MONTH
35    DAY_FINISH_BG     = CINTXY
36    MONTH_LAG_BG      = BCK_TIME_ON     !TIME ELAPSED BEFORE BACKGROUND EXPOSURE
37   BEGINS (MONTHS)
38    MONTH_PERIOD_BG = TIMELIMIT        !BACKGROUND EXPOSURE PERIOD (MONTHS)
39    MONTH_FINISH_BG = BCK_TIME_OFF     !LENGTH OF BACKGROUND EXPOSURE (MONTHS)
40
41      !INTRAVENOUS LATE
42    IV_FINISH = CINTXY
43    B = 1-A ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER
44
45
46   !FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUM
47   E
48     ! FROM OFLAHERTY_1992
49
50   RTESTGEST= T-CONCEPTION_T
51   TESTGEST=DIM(RTESTGEST,0.0)
52
53   WTFER_RODENT= (2.3d-3*EXP(1.49d-2*(TESTGEST))+1.3d-2)*Gest_on
54   WTFER = (WTFER_RODENT*RATIO_RATF_MOUSEF*N_FETUS)
55   WTFE = DIM(WTFER,0.0)
56
```

```fortran
 1      !
 2   FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME
 3      ! FAT GROWTH EXPRESSION LINEAR DURING PREGNANCY
 4      ! FROM O'FLAHERTY_1992
 5
 6   WF0= (((9.66d-5*(TESTGEST))*gest_on)+0.069)
 7
 8      ! PLACENTA,VOLUME, PLACENTA,VOLUME, PLACENTA,VOLUME, PLACENTA,VOLUME
 9      ! WPLA PLACENTA GROWTH EXPRESSION, SINGLE EXPONENTIAL WITH OFFSET
10      ! FROM O'FLAHERTY_1992  ! FOR EACH PUP
11
12   WPLA0N_RODENT = (0.6/(1+(5d+3*EXP(-0.0225*(TESTGEST)))))*N_FETUS
13   WPLA0R = (WPLA0N_RODENT/WT0)*Gest_on
14   WPLA0 = DIM(WPLA0R,0.0)
15
16      ! PLACENTA,FLOW RATE, PLACENTA,FLOW RATE, PLACENTA,FLOW RATE, PLACENTA,FLOW
17   RATE
18      ! QPLA PLACENTA GROWTH EXPRESSION, DOUBLE EXPONENTIAL WITH OFFSET
19      ! FROM O'FLAHERTY_1992
20
21    QPLARF = (1.67d-7 *exp(9.6d-3*(TESTGEST)) &
22      +1.6d-3*exp(7.9d-3*(TESTGEST))+0.0)*Gest_on*SWITCH_trans
23    QPLAF=DIM(QPLARF,0.0)                        !FRACTION OF FLOW RATE IN PLACENTA
24
25      ! GESTATION CONTROL
26   IF (T.LT.CONCEPTION_T) THEN
27      Gest_off = 1
28      Gest_on=   0.0
29   ELSE
30      Gest_off = 0.0
31      Gest_on  = 1
32   END IF
33
34      ! MOTHER BODY WEIGHT GROWTH EQUATION========
35      ! MODIFICATION TO ADAPT THIS MODEL AT HUMAN MODEL
36      ! BECAUSE LINEAR DESCRIPTION IS NOT GOOD ENOUGH FOR MOTHER GROWTH
37      ! MOTHER BODY WEIGHT GROWTH
38
39      PARAMETER (BW_RMN = 1.0E-30)
40      WT0= BW_T0 *(1.0+(0.41*T)/(1402.5+T+BW_RMN)) ! IN GRAMS
41
42      ! VARIABILITY OF REST OF THE BODY DEPENDS ON OTHER ORGANS
43      WRE0 = (0.91 - (WLIB0*WLI0 + WFB0*WF0 +WPLAB0*WPLA0 + WLI0 + WF0 +
44   WPLA0))/(1.0+WREB0)   ! REST OF THE BODY FRACTION; UPDATED FOR EPA ASSESSMENT
45      QREF = 1.0-(QFF+QLIF+QPLAF)              !REST OF BODY BLOOD FLOW RATE
46   FRACTION
47      QTTQF = QFF+QREF+QLIF+QPLAF          ! SUM MUST EQUAL 1
48
49      ! COMPARTMENT VOLUME (ML OR G) =========
50    WF  =   WF0  * WT0                        ! ADIPOSE TISSUE
51    WRE =   WRE0 * WT0                        ! REST OF THE BODY
52    WLI =   WLI0 * WT0                        ! LIVER
53    WPLA=   WPLA0* WT0                        ! PLACENTA
54
55      ! COMPARTMENT TISSUE BLOOD (ML OR G) =========
56    WFB  =   WFB0  * WF                       ! ADIPOSE TISSUE
57    WREB =   WREB0 * WRE                      ! REST OF THE BODY
```

```
 1    WLIB =  WLIB0 * WLI                      ! LIVER
 2     WPLAB = WPLAB0* WPLA                     ! PLACANTA
 3
 4        ! CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT
 5        !QC= QCCAR*60*(WT0/1000.0)**0.75
 6    CONSTANT QCC=16500                        ! EQUIVALENT TO 275 * 60
 7    QC= QCC*(WT0/UNITCORR)**0.75
 8
 9        !COMPARTMENT BLOOD FLOW RATE (ML/HR)
10    QF  = QFF*QC                              !ADIPOSE TISSUE BLOOD FLOW RATE
11    QLI = QLIF*QC                             !LIVER TISSUE BLOOD FLOW RATE
12    QRE = QREF*QC                             !REST OF THE BODY BLOOD FLOW RATE
13    QPLA = QPLAF*QC                           !PLACENTA TISSUE BLOOD FLOW RATE
14    QTTQ = QF+QRE+QLI+QPLA    !TOTAL FLOW RATE
15
16        !PERMEABILITY ORGAN FLOW (ML/HR)=========
17    PAF  = PAFF*QF                            ! ADIPOSE TISSUE
18    PARE = PAREF*QRE                          ! REST OF THE BODY
19    PALI = PALIF*QLI                          ! LIVER TISSUE
20    PAPLA = PAPLAF*QPLA                       ! PLACENTA
21
22        !************************************
23        ! ABSORPTION SECTION
24        ! ORAL,
25        ! INTRAPERITONEAL,
26        ! INTRAVENOUS
27        !************************************
28
29        !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIO
30
31    MSTOT_NMBCKGR = MSTOTBCKGR/322        !AMOUNT IN NMOL/G
32    MSTTBCKGR =MSTOT_NMBCKGR *WT0
33
34    DAY_EXPOSURE_BG   = PULSE(DAY_LAG_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
35    WEEK_EXPOSURE_BG  = PULSE(WEEK_LAG_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
36    MONTH_EXPOSURE_BG = PULSE(MONTH_LAG_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)
37
38    MSTTCH_BG = (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCKGR
39    MSTTFR_BG = MSTTBCKGR/CINT
40
41    CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG
42
43        ! CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
44
45    IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
46        ABSMSTT_GB= MSTTFR_BG
47    ELSE
48        ABSMSTT_GB = 0.0
49    END IF
50
51    CYCLETOTBG=INTEG(CYCLE_BG,0.0)
52
53        !REPETITIVE ORAL EXPOSURE SCENARIO
54
55    MSTT= MSTOT_NM * WT0                      !AMOUNT IN NMOL
56
57    DAY_EXPOSURE   = PULSE(DAY_LAG,DAY_PERIOD,DAY_FINISH)
```

```
1    WEEK_EXPOSURE  = PULSE(WEEK_LAG,WEEK_PERIOD,WEEK_FINISH)
2    MONTH_EXPOSURE = PULSE(MONTH_LAG,MONTH_PERIOD,MONTH_FINISH)
3
4    MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
5    MSTTFR = MSTT/CINT
6
7    CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
8    SUMEXPEVENT= INTEG (CYCLE,0.0)/cint !NUMBER OF CYCLES GENERATED DURING
9    SIMULATION
10
11      ! CONDITIONAL ORAL EXPOSURE
12   IF (MSTTCH.EQ.MSTT) THEN
13      ABSMSTT= MSTTFR
14   ELSE
15      ABSMSTT = 0.0
16   END IF
17
18
19    CYCLETOT=INTEG(CYCLE,0.0)
20
21      ! MASS CHANGE IN THE LUMEN
22    RMSTT= -(KST+KABS)*MST +ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE (NMOL/H)
23     MST = INTEG(RMSTT,0.0)                      !AMOUNT REMAINING IN DUODENUM
24   (NMOL)
25
26      ! ABSORPTION IN LYMPH CIRCULATION
27    LYRMLUM = KABS*MST*A
28     LYMLUM = INTEG(LYRMLUM,0.0)
29
30      ! ABSORPTION IN PORTAL CIRCULATION
31    LIRMLUM = KABS*MST*B
32     LIMLUM = INTEG(LIRMLUM,0.0)
33
34
35   ! -----IV EXPOSURE ---------
36
37    IV= DOSEIV_NM * WT0 !AMOUNT IN NMOL
38    IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
39    EXPIV= IVR * (1.0-STEP(PFUNC))
40    IVDOSE = integ(EXPIV,0.0)
41
42      !------IV late in the cycle
43      ! MODIFICATION ON January 13 2004
44    IV_RlateR = DOSEIVNMlate*WT0
45    IV_EXPOSURE=PULSE(IV_LAG,IV_PERIOD,IV_FINISH)
46
47    IV_lateT = IV_EXPOSURE *IV_RlateR
48    IV_late = IV_lateT/CINT
49
50   SUMEXPEVENTIV= integ (IV_EXPOSURE,0.0) !NUMBER OF CYCLES GENERATED DURING
51   SIMULATION
52
53      !SYSTEMIC CONCENTRATION OF TCDD
54      ! MODIFICATION ON OCTOBER 6, 2009
55    CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late)/(QC+CLURI) !
56    CA = CB ! CONCENTRATION (NMOL/ML)
57
```

```
     !URINARY EXCRETION BY KIDNEY
     !MODIFICATION ON OCTOBER 6, 2009
RAURI = CLURI *CB
  AURI = INTEG(RAURI,0.0)

  !UNIT CONVERSION POST SIMULATION
 CBSNGKGLIADJ=(CB*MW*UNITCORR*(1/B_TOTLIP)*(1/SERBLO))![NG of TCDD Serum/Kg
OF LIPID]
   AUCBS_NGKGLIADJ=integ(CBSNGKGLIADJ,0.0)


  CBNGKG= CB*MW*UNITCORR
  CBNGG = CB*MW

   !ADIPOSE COMPARTMENT
   !TISSUE BLOOD COMPARTMENT
RAFB= QF*(CA-CFB)-PAF*(CFB-CF/PF)    !(NMOL/H)
 AFB = INTEG(RAFB,0.0)                    !(NMOL)
  CFB = AFB/WFB                           !(NMOL/ML)
   !TISSUE COMPARTMENT
RAF = PAF*(CFB-CF/PF)                !(NMOL/H)
 AF = INTEG(RAF,0.0)                 !(NMOL)
  CF  = AF/WF                        !(NMOL/ML)

   !UNIT CONVERSION POST SIMULATION
  CFTOTAL= (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION IN NMOL/ML
  CFTFREE = CFB + CF !TOTAL FREE CONCENTRATION IN FAT  (NM/ML)

  CFNGKG=CFTOTAL*MW*UNITCORR ! FAT CONCENTRATION IN NG/KG
    AUCF_NGKGH=integ(CFNGKG,0.0)
  CFNGG = CFTOTAL*MW

   !REST OF THE BODY COMPARTMENT
RAREB= QRE *(CA-CREB)-PARE*(CREB-CRE/PRE)  !(NMOL/H)
 AREB = INTEG(RAREB,0.0)                   !(NMOL)
  CREB = AREB/WREB                         !(NMOL/H)
   !TISSUE COMPARTMENT
RARE = PARE*(CREB - CRE/PRE)            !(NMOL/H)
 ARE = INTEG(RARE,0.0)                  !(NMOL)
  CRE  = ARE/WRE                        !(NMOL/ML)

   !UNIT CONVERSION POST SIMULATION
  CRETOTAL= (ARE + AREB)/(WRE + WREB)         ! TOTAL CONCENTRATION IN
NMOL/ML
     CRENGKG=CRETOTAL*MW*UNITCORR ! REST OF THE BODY CONCENTRATION IN NG/KG


   !LIVER COMPARTMENT
   !TISSUE BLOOD COMPARTMENT
 RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM !
  ALIB = INTEG(RALIB,0.0)                     !(NMOL)
   CLIB = ALIB/WLIB                           !(NMOL/ML)
   !TISSUE COMPARTMENT
 RALI = PALI*(CLIB - CFLLIR)-REXCLI        !  (NMOL/HR)
  ALI = INTEG(RALI,0.0)                        !(NMOL)
   CLI  = ALI/WLI                             !(NMOL/ML)
```

```
 1      !FREE TCDD IN LIVER COMPARTMENT
 2    PARAMETER (LIVER_1RMN = 1.0E-30)
 3     CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
 4          +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2 + CFLLIR &
 5          +LIVER_1RMN)*IND_ACTIVE)))-CFLLI,CFLLI0)
 6       CFLLIR=DIM(CFLLI,0.0) ! FREE CONCENTRATION IN LIVER
 7
 8     CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND CONCENTRATION
 9
10     !VARIABLE ELIMINATION BASED ON THE CYP1A2
11    KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv ! INDUCED BILIARY
12    EXCRETION RATE CONSTANT
13     REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT EXCRETION RATE
14       EXCLI = INTEG(REXCLI,0.0)
15
16     !UNIT CONVERSION POST SIMULATION
17     CLITOTAL= (ALI + ALIB)/(WLI + WLIB) ! TOTAL CONCENTRATION IN NMOL/ML
18
19     Rec_occ= CFLLIR/(KDLI+CFLLIR)
20     CLINGKG=CLITOTAL*MW*UNITCORR ! LIVER CONCENTRATION IN NG/KG
21        AUCLI_NGKGH=INTEG(CLINGKG,0.0)
22     CBNDLINGKG = CBNDLI*MW*UNITCORR
23        AUCBNDLI_NGKGH =INTEG(CBNDLINGKG,0.0)
24     CLINGG = CLITOTAL*MW
25
26      !CHEMICAL IN CYP450 (1A2) COMPARTMENT
27    CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ ! BASAL RATE OF CYP1A2 PRODUCTION
28    SET EQUAL TO BASAL RATE OF DEGREDATION
29
30      ! MODIFICATION ON OCTOBER 6, 2009
31    CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-30)**HILL
32    &
33        /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
34         - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)
35
36    ! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
37    SIMULATIONS)
38
39         CYP1A2_1RO2 = (CYP1A2_1OUT - CYP1A2_1O2)/ CYP1A2_1TAU
40      CYP1A2_1O2 =INTEG(CYP1A2_1RO2, CYP1A2_1A1)
41
42    CYP1A2_1RO3 = (CYP1A2_1O2 - CYP1A2_1O3)/ CYP1A2_1TAU
43      CYP1A2_1O3 =INTEG(CYP1A2_1RO3, CYP1A2_1A2)
44
45    ! TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
46    ! FETAL EXPOSURE ONLY DURING EXPOSURE
47
48    IF (T.LT.TRANSTIME_ON) THEN
49     SWITCH_trans = 0.0
50    ELSE
51     SWITCH_trans = 1
52    END IF
53
54    !TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
55    ! MODIFICATION 26 SEPTEMBER 2003
56
57    CONSTANT PFETUS= 4 !
```

```
1    CONSTANT CLPLA_FET = 0.17 !
2
3    RAMPF = (CLPLA_FET*CPLA) *SWITCH_trans
4      AMPF=INTEG(RAMPF,0.0)
5
6    !TRANSFER OF DIOXIN FROM FETUS TO PLACENTA
7    RAFPM = (CLPLA_FET*CFETUS_v)*SWITCH_trans !
8      AFPM = INTEG(RAFPM,0.0)
9
10   ! TCDD IN PLACENTA MOTHER COMPARTMENT
11   RAPLAB= QPLA*(CA - CPLAB)-PAPLA*(CPLAB -CFLPLAR)    ! NMOL/H)
12    APLAB = INTEG(RAPLAB,0.0)                                ! (NMOL)
13    CPLAB = APLAB/(WPLAB+1E-30)                         ! (NMOL/ML)
14   RAPLA = PAPLA*(CPLAB-CFLPLAR)-RAMPF + RAFPM         ! (NMOL/H)
15    APLA = INTEG(RAPLA,0.0)                                 ! (NMOL)
16    CPLA  = APLA/(WPLA+1e-30)                           ! (NMOL/ML)
17
18   PARAMETER (PARA_ZERO = 1.0E-30)
19   CFLPLA= IMPLC(CPLA-(CFLPLAR*PPLA +(PLABMAX*CFLPLAR/(KDPLA&
20        +CFLPLAR+PARA_ZERO)))-CFLPLA,CFLPLA0)
21   CFLPLAR=DIM(CFLPLA,0.0)
22
23      !UNIT CONVERSION POST SIMULATION
24     CPLATOTAL= (APLA + APLAB)/((WPLA + WPLAB)+1e-30)! TOTAL CONCENTRATION IN
25   NMOL/ML
26
27     CPLANGG = CPLATOTAL*MW
28
29      !FETUS COMPARTMENT
30   RAFETUS= RAMPF-RAFPM
31    AFETUS=INTEG(RAFETUS,0.0)
32   CFETUS=AFETUS/(WTFE+1E-30)
33   CFETOTAL= CFETUS
34   CFETUS_v = CFETUS/PFETUS
35
36     ! UNIT CONVERSION POST SIMULATION
37   CFETUSNGKG = CFETUS*MW*UNITCORR                          !(NG/KG)
38   AUC_FENGKGH = INTEG(CFETUSNGKG,0.0)
39   CFETUSNGG = CFETOTAL*MW
40
41   ! ------------CONTROL MASS BALANCE ----------
42   BDOSE= IVDOSE +LYMLUM+LIMLUM
43   BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB+AFETUS
44   BDIFF = BDOSE-BMASSE
45
46        !BODY BURDEN (NG)
47   BODY_BURDEN = AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB !
48   BBFETUSNG      = AFETUS*MW*UNITCORR     ! NG
49        ! BODY BURDEN IN TERMS OF CONCENTRATION (NG/KG)
50    BBNGKG =(((AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB)/WT0)*MW*UNITCORR) !
51     AUC_BBNGKGH=INTEG(BBNGKG,0.0)
52
53
54   ! ------------COMMAND OF THE END OF SIMULATION ----------
55   TERMT (T.GE. TimeLimit, 'Time limit has been reached.')
56   END   ! END OF THE DERIVATIVE SECTION
57   END   ! END OF THE DYNAMIC SECTION
```

```
END   ! END OF THE PROGRAM
```

E.2.6.2. *Input Files*

E.2.6.2.1. *Keller et al. (2007)*

```
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH

%Keller et al. 2007
%protocol:  single oral dose at GD13
%dose levels: 0.01, 0.100 1 ug/kg at GD13
%dose levels:   10, 100 1000 ng/kg at GD13

 MAXT=0.01
 CINT =0.1
 EXP_TIME_ON     = 312.                %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 336                 %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 24                  %HOURS BETWEEN DOSES
 BCK_TIME_ON     = 0.                  %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF    = 0.                  %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT       = 336                 %SIMULATION DURATION (HOUR)
 BW_T0           = 24                  %BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)
 CONCEPTION_T        = 0.              %TIME OF CONCEPTION (HOUR)
 TRANSTIME_ON    = 144.                %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
 N_FETUS         = 10                  %NUMBER OF FETUSES

%EXPOSURE DOSE SCENARIOS (UG/KG)

   %MSTOT          = 0.01              %ORAL EXPOSURE DOSE (UG/KG)
   %MSTOT          = 0.1               %ORAL EXPOSURE DOSE (UG/KG)
   MSTOT          = 1                  %ORAL EXPOSURE DOSE (UG/KG)
```

E.2.6.2.2. *Li et al. (2006)*

```
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG AUCLI_NGKGH
AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH
CBNGKG AUC_CBNGKGH
%Li et al.2006
%protocol:  daily oral dose from GD1 to GD3
%dose levels: 0.002, 0.050, 0.10 ug/kg-day at GD1 to GD3
%dose levels: 2, 50, 100 ng/kg-day from GD1 to GD3

 MAXT=0.001
 CINT =0.1
 EXP_TIME_ON     = 0.                  %TIME EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 72                  %TIME EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 24                  %HOURS BETWEEN DOSES
 BCK_TIME_ON     = 0.                  %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF    = 0.                  %TIME BACKGROUND EXPOSURE ENDS (HOUR)
 TIMELIMIT       = 72.                 %SIMULATION DURATION (HOUR)
```

```
1   BW_T0            = 27              %BODY WEIGHT AT THE BEGINNING OF THE
2   SIMULATION (G)
3   CONCEPTION_T        = 0.           %TIME OF CONCEPTION (HOUR)
4   TRANSTIME_ON    = 144.            %TIME OF CONCEPATION + 6 DAYS(144 HOURS)
5   N_FETUS         = 10              %NUMBER OF FETUSES
6
7   %EXPOSURE DOSE SCENARIOS (UG/KG)
8
9     %MSTOT          = 0.002          %ORAL EXPOSURE DOSE (UG/KG)
10    %MSTOT         = 0.05           %ORAL EXPOSURE DOSE (UG/KG)
11     MSTOT         = 0.10           %ORAL EXPOSURE DOSE (UG/KG)
12
```

E.2.6.2.3. *Smith et al. ([1976](#))*

```
14        output @clear
15        prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG
16   AUCLI_NGKGH AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH AUC_FENGKGH CBNDLINGKG
17   AUCBNDLI_NGKGH CBNGKG AUC_CBNGKGH
18
19   %protocol:  daily oral dose from GD6 to GD15
20
21   %EXPOSURES SCENARIOS
22    MAXT=0.01
23    CINT =0.1
24    EXP_TIME_ON   = 120.            %TIME EXPOSURE BEGINS (HOUR)
25    EXP_TIME_OFF  = 337.            %TIME EXPOSURE ENDS (HOUR)
26    DAY_CYCLE     = 24              %HOURS BETWEEN DOSES
27    BCK_TIME_ON   = 0.              %TIME BACKGROUND EXPOSURE BEGINS (HOUR)
28    BCK_TIME_OFF  = 0.              %TIME BACKGROUND EXPOSURE ENDS (HOUR)
29    TIMELIMIT     = 360.            %SIMULATION DURATION (HOUR)
30    BW_T0         = 28.5            %BODY WEIGHT AT THE BEGINNING OF THE
31   SIMULATION (G)
32    CONCEPTION_T  = 0.              %TIME OF CONCEPTION (HOUR)
33    TRANSTIME_ON  = 144.            %TIME OF CONCEPTION + 6 DAYS(144 HOURS)
34    N_FETUS       = 10              %NUMBER OF FETUSES
35
36   %EXPOSURE DOSE SCENARIOS (UG/KG)
37
38     %MSTOT          = 0.001         %ORAL EXPOSURE DOSE (UG/KG)
39     %MSTOT         = 0.01          %ORAL EXPOSURE DOSE (UG/KG)
40     %MSTOT         = 0.10          %ORAL EXPOSURE DOSE (UG/KG)
41
```

E.3. TOXICOKINETIC MODELING RESULTS FOR KEY ANIMAL BIOASSAY STUDIES

The simulated TCDD serum-adjusted lipid concentrations reported in this appendix for

the rodent bioassays were converted to TCDD concentrations in rodent whole blood. Initially,

EPA multiplied the serum-adjusted lipid concentrations by 0.0033, the ratio of lipid content to

total serum volume, then by 0.55, the value of the hematocrit. This product yields the TCDD

concentration in whole rodent blood as predicted by the PBPK model. EPA assumed that the

same whole blood TCDD concentration would result in the same effects in humans and rodents.

1   This conversion accomplishes the following:

2
3
4   1. Allows the human equivalent dose to be based on equivalent blood concentration (that
5   represents serum plus erythrocyte TCDD), which is proportional to tissue exposure;

6   2. Avoids criticism that the total blood concentration is normalized to serum lipid alone in
7   an unbalanced way (thus EPA does not contradict Centers for Disease Control and
8   Prevention data or methods);

9   3. Factors out any impact of the lipid content used in the PBPK model; and

10   4. TCDD concentration in whole blood is encouraged for use in the assessments by the
11   National Academy of Sciences (2006, p. 43); see additional information in Section 3.3.
12
13
14 **E.3.1.   Nongestational Studies**

15 **E.3.1.1. *Cantoni et al. (1981)***

16
17

Type:	Rat	Dose:	10, 100, and 1,000 ng/kg-wk
Strain:	CD-COBS rats	Route:	Oral gavage exposure
Body weight:	BW = 125 g	Regime:	1 dose/wk for 45 wk
Sex:	Female	Simulation time:	7,560 hr (45 wk)

18
19 BW = body weight.
20

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max.	Terminal
1.43	Emond	1.85	3.70 (@ 7,392 hr)	1.82
	CADM	-	-	-
14.29	Emond	8.84	26.6 (@ 7,392 hr)	7.97
	CADM	-	-	-
142.86	Emond	50.0	227 (@ 7,392 hr)	41.9
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
1.43	Emond		328 (@ 7,398 hr)	
	CADM	382	431	431
14.29	Emond	2,176	2,860 (@ 7,231 hr)	1,928
	CADM	3,973	4,330	4,330
142.86	Emond	20,500	26,978 (@ 7,399 hr)	17,255
	CADM	39,955	43,329	43,329
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
1.43	Emond	175	200 (@ 7,431 hr)	181
	CADM	256	280	244
14.29	Emond	837	937 (@ 7,427 hr)	807
	CADM	1,237	1,352	1,167
142.86	Emond	4,741	5,374 (@ 7,424 hr)	4,349
	CADM	10,278	11,224	9,734
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
1.43	Emond	26.1	31.7 (@ 7,398 hr)	26.3
	CADM	32.4	35.0	35.0
14.29	Emond	170	210 (@ 7,230 hr)	156
	CADM	230	243	243
142.86	Emond	1,337	1,695 (@ 7,398 hr)	1,151
	CADM	2,154	2,266	2,266
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
1.43	Emond	6.04	7.76 (@ 7,396 hr)	6.01
	CADM	-	-	-
14.29	Emond	23.7	29.1 (@ 7,228 hr)	22.2
	CADM	-	-	-

| 142.86 | Emond | 66.8 | 80.0 (@ 1 hr) | 63.4 |
| | CADM | - | - | - |

1
2   Max = maximum.
3
4
5   **E.3.1.2. *Chu et al. (2007) and Chu et al. (2001)***
6
7

Type:	Rat	Dose:	2.5, 25, 250, and 1,000 ng/kg-day
Strain:	Sprague-Dawley	Route:	Oral exposure
Body weight:	200 g	Regime:	1 dose per day for 28 d
Sex:	Female	Simulation time:	672 hr

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
2.5	Emond	1.26	2.35 (@ 648 hr)	1.88
	CADM			
25	Emond	7.66	15.3 (@ 648 hr)	10.4
	CADM			
250	Emond	48.8	113 (@ 648 hr)	63.7
	CADM	-	-	-
1,000	Emond	169	418 (@ 648 hr)	222
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
2.5	Emond	148	268 (@ 652 hr)	255
	CADM	337	505	505
25	Emond	1,777	2,953 (@ 653 hr)	2,806
	CADM	4,422	5,786	5,786
250	Emond	19,232	30,262 (@ 653 hr)	28,668
	CADM	45,872	58,681	58,681
1,000	Emond	77,819	120,400 (@ 653 hr)	113,890
	CADM	184,076	234,992	234,992

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
2.5	Emond	108	180 (@ 668 hr)	180
	CADM	295	362	362
25	Emond	660	1,020 (@ 659 hr)	1,015
	CADM	1,703	2,057	2,057
250	Emond	4,210	6,433 (@ 655 hr)	6,354
	CADM	14,899	18,210	18,210
1,000	Emond	14,576	22,610 (@ 655 hr)	22,280
	CADM	58,824	72,002	72,002
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
2.5	Emond	16.1	27.5 (@ 652 hr)	26.9
	CADM	30.0	40.9	40.9
25	Emond	138	222 (@ 652 hr)	214
	CADM	261	336	336
250	Emond	1,239	1,935 (@ 652 hr)	1,842
	CADM	2,544	3,243	3,243
1,000	Emond	4,801	7,444 (@ 652 hr)	7,067
	CADM	10,150	12,930	12,930
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
2.5	Emond	4.15	6.51 (@ 652 hr)	6.21
	CADM	-	-	-
25	Emond	20.5	28.5 (@ 652 hr)	27.4
	CADM	-	-	-
250	Emond	63.3	76.0 (@ 652 hr)	74.7
	CADM	-	-	-
1,000	Emond	90.2	99.0 (@ 653 hr)	98.3
	CADM	-	-	-

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1 **E.3.1.3.** *Crofton et al. ([2005](#))*

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Type:	Rats	Dose:	0, 0.1, 3, 10, 30, 100, 300, 1,000, 3,000, and 10,000 ng/kg-day
Strain:	Long Evans	Route:	Oral exposure
Body weight:	BW = 190 g (4 wk old)	Regime:	One dose per day for 4 d
Sex:	Female	Simulation time:	96 hr

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5 The CADM model was not run because the dosing duration is lower than the resolution of the model (1 wk).

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max.	Terminal
0.1	Emond	0.0202	0.041 (@ 72 hr)	0.0244
	CADM	-	-	-
3	Emond	0.488	1.10 (@ 72 hr)	0.582
	CADM	-	-	-
10	Emond	1.38	3.40 (@ 72 hr)	1.62
	CADM	-	-	-
30	Emond	3.46	9.44 (@ 72 hr)	3.93
	CADM	-	-	-
100	Emond	9.26	29.0 (@ 72 hr)	10.2
	CADM	-	-	-
300	Emond	23.1	81.8 (@ 72 hr)	24.5
	CADM	-	-	-
1,000	Emond	65.7	260 (@ 72 hr)	68.2
	CADM	-	-	-
3,000	Emond	181	764 (@ 72 hr)	187
	CADM	-	-	-
10,000	Emond	583	2,527 (@ 72 hr)	607
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max.	Terminal
0.1	Emond	0.919	1.55 (@ 75 hr)	1.18
	CADM	-	-	-

3	Emond	37.4	62.6 (@ 76 hr)	53.3
	CADM	-	-	-
10	Emond	145	242 (@ 77 hr)	214
	CADM	-	-	-
30	Emond	494	818 (@ 78 hr)	742
	CADM	-	-	-
100	Emond	1,839	3,025 (@ 78 hr)	2,793
	CADM	-	-	-
300	Emond	5,925	9,692 (@ 78 hr)	9,028
	CADM	-	-	-
1,000	Emond	20,717	33,738 (@ 79 hr)	31,564
	CADM	-	-	-
3,000	Emond	63,511	103,140 (@ 79 hr)	96,545
	CADM	-	-	-
10,000	Emond	212,890	344,910 (@ 79 hr)	321,960
	CADM	-	-	-

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max.	Terminal
0.1	Emond	1.00	1.93 (@ 96 hr)	1.93
	CADM	-	-	-
3	Emond	24.6	45.9 (@ 96 hr)	45.9
	CADM	-	-	-
10	Emond	70.3	129 (@ 96 hr)	129
	CADM	-	-	-
30	Emond	177	317 (@ 96 hr)	317
	CADM	-	-	-
100	Emond	480	838 (@ 96 hr)	838
	CADM	-	-	-
300	Emond	1,206	2,065 (@ 96 hr)	2,065
	CADM	-	-	-
1,000	Emond	3,452	5,836 (@ 96 hr)	5,836
	CADM	-	-	-
3,000	Emond	9,522	16,050 (@ 96 hr)	16,050
	CADM	-	-	-

| 10,000 | Emond | 30,657 | 51,918 (@ 96 hr) | 51,918 |
| | CADM | - | - | - |

BODY BURDEN (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
0.1	Emond	0.138	0.224 (@ 79 hr)	0.223
	CADM	-	-	-
3	Emond	4.04	6.56 (@ 78 hr)	6.44
	CADM	-	-	-
10	Emond	13.3	21.5 (@ 78 hr)	21.0
	CADM	-	-	-
30	Emond	39.3	63.5 (@ 78 hr)	61.5
	CADM	-	-	-
100	Emond	129	208 (@ 78 hr)	200
	CADM	-	-	-
300	Emond	384	618 (@ 77 hr)	590
	CADM	-	-	-
1,000	Emond	1,270	2,041 (@ 77 hr)	1,942
	CADM	-	-	-
3,000	Emond	3,793	6,094 (@ 77 hr)	5,784
	CADM	-	-	-
10,000	Emond	12,595	20,226 (@ 77 hr)	19,154
	CADM	-	-	-

BOUND LIVER (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
0.1	Emond	0	0.115 (@ 75 hr)	0
	CADM	-	-	-
3	Emond	2	2.47 (@ 76 hr)	2
	CADM	-	-	-
10	Emond	4	6.42 (@ 76 hr)	5
	CADM	-	-	-
30	Emond	10	14.1 (@ 76 hr)	12
	CADM	-	-	-

100	Emond	22	29.9 (@ 76 hr)	27
	CADM	-	-	-
300	Emond	41	51.9 (@ 77 hr)	49
	CADM	-	-	-
1,000	Emond	68	80.2 (@ 1 hr)	77
	CADM	-	-	-
3,000	Emond	90	98.6 (@ 1 hr)	96
	CADM	-	-	-
10,000	Emond	104	108 (@ 1 hr)	107
	CADM	-	-	-

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3 ### E.3.1.4. *Croutch et al. ([2005](#))*
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Type:	Rat	**Dose:**	12.5, 50, 200, 800, and 3,200 ng/kg initial and 1.25, 5, 20, 80, and 320 ng/kg maintenance doses every 4 d (equivalent to 0.85, 3.4, 13.6, 54.3, and 217 ng/kg-day)
Strain:	Sprague-Dawley	**Route:**	Gavage
Body weight:	250 g	**Regime:**	One initial dose and maintenance doses every 3 d for 28 d
Sex:	Female	**Simulation time:**	672 hr

6 The CADM model was not run because the dosing protocol includes both initial and maintenance doses, which is
7 not supported in the model.
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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
0.85	Emond	0.340	0.723 (@ 648 hr)	0.513
	CADM	-	-	-
3.4	Emond	1.10	2.44 (@ 648 hr)	1.55
	CADM	-	-	-
13.6	Emond	3.29	8.69 (@ 0 hr)	4.36
	CADM	-	-	-
54.3	Emond	9.58	34.8 (@ 0 hr)	12.1
	CADM	-	-	-

| 217 | Emond | 28.7 | 139 (@ 0 hr) | 35.0 |
| | CADM | - | - | - |

LIVER CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
0.85	Emond	25.6	46.8 (@ 653 hr)	43.9
	CADM	-	-	-
3.4	Emond	119	206 (@ 654 hr)	195
	CADM	-	-	-
13.6	Emond	538	877 (@ 654 hr)	834
	CADM	-	-	-
54.3	Emond	2,339	3,617 (@ 655 hr)	3,444
	CADM	-	-	-
217	Emond	9,824	14,634 (@ 655 hr)	13,931
	CADM	-	-	-

FAT CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
0.85	Emond	29.0	46.9 (@ 672 hr)	46.9
	CADM	-	-	-
3.4	Emond	94.1	143 (@ 672 hr)	143
	CADM	-	-	-
13.6	Emond	284	409 (@ 672 hr)	409
	CADM	-	-	-
54.3	Emond	828	1,149 (@ 670 hr)	1,149
	CADM	-	-	-
217	Emond	2,480	3,389 (@ 666 hr)	3,384
	CADM	-	-	-

BODY BURDEN (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
0.85	Emond	3.67	6.09 (@ 654 hr)	6.00
	CADM	-	-	-
3.4	Emond	13.5	21.6 (@ 653 hr)	21.1
	CADM	-	-	-

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		Time-weighted average	Max	Terminal
13.6	Emond	48.9	75.0 (@ 653 hr)	72.8
	CADM	-	-	-
54.3	Emond	178	264 (@ 653 hr)	254
	CADM	-	-	-
217	Emond	661	963 (@ 653 hr)	922
	CADM	-	-	-

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
0.85	Emond	1.17	1.93 (@ 652 hr)	1.77
	CADM	-	-	-
3.4	Emond	3.65	5.59 (@ 652 hr)	5.18
	CADM	-	-	-
13.6	Emond	10.1	14.4 (@ 652 hr)	13.4
	CADM	-	-	-
54.3	Emond	24.7	35.8 (@ 1 hr)	30.6
	CADM	-	-	-
217	Emond	50.5	69.9 (@ 1 hr)	58.6
	CADM	-	-	-

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3 **E.3.1.5.** *Della Porta et al. ([1987](#)) Female*

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Type:	Mouse	**Dose:**	2,500 and 5,000 ng/kg-wk (equivalent to 357 and 714 ng/kg-day)
Strain:	B6C3	**Route:**	Gavage
Body weight:	BW = 20 g (6 wk old)	**Regime:**	Once a wk for 52 wk
Sex:	Female	**Simulation time:**	8,736 hr

6 The CADM model was not run because the study duration is longer than the allowed model duration.
7

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
357	Emond	67.0	741 (@ 8,568 hr)	46.8
	CADM	-	-	-

714	Emond	37.6	374 (@ 8,568 hr)	27.2
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
357	Emond	50,269	70,070 (@ 8,577 hr)	37,389
	CADM	-	-	-
714	Emond	25,422	35,352 (@ 8,577 hr)	19,105
	CADM	-	-	-

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
357	Emond	25,235	28,559 (@ 8,589 hr)	22,498
	CADM	-	-	-
714	Emond	14,162	15,914 (@ 8,590 hr)	12,810
	CADM	-	-	-

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
357	Emond	5,473	7,247 (@ 8,574 hr)	4,335
	CADM	-	-	-
714	Emond	2,878	3,774 (@ 8,574 hr)	2,318
	CADM	-	-	-

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
357	Emond	71.5	99.1 (@ 2 hr)	65.4
	CADM	-	-	-
714	Emond	56.4	88.6 (@ 2 hr)	50.4
	CADM	-	-	-

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1 **E.3.1.6.** *Della Porta et al. ([1987](#)) Male*

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Type:	Mouse	Dose:	2,500 and 5,000 ng/kg-wk (equivalent to 357 and 714 ng/kg-day)
Strain:	B6C3	Route:	Gavage
Body weight:	26 g (6 wk old)	Regime:	Once a week for 52 wk
Sex:	Male	Simulation time:	8,736 hr

4 The CADM model was not run because the study duration is longer than the allowed model duration.

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		WHOLE BLOOD CONCENTRATIONS (ng/kg)		
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
357	Emond	67.8	787 (@ 8,568 hr)	47.0
	CADM	-	-	-
714	Emond	38.0	398 (@ 8,568 hr)	27.3
	CADM	-	-	-
		LIVER CONCENTRATIONS (ng/kg)		
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
357	Emond	50,397	70,052 (@ 8,577 hr)	37,483
	CADM	-	-	-
714	Emond	25,493	35,347 (@ 8,577 hr)	19,155
	CADM	-	-	-
		FAT CONCENTRATIONS (ng/kg)		
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
357	Emond	25,516	28,851 (@ 8,589 hr)	22,861
	CADM	-	-	-
714	Emond	14,306	16,061 (@ 8,590 hr)	12,999
	CADM	-	-	-

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
357	Emond	5,504	7,282 (@ 8,574 hr)	4,368
	CADM	-	-	-
714	Emond	2,894	3,791 (@ 8,574 hr)	2,335
	CADM	-	-	-

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
357	Emond	71.6	99.2 (@ 2 hr)	65.4
	CADM	-	-	-
714	Emond	56.4	88.6 (@ 2 hr)	50.4
	CADM	-	-	-

E.3.1.7. *Fattore et al. ([2000](#))*

Type:	Rat	Dose:	20, 200, 2,000 ng/kg-day
Strain:	Sprague-Dawley	Route:	Dietary exposure
Body weight:	BW 150 g (7 wk old)	Regime:	Every day for 13 wk
Sex:	Female and male	Simulation time:	2,184 hr

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
20	Emond	9.59	15.0 (@ 2,160 hr)	11.1
	CADM	-	-	-
200	Emond	57.6	102 (@ 2,160 hr)	63.9
	CADM	-	-	-
2,000	Emond	476	903 (@ 2,160 hr)	522
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
20	Emond	2,448	3,228 (@ 2,164 hr)	3,078
	CADM	4,815	5,639	5,639
200	Emond	24,136	30,245 (@ 2,164 hr)	28,709
	CADM	48,824	56,499	56,499
2,000	Emond	234,170	288,020 (@ 2,164 hr)	272,590
	CADM	488,957	565,103	565,103
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
20	Emond	890	1,113 (@ 2,166 hr)	1,101
	CADM	1,663	1,796	1,756
200	Emond	5,355	6,542 (@ 2,165 hr)	6,430
	CADM	14,378	15,604	15,292
2,000	Emond	44,176	54,246 (@ 2,165 hr)	53,140
	CADM	141,356	153,534	150,516
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
20	Emond	187	242 (@ 2,164 hr)	233
	CADM	281	324	324
200	Emond	1,556	1,940 (@ 2,164 hr)	1,850
	CADM	2,688	3,084	3,084
2,000	Emond	14,432	17,797 (@ 2,164 hr)	16,891
	CADM	26,746	30,674	30,674
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
20	Emond	24.9	29.8 (@ 2,164 hr)	28.8
	CADM	-	-	-
200	Emond	69.4	76.0 (@ 2,164 hr)	74.7
	CADM	-	-	-

2,000	Emond	104	106 (@ 2,164 hr)	106
	CADM	-	-	-

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3 **E.3.1.8.** *Fox et al. ([1993](#))*

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Type:	Rat	**Dose:**	5, 2,500, and 12,000 ng/kg initial and 0.9, 600, or 3,500 ng/kg maintenance doses every 4 d (equivalent to 0.55, 307, and 1,607 ng/kg-day)
Strain:	Sprague-Dawley	**Route:**	Gavage
Body weight:	200 g (12 wk old)	**Regime:**	One initial dose and maintenance doses every 4 d for 14 d
Sex:	Male and Female	**Simulation time:**	336 hr

6 The CADM model was not run because the dosing protocol includes both initial and maintenance doses, which is
7 not supported in the model.
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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
0.55	Emond	0.119	0.314 (@ 288 hr)	0.173
	CADM	-	-	-
307	Emond	25.4	143 (@ 288 hr)	32.8
	CADM	-	-	-
1,607	Emond	112	797 (@ 288 hr)	150
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
0.55	Emond	6.95	14.3 (@ 292 hr)	11.1
	CADM	-	-	-
307	Emond	8,138	14,826 (@ 296 hr)	12,897
	CADM	-	-	-
1,607	Emond	46,701	86,754 (@ 296 hr)	75,253
	CADM	-	-	-

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
0.55	Emond	9.14	16.1 (@ 336 hr)	16.1
	CADM	-	-	-
307	Emond	1,997	3,197 (@ 324 hr)	3,186
	CADM	-	-	-
1,607	Emond	8,710	14,716 (@ 323 hr)	14,638
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
0.55	Emond	1.12	1.92 (@ 295 hr)	1.88
	CADM	-	-	-
307	Emond	545	952 (@ 294 hr)	857
	CADM	-	-	-
1,607	Emond	2,890	5,239 (@ 294 hr)	4,667
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
0.55	Emond	0.409	0.803 (@ 292 hr)	0.604
	CADM	-	-	-
307	Emond	45.9	63.7 (@ 1 hr)	56.8
	CADM	-	-	-
1,607	Emond	82.1	95.8 (@ 1 hr)	92.7
	CADM	-	-	-

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E.3.1.9. *Franc et al. ([2001](#)) Sprague-Dawley Rats*

Type:	Rats	Dose:	140, 420, and 1,400 ng/kg every 2 wk (equivalent to 10, 30, and 100 ng/kg-day)
Strain:	Sprague-Dawley	Route:	Oral gavage
Body weight:	200 g (10 wk old)	Regime:	Once every 2 wk for 22 wk
Sex:	Female	Simulation time:	3,696 hr

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max.	Terminal
10	Emond	6.59	34.6 (@ 3,360 hr)	5.52
	CADM	-	-	-
30	Emond	14.5	98.1 (@ 3,360 hr)	11.3
	CADM	-	-	-

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max.	Terminal
100	Emond	36.4	315 (@ 3,360 hr)	26.4
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max.	Terminal
10	Emond	1,447	2,458 (@ 3,368 hr)	1,150
	CADM	2,616	3,620	2,174
30	Emond	4,228	7,161 (@ 3,368 hr)	3,120
	CADM	7,936	10,899	6,510
100	Emond	13,821	23,417 (@ 3,368 hr)	9,658
	CADM	26,564	36,361	21,703

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max.	Terminal
10	Emond	619	787 (@ 3,417 hr)	560
	CADM	966	1,230	759

30	Emond	1,362	1,741 (@ 3,415 hr)	1,161
	CADM	2,448	3,203	1,849
100	Emond	3,430	4,464 (@ 3,412 hr)	2,755
	CADM	7,573	10,052	5,606

BODY BURDEN (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
10	Emond	119	177 (@ 3,366 hr)	99.5
	CADM	159	212	133
30	Emond	308	472 (@ 3,366 hr)	240
	CADM	450	603	367
100	Emond	921	1,445 (@ 3,366 hr)	671
	CADM	1,462	1,969	1,181

BOUND LIVER (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
10	Emond	18.6	32.9 (@ 1 hr)	16.4
	CADM	-	-	-
30	Emond	33.7	59.2 (@ 1 hr)	29.0
	CADM	-	-	-
100	Emond	57.5	86.9 (@ 1 hr)	50.4
	CADM	-	-	-

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3 **E.3.1.10.** *Franc et al. ([2001](#)) Long-Evans Rats*
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Type:	Rats	**Dose:**	140, 420, and 1,400 ng/kg every 2 wk (equivalent to 10, 30, and 100 ng/kg-day)
Strain:	Long-Evans	**Route:**	Oral gavage
Body weight:	190 g (10 wk old)	**Regime:**	Once every 2 wk for 22 wk
Sex:	Female	**Simulation time:**	3,696 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
10	Emond	6.58	34.2 (@ 3,360 hr)	5.52
	CADM	-	-	-
30	Emond	14.5	97.0 (@ 3,360 hr)	11.3
	CADM	-	-	-
100	Emond	36.4	312 (@ 3,360 hr)	26.4
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
10	Emond	1,447	2,458 (@ 3,368 hr)	1,150
	CADM	2,616	3,620	2,174
30	Emond	4,228	7,161 (@ 3,368 hr)	3,121
	CADM	7,936	10,899	6,510
100	Emond	13,821	23,421 (@ 3,368 hr)	9,659
	CADM	26,564	36,361	21,703
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
10	Emond	619	788 (@ 3,417 hr)	560
	CADM	966	1,230	759
30	Emond	1,362	1,742 (@ 3,414 hr)	1,160
	CADM	2,448	3,203	1,849
100	Emond	3,429	4,466 (@ 3,412 hr)	2,752
	CADM	7,573	10,052	5,606
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
10	Emond	119	177 (@ 3,366 hr)	99.5
	CADM	159	212	133
30	Emond	308	472 (@ 3,366 hr)	240
	CADM	450	603	367
100	Emond	921	1,445 (@ 3,366 hr)	671

	CADM	1,462	1,969	1,181

BOUND LIVER (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
10	Emond	18.6	32.9 (@ 1 hr)	16.4
	CADM	-	-	-
30	Emond	33.7	59.2 (@ 1 hr)	29.0
	CADM	-	-	-
100	Emond	57.5	86.9 (@ 1 hr)	50.4
	CADM	-	-	-

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3 **E.3.1.11. _Franc et al. ([2001]) Hans Wistar Rats_**

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Type:	Rats	**Dose:**	140, 420, and 1,400 ng/kg every 2 wk (equivalent to 10, 30, and 100 ng/kg-day)
Strain:	Hans Wistar	**Route:**	Oral gavage
Body weight:	205 g (10 wk old)	**Regime:**	Once every 2 wk for 22 wk
Sex:	Female	**Simulation time:**	3,696 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
10	Emond	6.59	34.7 (@ 3,360 hr)	5.52
	CADM	-	-	-
30	Emond	14.5	98.7 (@ 3,360 hr)	11.3
	CADM	-	-	-
100	Emond	36.4	317 (@ 3,360 hr)	26.4
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
10	Emond	1,447	2,458 (@ 3,368 hr)	1,150
	CADM	2,616	3,620	2,174

Dose (ng/kg-day) adjusted dose	Model			
30	Emond	4,228	7,160 (@ 3,368 hr)	3,120
	CADM	7,936	10,899	6,510
100	Emond	13,821	23,416 (@ 3,368 hr)	9,658
	CADM	26,564	36,361	21,703

FAT CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
10	Emond	619	787 (@ 3,418 hr)	560
	CADM	966	1,230	759
30	Emond	1,363	1,741 (@ 3,415 hr)	1,162
	CADM	2,448	3,203	1,849
100	Emond	3,431	4,463 (@ 3,412 hr)	2,757
	CADM	7,573	10,052	5,606

BODY BURDEN (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
10	Emond	119	177 (@ 3,366 hr)	99.5
	CADM	159	212	133
30	Emond	308	472 (@ 3,366 hr)	240
	CADM	450	603	367
100	Emond	921	1,446 (@ 3,366 hr)	671
	CADM	1,462	1,969	1,181

BOUND LIVER (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
10	Emond	18.6	32.9 (@ 1 hr)	16.4
	CADM	-	-	-
30	Emond	33.7	59.2 (@ 1 hr)	29.0
	CADM	-	-	-
100	Emond	57.5	86.9 (@ 1 hr)	50.4
	CADM	-	-	-

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1 **E.3.1.12.** *Hassoun et al. ([2000](#))*

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Type:	Rat	Dose:	0, 3, 10, 22, 46, 100 ng/kg-day (2.14, 7.14, 15.7, 32.9, and 71.4 ng/kg-day adjusted doses)
Strain:	Sprague-Dawley	Route:	Oral gavage
Body weight:	BW = 215 g (8 wk old)	Regime:	5 d/wk for 13 wk
Sex:	Female	Simulation time:	2,184 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max.	Terminal
2.14	Emond	1.94	3.12 (@ 2,112 hr)	1,303.17
	CADM	-	-	-
7.14	Emond	4.6136	7.71 (@ 2,112 hr)	2,901.26
	CADM	-	-	-
15.7	Emond	8.147	14.2 (@ 2,112 hr)	4,947.3
	CADM	-	-	-
32.9	Emond	14.009	25.8 (@ 2,112 hr)	8,277
	CADM	-	-	-
71.4	Emond	25.34	49.7 (@ 2,112 hr)	14,637
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max.	Terminal
2.14	Emond	266.8	399 (@ 2,116 hr)	349
	CADM	470	595	595
7.14	Emond	888	1,259 (@ 2,117 hr)	1,079
	CADM	1,678	2,001	2,001
15.7	Emond	1,948.499	2,689 (@ 2,117 hr)	2,278.182
	CADM	1,768	4,428	4,428
32.9	Emond	4,055.031	5,484 (@ 2,117 hr)	4,607.265
	CADM	7,957	9,272	9,272
71.4	Emond	8,774.97	11,692 (@ 2,117 hr)	9,754.31
	CADM	17,387	20,170	20,170

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
2.14	Emond	179.2	243 (@ 2,126 hr)	234.9
	CADM	325	355	349
7.14	Emond	427	553 (@ 2,124 hr)	528
	CADM	730	787	769
15.7	Emond	755	958 (@ 2,123 hr)	908
	CADM	1,356	1,463	1,430
32.9	Emond	1,299	1,627 (@ 2,122 hr)	1,529
	CADM	2,577	2,787	2,727
71.4	Emond	2,349.892	2,928 (@ 2,121 hr)	2,727.240
	CADM	5,304	5,748	5,630
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
2.14	Emond	27.425	38.9 (@ 2,116 hr)	35.720
	CADM	38.2	45.9	45.9
7.14	Emond	76.87	105 (@ 2,116 hr)	93.67
	CADM	108	126	126
15.7	Emond	153.1	205 (@ 2,116 hr)	180.2
	CADM	224	258	258
32.9	Emond	295	390 (@ 2,116 hr)	339
	CADM	453	522	522
71.4	Emond	600	785 (@ 2,116 hr)	674
	CADM	970	1,113	1,113
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
2.14	Emond	6	8.48 (@ 2,116 hr)	8
	CADM	-	-	-
7.14	Emond	13.7242	17.5 (@ 2,116 hr)	15.7348
	CADM	-	-	-
15.7	Emond	21.9703	27.1 (@ 2,116 hr)	24.4047
	CADM	-	-	-

32.9	Emond	32.817	39.2 (@ 2,116 hr)	35.608
	CADM	-	-	-
71.4	Emond	47.54	55.0 (@ 2,116 hr)	50.63
	CADM	-	-	-

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3 **E.3.1.13.** *Hutt et al. ([2008](#))*

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Type:	Rat	**Dose:**	50 ng/kg-wk (equivalent to 7.14 ng/kg-day)
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	4.5 g (weight at birth)	**Regime:**	1 per week for 13 wk
Sex:	Female	**Simulation time:**	2,184 hr (weekly exposure)

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
7.14	Emond	4.49	8.86 (@ 2,016 hr)	4.71
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
7.14	Emond	867.4	1,363 (@ 2,021 hr)	928.1
	CADM	1,678	2,007	2,007
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
7.14	Emond	423.6	555 (@ 2,040 hr)	459.9
	CADM	730	787.1	769
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
7.14	Emond	76	108 (@ 2,022 hr)	81
	CADM	108	126	126

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
7.14	Emond	14	19.4 (@ 2,020 hr)	14
	CADM	-	-	-

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3 ### E.3.1.14. *Ishihara et al. ([2007](#))*

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Type:	Mouse	Dose:	2 and 2,000 ng/kg-wk initial and 0.4 or 400 ng/kg-wk maintenance (equivalent to 0.024 and 2.4 ng/kg-day)
Strain:	ICR	Route:	Gavage
Body weight:	23 g (7 wk old)	Regime:	One initial dose and weekly maintenance doses for 5 wk
Sex:	Male and Female	Simulation time:	840 hr

6 The CADM model was not run because the dosing protocol includes both initial and maintenance doses, which is
7 not supported in the model.
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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
0.024	Emond	0.0172	0.076 (@ 672 hr)	0.0247
	CADM	-	-	-
2.4	Emond	7.04	61.2 (@ 672 hr)	6.47
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
0.024	Emond	1.45	3.65 (@ 677 hr)	2.13
	CADM	-	-	-
2.4	Emond	2,805	5,059 (@ 680 hr)	2,758
	CADM	-	-	-

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.024	Emond	5.48	9.88 (@ 749 hr)	9.63
	CADM	-	-	-
2.4	Emond	2,352	3,284 (@ 712 hr)	2,856
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.024	Emond	0.537	0.964 (@ 680 hr)	0.902
	CADM	-	-	-
2.4	Emond	381	617 (@ 678 hr)	413
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.024	Emond	0.0599	0.150 (@ 676 hr)	0.0861
	CADM	-	-	-
2.4	Emond	18.6	43.6 (@ 2 hr)	18.4
	CADM	-	-	-

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3 ### E.3.1.15. *Kitchin and Woods (1979)*
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Type:	Rats	**Dose:**	0, 0.6, 2, 4, 20, 60, 200, 600, 2,000, 5,000, 20,000 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral exposure
Body weight:	BW = 225 g (200 to 250 g)	**Regime:**	Single dose
Sex:	Female	**Simulation time:**	24 hr

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7 1 wk is the minimum that can be simulated with the CADM model, so the CADM model was not used.
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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
0.6	Emond	0.0645	0.126 (@ 0 hr)	0.0441
	CADM	-	-	-
2	Emond	0.202	0.421 (@ 0 hr)	0.137
	CADM	-	-	-
4	Emond	0.384	0.841 (@ 0 hr)	0.258
	CADM	-	-	-
20	Emond	1.61	4.21 (@ 0 hr)	1.04
	CADM	-	-	-
60	Emond	4.15	12.6 (@ 0 hr)	2.55
	CADM	-	-	-
200	Emond	11.6	42.1 (@ 0 hr)	6.61
	CADM	-	-	-
600	Emond	30.3	126 (@ 0 hr)	15.8
	CADM	-	-	-
2,000	Emond	90.9	422 (@ 0 hr)	42.8
	CADM	-	-	-
5,000	Emond	218	1,056 (@ 0 hr)	96.9
	CADM	-	-	-
20,000	Emond	863	4,233 (@ 0 hr)	365
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max.**	**Terminal**
0.6	Emond	2.95	3.81 (@ 4 hr)	2.31
	CADM	-	-	-
2	Emond	10.5	12.9 (@ 4 hr)	8.69
	CADM	-	-	-
4	Emond	22.2	26.3 (@ 4 hr)	18.9
	CADM	-	-	-
20	Emond	128	143 (@ 6 hr)	118
	CADM	-	-	-

60	Emond	420	463 (@ 8 hr)	406
	CADM	-	-	-
200	Emond	1,523	1,666 (@ 9 hr)	1,526
	CADM	-	-	-
600	Emond	4,821	5,258 (@ 10 hr)	4,932
	CADM	-	-	-
2,000	Emond	16,603	18,080 (@ 11 hr)	17,226
	CADM	-	-	-
5,000	Emond	41,971	45,674 (@ 11 hr)	43,803
	CADM	-	-	-
20,000	Emond	167,820	182,580 (@ 11 hr)	175,890
	CADM	-	-	-

FAT CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
0.6	Emond	1.60	2.47 (@ 24 hr)	2.47
	CADM	-	-	-
2	Emond	5.07	7.71 (@ 24 hr)	7.71
	CADM	-	-	-
4	Emond	9.68	14.6 (@ 24 hr)	14.6
	CADM	-	-	-
20	Emond	41.7	60.7 (@ 24 hr)	60.7
	CADM	-	-	-
60	Emond	110	155 (@ 24 hr)	155
	CADM	-	-	-
200	Emond	317	427 (@ 24 hr)	427
	CADM	-	-	-
600	Emond	851	1,102 (@ 24 hr)	1,102
	CADM	-	-	-
2,000	Emond	2,620	3,276 (@ 24 hr)	3,276
	CADM	-	-	-
5,000	Emond	6,361	7,816 (@ 24 hr)	7,816
	CADM	-	-	-
20,000	Emond	25,401	30,827 (@ 24 hr)	30,827
	CADM	-	-	-

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.6	Emond	0.322	0.341 (@ 9 hr)	0.338
	CADM	-	-	-
2	Emond	1.07	1.14 (@ 8 hr)	1.12
	CADM	-	-	-
4	Emond	2.14	2.27 (@ 8 hr)	2.23
	CADM	-	-	-
20	Emond	10.6	11.3 (@ 8 hr)	11.0
	CADM	-	-	-
60	Emond	31.7	33.8 (@ 7 hr)	32.8
	CADM	-	-	-
200	Emond	105	112 (@ 7 hr)	108
	CADM	-	-	-
600	Emond	315	337 (@ 7 hr)	324
	CADM	-	-	-
2,000	Emond	1,049	1,123 (@ 7 hr)	1,074
	CADM	-	-	-
5,000	Emond	2,621	2,806 (@ 7 hr)	2,680
	CADM	-	-	-
20,000	Emond	10,468	11,215 (@ 7 hr)	10,693
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.6	Emond	0.216	0.309 (@ 3 hr)	0.159
	CADM	-	-	-
2	Emond	0.668	0.975 (@ 3 hr)	0.494
	CADM	-	-	-
4	Emond	1.25	1.86 (@ 3 hr)	0.927
	CADM	-	-	-
20	Emond	4.87	7.67 (@ 2 hr)	3.66
	CADM	-	-	-

60	Emond	11.2	18.3 (@ 2 hr)	8.55
	CADM	-	-	-
200	Emond	25.1	40.8 (@ 1 hr)	19.7
	CADM	-	-	-
600	Emond	45.8	68.2 (@ 1 hr)	37.6
	CADM	-	-	-
2,000	Emond	73.3	93.1 (@ 1 hr)	64.7
	CADM	-	-	-
5,000	Emond	90.9	104 (@ 1 hr)	84.7
	CADM	-	-	-
20,000	Emond	106	110 (@ 1 hr)	104
	CADM	-	-	-

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3 **E.3.1.16.** *Kociba et al. ([1976](#))*

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Type:	Rats	**Dose:**	1, 10, 100, and 1,000 ng/kg-day
Strain:	Sprague-Dawley (Spartan)	**Route:**	Dietary exposure
Body weight:	BW = 180 g (170–190 g)	**Regime:**	5 d/wk for 13 wk
Sex:	Female	**Simulation time:**	2,184 hr (13 wk exposed)

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
0.714	Emond	0.859	1.38 (@ 2,112 hr)	1.13
	CADM	-	-	-
7.143	Emond	4.61	7.62 (@ 2,112 hr)	5.27
	CADM	-	-	-
71.43	Emond	25.3	48.8 (@ 2,112 hr)	26.6
	CADM	-	-	-
714.3	Emond	181	403 (@ 2,112 hr)	184
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
0.714	Emond	88.3	140 (@ 2,116 hr)	126
	CADM	136	192	192
7.143	Emond	888	1,259 (@ 2,117 hr)	1,079
	CADM	1,678	2,007	2,007
71.43	Emond	8,776	11,693 (@ 2,117 hr)	9,756
	CADM	17,387	20,170	20,170
714.3	Emond	86,329	112,580 (@ 2,117 hr)	92,835
	CADM	174,576	201,814	201,814

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
0.714	Emond	79.4	114 (@ 2,129 hr)	111
	CADM	165	190	189
7.143	Emond	427	553 (@ 2,124 hr)	528
	CADM	730	787	769
71.43	Emond	2,348	2,925 (@ 2,121 hr)	2,720
	CADM	5,305	5,748	5,630
714.3	Emond	16,815	21,126 (@ 2,120 hr)	19,233
	CADM	50,658	55,013	53,928

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
0.714	Emond	10.8	16.1 (@ 2,116 hr)	15.1
	CADM	15.9	20.0	20.0
7.143	Emond	76.9	105 (@ 2,116 hr)	93.6
	CADM	108	126	126
71.43	Emond	600	785 (@ 2,116 hr)	673
	CADM	969	1,113	1,113
714.3	Emond	5,366	6,960 (@ 2,116 hr)	5,842
	CADM	9,562	10,967	10,967

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
0.714	Emond	2.89	4.17 (@ 2,116 hr)	3.81
	CADM	-	-	-
7.143	Emond	13.7	17.5 (@ 2,116 hr)	15.7
	CADM	-	-	-
71.43	Emond	47.5	55.0 (@ 2,116 hr)	50.6
	CADM	-	-	-
714.3	Emond	93.4	98.2 (@ 2,117 hr)	95.7
	CADM	-	-	-

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3 **E.3.1.17.** *Kociba et al. ([1978]) Female*

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Type:	Rats	Dose:	0, 1, 10, and 100 ng/kg-day
Strain:	Sprague-Dawley (Spartan)	Route:	Dietary exposure
Body weight:	BW = 180 g (170−190 g)	Regime:	7 d/wk for 104 wk
Sex:	Female	Simulation time:	17,472 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	1.55	1.92 (@ 17,448 hr)	1.69
	CADM	-	-	-
10	Emond	7.15	9.25 (@ 17,448 hr)	7.16
	CADM	-	-	-
100	Emond	38.6	57.5 (@ 17,448 hr)	37.1
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	192	226 (@ 17,452 hr)	218
	CADM	295	334	334

10	Emond	1,618	1,742 (@ 17,452 hr)	1,665
	CADM	3,013	3,348	3,348
100	Emond	14,892	15,673 (@ 17,452 hr)	14,907
	CADM	30.239	33.488	33.488

FAT CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	147	165 (@ 17,457 hr)	164
	CADM	198	229	181
10	Emond	680	713 (@ 17,454 hr)	706
	CADM	869	1,015	788
100	Emond	3,663	3,788 (@ 17,454 hr)	3,731
	CADM	6.816	7,939	6.195

BODY BURDEN (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	21.2	24.3 (@ 17,452 hr)	23.8
	CADM	26.1	27.0	27.0
10	Emond	131	140 (@ 17,452 hr)	136
	CADM	171	176	176
100	Emond	989	1,039 (@ 17,452 hr)	994
	CADM	1,562	1,601	1,601

BOUND LIVER (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	5.11	5.77 (@ 17,452 hr)	5.59
	CADM	-	-	-
10	Emond	20.0	21.1 (@ 17,452 hr)	20.4
	CADM	-	-	-
100	Emond	59.9	61.5 (@ 17,452 hr)	60.1
	CADM	-	-	-

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1 **E.3.1.18.** *Kociba et al. (1978) Male*

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Type:	Rats	Dose:	0, 1, 10, and 100 ng/kg-day
Strain:	Sprague-Dawley (Spartan)	Route:	Dietary exposure
Body weight:	BW approximated to be 250 g	Regime:	7 d/wk for 104 wk
Sex:	Male	Simulation time:	17,472 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	1.56	1.96 (@ 17,448 hr)	1.70
	CADM	-	-	-
10	Emond	7.16	9.35 (@ 17,448 hr)	7.11
	CADM	-	-	-
100	Emond	38.7	59.3 (@ 17,448 hr)	37.1
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	194	229 (@ 17,452 hr)	221
	CADM	295	334	334
10	Emond	1,616	1,723 (@ 17,452 hr)	1,649
	CADM	3,013	3,348	3,348
100	Emond	14,898	15,671 (@ 17,452 hr)	14,912
	CADM	30.239	33.488	33.488
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	148	167 (@ 17,456 hr)	166
	CADM	198	229	181
10	Emond	680	709 (@ 17,454 hr)	703
	CADM	869	1,015	788
100	Emond	3,677	3,803 (@ 17,453 hr)	3,747
	CADM	6.816	7,939	6.195

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	21.4	24.6 (@ 17,452 hr	24.1
	CADM	26.1	27.0	27.0
10	Emond	131	139 (@ 17,452 hr)	134
	CADM	171	176	176
100	Emond	991	1,041 (@ 17,452 hr)	995
	CADM	1,562	1,601	1,601
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	5.15	5.83 (@ 17,452 hr)	5.64
	CADM	-	-	-
10	Emond	20.0	21.0 (@ 17,452 hr)	20.3
	CADM	-	-	-
100	Emond	60.0	61.5 (@ 17,452 hr)	60.1
	CADM	-	-	-

1 **E.3.1.19. *Kuchiiwa et al. ([2002](#))***

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Type:	Mouse	Dose:	4.9 and 490 ng/kg-wk (equivalent to 0.7 and 70 ng/kg-day)
Strain:	ddy	Route:	Gavage
Body weight:	25 g	Regime:	Once a week for 8 wk
Sex:	Female	Simulation time:	1,344 hr
WHOLE BLOOD CONCENTRATIONS (ng/kg)			

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
0.7	Emond	0.257	1.01 (@ 1,176 hr)	0.323
	CADM	-	-	-
70	Emond	9.12	77.7 (@ 1,176 hr)	8.10
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.7	Emond	33.7	68.0 (@ 1,182 hr)	44.7
	CADM	28.4	51.1	41.7
70	Emond	4,033	6,796 (@ 1,185 hr)	3,769
	CADM	5,306	8,597	3,914
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.7	Emond	88.3	138 (@ 1,236 hr)	131
	CADM	92.1	144	125
70	Emond	3,199	4,252 (@ 1,207 hr)	3,633
	CADM	2,072	2,848	1,739
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.7	Emond	9.32	15.3 (@ 1,182 hr)	13.3
	CADM	12.3	19.5	16.9
70	Emond	533	818 (@ 1,182 hr)	544
	CADM	499	749	748
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max.**	**Terminal**
0.7	Emond	0.877	1.67 (@ 1,181 hr)	1.11
	CADM	-	-	-
70	Emond	22.8	48.9 (@ 2 hr)	22.1
	CADM	-	-	-

E.3.1.20. *Latchoumycandane and Mathur (2002)*

Type:	Rat	Dose:	0, 1, 10, and 100 ng/kg-day
Strain:	Wistar	Route:	Oral gavage
Body weight:	BW = 200 g (45 d old)	Regime:	1 per day for 45 d
Sex:	Male	Simulation time:	1,080 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	0.785	1.37 (@ 1,056 hr)	1.18
	CADM	-	-	-
10	Emond	4.65	8.18 (@ 1,056 hr)	6.18
	CADM	-	-	-
100	Emond	27.3	53.9 (@ 1,056 hr)	33.8
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	78.5	138 (@ 1,060 hr)	133
	CADM	142	217	182
10	Emond	902	1,423 (@ 1,060 hr)	1,358
	CADM	1,952	2,550	1,980
100	Emond	9,579	14,015 (@ 1,061 hr)	13,306
	CADM	20,541	25,915	20,018
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	69.8	113 (@ 1,072 hr)	113
	CADM	179	220	198
10	Emond	416	608 (@ 1,065 hr)	604
	CADM	861	1,009	821
100	Emond	2,448	3,425 (@ 1,062 hr)	3,380
	CADM	6,581	7,866	6,035

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
1	Emond	9.56	15.9 (@ 1,060 hr)	15.6
	CADM	16.4	22.2	19.7
10	Emond	76.7	117 (@ 1,060 hr)	113
	CADM	124	157	125.2
100	Emond	646	933 (@ 1,060 hr)	891
	CADM	1,147	1,439	1,114
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
1	Emond	2.64	4.12 (@ 1,060 hr)	3.96
	CADM	-	-	-
10	Emond	13.7	18.8 (@ 1,060 hr)	18.1
	CADM	-	-	-
100	Emond	48.6	59.0 (@ 1,060 hr)	57.5
	CADM	-	-	-

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3 **E.3.1.21. *Li et al. (1997)***

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Type:	Rats	**Dose:**	0, 3, 10, 30, 100, 300, 1,000, 3,000, 10,000, and 30,000 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Gastric intubation
Body weight:	BW = 56.5 g (22 d old, 55 to 58 g)	**Regime:**	One dose for one day
Sex:	Female	**Simulation time:**	24 hr

6 The CADM model was not run because the dosing duration is lower than the resolution of the model (1 wk)
7

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
3	Emond	0.266	0.470 (@ 1 hr)	0.180
	CADM	-	-	-

10	Emond	0.799	1.57 (@ 1 hr)	0.535
	CADM	-	-	-
30	Emond	2.10	4.68 (@ 1 hr)	1.37
	CADM	-	-	-
100	Emond	5.87	15.6 (@ 1 hr)	3.68
	CADM	-	-	-
300	Emond	15.0	46.8 (@ 0 hr)	8.83
	CADM	-	-	-
1,000	Emond	43.3	156 (@ 0 hr)	23.4
	CADM	-	-	-
3,000	Emond	120	469 (@ 0 hr)	59.9
	CADM	-	-	-
10,000	Emond	386	1,570 (@ 0 hr)	182
	CADM	-	-	-
30,000	Emond	1,172	4,762 (@ 0 hr)	535
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
3	Emond	14.7	18.6 (@ 4 hr)	11.9
	CADM	-	-	-
10	Emond	55.0	65.2 (@ 5 hr)	47.6
	CADM	-	-	-
30	Emond	185	210 (@ 6 hr)	170
	CADM	-	-	-
100	Emond	690	768 (@ 7 hr)	666
	CADM	-	-	-
300	Emond	2,248	2,473 (@ 8 hr)	2,240
	CADM	-	-	-
1,000	Emond	7,938	8,671 (@ 9 hr)	8,094
	CADM	-	-	-
3,000	Emond	24,474	26,639 (@ 9 hr)	25,267
	CADM	-	-	-
10,000	Emond	82,349	89,464 (@ 9 hr)	85,597
	CADM	-	-	-

| 30,000 | Emond | 245,610 | 265,670 (@ 10 hr) | 255,390 |
| | CADM | - | - | - |

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
3	Emond	8.75	12.7 (@ 24 hr)	12.7
	CADM	-	-	-
10	Emond	26.6	38.0 (@ 24 hr)	38.0
	CADM	-	-	-
30	Emond	70.8	98.9 (@ 24 hr)	98.9
	CADM	-	-	-
100	Emond	202	273 (@ 24 hr)	273
	CADM	-	-	-
300	Emond	530	689 (@ 24 hr)	689
	CADM	-	-	-
1,000	Emond	1,573	1,958 (@ 24 hr)	1,958
	CADM	-	-	-
3,000	Emond	4,433	5,358 (@ 24 hr)	5,358
	CADM	-	-	-
10,000	Emond	14,428	17,119 (@ 24 hr)	17,119
	CADM	-	-	-
30,000	Emond	44,361	51,948 (@ 22 hr)	51,898
	CADM	-	-	-

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
3	Emond	1.60	1.70 (@ 8 hr)	1.68
	CADM	-	-	-
10	Emond	5.33	5.66 (@ 8 hr)	5.56
	CADM	-	-	-
30	Emond	15.9	16.9 (@ 8 hr)	16.5
	CADM	-	-	-
100	Emond	52.8	56.2 (@ 7 hr)	54.5
	CADM	-	-	-

Dose	Model	Time-weighted average	Max	Terminal
300	Emond	158	169 (@ 7 hr)	163
	CADM	-	-	-
1,000	Emond	525	561 (@ 7 hr)	539
	CADM	-	-	-
3,000	Emond	1,574	1,684 (@ 7 hr)	1,611
	CADM	-	-	-
10,000	Emond	5,240	5,610 (@ 7 hr)	5,360
	CADM	-	-	-
30,000	Emond	15,758	16,815 (@ 7 hr)	16,041
	CADM	-	-	-

BOUND LIVER (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
3	Emond	0.89	1.37 (@ 3 hr)	0.64
	CADM	-	-	-
10	Emond	2.58	4.10 (@ 2 hr)	1.88
	CADM	-	-	-
30	Emond	6.37	10.5 (@ 2 hr)	4.71
	CADM	-	-	-
100	Emond	15.54	25.9 (@ 2 hr)	11.77
	CADM	-	-	-
300	Emond	31.25	50.1 (@ 1 hr)	24.57
	CADM	-	-	-
1,000	Emond	56.75	79.8 (@ 1 hr)	47.62
	CADM	-	-	-
3,000	Emond	81.28	98.4 (@ 1 hr)	73.32
	CADM	-	-	-
10,000	Emond	99.77	108 (@ 1 hr)	95.68
	CADM	-	-	-
30,000	Emond	107.69	111 (@ 1 hr)	106.24
	CADM	-	-	-

1 **E.3.1.22.** *Murray et al. ([1979](#)) Adult Portion*

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Type:	Rat	Dose:	1, 10, and 100 ng/kg-day
Strain:	Sprague-Dawley	Route:	Dietary exposure
Body weight:	BW = 4.5 g	Regime:	Once per day for 120 d
Sex:	Female	Simulation time:	2,880 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	1.12	1.51 (@ 2,856 hr)	1.42
	CADM	-	-	-
10	Emond	5.88	7.59 (@ 2,856 hr)	6.75
	CADM	-	-	-
100	Emond	32.7	44.3 (@ 2,856 hr)	36.0
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	128	180 (@ 2,859 hr)	173
	CADM	232	312	312
10	Emond	1,273	1,618 (@ 2,860 hr)	1,540
	CADM	2,613	3,179	3,179
100	Emond	12,601	15,281 (@ 2,860 hr)	14,460
	CADM	26,609	31,868	31,868
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	106	139 (@ 2,865 hr)	138
	CADM	209	243	236
10	Emond	556	665 (@ 2,864 hr)	657
	CADM	975	1,103	1,053
100	Emond	3,095	3,604 (@ 2,862 hr)	3,534
	CADM	7,742	8,790	8,427

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
1	Emond	14.8	20.0 (@ 2,860 hr)	19.6
	CADM	22.5	28.3	28.3
10	Emond	105	130 (@ 2,860 hr)	126
	CADM	159	189	189
100	Emond	837	1,003 (@ 2,860 hr)	957
	CADM	1,468	1,738	1,738
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
1	Emond	3.77	4.95 (@ 2,859 hr)	4.77
	CADM	-	-	-
10	Emond	17.1	20.3 (@ 2,859 hr)	19.5
	CADM	-	-	-
100	Emond	55.3	60.9 (@ 2,860 hr)	59.4
	CADM	-	-	-

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3 **E.3.1.23. *NTP (1982) Female Rats, Chronic***

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Type:	Rat	**Dose:**	10, 50, and 500 ng/kg-wk, 2 doses/wk
Strain:	Osborne-Mendel	**Route:**	Oral exposure
Body weight	BW = 250 g (6 wk old)	**Regime:**	2 doses/wk
Sex:	Female	**Simulation time**	17,472 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
1.4	Emond	1.96	3.11 (@ 17,220 hr)	1.94
	CADM	-	-	-
7.1	Emond	5.69	11.0 (@ 17,388 hr)	5.40
	CADM	-	-	-

| 71 | Emond | 29.8 | 82.2 (@ 17,388 hr) | 26.9 |
| | CADM | - | - | - |

LIVER CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1.4	Emond	265	308 (@ 17,226 hr)	265
	CADM	424	477	477
7.1	Emond	1,175	1,338 (@ 17,394 hr)	1,117
	CADM	2,150	2,391	2,391
71	Emond	10,734	12,182 (@ 17,395 hr)	9,882
	CADM	21,596	23,920	23,920

FAT CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1.4	Emond	186	200 (@ 17,328 hr)	193
	CADM	241	280	220
7.1	Emond	541	569 (@ 17,409 hr)	544
	CADM	673	787	610
71	Emond	2,826	2,973 (@ 17,404 hr)	2,769
	CADM	4,934	5,748	4,483

BODY BURDEN (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1.4	Emond	27.9	31.1 (@ 17,225 hr)	
	CADM	33.9	35.0	35.0
7.1	Emond	99.4	110 (@ 17,393 hr)	96.7
	CADM	126.4	129.8	129.8
71	Emond	729	814 (@ 17,393 hr)	683
	CADM	1,121	1,149	1,149

BOUND LIVER (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1.4	Emond	6.37	7.26 (@ 17,224 hr)	6.38
	CADM	-	-	-

7.1	Emond	16.6	18.5 (@ 17,392 hr)	16.1
	CADM	-	-	-
71	Emond	52.7	56.4 (@ 17,393 hr)	50.9
	CADM	-	-	-

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3 **E.3.1.24.** *NTP (1982) Male Rats, Chronic*

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Type:	Rat	Dose:	10, 50, and 500 ng/kg-wk, 2 doses/wk
Strain:	Osborne-Mendel	Route:	Oral exposure
Body weight	BW = 350 g (6 wk old)	Regime:	2 doses/wk
Sex:	Male	Simulation time	17,472 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max	Terminal
1.4	Emond	1.96	3.18 (@ 17,388 hr)	1.93
	CADM	-	-	-
7.1	Emond	5.70	11.4 (@ 17,388 hr)	5.39
	CADM	-	-	-
71	Emond	29.9	87.0 (@ 17,388 hr)	26.9
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max	Terminal
1.4	Emond	265	306 (@ 17,394 hr)	263
	CADM	424	477	477
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max	Terminal
7.1	Emond	1,174	1,334 (@ 17,394 hr)	1,114
	CADM	2,150	2,391	2,391
71	Emond	10,736	12,170 (@ 17,395 hr)	9,881
	CADM	21,596	23,920	23,920

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1.4	Emond	186	199 (@ 17,412 hr)	193
	CADM	241	280	220
7.1	Emond	541	569 (@ 17,409 hr)	544
	CADM	673	787	610
71	Emond	2,836	2,983 (@ 17,404 hr)	2,784
	CADM	4,934	5,748	4,483
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1.4	Emond	27.8	30.9 (@ 17,393 hr)	28.2
	CADM	33.9	35.0	35.0
7.1	Emond	99.5	110 (@ 17,393 hr)	96.6
	CADM	126.4	129.8	129.8
71	Emond	730	816 (@ 17,393 hr)	684
	CADM	1,121	1,149	1,149
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1.4	Emond	6.36	7.22 (@ 17,392 hr)	6.35
	CADM	-	-	-
7.1	Emond	16.6	18.4 (@ 17,392 hr)	16.0
	CADM	-	-	-
71	Emond	52.7	56.3 (@ 17,393 hr)	50.9
	CADM	-	-	-

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1 **E.3.1.25.** *NTP ([1982](#)) Female Mice, Chronic*

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Type:	Mice	Dose:	40, 200, and 2,000 ng/kg-wk, 2 doses/wk
Strain:	B6C3F$_1$	Route:	Oral exposure
Body weight	BW = 23 g (6 wk old)	Regime:	2 doses/wk
Sex:	Female	Simulation time	17,472 hr

4 The CADM model was not run because the study duration is longer than the allowed model duration.
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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
5.7	Emond	1.95	4.86 (@ 16,800 hr)	1.82
	CADM	-	-	-
28.6	Emond	5.84	19.8 (@ 17,388 hr)	5.17
	CADM	-	-	-
286	Emond	32.1	171 (@ 16,884 hr)	26.0
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
5.7	Emond	490	582 (@ 16,807 hr)	463
	CADM	-	-	-
28.6	Emond	2,236	2,629 (@ 17,395 hr)	2,025
	CADM	-	-	-
286	Emond	20,841	24,353 (@ 17,396 hr)	18,182
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
5.7	Emond	737	785 (@ 17,408 hr)	757
	CADM	-	-	-
28.6	Emond	2,213	2,337 (@ 17,404 hr)	2,216
	CADM	-	-	-
286	Emond	12,138	12,861 (@ 17,400 hr)	11,775
	CADM	-	-	-

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
5.7	Emond	91.9	103 (@ 17,393 hr)	91.2
	CADM	-	-	-
28.6	Emond	329	370 (@ 17,393 hr)	313
	CADM	-	-	-
286	Emond	2,400	2,740 (@ 17,393 hr)	2,176
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
5.7	Emond	6.18	7.29 (@ 16,805 hr)	5.93
	CADM	-	-	-
28.6	Emond	16.3	18.9 (@ 17,393 hr)	15.3
	CADM	-	-	-
286	Emond	52.3	67.8 (@ 2 hr)	49.3
	CADM	-	-	-

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3 **E.3.1.26.** *NTP (1982) Male Mice, Chronic*

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Type:	Mice	**Dose:**	10, 50, and 500 ng/kg-wk, 2 doses during the week
Strain:	B6C3F$_1$	**Route:**	Oral exposure
Body weight	BW = 25 g (6 wk old)	**Regime:**	2 doses/wk
Sex:	Male	**Simulation time**	17,472 hr (104 wk of exposure)

6 The CADM model was not run because the study duration is longer than the allowed model duration.
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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	0.767	1.53 (@ 17,304 hr)	0.749
	CADM	-	-	-
7.1	Emond	2.27	5.99 (@ 17,052 hr)	2.11
	CADM	-	-	-
71	Emond	11.2	46.7 (@ 17,388 hr)	9.59
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	138	165 (@ 17,310 hr)	136
	CADM	-	-	-
7.1	Emond	606	722 (@ 17,059 hr)	571
	CADM	-	-	-
71	Emond	5,409	6,328 (@ 17,395 hr)	4,805
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	290	314 (@ 17,411 hr)	306
	CADM	-	-	-
7.1	Emond	860	918 (@ 17,155 hr)	883
	CADM	-	-	-
71	Emond	4,257	4,490 (@ 17,402 hr)	4,204
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.4	Emond	32.3	36.2 (@ 17,309 hr)	33.3
	CADM	-	-	-
7.1	Emond	110	123 (@ 17,057 hr)	108
	CADM	-	-	-

71	Emond	710	802 (@ 17,393 hr)	660
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1.4	Emond	2.56	3.03 (@ 17,309 hr)	2.53
	CADM	-	-	-
7.1	Emond	7.12	8.40 (@ 17,057 hr)	6.82
	CADM	-	-	-
71	Emond	27.1	32.4 (@ 2 hr)	25.3
	CADM	-	-	-

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3 **E.3.1.27.** *NTP ([2006](#)) 14 Weeks*

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Type:	Rat	Dose:	0, 3, 10, 22, 46, and 100 ng/kg-day
Strain:	Sprague-Dawley	Route:	Oral gavage
Body weight:	BW = 215 g (8 wk old)	Regime:	5 d/wk for 14 wk
Sex:	Female and male	Simulation time:	2,352 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
2.14	Emond	1.98	3.15 (@ 2,280 hr)	2.39
	CADM	-	-	-
7.14	Emond	4.69	7.75 (@ 2,280 hr)	5.30
	CADM	-	-	-
15.7	Emond	8.27	14.3 (@ 2,280 hr)	9.02
	CADM	-	-	-
32.9	Emond	14.2	25.9 (@ 2,280 hr)	15.1
	CADM	-	-	-
71.4	Emond	25.7	49.8 (@ 2,280 hr)	26.6
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
2.14	Emond	275	404 (@ 2,284 hr)	354
	CADM	479	599	599
7.14	Emond	909	1,270 (@ 2,285 hr)	1,089
	CADM	1,702	2,017	2,017
15.7	Emond	1,988	2,703 (@ 2,285 hr)	2,291
	CADM	3,817	4,449	4,449
32.9	Emond	4,129	5,508 (@ 2,285 hr)	4,628
	CADM	8,054	9,314	9,314
71.4	Emond	8,921	11,734 (@ 2,285 hr)	9,792
	CADM	17,592	20,262	20,262
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
2.14	Emond	184	246 (@ 2,294 hr)	237
	CADM	326	355	347
7.14	Emond	436	557 (@ 2,292 hr)	532
	CADM	733	787	765
15.7	Emond	768	962 (@ 2,291 hr)	912
	CADM	1,361	1,463	1,422
32.9	Emond	1,319	1,633 (@ 2,289 hr)	1,535
	CADM	2,587	2,787	2,712
71.4	Emond	2,385	2,938 (@ 2,289 hr)	2,736
	CADM	5,326	5,748	5,599
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
2.14	Emond	28.2	39.4 (@ 2,284 hr)	36.1
	CADM	38.8	46.1	46.1
7.14	Emond	78.5	106 (@ 2,284 hr)	94.4
	CADM	109	126	126
15.7	Emond	156	206 (@ 2,284 hr)	181
	CADM	226	259	259

32.9	Emond	300	391 (@ 2,284 hr)	340
	CADM	459	523	523
71.4	Emond	610	788 (@ 2,284 hr)	676
	CADM	980	1,117	1,117

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
2.14	Emond	6.41	8.55 (@ 2,284 hr)	7.74
	CADM	-	-	-
7.14	Emond	13.9	17.6 (@ 2,284 hr)	15.8
	CADM	-	-	-
15.7	Emond	22.2	27.2 (@ 2,284 hr)	24.5
	CADM	-	-	-
32.9	Emond	33.2	39.3 (@ 2,284 hr)	35.7
	CADM	-	-	-
71.4	Emond	47.9	55.1 (@ 2,284 hr)	50.7
	CADM	-	-	-

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3 **E.3.1.28.** *NTP (2006) 31 Weeks*

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Type:	Rat	**Dose:**	0, 3, 10, 22, 46, 100 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	BW = 215 g (8 wk old)	**Regime:**	5 d/wk for 31 wk
Sex:	Female and male	**Simulation time:**	5,208 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
2.14	Emond	2.33	3.25 (@ 3,960 hr)	2.48
	CADM	-	-	-
7.14	Emond	5.32	7.89 (@ 3,960 hr)	5.40
	CADM	-	-	-

15.7	Emond	9.21	14.5 (@ 3,960 hr)	9.15
	CADM	-	-	-
32.9	Emond	15.7	26.2 (@ 5,136 hr)	15.3
	CADM	-	-	-
71.4	Emond	28.1	50.4 (@ 5,136 hr)	27.0
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
2.14	Emond	341	425 (@ 5,140 hr)	373
	CADM	555	631	631
7.14	Emond	1,075	1,308 (@ 3,965 hr)	1,117
	CADM	1,906	2,112	2,112
15.7	Emond	2,296	2,756 (@ 3,965 hr)	2,336
	CADM	4,229	4,652	4,652
32.9	Emond	4,696	5,597 (@ 5,141 hr)	4,712
	CADM	8,880	9,732	9,732
71.4	Emond	10,033	11,905 (@ 5,141 hr)	9,953
	CADM	19,347-	21,163	21,163

FAT CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
2.14	Emond	220	256 (@ 5,149 hr)	246
	CADM	329	355	320
7.14	Emond	501	570 (@ 4,139 hr)	542
	CADM	732	787	706
15.7	Emond	868	978 (@ 4,138 hr)	926
	CADM	1,361	1,463	1,315
32.9	Emond	1,476	1,657 (@ 5,145 hr)	1,558
	CADM	2,591	2,787	2,509
71.4	Emond	2,652	2,978 (@ 5,144 hr)	2,775
	CADM	5,344	5,748	5,183

BODY BURDEN (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
2.14	Emond	34.2	41.2 (@ 5,140 hr)	37.8
	CADM	43.2	47.1	47.1

7.14	Emond	91.6	108 (@ 3,964 hr)	96.6
	CADM	119	129	129
15.7	Emond	178	209 (@ 3,964 hr)	184
	CADM	246	264	264
32.9	Emond	339	398 (@ 5,140 hr)	346
	CADM	498	533	533
71.4	Emond	682	799 (@ 5,140 hr)	687
	CADM	1,063	1,138	1,138

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
2.14	Emond	7.48	8.83 (@ 5,140 hr)	8.01
	CADM	-	-	-
7.14	Emond	15.6	17.9 (@ 3,964 hr)	16.1
	CADM	-	-	-
15.7	Emond	24.3	27.4 (@ 3,964 hr)	24.8
	CADM	-	-	-
32.9	Emond	35.7	39.6 (@ 5,140 hr)	36.0
	CADM	-	-	-
71.4	Emond	50.9	55.4 (@ 5,140 hr)	51.1
	CADM	-	-	-

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3 **E.3.1.29.** *NTP (2006) 53 Weeks*

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Type:	Rat	**Dose:**	0, 3, 10, 22, 46, 100 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	BW = 215 g (8 wk old)	**Regime:**	5 d/wk for 53 wk
Sex:	Female and male	**Simulation time:**	8,904 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
2.14	Emond	2.46	3.25 (@ 6,312 hr)	2.48
	CADM	-	-	-
7.14	Emond	5.53	7.89 (@ 3,960 hr)	5.41
	CADM	-	-	-

Dose (ng/kg-day) adjusted dose	Model	Time-weighted average	Max	Terminal
15.7	Emond	9.54	14.5 (@ 8,832 hr)	9.17
	CADM	-	-	-
32.9	Emond	16.2	26.3 (@ 8,832 hr)	15.3
	CADM	-	-	-
71.4	Emond	29.0	50.6 (@ 8,832 hr)	27.1
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
2.14	Emond	366	426 (@ 6,316 hr)	373
	CADM	593	656	656
7.14	Emond	1,134	1,308 (@ 3,965 hr)	1,121
	CADM	2,010	2,197	2,197
15.7	Emond	2,406	2,759 (@ 8,837 hr)	2,345
	CADM	4,446	4,836	4,836
32.9	Emond	4,902	5,612 (@ 8,837 hr)	4,727
	CADM	9,318	10,115	10,115
71.4	Emond	10,439	11,938 (@ 8,837 hr)	9,985
	CADM	20,284	21,993	21,993

FAT CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
2.14	Emond	233	256 (@ 6,325 hr)	247
	CADM	321	355	301
7.14	Emond	524	570 (@ 4,139 hr)	544
	CADM	711	787	663
15.7	Emond	904	980 (@ 8,842 hr)	929
	CADM	1,323	1,463	1,236
32.9	Emond	1,533	1,661 (@ 8,841 hr)	1,562
	CADM	2,522	2,787	2,359
71.4	Emond	2,749	2,986 (@ 8,840 hr)	2,784
	CADM	5,205	5,748	4,873

BODY BURDEN (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
2.14	Emond	36.4	41.2 (@ 6,316 hr)	37.8
	CADM	44.9	47.4	47.4

		Time-weighted average	Max	Terminal
7.14	Emond	96.1	108 (@ 3,964 hr)	96.9
	CADM	123	129	129
15.7	Emond	186	210 (@ 8,836 hr)	185
	CADM	254	266	266
32.9	Emond	353	399 (@ 8,836 hr)	347
	CADM	513	536	536
71.4	Emond	709	801 (@ 8,836 hr)	689
	CADM	1,096	1,144	1,144

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
2.14	Emond	7.87	8.84 (@ 6,316 hr)	8.01
	CADM	-	-	-
7.14	Emond	16.2	17.9 (@ 3,964 hr)	16.1
	CADM	-	-	-
15.7	Emond	25.1	27.5 (@ 8,836 hr)	24.8
	CADM	-	-	-
32.9	Emond	36.6	39.7 (@ 8,836 hr)	36.1
	CADM	-	-	-
71.4	Emond	51.9	55.4 (@ 8,836 hr)	51.1
	CADM	-	-	-

E.3.1.30. *NTP ([2006](#)) 2 Years*

Type:	Rat	**Dose:**	0, 3, 10, 22, 46, 100 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	BW = 215 g (8 wk old)	**Regime:**	5 d/wk for 105 wk
Sex:	Female and male	**Simulation time:**	17,640 hr

The CADM model simulates for 104 wk only (17,472 hr). As a result, the terminal values from the CADM model may be underestimated compared to the Emond model, which considers the full 105 wk of exposure.

WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
2.14	Emond	2.56	3.47 (@ 17,568 hr)	2.62
	CADM	-	-	-

7.14	Emond	5.69	7.97 (@ 17,568 hr)	5.46
	CADM	-	-	-
15.7	Emond	9.79	14.6 (@ 17,568 hr)	9.22
	CADM	-	-	-
32.9	Emond	16.6	26.4 (@ 17,568 hr)	15.4
	CADM	-	-	-
71.4	Emond	29.7	50.8 (@ 17,568 hr)	27.1
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
2.14	Emond	385	460 (@ 17,572 hr)	403
	CADM	639	717	717
7.14	Emond	1,177	1,320 (@ 17,573 hr)	1,135
	CADM	2,150	2,391	2,391
15.7	Emond	2,487	2,779 (@ 17,573 hr)	2,361
	CADM	4,742	5,261	5,261
32.9	Emond	5,051	5,637 (@ 17,573 hr)	4,749
	CADM	9,927	11,002	11,002
71.4	Emond	10,734	11,976 (@ 17,573hr)	10,018
	CADM	21,596	23,920	23,920

FAT CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
2.14	Emond	243	271 (@ 17,581 hr)	261
	CADM	304	355	277
7.14	Emond	541	575 (@ 17,579 hr)	549
	CADM	673	787	610
15.7	Emond	930	985 (@ 17,578 hr)	934
	CADM	1,253	1,463	1,137
32.9	Emond	1,574	1,667 (@ 17,577 hr)	1,568
	CADM	2,390	2,787	2,170
71.4	Emond	2,821	2,995 (@ 17,576 hr)	2,792
	CADM	4,934	5,748	4,934

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
2.14	Emond	38.1	44.0 (@ 17,572 hr)	40.4
	CADM	46.2	47.6	47.6
7.14	Emond	99.5	109 (@ 17,572 hr)	97.9
	CADM	126	130	130
15.7	Emond	192	211 (@ 17,572 hr)	186
	CADM	260	267	267
32.9	Emond	364	400 (@ 17,572 hr)	348
	CADM	525	538	538
71.4	Emond	729	804 (@ 17,572 hr)	691
	CADM	1,121	1,149	1,149
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
2.14	Emond	8.17	9.30 (@ 17,572 hr)	8.43
	CADM	-	-	-
7.14	Emond	16.6	18.0 (@ 17,572 hr)	16.2
	CADM	-	-	-
15.7	Emond	25.6	27.6 (@ 17,572 hr)	24.9
	CADM	-	-	-
32.9	Emond	37.3	39.7 (@ 17,572 hr)	36.2
	CADM	-	-	-
71.4	Emond	52.7	55.5 (@ 17,572 hr)	51.2
	CADM	-	-	-

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3   **E.3.1.31. *Nohara et al. ([2002])***

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Type:	Mice	**Dose:**	5, 20, 100, and 500 ng/kg
Strain:	Four strains	**Route:**	Gavage
Body weight:	BW = 23 g (8 wk old)	**Regime:**	Single dose
Sex:	Female	**Simulation time:**	24 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
5	Emond	0.229	0.686 (@ 0 hr)	0.135
	CADM	-	-	-
20	Emond	0.817	2.74 (@ 0 hr)	0.448
	CADM	-	-	-
100	Emond	3.41	13.7 (@ 0 hr)	1.65
	CADM	-	-	-
500	Emond	14.2	68.6 (@ 0 hr)	5.70
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
5	Emond	19.8	23.6 (@ 5 hr)	16.8
	CADM	6.80	6.80	6.80
20	Emond	85.7	96.3 (@ 6 hr)	77.8
	CADM	38.7	38.7	38.7
100	Emond	472	517 (@ 10 hr)	458
	CADM	416	416	416
500	Emond	2,541	2,785 (@ 11 hr)	2,578
	CADM	3,998	3,998	3,998
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
5	Emond	13.5	20.4 (@ 24 hr)	20.4
	CADM	31.1	31.1	31.1
20	Emond	49.6	72.3 (@ 24 hr)	72.3
	CADM	119	119	119
100	Emond	217	299 (@ 24 hr)	299
	CADM	506	506	506
500	Emond	952	1,231 (@ 24 hr)	1,231
	CADM	1,761	1,761	1,761

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
5	Emond	2.84	3.03 (@ 8 hr)	2.96
	CADM	4.00	4.00	4.00
20	Emond	11.3	12.1 (@ 8 hr)	11.7
	CADM	16.0	16.0	16.0
100	Emond	55.9	60.0 (@ 7 hr)	57.4
	CADM	80.0	80.0	80.0
500	Emond	276	298 (@ 7 hr)	282
	CADM	400	400	400
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
5	Emond	0.715	1.07 (@ 3 hr)	0.507
	CADM	-	-	-
20	Emond	2.40	3.99 (@ 3 hr)	1.67
	CADM	-	-	-
100	Emond	8.61	16.4 (@ 2 hr)	5.88
	CADM	-	-	-
500	Emond	25.5	49.4 (@ 2 hr)	17.8
	CADM	-	-	-

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3 **E.3.1.32.** *Sewall et al. ([1995](#)) and Maronpot et al. ([1993](#))*

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Type:	Rat	**Dose:**	49, 149.8, 490, and 1,750 ng/kg every 2 wk (equivalent to 3.5, 10.7, 35, and 125 ng/kg-day)
Strain:	Sprauge-Dawley	**Route:**	Oral gavage
Body weight:	BW = 250 g (12 wk old)	**Regime:**	Once every 2 wk for 30 wk
Sex:	Female	**Simulation time:**	5,040 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
3.5	Emond	3.29	13.7 (@ 4,704 hr)	2.88
	CADM	-	-	-
10.7	Emond	7.11	38.7 (@ 4,704 hr)	5.79
	CADM	-	-	-
35	Emond	16.6	120 (@ 4,704 hr)	12.6
	CADM	-	-	-
125	Emond	44.7	414 (@ 4,704 hr)	31.4
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
3.5	Emond	550	901 (@ 4,711 hr)	459
	CADM	928	1,273	786
10.7	Emond	1,605	2,632 (@ 4,712 hr)	1,229
	CADM	2,891	3,940	2,373
35	Emond	5,072	8,350 (@ 4,712 hr)	3,618
	CADM	9,534	12,926	7,744
125	Emond	17,683	29,256 (@ 4,713 hr)	12,011
	CADM	34,145	46,190	27,659
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
3.5	Emond	310	383 (@ 4,765 hr)	290
	CADM	451	560	367
10.7	Emond	670	827 (@ 4,763 hr)	590
	CADM	1,008	1,300	774
35	Emond	1,569	1,957 (@ 4,760 hr)	1,304
	CADM	2,786	3,693	2,054
125	Emond	4,217	5,376 (@ 4,757 hr)	3,303
	CADM	9,308	12,496	6,738

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
3.5	Emond	51.4	72.5 (@ 4,710 hr)	45.3
	CADM	64.8	83.25	56.0
10.7	Emond	130	189 (@ 4,710 hr)	106
	CADM	173	227	143
35	Emond	364	546 (@ 4,710 hr)	274
	CADM	534	704	429
125	Emond	1,164	1,793 (@ 4,710 hr)	824
	CADM	1,863	2,468	-1,483
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
3.5	Emond	10.2	15.8 (@ 2 hr)	9.18
	CADM	-	-	-
10.7	Emond	19.8	34.4 (@ 1 hr)	17.0
	CADM	-	-	-
35	Emond	37.0	63.2 (@ 1 hr)	31.4
	CADM	-	-	-
125	Emond	63.1	90.9 (@ 1 hr)	55.2
	CADM	-	-	-

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3 **E.3.1.33.** *Shi et al. ([2007](#)) Adult Portion*

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Type:	Rat	Dose:	1, 5, 50, and 200 ng/kg-wk (equivalent to 0.143, 0.714, 7.14, and 28.6 ng/kg-day)
Strain:	Sprague-Dawley	Route:	Oral exposure
Body weight:	BW = 4.5 g	Regime:	Weekly doses for 11 mo
Sex:	Female	Simulation time:	8,040 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.143	Emond	0.342	0.475 (@ 7,561 hr)	0.380
	CADM	-	-	-
0.714	Emond	1.07	1.53 (@ 7,560 hr)	1.09
	CADM	-	-	-
7.14	Emond	5.23	9.12 (@ 7,560 hr)	4.86
	CADM	-	-	-
28.6	Emond	13.9	29.2 (@ 7,560 hr)	12.4
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.143	Emond	26.1	36.5 (@ 7,564 hr)	29.6
	CADM	33.6	42.6	42.6
0.714	Emond	118	159 (@ 7,564 hr)	120
	CADM	189	216	216
7.14	Emond	1,068	1,415 (@ 7,565 hr)	970
	CADM	1,992	2,178	2,178
28.6	Emond	4,119	5,450 (@ 7,565 hr)	3,574
	CADM	8,031	8,722	8,722
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.143	Emond	32.5	40.0 (@ 7,583 hr)	36.7
	CADM	71.0	78.6	73.8
0.714	Emond	102	120 (@ 7,584 hr)	106
	CADM	173	190	167
7.14	Emond	497	571 (@ 7,584 hr)	475
	CADM	716	787	671
28.6	Emond	1,322	1,527 (@ 7,584 hr)	1,217
	CADM	2,237	2,457	2,104

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.143	Emond	3.94	4.99 (@ 7,566 hr)	4.45
	CADM	6.6	7.6	7.6
0.714	Emond	14.0	17.2 (@ 7,566 hr)	14.5
	CADM	19.6	21.2	21.2
7.14	Emond	90.8	112 (@ 7,566 hr)	84.4
	CADM	123	129	129
28.6	Emond	300	374 (@ 7,566 hr)	266
	CADM	446	468	468
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
0.143	Emond	1.18	1.60 (@ 7,563 hr)	1.31
	CADM	-	-	-
0.714	Emond	3.62	4.75 (@ 7,563 hr)	3.70
	CADM	-	-	-
7.14	Emond	15.6	19.7 (@ 7,564 hr)	14.7
	CADM	-	-	-
28.6	Emond	33.5	40.7 (@ 7,564 hr)	31.2
	CADM	-	-	-

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3 **E.3.1.34.** *Simanainen et al. ([2002](#)) and Simanainen et al. ([2003](#))*

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Type:	Rats	**Dose:**	100 and 300 ng/kg
Strain:	Hans/Wistar and Long-Evans	**Route:**	Oral gavage
Body weight:	BW = 200 g	**Regime:**	Single dose
Sex:	Female	**Simulation time:**	24 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
100	Emond	6.36	20.5 (@ 0 hr)	3.82
	CADM	-	-	-
300	Emond	16.3	61.5 (@ 0 hr)	9.07
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
100	Emond	725	796 (@ 8 hr)	711
	CADM	-	-	-
300	Emond	2,331	2,547 (@ 9 hr)	2,352
	CADM	-	-	-

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
100	Emond	174	241 (@ 24 hr)	241
	CADM	-	-	-
300	Emond	461	611 (@ 24 hr)	611
	CADM	-	-	-

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
100	Emond	52.8	56.3 (@ 7 hr)	54.5
	CADM	-	-	-
300	Emond	158	169 (@ 7 hr)	162
	CADM	-	-	-

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max.	Terminal
100	Emond	16.0	26.4 (@ 2 hr)	12.3
	CADM	-	-	-

300	Emond	31.8	50.6 (@ 1 hr)	25.3
	CADM	-	-	-

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3 **E.3.1.35.** *Smialowicz et al. ([2004](#))*

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Type:	Mice	Dose:	30, 100, 300, 1,000, 3,000, and 10,000 ng/kg
Strain:	C57BL/6N	**Route:**	Oral gavage
Body weight:	BW = 25 g (Age not specified)	**Regime:**	Single dose
Sex:	Female	**Simulation time:**	24 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
30	Emond	1.19	4.19 (@ 0 hr)	0.632
	CADM	-	-	-
100	Emond	3.44	14.0 (@ 0 hr)	1.65
	CADM	-	-	-
300	Emond	9.08	42.0 (@ 0 hr)	3.87
	CADM	-	-	-
1,000	Emond	26.9	140 (@ 0 hr)	9.76
	CADM	-	-	-
3,000	Emond	75.1	420 (@ 0 hr)	23.5
	CADM	-	-	-
10,000	Emond	242	1,403 (@ 0 hr)	66.7
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
30	Emond	132	147 (@ 7 hr)	123
	CADM	68.6	68.6	68.6
100	Emond	473	518 (@ 10 hr)	461
	CADM	416	416	416

300	Emond	1,498	1,641 (@ 11 hr)	1,506
	CADM	2,039	2,039	2,039
1,000	Emond	5,199	5,700 (@ 12 hr)	5,345
	CADM	9,294	9,294	9,294
3,000	Emond	15,934	17,473 (@ 12 hr)	16,586
	CADM	31,419	31,419	31,419
10,000	Emond	53,457	58,629 (@ 13 hr)	56,056
	CADM	109,703	109,703	109,703

FAT CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
30	Emond	71.4	103 (@ 24 hr)	103
	CADM	174	174	174
100	Emond	215	296 (@ 24 hr)	296
	CADM	506	506	506
300	Emond	588	776 (@ 24 hr)	776
	CADM	1,201	1,201	1,201
1,000	Emond	1,804	2,278 (@ 24 hr)	2,278
	CADM	3,002	3,002	3,002
3,000	Emond	5,165	6,333 (@ 24 hr)	6,333
	CADM	7,593	7,593	7,593
10,000	Emond	16,888	20,306 (@ 24 hr)	20,306
	CADM	23,319	23,319	23,319

BODY BURDEN (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
30	Emond	16.9	18.1 (@ 7 hr)	17.5
	CADM	24.0	24.0	24.0
100	Emond	55.9	60.0 (@ 7 hr)	57.4
	CADM	80.0	80.0	80.0
300	Emond	166	179 (@ 7 hr)	170
	CADM	240	240	240
1,000	Emond	550	594 (@ 7 hr)	560
	CADM	800	800	800

3,000	Emond	1,646	1,778 (@ 7 hr)	1,668
	CADM	2,400	2,400	2,400
10,000	Emond	5,469	5,916 (@ 7 hr)	5,528
	CADM	8,000	8,000	8,000

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
30	Emond	3.37	5.79 (@ 3 hr)	2.34
	CADM	-	-	-
100	Emond	8.63	16.4 (@ 2 hr)	5.90
	CADM	-	-	-
300	Emond	18.6	36.6 (@ 2 hr)	12.8
	CADM	-	-	-
1,000	Emond	37.6	67.8 (@ 2 hr)	27.2
	CADM	-	-	-
3,000	Emond	61.3	91.8 (@ 2 hr)	48.3
	CADM	-	-	-
10,000	Emond	86.5	106 (@ 2 hr)	76.1
	CADM	-	-	-

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3 **E.3.1.36. *Smialowicz et al. (2008)***
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Type:	Mice	**Dose:**	0, 1.5, 15, 150, and 450 ng/kg-day
Strain:	B6C3F$_1$	**Route:**	Oral gavage
Body weight:	BW = 28 g (13 wk old)	**Regime:**	5 d/wk for 13 wk
Sex:	Female	**Simulation time:**	2,184 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1.07	Emond	0.438	0.815 (@ 2,112 hr)	0.557
	CADM	-	-	-
10.7	Emond	2.46	5.12 (@ 2,112 hr)	2.65
	CADM	-	-	-

107	Emond	13.4	36.4 (@ 2,112 hr)	12.7
	CADM	-	-	-
321	Emond	31.6	98.6 (@ 2,112 hr)	28.4
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max	Terminal
1.07	Emond	67.1	107 (@ 2,116 hr)	91.5
	CADM	59.8	91.9	84.2
10.7	Emond	683	971 (@ 2,117 hr)	787
	CADM	776	1,000	825
107	Emond	6,784	9,010 (@ 2,117 hr)	7,043
	CADM	8,441	10,306	7,863
321	Emond	20,218	26,379 (@ 2,117 hr)	20,405
	CADM	25.626	31,006	23.460

FAT CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max	Terminal
1.07	Emond	156	229 (@ 2,130 hr)	225
	CADM	153	210	199
10.7	Emond	885	1,155 (@ 2,124 hr)	1,111
	CADM	697	815	735
107	Emond	4,831	5,979 (@ 2,120 hr)	5,591
	CADM	2,802	3,224	2,684
321	Emond	11,420	14,037 (@ 2,119 hr)	12,920
	CADM	6,408	7,509	5.972

BODY BURDEN (ng/kg)

Dose (ng/kg-day) adjusted dose		Metric		
	Model	Time-weighted average	Max	Terminal
1.07	Emond	17.0	25.5 (@ 2,116 hr)	23.9
	CADM	21.1	29.3	27.7
10.7	Emond	117	159 (@ 2,116 hr)	141
	CADM	120	145	127
107	Emond	852	1,103 (@ 2,116 hr)	923
	CADM	736	875	694

321	Emond	2,304	2,958 (@ 2,116 hr)	2,419
	CADM	1.983	2,370	1.828
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1.07	Emond	1.48	2.17 (@ 2,116 hr)	1.90
	CADM	-	-	-
10.7	Emond	7.60	9.86 (@ 2,116 hr)	8.42
	CADM	-	-	-
107	Emond	30.3	36.0 (@ 2,117 hr)	31.1
	CADM	-	-	-
321	Emond	51.1	58.1 (@ 2,117 hr)	51.8
	CADM	-	-	-

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3 **E.3.1.37.** *Toth et al. ([1979](#)) 1 Year*

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Type:	Mice	**Dose:**	7, 700, and 7,000 ng/kg-wk
Strain:	Swiss/H/Riop	**Route:**	Oral gavage In gastric tube
Body weight:	BW = 27 g (10 wk old)	**Regime:**	Once per week for 1 yr (365 d)
Sex:	Female and male	**Simulation time:**	8,760 hr

6 The CADM model was not run because the study duration is longer than the allowed model duration.
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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
1	Emond	0.573	1.61 (@ 8,736 hr)	0.682
	CADM	-	-	-
100	Emond	14.2	116 (@ 8,736 hr)	15.7
	CADM	-	-	-
1,000	Emond	91.2	1,108 (@ 8,736 hr)	99.3
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	94.2	131 (@ 8,743 hr)	123
	CADM	-	-	-
100	Emond	7,343	10,134 (@ 8,745 hr)	9,604
	CADM	-	-	-
1,000	Emond	70,243	97,658 (@ 8,745 hr)	92,506
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	215	247 (@ 8,613 hr)	245
	CADM	-	-	-
100	Emond	5,339	5,914 (@ 8,760 hr)	5,914
	CADM	-	-	-
1,000	Emond	34,249	38,828 (@ 8,756 hr)	38,807
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	23.4	28.4 (@ 8,742 hr)	27.9
	CADM	-	-	-
100	Emond	929	1,189 (@ 8,742 hr)	1,132
	CADM	-	-	-
1,000	Emond	7,569	10,045 (@ 8,742 hr)	9,471
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
1	Emond	1.93	2.65 (@ 8,741 hr)	2.35
	CADM	-	-	-
100	Emond	31.8	58.4 (@ 2 hr)	36.7
	CADM	-	-	-

1,000	Emond	78.6	103 (@ 2 hr)	84.8
	CADM	-	-	-

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3 **E.3.1.38. *Van Birgelen et al. ([1995](#))***

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Type:	Rat	**Dose:**	0, 13.5, 26.4, 46.9, 320, and 1,024 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	BW = 150 g	**Regime:**	Once per day for 13 wk
Sex:	Female	**Simulation time:**	2,184 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
13.5	Emond	7.20	11.1 (@ 2,160 hr)	8.47
	CADM	-	-	-
26.4	Emond	11.8	18.6 (@ 2,160 hr)	13.5
	CADM	-	-	-
46.9	Emond	18.1	29.6 (@ 2,160 hr)	20.5
	CADM	-	-	-
320	Emond	86.4	156 (@ 2,160 hr)	95.4
	CADM	-	-	-
1,024	Emond	250	470 (@ 2,160 hr)	275
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose		**Metric**		
	Model	**Time-weighted average**	**Max**	**Terminal**
13.5	Emond	1,655	2,208 (@ 2,164 hr)	2,107
	CADM	3,228	3,802	3,802
26.4	Emond	3,228	4,216 (@ 2,164 hr)	4,017
	CADM	6,379	7,447	7,447
46.9	Emond	5,719	7,366 (@ 2,164 hr)	7,008
	CADM	11,390	13,240	13,240

Dose (ng/kg-day) adjusted dose	Model	Time-weighted average	Max	Terminal
320	Emond	38,484	47,999 (@ 2,164 hr)	45,537
	CADM	78,166	90,406	90,406
1,024	Emond	121,640	150,410 (@ 2,164 hr)	142,510
	CADM	250,307	289,326	289,326

FAT CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
13.5	Emond	669	843 (@ 2,167 hr)	835
	CADM	1,197	1,291	1,261
26.4	Emond	1,092	1,357 (@ 2,166 hr)	1,342
	CADM	2,119	2,290	2,240
46.9	Emond	1,680	2,071 (@ 2,166 hr)	2,045
	CADM	3,572	3,866	3,785
320	Emond	8,027	9,816 (@ 2,165 hr)	9,639
	CADM	22,844	24,800	24,308
1,024	Emond	23,234	28,519 (@ 2,165 hr)	27,954
	CADM	72,506	78,746	77,195

BODY BURDEN (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
13.5	Emond	132	173 (@ 2,164 hr)	167
	CADM	194	224	224
26.4	Emond	240	308 (@ 2,164 hr)	296
	CADM	367	423	423
46.9	Emond	404	513 (@ 2,164 hr)	492
	CADM	641	737	737
320	Emond	2,437	3,031 (@ 2,164 hr)	2,887
	CADM	4,292	4,294	4,294
1,024	Emond	7,521	9,310 (@ 2,164 hr)	8,846
	CADM	13,702	15,714	15,714

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	**Metric**		
		Time-weighted average	Max	Terminal
13.5	Emond	19.9	24.2 (@ 2,164 hr)	23.4
	CADM	-	-	-
26.4	Emond	29.0	34.3 (@ 2,164 hr)	33.2
	CADM	-	-	-
46.9	Emond	38.8	45.0 (@ 2,164 hr)	43.7
	CADM	-	-	-
320	Emond	79.1	85.2 (@ 2,164 hr)	84.1
	CADM	-	-	-
1,024	Emond	97.5	101 (@ 2,164 hr)	101
	CADM	-	-	-

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E.3.1.39. *Vanden Heuvel et al. ([1994](#))*

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Type:	Rat	Dose:	0.05, 0.1, 1, 10, 100, 1,000, 10,000 ng/kg-day
Strain:	Sprague-Dawley	Route:	Oral gavage
Body weight:	BW = 250 g (10 wk old; BW 225 to 275 g)	Regime:	Single dose
Sex:	Female	Simulation time:	24 hr

6 The CADM model was not run because the study duration is longer than the allowed model duration.
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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	Model	**Metric**		
		Time-weighted average	Max	Terminal
0.05	Emond	0.01	0.011 (@ 0 hr)	0.0039
	CADM	-	-	-
0.1	Emond	0.0113	0.022 (@ 0 hr)	0.008
	CADM	-	-	-
1	Emond	0.106	0.215 (@ 0 hr)	0.0723
	CADM	-	-	-

Dose (ng/kg-day) adjusted dose	Model	Time-weighted average	Max	Terminal
10	Emond	0.883	2.15 (@ 0 hr)	0.583
	CADM	-	-	-
100	Emond	6.45	21.5 (@ 0 hr)	3.85
	CADM	-	-	-
1,000	Emond	48.3	216 (@ 0 hr)	23.9
	CADM	-	-	-
10,000	Emond	435	2,166 (@ 0 hr)	186
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
0.05	Emond	0.232	0.315 (@ 3 hr)	0.173
	CADM	-	-	0.0140
0.1	Emond	0.469	0.631 (@ 3 hr)	0.353
	CADM	-	-	0.0320
1	Emond	5.08	6.42 (@ 4 hr)	4.08
	CADM	-	-	0.950
10	Emond	60.2	68.7 (@ 5 hr)	54.1
	CADM	-	-	52.7
100	Emond	730	800 (@ 9 hr)	719
	CADM	-	-	1,342
1,000	Emond	8,186	8,919 (@ 11 hr)	8,442
	CADM	-	-	15,967
10,000	Emond	84,254	91,675 (@ 11 hr)	88,230
	CADM	-	-	162,773

FAT CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
0.05	Emond	0.138	0.215 (@ 24 hr)	0.215
	CADM	-	-	0.780
0.1	Emond	0.274	0.427 (@ 24 hr)	0.427
	CADM	-	-	1.57
1	Emond	2.58	3.97 (@ 24 hr)	3.97
	CADM	-	-	15.3

10	Emond	22.1	32.8 (@ 24 hr)	32.8
	CADM	-	-	125
100	Emond	170	235 (@ 24 hr)	235
	CADM	-	-	739
1,000	Emond	1,348	1,720 (@ 24 hr)	1,720
	CADM	-	-	5,779
10,000	Emond	12,500	15,265 (@ 24 hr)	15,265
	CADM	-	-	55,825

BODY BURDEN (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
0.05	Emond	0.0269	0.028 (@ 9 hr)	0.0283
	CADM	-	-	0.0450
0.1	Emond	0.0538	0.057 (@ 9 hr)	0.0565
	CADM	-	-	0.0900
1	Emond	0.536	0.568 (@ 9 hr)	0.562
	CADM	-	-	0.900
10	Emond	5.32	5.65 (@ 8 hr)	5.55
	CADM	-	-	9.00
100	Emond	52.8	56.3 (@ 7 hr)	54.4
	CADM	-	-	90.0
1,000	Emond	525	562 (@ 7 hr)	538
	CADM	-	-	900
10,000	Emond	5,238	5,610 (@ 7 hr)	5,353
	CADM	-	-	9,000

BOUND LIVER (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
0.05	Emond	0.0194	0.027 (@ 3 hr)	0.0142
	CADM	-	-	-
0.1	Emond	0.0383	0.054 (@ 3 hr)	0.0281
	CADM	-	-	-
1	Emond	0.353	0.506 (@ 3 hr)	0.261
	CADM	-	-	-

10	Emond	2.77	4.24 (@ 2 hr)	2.08
	CADM	-	-	-
100	Emond	16.1	26.4 (@ 2 hr)	12.4
	CADM	-	-	-
1,000	Emond	57.4	80.2 (@ 1 hr)	48.5
	CADM	-	-	-
10,000	Emond	100	108 (@ 1 hr)	96.1
	CADM	-	-	-

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3 **E.3.1.40.** *Weber et al. ([1995](#)) C57 Mice*

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Type:	Mouse	**Dose:**	30, 100, 300, 1,000, 3,000, 9,400, 37,500, 75,000, 100,000, 133,000, 150,000, and 235,000 ng/kg
Strains:	C57BL/6J (C57)	**Route:**	Gavage
Body weight:	24.1 g (7−8 wk old)	**Regime:**	Single dose
Sex:	Male	**Simulation time:**	24 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
30	Emond	1.18	4.16 (@ 0 hr)	0.630
	CADM	-	-	-
100	Emond	3.43	13.9 (@ 0 hr)	1.65
	CADM	-	-	-
300	Emond	9.05	41.6 (@ 0 hr)	3.86
	CADM	-	-	-
1,000	Emond	26.8	139 (@ 0 hr)	9.74
	CADM	-	-	-
3,000	Emond	74.8	417 (@ 0 hr)	23.5
	CADM	-	-	-
9,400	Emond	226	1,307 (@ 0 hr)	63.0
	CADM	-	-	-

Dose	Model			
37,500	Emond	917	5,223 (@ 0 hr)	231
	CADM	-	-	-
75,000	Emond	1,929	10,464 (@ 0 hr)	459
	CADM	-	-	-
100,000	Emond	2,668	13,967 (@ 0 hr)	612
	CADM	-	-	-
133,000	Emond	3,725	18,603 (@ 0 hr)	815
	CADM	-	-	-
150,000	Emond	4,301	21,287 (@ 1 hr)	920
	CADM	-	-	-
235,000	Emond	7,426	39,404 (@ 1 hr)	1,456
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
30	Emond	132	146 (@ 7 hr)	122
	CADM	68.6	68.6	68.6
100	Emond	473	517 (@ 10 hr)	460
	CADM	416	416	416
300	Emond	1,497	1,639 (@ 11 hr)	1,503
	CADM	2,039	2,039	2,039
1,000	Emond	5,194	5,695 (@ 12 hr)	5,337
	CADM	9,294	9,294	9,294
3,000	Emond	15,923	17,461 (@ 12 hr)	16,565
	CADM	31,419	31,419	31,419
9,400	Emond	50,222	55,080 (@ 13 hr)	52,624
	CADM	102,986	102,986	102,986
37,500	Emond	196,690	216,050 (@ 13 hr)	207,410
	CADM	417,663	417,663	417,663
75,000	Emond	379,350	418,260 (@ 13 hr)	402,930
	CADM	837,656	837,656	837,656
100,000	Emond	491,890	544,360 (@ 14 hr)	525,670
	CADM	1,117,654	1,117,654	1,117,654
133,000	Emond	629,230	700,560 (@ 14 hr)	678,650
	CADM	1,487,253	1,487,253	1,487,253

Dose	Model	695,520	777,030 (@ 15 hr)	753,880
150,000	Emond	695,520	777,030 (@ 15 hr)	753,880
	CADM	1,677,652	1,677,652	1,677,652
235,000	Emond	993,260	1,128,600 (@ 16 hr)	1,101,800
	CADM	2,629,651	2,629,651	2,629,651

<div align="center">FAT CONCENTRATIONS (ng/kg)</div>

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
30	Emond	71.8	103 (@ 24 hr)	103
	CADM	174	174	174
100	Emond	216	297 (@ 24 hr)	297
	CADM	506	506	506
300	Emond	591	779 (@ 24 hr)	779
	CADM	1,201	1,201	1,201
1,000	Emond	1,810	2,286 (@ 24 hr)	2,286
	CADM	3,002	3,002	3,002
3,000	Emond	5,183	6,354 (@ 24 hr)	6,354
	CADM	7,593	7,593	7,593
9,400	Emond	15,932	19,164 (@ 24 hr)	19,164
	CADM	21,974	21,974	21,974
37,500	Emond	65,208	77,479 (@ 24 hr)	77,479
	CADM	84,935	84,935	84,935
75,000	Emond	137,960	162,720 (@ 24 hr)	162,720
	CADM	168,938	168,938	168,938
100,000	Emond	191,630	224,920 (@ 24 hr)	224,920
	CADM	224,938	224,938	224,938
133,000	Emond	268,900	313,670 (@ 23 hr)	313,580
	CADM	298,859	298,859	298,859
150,000	Emond	311,290	362,150 (@ 22 hr)	361,880
	CADM	336,939	336,939	336,939
235,000	Emond	542,350	625,850 (@ 19 hr)	623,390
	CADM	527,340	527,340	527,340

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	Metric		
		Time-weighted average	**Max**	**Terminal**
30	Emond	16.9	18.1 (@ 7 hr)	17.5
	CADM	24.0	24.0	24.0
100	Emond	55.9	60.0 (@ 7 hr)	57.4
	CADM	80.0	80.0	80.0
300	Emond	166	179 (@ 7 hr)	170
	CADM	240	240	240
1,000	Emond	550	594 (@ 7 hr)	560
	CADM	800	800	800
3,000	Emond	1,646	1,778 (@ 7 hr)	1,668
	CADM	2,400	2,400	2,400
9,400	Emond	5,141	5,561 (@ 7 hr)	5,197
	CADM	7,520	7,520	7,520
37,500	Emond	20,411	22,102 (@ 7 hr)	20,591
	CADM	30,000	30,000	30,000
75,000	Emond	40,607	43,991 (@ 6 hr)	40,914
	CADM	60,000	60,000	60,000
100,000	Emond	53,951	58,459 (@ 6 hr)	54,329
	CADM	80,000	80,000	80,000
133,000	Emond	71,431	77,411 (@ 6 hr)	71,888
	CADM	106,400	106,400	106,400
150,000	Emond	80,385	87,121 (@ 6 hr)	80,879
	CADM	120,000	120,000	120,000
235,000	Emond	124,740	135,260 (@ 6 hr)	125,340
	CADM	188,000	188,000	188,000
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	Metric		
		Time-weighted average	**Max**	**Terminal**
30	Emond	3.37	5.79 (@ 3 hr)	2.33
	CADM	-	-	-
100	Emond	8.62	16.4 (@ 2 hr)	5.89
	CADM	-	-	-

300	Emond	18.6	36.6 (@ 2 hr)	12.8
	CADM	-	-	-
1,000	Emond	37.6	67.8 (@ 2 hr)	27.1
	CADM	-	-	-
3,000	Emond	61.3	91.8 (@ 2 hr)	48.3
	CADM	-	-	-
9,400	Emond	85.4	105 (@ 2 hr)	74.7
	CADM	-	-	-
37,500	Emond	103.3	111 (@ 2 hr)	98.7
	CADM	-	-	-
75,000	Emond	107.6	112 (@ 2 hr)	105.1
	CADM	-	-	-
100,000	Emond	108.7	112 (@ 2 hr)	106.9
	CADM	-	-	-
133,000	Emond	109.6	112 (@ 1 hr)	108.2
	CADM	-	-	-
150,000	Emond	109.9	112 (@ 1 hr)	108.7
	CADM	-	-	-
235,000	Emond	110.7	113 (@ 1 hr)	110.1
	CADM	-	-	-

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3 **E.3.1.41.** *White et al. ([1986](#))*

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Type:	Mice	**Dose:**	10, 50, 100, 500, 1,000, 2,000 ng/kg-day
Strain:	B6C3F$_1$	**Route:**	Oral gavage
Body weight:	BW = 23 g (7 wk old)	**Regime:**	Once per day for 14 d
Sex:	Female	**Simulation time:**	336 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
10	Emond	1.09	2.73 (@ 312 hr)	1.42
	CADM	-	-	-

Dose	Model	Time-weighted average	Max	Terminal
50	Emond	4.08	11.6 (@ 312 hr)	4.98
	CADM	-	-	-
100	Emond	7.14	21.7 (@ 312 hr)	8.44
	CADM	-	-	-
500	Emond	26.8	96.5 (@ 312 hr)	29.8
	CADM	-	-	-
1,000	Emond	48.7	187 (@ 312 hr)	53.1
	CADM	-	-	-
2,000	Emond	90.6	365 (@ 312 hr)	97.5
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
10	Emond	216	375 (@ 317 hr)	343
	CADM	232	463	463
50	Emond	1,279	2,164 (@ 317 hr)	1,997
	CADM	1,902	3,261	3,261
100	Emond	2,707	4,525 (@ 317 hr)	4,184
	CADM	4,285	6,923	6,923
500	Emond	14,802	24,165 (@ 317 hr)	22,383
	CADM	24,327	36,362	36,362
1,000	Emond	30,278	49,034 (@ 317 hr)	45,414
	CADM	49,617	73,145	73,145
2,000	Emond	61,381	98,703 (@ 317 hr)	91,363
	CADM	100,261	146,695	146,695

FAT CONCENTRATIONS (ng/kg)

Dose (ng/kg-day) adjusted dose	Model	Metric		
		Time-weighted average	Max	Terminal
10	Emond	279	507 (@ 336 hr)	507
	CADM	338	537	537
50	Emond	1,056	1,846 (@ 336 hr)	1,846
	CADM	1,103	1,564	1,564
100	Emond	1,854	3,195 (@ 333 hr)	3,195
	CADM	1,781	2,470	2,470

500	Emond	7,008	11,868 (@ 324 hr)	11,816
	CADM	6,119	8,594	8,594
1,000	Emond	12,746	21,566 (@ 323 hr)	21,424
	CADM	11,248	15,993	15,993
2,000	Emond	23,691	40,177 (@ 322 hr)	39,843
	CADM	21,417	30,726	30,726

			BODY BURDEN (ng/kg)	
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
10	Emond	37.7	65.9 (@ 317 hr)	63.8
	CADM	51.3	85.9	85.9
50	Emond	175	297 (@ 317 hr)	284
	CADM	222	342	342
100	Emond	338	570 (@ 316 hr)	542
	CADM	416	624	624
500	Emond	1,597	2,637 (@ 316 hr)	2,480
	CADM	1,887	2,754	2,754
1,000	Emond	3,137	5,153 (@ 316 hr)	4,830
	CADM	3,702	5,387	5,387
2,000	Emond	6,186	10,118 (@ 316 hr)	9,459
	CADM	7,324	10,643	10,643

			BOUND LIVER (ng/kg)	
Dose (ng/kg-day) adjusted dose	**Model**	**Metric**		
		Time-weighted average	**Max**	**Terminal**
10	Emond	3.49	5.32 (@ 316 hr)	4.82
	CADM	-	-	-
50	Emond	11.4	16.4 (@ 317 hr)	15.1
	CADM	-	-	-
100	Emond	18.1	25.1 (@ 317 hr)	23.4
	CADM	-	-	-
500	Emond	44.2	56.2 (@ 317 hr)	53.8
	CADM	-	-	-
1,000	Emond	59.3	71.9 (@ 317 hr)	69.7
	CADM	-	-	-

| 2,000 | Emond | 74.4 | 86.1 (@ 317 hr) | 84.3 |
| | CADM | - | - | - |

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E.3.2. Gestational Studies

E.3.2.1. *Bell et al. ([2007])*

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Type:	Rat	Dose:	2.4, 8, and 46 ng/kg-day with a 0.03 ng/kg-day background
Strain:	Han/Wistar	Route:	Dietary exposure
Body weight:	BW = 85 g (6 wk old)	Regime:	Once per day for 12 wk prior to mating, during the 2 wk mating period, and during gestation
Sex:	Female	Simulation time:	2,352 hr (98 d) prior to gestation + 504 hr (21 d) during gestation for a total simulation of 2,856 hr

7   Time averages are computed during the gestation period only.
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Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
2.43	2.20	6,295	3.10 (@ 2,352 hr)	2.20
8.03	5.14	14,674	7.31 (@ 2,352 hr)	5.08
46.03	18.4	52,584	28.1 (@ 2,352 hr)	18.1
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Time-weighted average	Area under the curve	Max	Terminal
2.43	320	914,290	437 (@ 2,356 hr)	321
8.03	1,040	2,969,800	1,349 (@ 2,356 hr)	1,042
46.03	5,892	16,829,000	7,289 (@ 2,356 hr)	6,007
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Time-weighted average	Area under the curve	Max	Terminal
2.43	205	585,530	263 (@ 2,336 hr)	211
8.03	478	1,365,100	589 (@ 2,335 hr)	486
46.03	1,713	4,891,500	2,045 (@ 2,334 hr)	1,745

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
2.43	33.0	94,390	44.4 (@ 2,836 hr)	43.4
8.03	90.4	258,110	117 (@ 2,836 hr)	114
46.03	422	1,206,500	531 (@ 2,836 hr)	511
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
2.43	3.03	8,648	39.6 (@ 2,530 hr)	6.48
8.03	6.65	18,999	86.7 (@ 2,529 hr)	14.4
46.03	20.9	59,794	272 (@ 2,527 hr)	46.0
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
2.43	7.10	20,289	8.98 (@ 2,356 hr)	7.23
8.03	15.1	43,242	18.2 (@ 2,356 hr)	15.4
46.03	39.6	113,070	44.8 (@ 2,356 hr)	40.6

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3 **E.3.2.2. *Hojo et al. (2002)***

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Type:	Rat	Dose:	20, 60, and 180 ng/kg
Strain:	Sprague-Dawley	Route:	Oral exposure
Body weight	20 ng/kg BW = 271 g 60 ng/kg BW = 275 g 180 ng/kg BW = 262 g	Regime:	Single dose on GD 8
Sex:	Female	Simulation time	216 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
20	1.62	39.1	4.47 (@ 192 hr)	1.02
60	4.17	100	13.3 (@ 192 hr)	2.50

| 180 | 10.7 | 258 | 40.3 (@ 192 hr) | 5.96 |

LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)

Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
20	128	20,554	144 (@ 198 hr)	43.2
60	420	72,340	465 (@ 200 hr)	147
180	1,364	250,820	1,497 (@ 201 hr)	497

FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)

Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
20	32.5	17,253	63.0 (@ 281 hr)	49.4
60	86.4	44,093	161 (@ 284 hr)	124
180	226	108,730	398 (@ 286 hr)	301

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)

Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
20	10.6	3,054	11.3 (@ 200 hr)	8.67
60	31.8	8,702	33.8 (@ 199 hr)	23.6
180	95.0	24,747	101 (@ 199 hr)	63.4

FETUS (ng/kg) and AUC ((ng/kg) • hr)

Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
20	15.9	2,334	18.4 (@ 206 hr)	1.64
60	39.8	5,829	45.7 (@ 205 hr)	4.10
180	96.3	13,866	110 (@ 203 hr)	9.72

BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)

Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
20	4.88	759	7.74 (@ 194 hr)	1.75
60	11.2	1,848	18.5 (@ 194 hr)	4.26
180	23.6	4,157	38.5 (@ 193 hr)	9.65

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E.3.2.3. *Ikeda et al. (2005)*

Type:	Rat	Dose:	400 ng/kg single dose and 80 ng/kg weekly maintenance dose
Strain:	Sprague-Dawley	Route:	Oral gavage
Body weight:	BW = 250 g (10 wk old)	Regime:	400 ng/kg single dose, two weekly maintenance doses prior to gestation and weekly maintenance doses during gestation
Sex:	Female	Simulation time:	504 hr (21 d) prior to gestation + 504 hr (21 d) during gestation for a total simulation of 1,008 hr

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
16.5	22.9	23,086	101 (@ 144 hr)	10.1
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
16.5	7,755	7,817,300	17,016 (@ 150 hr)	2,698
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
16.5	2,087	2,103,900	3,663 (@ 184 hr)	1,028
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
16.5	548	552,590	1,085 (@ 149 hr)	262
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
16.5	45.9	46,290	245 (@ 679 hr)	30.2

BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
16.5	44.0	44,361	63.8 (@ 149 hr)	26.8

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3 **E.3.2.4.** *Kattainen et al. (2001) and Simanainen et al. (2004)*

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Type:	Rat	Dose:	30, 100, 300, and 1,000 ng/kg
Strain:	Han/Wistar (Kuopio) and Long/Evans (Turku/AB) crossing.	Route:	Oral exposure
Body weight:	BW = 190 g (BW not specified)*	Regime:	Single dose on GD 15
Sex:	Female	Simulation time:	360 hr

6 *Derelanko and Hollinger (1995).
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WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	2.23	53.7	5.95 (@ 336 hr)	1.36
100	6.25	150	19.8 (@ 336 hr)	3.62
300	16.1	387	59.8 (@ 336 hr)	8.62
1,000	46.9	1,128	200 (@ 336 hr)	22.7
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	193	4,648	219 (@ 342 hr)	175
100	713	17,141	793 (@ 344 hr)	680
300	2,298	55,266	2,533 (@ 345 hr)	2,267
1,000	8,055	193,720	8,831 (@ 345 hr)	8,134

FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	42.8	1,027	62.8 (@ 360 hr)	62.8
100	123	2,964	175 (@ 360 hr)	175
300	327	7,853	446 (@ 360 hr)	446
1,000	981	23,588	1,289 (@ 360 hr)	1,289

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	15.9	382	16.9 (@ 343 hr)	16.4
100	52.7	1,266	56.2 (@ 343 hr)	54.3
300	158	3,791	168 (@ 343 hr)	162
1,000	524	12,612	561 (@ 343 hr)	538

FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	4.86	117	6.66 (@ 360 hr)	6.66
100	13.2	317	17.6 (@ 360 hr)	17.6
300	31.5	758	41.2 (@ 360 hr)	41.2
1,000	82.2	1,975	104 (@ 360 hr)	104

BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	6.57	158	10.7 (@ 338 hr)	4.80
100	15.8	381	26.3 (@ 338 hr)	11.9
300	31.6	760	50.6 (@ 337 hr)	24.7
1,000	57.1	1,373	80.1 (@ 337 hr)	47.7

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E.3.2.5. *Keller et al. ([2007])*

Type:	Mouse	Dose:	10, 100, and 1,000 ng/kg
Strain:	CBA/J and C3H/HeJ	Route:	Oral
Body weight:	BW = 24 g (BW not specified)	Regime:	Single dose on GD 13
Sex:	Female	Simulation time:	336 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
10	0.537	12.9	1.43 (@ 312 hr)	0.269
100	4.29	103	14.3 (@ 312 hr)	1.95
1,000	34.1	820	143 (@ 312 hr)	12.3
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
10	30.6	737	39.8 (@ 316 hr)	22.2
100	371	8,922	421 (@ 319 hr)	317
1,000	4,214	101,360	4,697 (@ 321 hr)	3,940
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
10	22.4	538	33.3 (@ 336 hr)	33.3
100	188	4,523	264 (@ 336 hr)	264
1,000	1,591	38,233	2,080 (@ 336 hr)	2,080
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
10	5.57	134	5.99 (@ 319 hr)	5.72
100	54.3	1,306	59.0 (@ 318 hr)	54.7
1,000	530	12,747	581 (@ 318 hr)	524

FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
10	2.57	61.7	3.80 (@ 336 hr)	3.80
100	21.7	522	30.0 (@ 334 hr)	29.9
1,000	179	4,312	233 (@ 329 hr)	225
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
10	1.74	41.8	3.14 (@ 315 hr)	1.01
100	11.5	276	23.5 (@ 314 hr)	6.99
1,000	46.7	1,123	79.8 (@ 314 hr)	32.9

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3 **E.3.2.6.** *Li et al. ([2006](#)) 3 Day*

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Type:	Mouse	**Dose:**	2, 50, and 100 ng/kg-day
Strain:	NIH	**Route:**	Oral
Body weight:	BW = 27 g (25-28 g)	**Regime:**	Daily exposure from GD 1 to GD 3
Sex:	Female	**Simulation time:**	72 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ([ng/kg] • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2	0.159	11.4	0.392 (@ 48 hr)	0.136
50	2.84	205	8.90 (@ 48 hr)	2.38
100	5.12	369	17.3 (@ 48 hr)	4.20
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2	8.98	647	15.1 (@ 52 hr)	9.10
50	333	23,971	539 (@ 53 hr)	402
100	718	51,738	1,156 (@ 53 hr)	888

FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2	17.0	1,227	31.1 (@ 72 hr)	31.1
50	315	22,704	548 (@ 72 hr)	548
100	576	41,460	984 (@ 72 hr)	984

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2	2.29	165	3.51 (@ 55 hr)	3.43
50	53.6	3,863	82.2 (@ 54 hr)	77.1
100	105	7,598	162 (@ 53 hr)	150

FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2	0.0	0	0.000 (@ 72 hr)	0.00
50	0.0	0	0.000 (@ 72 hr)	0.00
100	0.0	0	0.000 (@ 72 hr)	0.00

BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
2	0.538	38.8	0.864 (@ 51 hr)	0.498
50	8.24	594	13.5 (@ 2 hr)	8.16
100	13.6	981	23.7 (@ 2 hr)	13.6

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3 **E.3.2.7.** *Markowski et al. (2001)*

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Type:	Rat	**Dose:**	20, 60, and 180 ng/kg
Strain:	Holtzman rats	**Route:**	Oral exposure
Body weight:	BW = 190 g (BW not specified)*	**Regime:**	Single dose on GD 18
Sex:	Female	**Simulation time:**	432 hr

5 *Derelanko and Hollinger (1995).

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
20	1.56	37.5	3.82 (@ 408 hr)	0.958
60	4.03	97.0	11.5 (@ 408 hr)	2.38
180	10.3	248	34.8 (@ 408 hr)	5.72

LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
20	123	2,959	141 (@ 414 hr)	109
60	409	9,843	459 (@ 415 hr)	382
180	1,334	32,086	1,479 (@ 416 hr)	1,295

FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
20	27.9	670	41.6 (@ 432 hr)	41.6
60	74.0	1,778	107 (@ 432 hr)	107
180	195	4,685	273 (@ 432 hr)	273

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
20	10.6	254	11.2 (@ 415 hr)	10.9
60	31.7	762	33.8 (@ 415 hr)	32.7
180	94.7	2,278	101 (@ 415 hr)	97.5

FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
20	1.26	30.2	1.80 (@ 432 hr)	1.80
60	3.21	77.2	4.49 (@ 432 hr)	4.49
180	7.81	188	10.7 (@ 432 hr)	10.7

BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
20	4.74	114	7.59 (@ 410 hr)	3.43
60	11.0	265	18.2 (@ 410 hr)	8.16
180	23.2	559	38.1 (@ 409 hr)	17.7

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3 **E.3.2.8.** *Mietinnen et al. (2006)*

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Type:	Rat	Dose:	30, 100, 300, and 1,000 ng/kg
Strain:	Cross-breeding of Han/Wistar and Long-Evans rats	Route:	Oral exposure
Body weight:	BW = 180 g (11 wk old)	Regime:	Single dose on GD 15
Sex:	Female	Simulation time:	360 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	2.22	53.4	5.87 (@ 336 hr)	1.36
100	6.23	150	19.6 (@ 336 hr)	3.61
300	16.0	386	59.0 (@ 336 hr)	8.61
1,000	46.6	1,123	198 (@ 336 hr)	22.7
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	193	4,631	219 (@ 342 hr)	174
100	711	17,096	791 (@ 344 hr)	677
300	2,294	55,166	2,530 (@ 345 hr)	2,260
1,000	8,042	193,410	8,820 (@ 345 hr)	8,114

FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	43.0	1,034	63.2 (@ 360 hr)	63.2
100	124	2,984	176 (@ 360 hr)	176
300	329	7,905	449 (@ 360 hr)	449
1,000	987	23,729	1,296 (@ 360 hr)	1,296

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	15.9	381	16.9 (@ 343 hr)	16.4
100	52.6	1,266	56.1 (@ 343 hr)	54.3
300	158	3,791	168 (@ 343 hr)	162
1,000	524	12,609	561 (@ 343 hr)	538

FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	4.83	116	6.62 (@ 360 hr)	6.62
100	13.1	315	17.5 (@ 360 hr)	17.5
300	31.3	753	41.0 (@ 360 hr)	41.0
1,000	81.7	1,963	104 (@ 360 hr)	104

BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	6.56	158	10.7 (@ 338 hr)	4.78
100	15.8	381	26.3 (@ 338 hr)	11.9
300	31.6	760	50.5 (@ 337 hr)	24.6
1,000	57.0	1,372	80.1 (@ 337 hr)	47.6

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1 **E.3.2.9.** *Nohara et al. ([2000](#))*

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Type:	Rat	Dose:	12.5, 50, 200, or 800 ng TCDD/kg
Strain:	Holtzman rats	Route:	Oral exposure
Body weight:	BW = 190 g (BW not specified)[a]	Regime:	Single dose on GD 15
Sex:	Female	Simulation time:	360 hr

4 [a]Derelanko and Hollinger ([1995](#)).
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WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	1.03	24.8	2.44 (@ 336 hr)	0.645
50	3.45	82.9	9.78 (@ 336 hr)	2.07
200	11.3	271	39.2 (@ 336 hr)	6.25
800	38.1	918	158 (@ 336 hr)	18.9
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	73.8	1,776	86.1 (@ 341 hr)	63.6
50	336	8,084	378 (@ 343 hr)	311
200	1,492	35,890	1,651 (@ 344 hr)	1,454
800	6,389	153,640	7,012 (@ 345 hr)	6,423
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	19.7	473	29.5 (@ 360 hr)	29.5
50	67.6	1,624	97.8 (@ 360 hr)	97.8
200	229	5,504	317 (@ 360 hr)	317
800	803	19,292	1,061 (@ 360 hr)	1,061

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
12.5	6.62	159	7.04 (@ 343 hr)	6.88
50	26.4	635	28.1 (@ 343 hr)	27.3
200	105	2,528	112 (@ 343 hr)	108
800	420	10,092	449 (@ 343 hr)	430
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
12.5	2.25	54.0	3.14 (@ 360 hr)	3.14
50	7.43	179	10.1 (@ 360 hr)	10.1
200	22.8	548	30.1 (@ 360 hr)	30.1
800	68.1	1,638	87.0 (@ 360 hr)	87.0
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
12.5	3.24	77.9	5.12 (@ 338 hr)	2.32
50	9.66	232	16.0 (@ 338 hr)	7.12
200	24.8	597	40.7 (@ 337 hr)	19.0
800	51.9	1,248	75.0 (@ 337 hr)	42.7

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3 **E.3.2.10. *Ohsako et al. (2001)***

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Type:	Rat	**Dose:**	12.5, 50, 200, and 800 ng/kg-day
Strain:	Holtzmann	**Route:**	Oral exposure
Body weight	10 wk old (200 g)	**Regime:**	Single dose on GD 15
Sex:	Female	**Simulation time**	384 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	1.04	25.0	2.48 (@ 360 hr)	0.649
50	3.47	83.6	9.93 (@ 360 hr)	2.07
200	11.4	273	39.9 (@ 360 hr)	6.26
800	38.4	925	161 (@ 360 hr)	18.9
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	74.3	1,788	86.5 (@ 365 hr)	64.2
50	338	8,126	379 (@ 367 hr)	314
200	1,497	36,006	1,655 (@ 368 hr)	1,461
800	6,402	153,960	7,025 (@ 369 hr)	6,443
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	19.0	457	28.6 (@ 384 hr)	28.6
50	65.3	1,569	94.7 (@ 384 hr)	94.7
200	221	5,321	307 (@ 384 hr)	307
800	777	18,671	1,029 (@ 384 hr)	1,029
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	6.63	159	7.05 (@ 367 hr)	6.89
50	26.4	635	28.2 (@ 367 hr)	27.3
200	105	2,529	112 (@ 367 hr)	108
800	420	10,093	449 (@ 367 hr)	430
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	1.65	39.5	2.33 (@ 384 hr)	2.33

50	5.44	131	7.48 (@ 384 hr)	7.48
200	16.7	401	22.3 (@ 384 hr)	22.3
800	49.9	1,200	64.6 (@ 384 hr)	64.6

BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
12.5	3.25	78.3	5.13 (@ 362 hr)	2.34
50	9.69	233	16.0 (@ 362 hr)	7.16
200	24.9	598	40.7 (@ 361 hr)	19.1
800	51.9	1,249	75.0 (@ 361 hr)	42.8

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3 **E.3.2.11.** *Schantz et al. (1996) and Amin et al. (2000)*

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Type:	Rat	**Dose:**	25 and 100 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral exposure
Body weight:	BW = 250 g (BW not specified)	**Regime:**	Daily doses from GD 10−16
Sex:	Female	**Simulation time:**	384 hr; time averages are calculated from the beginning of the dosing

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WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
25	3.38	487	8.63 (@ 360 hr)	4.03
100	10.6	1,522	31.1 (@ 360 hr)	12.3
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
25	512	73,686	871 (@ 365 hr)	778
100	2,374	341,960	4,012 (@ 366 hr)	3,665

FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
25	169	24,323	306 (@ 384 hr)	306
100	532	76,675	950 (@ 384 hr)	950
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
25	45.1	6,490	76.6 (@ 365 hr)	74.3
100	177	25,438	298 (@ 365 hr)	287
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
25	25.2	3,627	30.4 (@ 343 hr)	27.3
100	74.1	10,672	88.1 (@ 342 hr)	77.9
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
25	9.99	1,439	14.4 (@ 364 hr)	12.8
100	25.2	3,632	34.2 (@ 364 hr)	31.6

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3 **E.3.2.12. *Seo et al. ([1995])***

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Type:	Rat	**Dose:**	25 and 100 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral exposure
Body weight:	BW = 190 g (BW not specified)	**Regime:**	Daily doses from GD 10−16
Sex:	Female	**Simulation time:**	384 hr; time averages are calculated from the beginning of the dosing

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WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
25	3.33	479	8.25 (@ 360 hr)	4.00
100	10.4	1,498	29.6 (@ 360 hr)	12.2

LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
25	504	72,592	861 (@ 365 hr)	767
100	2,347	337,970	3,978 (@ 365 hr)	3,627

FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
25	172	24,807	310 (@ 384 hr)	310
100	542	78,097	962 (@ 384 hr)	962

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
25	45.0	6,486	76.5 (@ 365 hr)	74.2
100	176	25,387	298 (@ 365 hr)	287

FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
25	24.7	3,551	29.8 (@ 343 hr)	26.8
100	72.6	10,456	86.6 (@ 342 hr)	76.8

BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
25	9.90	1,426	14.3 (@ 364 hr)	12.7
100	25.0	3,607	34.1 (@ 364 hr)	31.4

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1 **E.3.2.13.** *Smith et al. ([1976](#))*

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Type:	Mouse	Dose:	1, 10, 100, 1,000, and 3,000 ng/kg-day
Strain:	CF-1	Route:	Gavage
Body weight:	Mean 28–29 g (GD 6)	Regime:	Daily doses from GD 6−15
Sex:	Female	Simulation time:	360 hr

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WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
1	0.124	29.8	0.274 (@ 336 hr)	0.136
10	1.01	243	2.47 (@ 336 hr)	1.08
100	7.11	1,707	21.1 (@ 336 hr)	7.16
1,000	50.6	12,145	188 (@ 336 hr)	47.4
3,000	138	33,142	554 (@ 336 hr)	127
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
1	7.23	1,735	12.3 (@ 339 hr)	8.71
10	101	24,194	167 (@ 340 hr)	128
100	1,381	331,570	2,196 (@ 341 hr)	1,788
1,000	16,329	3,919,700	25,189 (@ 341 hr)	20,932
3,000	50,491	12,120,000	77,170 (@ 341 hr)	64,246
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
1	22.8	5,477	41.1 (@ 360 hr)	41.1
10	188	45,189	331 (@ 360 hr)	331
100	1,344	322,580	2,289 (@ 360 hr)	2,289
1,000	9,659	2,318,300	16,123 (@ 357 hr)	16,117
3,000	26,368	6,328,900	44,004 (@ 355 hr)	43,959

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
1	3.07	736	5.48 (@ 342 hr)	5.40
10	28.1	6,745	49.1 (@ 341 hr)	47.5
100	246	59,076	415 (@ 340 hr)	390
1,000	2,211	530,720	3,626 (@ 340 hr)	3,316
3,000	6,446	1,547,200	10,500 (@ 340 hr)	9,535

FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
1	1.90	456	2.45 (@ 274 hr)	2.15
10	15.4	3,703	19.9 (@ 249 hr)	16.9
100	105	25,190	137 (@ 247 hr)	111
1,000	659	158,110	880 (@ 246 hr)	686
3,000	1,663	399,230	2,254 (@ 246 hr)	1,744

BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
1	0.428	103	0.694 (@ 339 hr)	0.485
10	3.30	791	4.93 (@ 340 hr)	3.77
100	18.5	4,435	24.9 (@ 340 hr)	20.9
1,000	61.9	14,855	79.8 (@ 122 hr)	67.4
3,000	85.2	20,450	98.9 (@ 122 hr)	90.1

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3 **E.3.2.14.** *Sparschu et al. (1971)*

4
5

Type:	Rat	Dose:	30, 125, 500, 2,000, and 8,000 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Gavage
Body weight:	BW = 295 g (290−300 g)	**Regime:**	Daily doses from GD 6−15
Sex:	Female	**Simulation time:**	360 hr

WHOLE BLOOD CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	5.09	1,222	12.4 (@ 336 hr)	6.52
125	16.3	3,908	45.5 (@ 336 hr)	20.4
500	52.9	12,690	168 (@ 336 hr)	65.6
2,000	188	45,188	646 (@ 336 hr)	235
8,000	732	175,750	2,572 (@ 336 hr)	928

LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	946	227,090	1,636 (@ 341 hr)	1,507
125	4,480	1,075,300	7,644 (@ 341 hr)	7,105
500	19,233	4,616,400	32,428 (@ 341 hr)	30,252
2,000	79,288	19,031,000	132,390 (@ 341 hr)	123,500
8,000	316,550	75,979,000	522,920 (@ 341 hr)	485,720

FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	317	75,978	547 (@ 360 hr)	547
125	1,016	243,930	1,739 (@ 360 hr)	1,739
500	3,295	790,910	5,663 (@ 360 hr)	5,663
2,000	11,671	2,801,200	20,374 (@ 360 hr)	20,374
8,000	45,125	10,831,000	80,136 (@ 360 hr)	80,136

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	Metric			
	Time-weighted average	Area under the curve	Max	Terminal
30	80.6	19,348	140 (@ 341 hr)	136
125	324	77,864	559 (@ 341 hr)	537
500	1,266	303,960	2,169 (@ 341 hr)	2,071
2,000	4,996	1,199,100	8,527 (@ 341 hr)	8,117
8,000	19,780	4,747,500	33,634 (@ 340 hr)	31,926

FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	53.8	12,906	69.5 (@ 247 hr)	54.1
125	156	37,342	202 (@ 246 hr)	153
500	430	103,180	560 (@ 245 hr)	424
2,000	1,311	314,680	1,721 (@ 269 hr)	1,334
8,000	4,694	1,126,700	6,255 (@ 269 hr)	4,943
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) adjusted dose	**Metric**			
	Time-weighted average	**Area under the curve**	**Max**	**Terminal**
30	14.4	3,452	20.7 (@ 340 hr)	19.2
125	34.5	8,279	46.2 (@ 340 hr)	43.9
500	64.0	15,367	77.7 (@ 341 hr)	75.8
2,000	91.2	21,890	100 (@ 341 hr)	99.2
8,000	106	25,389	109 (@ 341 hr)	109

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2

Table E-1. Model input parameters potentially addressed by selected articles

Articles	Absorption	Desorption	Distribution	Elimination	Kinetics	Induction CYP1A1	Interspecies differences	Age Differences	Aryl hydrocarbon receptor	Mode of action	Partition coefficient
Aylward et al. (2005a)	●	●	●	●	●						
Aylward et al. (2005b)	●	●	●	●	●						
Aylward et al. (2009)				●							
Bohonowych and Denison (2007)						●	●		●		
Boverhof et al. (2005)						●	●				
Connor and Aylward (2006)							●	●	●		
Heinzl et al. (2007)			●						●		
Irigaray et al. (2005)			●				●				
Kerger et al. (2006)			●		●			●			
Kerger et al. (2007)								●			
Kim et al. (2003)			●								
Korenaga et al. (2007)						●	●				
Korkalainen et al. (2004)							●	●			
Kransler et al. (2007)							●	●			
Maruyama et al. (2002)	●		●	●							
Maruyama et al. (2003)	●		●	●							
Maruyama and Aoki (2006)	●		●	●							
Milbrath et al. (2009)			●	●	●		●				
Moser and McLachlan (2002)		●		●							
Mullerova and Kopecky(2007)			●								
Nadal et al. (2009)				●	●						
Nohara et al. (2006)							●		●		
Olsman et al. (2007)									●		
Saghir et al. (2005)			●	●	●						
Schecter et al. (2003)				●				●			
Staskal et al. (2005)						●			●		
Toyoshiba et al. (2004)			●			●			●		
Wilkes et al. (2008)						●					

Partition coefficient estimates and CYP parameter value estimates were derived from Wang et al., (2000; 1997) and Santostefano et al. (1998).

E.4. RESPONSE SURFACE TABLES

1

2   In order to calculate human equivalent doses, the human model must be run with a daily

3 intake which gives average blood concentrations which match the average concentrations in the

4 rodent models. However, such calculation can require numerous human model runs with

5 repeated intake adjustments in order to reach the target blood concentrations. To facilitate this

6 process, a response surface was created for the human model. In the response surface, numerous

7 intakes were run and the blood, fat, and body burden average concentrations were recorded.

8 These tables can then be used to estimate the intake which would give a target blood

9 concentration. The two closest intakes are found and the intake is estimated by linearly

10 interpolating between the two doses. Then, this intake is run through the human model to

11 confirm that the average blood concentration is within a specified tolerance of the target blood

12 concentration.

13   For the current analysis, three different response surfaces were created: nongestational

14 lifetime to be used with long-term animal bioassays, nongestational 5 year average runs to be

15 used with shorter term animal bioassays, and gestational to be used with gestational animal

16 bioassays. All three response surfaces are shown in the following tables.

E.4.1. Nongestational Lifetime

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.03E-09	2.78E-05	8.69E-06	2.93E-07
1.09E-09	2.95E-05	9.21E-06	3.11E-07
1.16E-09	3.13E-05	9.77E-06	3.30E-07
1.23E-09	3.32E-05	1.04E-05	3.49E-07
1.30E-09	3.52E-05	1.10E-05	3.70E-07
1.38E-09	3.73E-05	1.16E-05	3.93E-07
1.46E-09	3.95E-05	1.23E-05	4.16E-07
1.55E-09	4.19E-05	1.31E-05	4.41E-07
1.64E-09	4.44E-05	1.38E-05	4.68E-07
1.74E-09	4.70E-05	1.47E-05	4.96E-07
1.84E-09	4.99E-05	1.56E-05	5.25E-07
1.95E-09	5.28E-05	1.65E-05	5.57E-07
2.07E-09	5.60E-05	1.75E-05	5.90E-07
2.20E-09	5.94E-05	1.85E-05	6.26E-07
2.33E-09	6.29E-05	1.96E-05	6.63E-07
2.47E-09	6.67E-05	2.08E-05	7.03E-07
2.62E-09	7.07E-05	2.21E-05	7.45E-07
2.77E-09	7.49E-05	2.34E-05	7.90E-07
2.94E-09	7.94E-05	2.48E-05	8.37E-07
3.12E-09	8.42E-05	2.63E-05	8.87E-07
3.30E-09	8.92E-05	2.79E-05	9.40E-07
3.50E-09	9.46E-05	2.95E-05	9.97E-07
3.71E-09	1.00E-04	3.13E-05	1.06E-06
3.93E-09	1.06E-04	3.32E-05	1.12E-06
4.17E-09	1.13E-04	3.52E-05	1.19E-06
4.42E-09	1.19E-04	3.73E-05	1.26E-06
4.68E-09	1.27E-04	3.95E-05	1.33E-06
4.97E-09	1.34E-04	4.19E-05	1.41E-06
5.26E-09	1.42E-04	4.44E-05	1.50E-06
5.58E-09	1.51E-04	4.70E-05	1.59E-06
5.91E-09	1.60E-04	4.99E-05	1.68E-06
6.27E-09	1.69E-04	5.28E-05	1.78E-06
6.65E-09	1.79E-04	5.60E-05	1.89E-06
7.04E-09	1.90E-04	5.94E-05	2.00E-06
7.47E-09	2.02E-04	6.29E-05	2.12E-06

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
7.92E-09	2.14E-04	6.67E-05	2.25E-06
8.39E-09	2.26E-04	7.07E-05	2.39E-06
8.89E-09	2.40E-04	7.49E-05	2.53E-06
9.43E-09	2.54E-04	7.94E-05	2.68E-06
9.99E-09	2.70E-04	8.42E-05	2.84E-06
1.06E-08	2.86E-04	8.92E-05	3.01E-06
1.12E-08	3.03E-04	9.46E-05	3.19E-06
1.19E-08	3.21E-04	1.00E-04	3.38E-06
1.26E-08	3.40E-04	1.06E-04	3.58E-06
1.34E-08	3.61E-04	1.13E-04	3.80E-06
1.42E-08	3.82E-04	1.19E-04	4.03E-06
1.50E-08	4.05E-04	1.26E-04	4.27E-06
1.59E-08	4.29E-04	1.34E-04	4.52E-06
1.69E-08	4.55E-04	1.42E-04	4.79E-06
1.79E-08	4.82E-04	1.51E-04	5.08E-06
1.90E-08	5.11E-04	1.60E-04	5.38E-06
2.01E-08	5.42E-04	1.69E-04	5.71E-06
2.13E-08	5.74E-04	1.79E-04	6.05E-06
2.26E-08	6.08E-04	1.90E-04	6.41E-06
2.39E-08	6.45E-04	2.01E-04	6.79E-06
2.54E-08	6.83E-04	2.13E-04	7.20E-06
2.69E-08	7.24E-04	2.26E-04	7.63E-06
2.85E-08	7.67E-04	2.40E-04	8.08E-06
3.02E-08	8.13E-04	2.54E-04	8.57E-06
3.20E-08	8.62E-04	2.69E-04	9.08E-06
3.40E-08	9.13E-04	2.85E-04	9.62E-06
3.60E-08	9.68E-04	3.02E-04	1.02E-05
3.82E-08	1.03E-03	3.21E-04	1.08E-05
4.05E-08	1.09E-03	3.40E-04	1.15E-05
4.29E-08	1.15E-03	3.60E-04	1.21E-05
4.55E-08	1.22E-03	3.81E-04	1.29E-05
4.82E-08	1.29E-03	4.04E-04	1.36E-05
5.11E-08	1.37E-03	4.28E-04	1.44E-05
5.41E-08	1.45E-03	4.54E-04	1.53E-05
5.74E-08	1.54E-03	4.81E-04	1.62E-05
6.08E-08	1.63E-03	5.10E-04	1.72E-05
6.45E-08	1.73E-03	5.40E-04	1.82E-05

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
6.84E-08	1.83E-03	5.73E-04	1.93E-05
7.25E-08	1.94E-03	6.07E-04	2.04E-05
7.68E-08	2.06E-03	6.43E-04	2.17E-05
8.14E-08	2.18E-03	6.81E-04	2.30E-05
8.63E-08	2.31E-03	7.22E-04	2.43E-05
9.15E-08	2.45E-03	7.65E-04	2.58E-05
9.70E-08	2.59E-03	8.11E-04	2.73E-05
1.03E-07	2.75E-03	8.59E-04	2.89E-05
1.09E-07	2.91E-03	9.10E-04	3.06E-05
1.15E-07	3.08E-03	9.64E-04	3.25E-05
1.22E-07	3.27E-03	1.02E-03	3.44E-05
1.30E-07	3.46E-03	1.08E-03	3.64E-05
1.38E-07	3.67E-03	1.15E-03	3.86E-05
1.46E-07	3.88E-03	1.22E-03	4.09E-05
1.55E-07	4.11E-03	1.29E-03	4.33E-05
1.64E-07	4.36E-03	1.36E-03	4.59E-05
1.74E-07	4.62E-03	1.45E-03	4.86E-05
1.84E-07	4.89E-03	1.53E-03	5.15E-05
1.95E-07	5.18E-03	1.62E-03	5.46E-05
2.07E-07	5.49E-03	1.72E-03	5.78E-05
2.19E-07	5.81E-03	1.82E-03	6.12E-05
2.32E-07	6.16E-03	1.93E-03	6.49E-05
2.46E-07	6.52E-03	2.04E-03	6.87E-05
2.61E-07	6.91E-03	2.17E-03	7.28E-05
2.77E-07	7.32E-03	2.29E-03	7.71E-05
2.93E-07	7.75E-03	2.43E-03	8.16E-05
3.11E-07	8.21E-03	2.57E-03	8.65E-05
3.30E-07	8.69E-03	2.73E-03	9.16E-05
3.49E-07	9.21E-03	2.89E-03	9.70E-05
3.70E-07	9.75E-03	3.06E-03	1.03E-04
3.93E-07	1.03E-02	3.24E-03	1.09E-04
4.16E-07	1.09E-02	3.43E-03	1.15E-04
4.41E-07	1.16E-02	3.63E-03	1.22E-04
4.68E-07	1.23E-02	3.85E-03	1.29E-04
4.96E-07	1.30E-02	4.08E-03	1.37E-04
5.25E-07	1.37E-02	4.32E-03	1.45E-04
5.57E-07	1.46E-02	4.57E-03	1.53E-04

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
5.90E-07	1.54E-02	4.84E-03	1.62E-04
6.26E-07	1.63E-02	5.13E-03	1.72E-04
6.63E-07	1.73E-02	5.43E-03	1.82E-04
7.03E-07	1.83E-02	5.75E-03	1.93E-04
7.45E-07	1.93E-02	6.09E-03	2.04E-04
7.90E-07	2.05E-02	6.45E-03	2.16E-04
8.37E-07	2.17E-02	6.82E-03	2.28E-04
8.88E-07	2.29E-02	7.22E-03	2.42E-04
9.41E-07	2.43E-02	7.65E-03	2.56E-04
9.97E-07	2.57E-02	8.10E-03	2.71E-04
1.01E-06	2.61E-02	8.21E-03	2.75E-04
1.03E-06	2.64E-02	8.33E-03	2.79E-04
1.04E-06	2.68E-02	8.45E-03	2.83E-04
1.06E-06	2.72E-02	8.58E-03	2.87E-04
1.07E-06	2.76E-02	8.70E-03	2.91E-04
1.09E-06	2.80E-02	8.83E-03	2.95E-04
1.11E-06	2.84E-02	8.96E-03	2.99E-04
1.12E-06	2.88E-02	9.09E-03	3.04E-04
1.14E-06	2.92E-02	9.22E-03	3.08E-04
1.16E-06	2.97E-02	9.35E-03	3.12E-04
1.17E-06	3.01E-02	9.49E-03	3.17E-04
1.19E-06	3.05E-02	9.63E-03	3.21E-04
1.21E-06	3.10E-02	9.77E-03	3.26E-04
1.23E-06	3.14E-02	9.91E-03	3.31E-04
1.24E-06	3.19E-02	1.01E-02	3.36E-04
1.26E-06	3.23E-02	1.02E-02	3.40E-04
1.28E-06	3.28E-02	1.03E-02	3.45E-04
1.30E-06	3.33E-02	1.05E-02	3.50E-04
1.32E-06	3.37E-02	1.06E-02	3.55E-04
1.34E-06	3.42E-02	1.08E-02	3.60E-04
1.36E-06	3.47E-02	1.10E-02	3.66E-04
1.38E-06	3.52E-02	1.11E-02	3.71E-04
1.40E-06	3.57E-02	1.13E-02	3.76E-04
1.42E-06	3.62E-02	1.14E-02	3.82E-04
1.44E-06	3.67E-02	1.16E-02	3.87E-04
1.46E-06	3.73E-02	1.18E-02	3.93E-04
1.49E-06	3.78E-02	1.19E-02	3.98E-04

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.53E-06	3.89E-02	1.23E-02	4.10E-04
1.58E-06	4.00E-02	1.27E-02	4.22E-04
1.62E-06	4.12E-02	1.30E-02	4.34E-04
1.67E-06	4.24E-02	1.34E-02	4.46E-04
1.72E-06	4.36E-02	1.38E-02	4.59E-04
1.77E-06	4.49E-02	1.42E-02	4.72E-04
1.83E-06	4.61E-02	1.46E-02	4.86E-04
1.88E-06	4.75E-02	1.50E-02	5.00E-04
1.94E-06	4.88E-02	1.55E-02	5.14E-04
2.00E-06	5.02E-02	1.59E-02	5.29E-04
2.06E-06	5.17E-02	1.64E-02	5.44E-04
2.12E-06	5.32E-02	1.68E-02	5.60E-04
2.18E-06	5.47E-02	1.73E-02	5.76E-04
2.25E-06	5.63E-02	1.78E-02	5.93E-04
2.32E-06	5.79E-02	1.84E-02	6.10E-04
2.39E-06	5.95E-02	1.89E-02	6.27E-04
2.46E-06	6.12E-02	1.94E-02	6.45E-04
2.53E-06	6.30E-02	2.00E-02	6.64E-04
2.61E-06	6.48E-02	2.06E-02	6.83E-04
2.68E-06	6.66E-02	2.12E-02	7.02E-04
2.76E-06	6.85E-02	2.18E-02	7.22E-04
2.85E-06	7.05E-02	2.24E-02	7.43E-04
2.93E-06	7.25E-02	2.30E-02	7.64E-04
3.02E-06	7.46E-02	2.37E-02	7.86E-04
3.11E-06	7.67E-02	2.44E-02	8.08E-04
3.21E-06	7.89E-02	2.51E-02	8.31E-04
3.30E-06	8.11E-02	2.58E-02	8.54E-04
3.40E-06	8.34E-02	2.65E-02	8.79E-04
3.50E-06	8.58E-02	2.73E-02	9.04E-04
3.61E-06	8.82E-02	2.81E-02	9.29E-04
3.72E-06	9.07E-02	2.89E-02	9.55E-04
3.83E-06	9.33E-02	2.97E-02	9.82E-04
3.94E-06	9.59E-02	3.06E-02	1.01E-03
4.06E-06	9.86E-02	3.14E-02	1.04E-03
4.18E-06	1.01E-01	3.23E-02	1.07E-03
4.31E-06	1.04E-01	3.33E-02	1.10E-03
4.44E-06	1.07E-01	3.42E-02	1.13E-03

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.57E-06	1.10E-01	3.52E-02	1.16E-03
4.71E-06	1.13E-01	3.62E-02	1.19E-03
4.85E-06	1.16E-01	3.72E-02	1.23E-03
4.99E-06	1.20E-01	3.83E-02	1.26E-03
5.14E-06	1.23E-01	3.94E-02	1.30E-03
5.30E-06	1.27E-01	4.05E-02	1.33E-03
5.46E-06	1.30E-01	4.16E-02	1.37E-03
5.62E-06	1.34E-01	4.28E-02	1.41E-03
5.79E-06	1.37E-01	4.40E-02	1.45E-03
5.96E-06	1.41E-01	4.53E-02	1.49E-03
6.14E-06	1.45E-01	4.65E-02	1.53E-03
6.33E-06	1.49E-01	4.78E-02	1.57E-03
6.52E-06	1.53E-01	4.92E-02	1.62E-03
6.71E-06	1.58E-01	5.06E-02	1.66E-03
6.91E-06	1.62E-01	5.20E-02	1.71E-03
7.12E-06	1.66E-01	5.35E-02	1.75E-03
7.33E-06	1.71E-01	5.50E-02	1.80E-03
7.55E-06	1.76E-01	5.65E-02	1.85E-03
7.78E-06	1.81E-01	5.81E-02	1.90E-03
8.01E-06	1.86E-01	5.97E-02	1.95E-03
8.25E-06	1.91E-01	6.14E-02	2.01E-03
8.50E-06	1.96E-01	6.31E-02	2.06E-03
8.76E-06	2.01E-01	6.49E-02	2.12E-03
9.02E-06	2.07E-01	6.67E-02	2.18E-03
9.29E-06	2.12E-01	6.86E-02	2.24E-03
9.57E-06	2.18E-01	7.05E-02	2.30E-03
9.86E-06	2.24E-01	7.24E-02	2.36E-03
1.02E-05	2.30E-01	7.45E-02	2.43E-03
1.05E-05	2.37E-01	7.65E-02	2.49E-03
1.08E-05	2.43E-01	7.86E-02	2.56E-03
1.11E-05	2.50E-01	8.08E-02	2.63E-03
1.14E-05	2.56E-01	8.31E-02	2.70E-03
1.18E-05	2.63E-01	8.54E-02	2.77E-03
1.21E-05	2.71E-01	8.77E-02	2.85E-03
1.25E-05	2.78E-01	9.01E-02	2.93E-03
1.29E-05	2.85E-01	9.26E-02	3.01E-03
1.32E-05	2.93E-01	9.52E-02	3.09E-03

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.36E-05	3.01E-01	9.78E-02	3.17E-03
1.41E-05	3.09E-01	1.00E-01	3.25E-03
1.45E-05	3.17E-01	1.03E-01	3.34E-03
1.49E-05	3.26E-01	1.06E-01	3.43E-03
1.54E-05	3.34E-01	1.09E-01	3.52E-03
1.58E-05	3.43E-01	1.12E-01	3.62E-03
1.63E-05	3.53E-01	1.15E-01	3.71E-03
1.68E-05	3.62E-01	1.18E-01	3.81E-03
1.73E-05	3.72E-01	1.21E-01	3.91E-03
1.78E-05	3.81E-01	1.25E-01	4.02E-03
1.83E-05	3.92E-01	1.28E-01	4.12E-03
1.89E-05	4.02E-01	1.32E-01	4.23E-03
1.95E-05	4.13E-01	1.35E-01	4.34E-03
2.00E-05	4.23E-01	1.39E-01	4.46E-03
2.06E-05	4.35E-01	1.43E-01	4.58E-03
2.13E-05	4.46E-01	1.46E-01	4.70E-03
2.19E-05	4.58E-01	1.50E-01	4.82E-03
2.25E-05	4.70E-01	1.54E-01	4.95E-03
2.32E-05	4.82E-01	1.59E-01	5.07E-03
2.39E-05	4.94E-01	1.63E-01	5.21E-03
2.46E-05	5.07E-01	1.67E-01	5.34E-03
2.54E-05	5.21E-01	1.72E-01	5.48E-03
2.61E-05	5.34E-01	1.76E-01	5.62E-03
2.69E-05	5.48E-01	1.81E-01	5.77E-03
2.77E-05	5.62E-01	1.86E-01	5.92E-03
2.86E-05	5.77E-01	1.91E-01	6.07E-03
2.94E-05	5.92E-01	1.96E-01	6.23E-03
3.03E-05	6.07E-01	2.01E-01	6.39E-03
3.12E-05	6.22E-01	2.06E-01	6.55E-03
3.21E-05	6.38E-01	2.12E-01	6.72E-03
3.31E-05	6.55E-01	2.18E-01	6.90E-03
3.41E-05	6.72E-01	2.23E-01	7.07E-03
3.51E-05	6.89E-01	2.29E-01	7.25E-03
3.62E-05	7.06E-01	2.35E-01	7.44E-03
3.73E-05	7.25E-01	2.42E-01	7.63E-03
3.84E-05	7.43E-01	2.48E-01	7.82E-03
3.95E-05	7.62E-01	2.54E-01	8.02E-03

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.07E-05	7.81E-01	2.61E-01	8.22E-03
4.19E-05	8.01E-01	2.68E-01	8.43E-03
4.32E-05	8.21E-01	2.75E-01	8.64E-03
4.45E-05	8.42E-01	2.82E-01	8.86E-03
4.58E-05	8.63E-01	2.90E-01	9.08E-03
4.72E-05	8.84E-01	2.97E-01	9.31E-03
4.86E-05	9.07E-01	3.05E-01	9.55E-03
5.01E-05	9.29E-01	3.13E-01	9.78E-03
5.16E-05	9.53E-01	3.21E-01	1.00E-02
5.31E-05	9.76E-01	3.29E-01	1.03E-02
5.47E-05	1.00E+00	3.38E-01	1.05E-02
5.64E-05	1.03E+00	3.47E-01	1.08E-02
5.81E-05	1.05E+00	3.56E-01	1.11E-02
5.98E-05	1.08E+00	3.65E-01	1.13E-02
6.16E-05	1.10E+00	3.74E-01	1.16E-02
6.34E-05	1.13E+00	3.84E-01	1.19E-02
6.54E-05	1.16E+00	3.94E-01	1.22E-02
6.73E-05	1.19E+00	4.04E-01	1.25E-02
6.93E-05	1.22E+00	4.14E-01	1.28E-02
7.14E-05	1.25E+00	4.25E-01	1.31E-02
7.36E-05	1.28E+00	4.36E-01	1.34E-02
7.58E-05	1.31E+00	4.47E-01	1.38E-02
7.80E-05	1.34E+00	4.58E-01	1.41E-02
8.04E-05	1.37E+00	4.70E-01	1.44E-02
8.28E-05	1.40E+00	4.82E-01	1.48E-02
8.53E-05	1.44E+00	4.94E-01	1.51E-02
8.78E-05	1.47E+00	5.07E-01	1.55E-02
9.05E-05	1.51E+00	5.19E-01	1.59E-02
9.32E-05	1.55E+00	5.33E-01	1.63E-02
9.60E-05	1.58E+00	5.46E-01	1.67E-02
9.89E-05	1.62E+00	5.60E-01	1.71E-02
1.02E-04	1.66E+00	5.74E-01	1.75E-02
1.05E-04	1.70E+00	5.89E-01	1.79E-02
1.08E-04	1.74E+00	6.04E-01	1.83E-02
1.11E-04	1.78E+00	6.19E-01	1.88E-02
1.15E-04	1.82E+00	6.34E-01	1.92E-02
1.18E-04	1.87E+00	6.50E-01	1.96E-02

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.22E-04	1.91E+00	6.66E-01	2.01E-02
1.25E-04	1.96E+00	6.83E-01	2.06E-02
1.29E-04	2.00E+00	7.00E-01	2.11E-02
1.33E-04	2.05E+00	7.17E-01	2.16E-02
1.37E-04	2.10E+00	7.35E-01	2.21E-02
1.41E-04	2.15E+00	7.53E-01	2.26E-02
1.45E-04	2.20E+00	7.72E-01	2.31E-02
1.50E-04	2.25E+00	7.91E-01	2.36E-02
1.54E-04	2.30E+00	8.11E-01	2.42E-02
1.59E-04	2.35E+00	8.31E-01	2.48E-02
1.63E-04	2.41E+00	8.51E-01	2.53E-02
1.68E-04	2.46E+00	8.72E-01	2.59E-02
1.73E-04	2.52E+00	8.94E-01	2.65E-02
1.79E-04	2.58E+00	9.16E-01	2.71E-02
1.84E-04	2.64E+00	9.39E-01	2.78E-02
1.89E-04	2.70E+00	9.62E-01	2.84E-02
1.95E-04	2.76E+00	9.85E-01	2.90E-02
2.01E-04	2.82E+00	1.01E+00	2.97E-02
2.07E-04	2.89E+00	1.03E+00	3.04E-02
2.13E-04	2.96E+00	1.06E+00	3.11E-02
2.20E-04	3.02E+00	1.09E+00	3.18E-02
2.26E-04	3.09E+00	1.11E+00	3.25E-02
2.33E-04	3.16E+00	1.14E+00	3.33E-02
2.40E-04	3.23E+00	1.17E+00	3.40E-02
2.47E-04	3.31E+00	1.20E+00	3.48E-02
2.55E-04	3.38E+00	1.23E+00	3.56E-02
2.62E-04	3.46E+00	1.26E+00	3.64E-02
2.70E-04	3.54E+00	1.29E+00	3.72E-02
2.78E-04	3.62E+00	1.32E+00	3.81E-02
2.86E-04	3.70E+00	1.35E+00	3.89E-02
2.95E-04	3.78E+00	1.38E+00	3.98E-02
3.04E-04	3.86E+00	1.42E+00	4.07E-02
3.13E-04	3.95E+00	1.45E+00	4.16E-02
3.22E-04	4.04E+00	1.49E+00	4.25E-02
3.32E-04	4.13E+00	1.52E+00	4.34E-02
3.42E-04	4.22E+00	1.56E+00	4.44E-02
3.52E-04	4.31E+00	1.59E+00	4.54E-02

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.63E-04	4.41E+00	1.63E+00	4.64E-02
3.74E-04	4.50E+00	1.67E+00	4.74E-02
3.85E-04	4.60E+00	1.71E+00	4.85E-02
3.97E-04	4.71E+00	1.75E+00	4.95E-02
4.08E-04	4.81E+00	1.80E+00	5.06E-02
4.21E-04	4.92E+00	1.84E+00	5.17E-02
4.33E-04	5.02E+00	1.89E+00	5.29E-02
4.46E-04	5.13E+00	1.93E+00	5.40E-02
4.60E-04	5.25E+00	1.98E+00	5.52E-02
4.74E-04	5.36E+00	2.03E+00	5.64E-02
4.88E-04	5.48E+00	2.07E+00	5.77E-02
5.02E-04	5.60E+00	2.12E+00	5.89E-02
5.17E-04	5.72E+00	2.18E+00	6.02E-02
5.33E-04	5.85E+00	2.23E+00	6.15E-02
5.49E-04	5.97E+00	2.28E+00	6.29E-02
5.65E-04	6.10E+00	2.34E+00	6.42E-02
5.82E-04	6.24E+00	2.39E+00	6.56E-02
6.00E-04	6.37E+00	2.45E+00	6.71E-02
6.18E-04	6.51E+00	2.51E+00	6.85E-02
6.36E-04	6.65E+00	2.57E+00	7.00E-02
6.55E-04	6.79E+00	2.63E+00	7.15E-02
6.75E-04	6.94E+00	2.69E+00	7.30E-02
6.95E-04	7.09E+00	2.76E+00	7.46E-02
7.16E-04	7.24E+00	2.82E+00	7.62E-02
7.38E-04	7.39E+00	2.89E+00	7.78E-02
7.60E-04	7.55E+00	2.96E+00	7.94E-02
7.83E-04	7.71E+00	3.03E+00	8.11E-02
8.06E-04	7.87E+00	3.10E+00	8.29E-02
8.30E-04	8.04E+00	3.17E+00	8.46E-02
8.55E-04	8.21E+00	3.25E+00	8.64E-02
8.81E-04	8.38E+00	3.33E+00	8.82E-02
9.07E-04	8.56E+00	3.41E+00	9.01E-02
9.21E-04	8.65E+00	3.45E+00	9.11E-02
9.35E-04	8.74E+00	3.49E+00	9.20E-02
9.49E-04	8.84E+00	3.53E+00	9.30E-02
9.63E-04	8.93E+00	3.57E+00	9.40E-02
9.69E-04	8.97E+00	3.59E+00	9.44E-02

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
9.77E-04	9.02E+00	3.61E+00	9.49E-02
9.84E-04	9.07E+00	3.63E+00	9.54E-02
9.91E-04	9.12E+00	3.66E+00	9.59E-02
9.98E-04	9.16E+00	3.68E+00	9.64E-02
1.01E-03	9.21E+00	3.70E+00	9.69E-02
1.02E-03	9.31E+00	3.74E+00	9.80E-02
1.04E-03	9.41E+00	3.79E+00	9.90E-02
1.05E-03	9.50E+00	3.83E+00	1.00E-01
1.07E-03	9.60E+00	3.88E+00	1.01E-01
1.08E-03	9.70E+00	3.92E+00	1.02E-01
1.10E-03	9.81E+00	3.97E+00	1.03E-01
1.12E-03	9.91E+00	4.02E+00	1.04E-01
1.13E-03	1.00E+01	4.06E+00	1.05E-01
1.15E-03	1.01E+01	4.11E+00	1.06E-01
1.17E-03	1.02E+01	4.16E+00	1.08E-01
1.18E-03	1.03E+01	4.21E+00	1.09E-01
1.20E-03	1.04E+01	4.26E+00	1.10E-01
1.22E-03	1.05E+01	4.31E+00	1.11E-01
1.24E-03	1.07E+01	4.36E+00	1.12E-01
1.26E-03	1.08E+01	4.41E+00	1.13E-01
1.27E-03	1.09E+01	4.46E+00	1.14E-01
1.29E-03	1.10E+01	4.52E+00	1.16E-01
1.31E-03	1.11E+01	4.57E+00	1.17E-01
1.33E-03	1.12E+01	4.62E+00	1.18E-01
1.35E-03	1.13E+01	4.68E+00	1.19E-01
1.37E-03	1.14E+01	4.73E+00	1.20E-01
1.39E-03	1.16E+01	4.79E+00	1.22E-01
1.41E-03	1.17E+01	4.85E+00	1.23E-01
1.43E-03	1.18E+01	4.91E+00	1.24E-01
1.46E-03	1.19E+01	4.96E+00	1.26E-01
1.48E-03	1.21E+01	5.02E+00	1.27E-01
1.50E-03	1.22E+01	5.08E+00	1.28E-01
1.52E-03	1.23E+01	5.14E+00	1.29E-01
1.54E-03	1.24E+01	5.20E+00	1.31E-01
1.57E-03	1.26E+01	5.26E+00	1.32E-01
1.59E-03	1.28E+01	5.39E+00	1.35E-01
1.61E-03	1.31E+01	5.54E+00	1.38E-01

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.64E-03	1.33E+01	5.60E+00	1.39E-01
1.66E-03	1.33E+01	5.62E+00	1.40E-01
1.69E-03	1.34E+01	5.67E+00	1.41E-01
1.71E-03	1.35E+01	5.73E+00	1.42E-01
1.74E-03	1.36E+01	5.77E+00	1.43E-01
1.76E-03	1.37E+01	5.80E+00	1.44E-01
1.79E-03	1.38E+01	5.87E+00	1.45E-01
1.82E-03	1.39E+01	5.94E+00	1.47E-01
1.84E-03	1.41E+01	6.01E+00	1.48E-01
1.87E-03	1.43E+01	6.11E+00	1.50E-01
1.90E-03	1.46E+01	6.31E+00	1.54E-01
1.93E-03	1.49E+01	6.45E+00	1.57E-01
1.96E-03	1.49E+01	6.42E+00	1.57E-01
1.99E-03	1.50E+01	6.48E+00	1.58E-01
2.02E-03	1.51E+01	6.55E+00	1.59E-01
2.08E-03	1.54E+01	6.66E+00	1.62E-01
2.14E-03	1.56E+01	6.77E+00	1.64E-01
2.20E-03	1.59E+01	6.93E+00	1.68E-01
2.27E-03	1.62E+01	7.09E+00	1.71E-01
2.34E-03	1.66E+01	7.25E+00	1.74E-01
2.41E-03	1.69E+01	7.42E+00	1.78E-01
2.48E-03	1.72E+01	7.60E+00	1.81E-01
2.55E-03	1.76E+01	7.78E+00	1.85E-01
2.63E-03	1.79E+01	7.96E+00	1.89E-01
2.71E-03	1.83E+01	8.15E+00	1.93E-01
2.79E-03	1.87E+01	8.35E+00	1.97E-01
2.87E-03	1.91E+01	8.55E+00	2.00E-01
2.96E-03	1.94E+01	8.75E+00	2.05E-01
3.05E-03	1.98E+01	8.96E+00	2.09E-01
3.14E-03	2.02E+01	9.17E+00	2.13E-01
3.23E-03	2.07E+01	9.41E+00	2.18E-01
3.33E-03	2.11E+01	9.63E+00	2.22E-01
3.43E-03	2.15E+01	9.85E+00	2.26E-01
3.53E-03	2.19E+01	1.01E+01	2.31E-01
3.64E-03	2.23E+01	1.03E+01	2.35E-01
3.75E-03	2.29E+01	1.06E+01	2.41E-01
3.81E-03	2.31E+01	1.08E+01	2.43E-01

Nongestational Lifetime Average				Nongestational Lifetime Average				Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)	Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)	Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.86E-03	2.32E+01	1.08E+01	2.44E-01	1.06E-02	4.54E+01	2.45E+01	4.78E-01	3.15E-02	9.33E+01	6.14E+01	9.81E-01
3.98E-03	2.36E+01	1.10E+01	2.48E-01	1.09E-02	4.63E+01	2.51E+01	4.87E-01	3.24E-02	9.51E+01	6.30E+01	1.00E+00
4.10E-03	2.40E+01	1.12E+01	2.52E-01	1.12E-02	4.73E+01	2.58E+01	4.98E-01	3.34E-02	9.69E+01	6.46E+01	1.02E+00
4.22E-03	2.44E+01	1.14E+01	2.56E-01	1.15E-02	4.83E+01	2.65E+01	5.08E-01	3.44E-02	9.88E+01	6.62E+01	1.04E+00
4.35E-03	2.48E+01	1.17E+01	2.61E-01	1.19E-02	4.93E+01	2.72E+01	5.19E-01	3.54E-02	1.01E+02	6.79E+01	1.06E+00
4.48E-03	2.53E+01	1.19E+01	2.66E-01	1.22E-02	5.02E+01	2.78E+01	5.28E-01	3.65E-02	1.03E+02	6.97E+01	1.08E+00
4.61E-03	2.58E+01	1.22E+01	2.71E-01	1.26E-02	5.11E+01	2.84E+01	5.38E-01	3.76E-02	1.05E+02	7.15E+01	1.10E+00
4.75E-03	2.63E+01	1.25E+01	2.77E-01	1.30E-02	5.22E+01	2.91E+01	5.49E-01	3.87E-02	1.07E+02	7.33E+01	1.12E+00
4.89E-03	2.68E+01	1.28E+01	2.82E-01	1.34E-02	5.31E+01	2.98E+01	5.59E-01	3.99E-02	1.09E+02	7.52E+01	1.14E+00
5.04E-03	2.75E+01	1.32E+01	2.89E-01	1.38E-02	5.42E+01	3.06E+01	5.70E-01	4.11E-02	1.11E+02	7.71E+01	1.17E+00
5.19E-03	2.82E+01	1.36E+01	2.97E-01	1.42E-02	5.53E+01	3.14E+01	5.82E-01	4.23E-02	1.13E+02	7.91E+01	1.19E+00
5.35E-03	2.89E+01	1.41E+01	3.04E-01	1.46E-02	5.66E+01	3.24E+01	5.95E-01	4.36E-02	1.15E+02	8.12E+01	1.21E+00
5.51E-03	2.96E+01	1.45E+01	3.11E-01	1.50E-02	5.76E+01	3.31E+01	6.07E-01	4.49E-02	1.18E+02	8.33E+01	1.24E+00
5.67E-03	3.04E+01	1.50E+01	3.20E-01	1.55E-02	5.87E+01	3.39E+01	6.18E-01	4.63E-02	1.20E+02	8.54E+01	1.26E+00
5.84E-03	3.10E+01	1.53E+01	3.26E-01	1.60E-02	5.99E+01	3.47E+01	6.30E-01	4.76E-02	1.22E+02	8.77E+01	1.29E+00
5.93E-03	3.13E+01	1.55E+01	3.29E-01	1.64E-02	6.10E+01	3.56E+01	6.42E-01	4.91E-02	1.25E+02	9.00E+01	1.31E+00
6.02E-03	3.16E+01	1.57E+01	3.32E-01	1.69E-02	6.22E+01	3.65E+01	6.55E-01	5.05E-02	1.27E+02	9.24E+01	1.34E+00
6.20E-03	3.22E+01	1.61E+01	3.39E-01	1.74E-02	6.34E+01	3.73E+01	6.67E-01	5.21E-02	1.30E+02	9.47E+01	1.36E+00
6.38E-03	3.29E+01	1.65E+01	3.46E-01	1.80E-02	6.46E+01	3.83E+01	6.80E-01	5.36E-02	1.32E+02	9.71E+01	1.39E+00
6.57E-03	3.34E+01	1.68E+01	3.51E-01	1.85E-02	6.59E+01	3.92E+01	6.93E-01	5.52E-02	1.34E+02	9.95E+01	1.41E+00
6.77E-03	3.40E+01	1.72E+01	3.58E-01	1.91E-02	6.71E+01	4.02E+01	7.06E-01	5.69E-02	1.37E+02	1.02E+02	1.44E+00
6.98E-03	3.45E+01	1.75E+01	3.63E-01	1.96E-02	6.88E+01	4.15E+01	7.24E-01	5.86E-02	1.40E+02	1.05E+02	1.47E+00
7.18E-03	3.54E+01	1.80E+01	3.72E-01	2.02E-02	7.01E+01	4.25E+01	7.38E-01	6.03E-02	1.43E+02	1.08E+02	1.50E+00
7.40E-03	3.61E+01	1.85E+01	3.80E-01	2.08E-02	7.14E+01	4.35E+01	7.52E-01	6.22E-02	1.45E+02	1.10E+02	1.53E+00
7.51E-03	3.64E+01	1.87E+01	3.83E-01	2.14E-02	7.26E+01	4.44E+01	7.64E-01	6.40E-02	1.48E+02	1.13E+02	1.56E+00
7.62E-03	3.68E+01	1.89E+01	3.87E-01	2.21E-02	7.40E+01	4.55E+01	7.79E-01	6.59E-02	1.51E+02	1.16E+02	1.59E+00
7.85E-03	3.75E+01	1.93E+01	3.94E-01	2.28E-02	7.55E+01	4.67E+01	7.94E-01	6.79E-02	1.54E+02	1.19E+02	1.62E+00
8.09E-03	3.82E+01	1.98E+01	4.02E-01	2.34E-02	7.69E+01	4.78E+01	8.10E-01	7.00E-02	1.57E+02	1.22E+02	1.65E+00
8.33E-03	3.89E+01	2.02E+01	4.09E-01	2.41E-02	7.85E+01	4.91E+01	8.26E-01	7.21E-02	1.60E+02	1.26E+02	1.69E+00
8.58E-03	3.96E+01	2.07E+01	4.17E-01	2.49E-02	8.00E+01	5.04E+01	8.42E-01	7.42E-02	1.63E+02	1.29E+02	1.72E+00
8.71E-03	4.00E+01	2.10E+01	4.21E-01	2.56E-02	8.16E+01	5.16E+01	8.59E-01	7.64E-02	1.66E+02	1.32E+02	1.75E+00
8.84E-03	4.04E+01	2.12E+01	4.25E-01	2.64E-02	8.32E+01	5.30E+01	8.76E-01	7.87E-02	1.70E+02	1.36E+02	1.79E+00
9.10E-03	4.12E+01	2.17E+01	4.34E-01	2.72E-02	8.48E+01	5.43E+01	8.93E-01	8.11E-02	1.73E+02	1.39E+02	1.82E+00
9.37E-03	4.20E+01	2.23E+01	4.42E-01	2.80E-02	8.64E+01	5.56E+01	9.09E-01	8.35E-02	1.76E+02	1.43E+02	1.86E+00
9.66E-03	4.29E+01	2.28E+01	4.51E-01	2.88E-02	8.81E+01	5.70E+01	9.27E-01	8.60E-02	1.80E+02	1.47E+02	1.89E+00
9.94E-03	4.37E+01	2.34E+01	4.60E-01	2.97E-02	8.98E+01	5.85E+01	9.45E-01	8.86E-02	1.84E+02	1.51E+02	1.93E+00
1.02E-02	4.46E+01	2.39E+01	4.69E-01	3.06E-02	9.15E+01	5.99E+01	9.63E-01	9.13E-02	1.87E+02	1.55E+02	1.97E+00

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
9.40E-02	1.91E+02	1.59E+02	2.01E+00
9.68E-02	1.95E+02	1.63E+02	2.05E+00
9.97E-02	1.98E+02	1.68E+02	2.09E+00
1.03E-01	2.02E+02	1.72E+02	2.13E+00
1.06E-01	2.06E+02	1.77E+02	2.17E+00
1.09E-01	2.10E+02	1.81E+02	2.21E+00
1.12E-01	2.14E+02	1.86E+02	2.26E+00
1.16E-01	2.19E+02	1.91E+02	2.30E+00
1.19E-01	2.23E+02	1.96E+02	2.35E+00
1.23E-01	2.27E+02	2.02E+02	2.39E+00
1.26E-01	2.32E+02	2.07E+02	2.44E+00
1.30E-01	2.36E+02	2.12E+02	2.48E+00
1.34E-01	2.41E+02	2.18E+02	2.53E+00
1.38E-01	2.45E+02	2.24E+02	2.58E+00
1.42E-01	2.50E+02	2.30E+02	2.63E+00
1.46E-01	2.55E+02	2.36E+02	2.69E+00
1.51E-01	2.60E+02	2.43E+02	2.74E+00
1.55E-01	2.65E+02	2.49E+02	2.79E+00
1.60E-01	2.71E+02	2.56E+02	2.85E+00
1.65E-01	2.76E+02	2.63E+02	2.90E+00
1.70E-01	2.81E+02	2.70E+02	2.96E+00
1.75E-01	2.87E+02	2.77E+02	3.02E+00
1.80E-01	2.93E+02	2.85E+02	3.08E+00
1.86E-01	2.98E+02	2.92E+02	3.14E+00
1.91E-01	3.04E+02	3.00E+02	3.20E+00
1.97E-01	3.10E+02	3.08E+02	3.26E+00
2.03E-01	3.16E+02	3.17E+02	3.33E+00
2.09E-01	3.23E+02	3.25E+02	3.39E+00
2.15E-01	3.29E+02	3.34E+02	3.46E+00
2.22E-01	3.35E+02	3.43E+02	3.53E+00
2.28E-01	3.42E+02	3.53E+02	3.60E+00
2.35E-01	3.49E+02	3.62E+02	3.67E+00
2.42E-01	3.56E+02	3.72E+02	3.74E+00
2.49E-01	3.63E+02	3.82E+02	3.82E+00
2.57E-01	3.70E+02	3.93E+02	3.89E+00
2.65E-01	3.77E+02	4.03E+02	3.97E+00
2.72E-01	3.85E+02	4.14E+02	4.05E+00

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
2.81E-01	3.93E+02	4.26E+02	4.13E+00
2.89E-01	4.00E+02	4.38E+02	4.21E+00
2.98E-01	4.08E+02	4.50E+02	4.30E+00
3.07E-01	4.16E+02	4.62E+02	4.38E+00
3.16E-01	4.25E+02	4.75E+02	4.47E+00
3.25E-01	4.33E+02	4.88E+02	4.56E+00
3.35E-01	4.42E+02	5.01E+02	4.65E+00
3.45E-01	4.51E+02	5.15E+02	4.74E+00
3.56E-01	4.60E+02	5.29E+02	4.84E+00
3.66E-01	4.69E+02	5.44E+02	4.94E+00
3.77E-01	4.78E+02	5.59E+02	5.03E+00
3.89E-01	4.88E+02	5.74E+02	5.14E+00
4.00E-01	4.98E+02	5.90E+02	5.24E+00
4.12E-01	5.08E+02	6.07E+02	5.34E+00
4.25E-01	5.18E+02	6.23E+02	5.45E+00
4.37E-01	5.28E+02	6.41E+02	5.56E+00
4.50E-01	5.39E+02	6.58E+02	5.67E+00
4.64E-01	5.50E+02	6.77E+02	5.79E+00
4.78E-01	5.61E+02	6.96E+02	5.90E+00
4.92E-01	5.72E+02	7.15E+02	6.02E+00
5.07E-01	5.84E+02	7.35E+02	6.14E+00
5.22E-01	5.96E+02	7.55E+02	6.27E+00
5.38E-01	6.08E+02	7.76E+02	6.40E+00
5.54E-01	6.20E+02	7.98E+02	6.53E+00
5.71E-01	6.33E+02	8.20E+02	6.66E+00
5.88E-01	6.46E+02	8.43E+02	6.79E+00
6.05E-01	6.59E+02	8.67E+02	6.93E+00
6.23E-01	6.72E+02	8.91E+02	7.07E+00
6.42E-01	6.86E+02	9.16E+02	7.22E+00
6.61E-01	7.00E+02	9.42E+02	7.37E+00
6.81E-01	7.14E+02	9.68E+02	7.52E+00
7.02E-01	7.29E+02	9.95E+02	7.67E+00
7.23E-01	7.44E+02	1.02E+03	7.83E+00
7.44E-01	7.59E+02	1.05E+03	7.99E+00
7.67E-01	7.75E+02	1.08E+03	8.15E+00
7.90E-01	7.91E+02	1.11E+03	8.32E+00
8.13E-01	8.07E+02	1.14E+03	8.49E+00

Nongestational Lifetime Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
8.38E-01	8.24E+02	1.18E+03	8.67E+00
8.63E-01	8.41E+02	1.21E+03	8.85E+00
8.89E-01	8.58E+02	1.24E+03	9.03E+00
9.16E-01	8.76E+02	1.28E+03	9.22E+00
9.43E-01	8.94E+02	1.31E+03	9.41E+00
9.71E-01	9.13E+02	1.35E+03	9.60E+00
1.00E+00	9.32E+02	1.39E+03	9.80E+00
1.03E+00	9.51E+02	1.43E+03	1.00E+01
1.06E+00	9.71E+02	1.47E+03	1.02E+01
1.09E+00	9.91E+02	1.51E+03	1.04E+01
1.13E+00	1.01E+03	1.55E+03	1.06E+01
1.16E+00	1.03E+03	1.60E+03	1.09E+01
1.19E+00	1.05E+03	1.64E+03	1.11E+01
1.23E+00	1.08E+03	1.69E+03	1.13E+01
1.27E+00	1.10E+03	1.74E+03	1.16E+01
1.31E+00	1.12E+03	1.79E+03	1.18E+01
1.34E+00	1.15E+03	1.84E+03	1.21E+01
1.38E+00	1.17E+03	1.89E+03	1.23E+01
1.43E+00	1.20E+03	1.94E+03	1.26E+01
1.47E+00	1.22E+03	2.00E+03	1.29E+01
1.51E+00	1.25E+03	2.06E+03	1.31E+01
1.56E+00	1.27E+03	2.12E+03	1.34E+01
1.61E+00	1.30E+03	2.18E+03	1.37E+01
1.65E+00	1.33E+03	2.24E+03	1.40E+01
1.70E+00	1.36E+03	2.30E+03	1.43E+01
1.75E+00	1.39E+03	2.37E+03	1.46E+01
1.81E+00	1.42E+03	2.44E+03	1.49E+01
1.86E+00	1.45E+03	2.51E+03	1.52E+01
1.92E+00	1.48E+03	2.58E+03	1.56E+01
1.97E+00	1.51E+03	2.65E+03	1.59E+01
2.03E+00	1.54E+03	2.73E+03	1.62E+01
2.09E+00	1.58E+03	2.80E+03	1.66E+01
2.16E+00	1.61E+03	2.89E+03	1.70E+01
2.22E+00	1.65E+03	2.97E+03	1.73E+01
2.29E+00	1.68E+03	3.05E+03	1.77E+01
2.36E+00	1.72E+03	3.14E+03	1.81E+01
2.43E+00	1.76E+03	3.23E+03	1.85E+01

Nongestational Lifetime Average

Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
2.50E+00	1.80E+03	3.32E+03	1.89E+01
2.58E+00	1.84E+03	3.42E+03	1.93E+01
2.65E+00	1.88E+03	3.52E+03	1.97E+01
2.73E+00	1.92E+03	3.62E+03	2.02E+01
2.82E+00	1.96E+03	3.73E+03	2.06E+01
2.90E+00	2.00E+03	3.83E+03	2.11E+01
2.99E+00	2.05E+03	3.94E+03	2.16E+01
3.08E+00	2.09E+03	4.06E+03	2.20E+01
3.17E+00	2.14E+03	4.17E+03	2.25E+01
3.26E+00	2.19E+03	4.30E+03	2.30E+01
3.36E+00	2.24E+03	4.42E+03	2.36E+01
3.46E+00	2.29E+03	4.55E+03	2.41E+01
3.57E+00	2.34E+03	4.68E+03	2.46E+01
3.67E+00	2.39E+03	4.81E+03	2.52E+01
3.78E+00	2.45E+03	4.95E+03	2.58E+01
3.90E+00	2.51E+03	5.10E+03	2.64E+01
4.01E+00	2.56E+03	5.25E+03	2.70E+01
4.13E+00	2.62E+03	5.40E+03	2.76E+01
4.26E+00	2.68E+03	5.55E+03	2.82E+01
4.39E+00	2.74E+03	5.72E+03	2.89E+01
4.52E+00	2.81E+03	5.88E+03	2.95E+01
4.65E+00	2.87E+03	6.05E+03	3.02E+01
4.79E+00	2.94E+03	6.23E+03	3.09E+01
4.94E+00	3.01E+03	6.41E+03	3.16E+01
5.08E+00	3.08E+03	6.60E+03	3.24E+01
5.24E+00	3.15E+03	6.79E+03	3.31E+01
5.39E+00	3.22E+03	6.99E+03	3.39E+01
5.56E+00	3.30E+03	7.19E+03	3.47E+01
5.72E+00	3.38E+03	7.40E+03	3.55E+01
5.89E+00	3.46E+03	7.61E+03	3.64E+01
6.07E+00	3.54E+03	7.84E+03	3.72E+01
6.25E+00	3.62E+03	8.07E+03	3.81E+01
6.44E+00	3.71E+03	8.30E+03	3.90E+01
6.63E+00	3.80E+03	8.54E+03	3.99E+01
6.83E+00	3.89E+03	8.79E+03	4.09E+01
7.04E+00	3.98E+03	9.05E+03	4.19E+01
7.25E+00	4.08E+03	9.31E+03	4.29E+01

Nongestational Lifetime Average

Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
7.47E+00	4.18E+03	9.59E+03	4.39E+01
7.69E+00	4.28E+03	9.87E+03	4.50E+01
7.92E+00	4.38E+03	1.02E+04	4.61E+01
8.16E+00	4.49E+03	1.05E+04	4.72E+01
8.40E+00	4.60E+03	1.08E+04	4.84E+01
8.66E+00	4.71E+03	1.11E+04	4.95E+01
8.92E+00	4.82E+03	1.14E+04	5.08E+01
9.18E+00	4.94E+03	1.17E+04	5.20E+01
9.46E+00	5.07E+03	1.21E+04	5.33E+01
9.74E+00	5.19E+03	1.24E+04	5.46E+01
1.00E+01	5.32E+03	1.28E+04	5.60E+01
1.06E+01	5.58E+03	1.35E+04	5.88E+01
1.13E+01	5.86E+03	1.43E+04	6.17E+01
1.20E+01	6.16E+03	1.52E+04	6.48E+01
1.27E+01	6.47E+03	1.61E+04	6.81E+01
1.34E+01	6.80E+03	1.70E+04	7.15E+01
1.42E+01	7.14E+03	1.80E+04	7.52E+01
1.51E+01	7.51E+03	1.91E+04	7.90E+01
1.60E+01	7.90E+03	2.02E+04	8.31E+01
1.70E+01	8.31E+03	2.14E+04	8.74E+01
1.80E+01	8.74E+03	2.26E+04	9.20E+01
1.90E+01	9.20E+03	2.40E+04	9.68E+01
2.02E+01	9.68E+03	2.54E+04	1.02E+02
2.14E+01	1.02E+04	2.69E+04	1.07E+02
2.27E+01	1.07E+04	2.85E+04	1.13E+02
2.40E+01	1.13E+04	3.01E+04	1.19E+02
2.55E+01	1.19E+04	3.19E+04	1.25E+02
2.70E+01	1.26E+04	3.38E+04	1.32E+02
2.86E+01	1.32E+04	3.58E+04	1.39E+02
3.04E+01	1.40E+04	3.79E+04	1.47E+02
3.22E+01	1.47E+04	4.01E+04	1.55E+02
3.41E+01	1.55E+04	4.25E+04	1.63E+02
3.62E+01	1.64E+04	4.50E+04	1.72E+02
3.83E+01	1.73E+04	4.77E+04	1.82E+02
4.06E+01	1.82E+04	5.05E+04	1.92E+02
4.31E+01	1.92E+04	5.34E+04	2.02E+02
4.57E+01	2.03E+04	5.66E+04	2.14E+02

Nongestational Lifetime Average

Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.84E+01	2.14E+04	5.99E+04	2.26E+02
5.13E+01	2.27E+04	6.34E+04	2.38E+02
5.44E+01	2.39E+04	6.71E+04	2.52E+02
5.76E+01	2.53E+04	7.11E+04	2.66E+02
6.11E+01	2.67E+04	7.52E+04	2.81E+02
6.48E+01	2.82E+04	7.97E+04	2.97E+02
6.86E+01	2.98E+04	8.43E+04	3.14E+02
7.28E+01	3.15E+04	8.93E+04	3.32E+02
7.71E+01	3.33E+04	9.45E+04	3.51E+02
8.18E+01	3.53E+04	1.00E+05	3.71E+02
8.67E+01	3.73E+04	1.06E+05	3.92E+02
9.19E+01	3.94E+04	1.12E+05	4.15E+02
9.74E+01	4.17E+04	1.19E+05	4.39E+02
1.03E+02	4.41E+04	1.25E+05	4.64E+02
1.09E+02	4.67E+04	1.33E+05	4.91E+02
1.16E+02	4.94E+04	1.40E+05	5.20E+02
1.23E+02	5.23E+04	1.48E+05	5.50E+02
1.30E+02	5.54E+04	1.57E+05	5.82E+02
1.38E+02	5.86E+04	1.66E+05	6.17E+02
1.46E+02	6.20E+04	1.76E+05	6.53E+02

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E.4.2. Nongestational 5-Year Peak Average

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.03E-09	6.14E-05	1.92E-05	6.46E-07
1.09E-09	6.51E-05	2.03E-05	6.85E-07
1.16E-09	6.90E-05	2.15E-05	7.26E-07
1.23E-09	7.32E-05	2.28E-05	7.69E-07
1.30E-09	7.75E-05	2.42E-05	8.15E-07
1.38E-09	8.22E-05	2.56E-05	8.64E-07
1.46E-09	8.71E-05	2.72E-05	9.16E-07
1.55E-09	9.23E-05	2.88E-05	9.71E-07
1.64E-09	9.79E-05	3.05E-05	1.03E-06
1.74E-09	1.04E-04	3.24E-05	1.09E-06
1.84E-09	1.10E-04	3.43E-05	1.16E-06
1.95E-09	1.17E-04	3.64E-05	1.23E-06
2.07E-09	1.24E-04	3.85E-05	1.30E-06
2.20E-09	1.31E-04	4.08E-05	1.38E-06
2.33E-09	1.39E-04	4.33E-05	1.46E-06
2.47E-09	1.47E-04	4.59E-05	1.55E-06
2.62E-09	1.56E-04	4.86E-05	1.64E-06
2.77E-09	1.65E-04	5.15E-05	1.74E-06
2.94E-09	1.75E-04	5.46E-05	1.84E-06
3.12E-09	1.86E-04	5.79E-05	1.95E-06
3.30E-09	1.97E-04	6.14E-05	2.07E-06
3.50E-09	2.09E-04	6.51E-05	2.19E-06
3.71E-09	2.21E-04	6.90E-05	2.32E-06
3.93E-09	2.34E-04	7.31E-05	2.46E-06
4.17E-09	2.48E-04	7.75E-05	2.61E-06
4.42E-09	2.63E-04	8.21E-05	2.77E-06
4.68E-09	2.79E-04	8.70E-05	2.93E-06
4.97E-09	2.96E-04	9.22E-05	3.11E-06
5.26E-09	3.13E-04	9.78E-05	3.29E-06
5.58E-09	3.32E-04	1.04E-04	3.49E-06
5.91E-09	3.52E-04	1.10E-04	3.70E-06
6.27E-09	3.73E-04	1.16E-04	3.92E-06
6.65E-09	3.95E-04	1.23E-04	4.16E-06

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
7.04E-09	4.19E-04	1.31E-04	4.41E-06
7.47E-09	4.44E-04	1.39E-04	4.67E-06
7.92E-09	4.71E-04	1.47E-04	4.95E-06
8.39E-09	4.99E-04	1.56E-04	5.24E-06
8.89E-09	5.29E-04	1.65E-04	5.56E-06
9.43E-09	5.60E-04	1.75E-04	5.89E-06
9.99E-09	5.94E-04	1.85E-04	6.24E-06
1.06E-08	6.29E-04	1.96E-04	6.62E-06
1.12E-08	6.67E-04	2.08E-04	7.01E-06
1.19E-08	7.07E-04	2.21E-04	7.43E-06
1.26E-08	7.49E-04	2.34E-04	7.88E-06
1.34E-08	7.94E-04	2.48E-04	8.35E-06
1.42E-08	8.41E-04	2.63E-04	8.84E-06
1.50E-08	8.91E-04	2.78E-04	9.37E-06
1.59E-08	9.45E-04	2.95E-04	9.93E-06
1.69E-08	1.00E-03	3.13E-04	1.05E-05
1.79E-08	1.06E-03	3.31E-04	1.12E-05
1.90E-08	1.12E-03	3.51E-04	1.18E-05
2.01E-08	1.19E-03	3.72E-04	1.25E-05
2.13E-08	1.26E-03	3.94E-04	1.33E-05
2.26E-08	1.34E-03	4.18E-04	1.41E-05
2.39E-08	1.42E-03	4.43E-04	1.49E-05
2.54E-08	1.50E-03	4.69E-04	1.58E-05
2.69E-08	1.59E-03	4.97E-04	1.67E-05
2.85E-08	1.69E-03	5.27E-04	1.77E-05
3.02E-08	1.79E-03	5.58E-04	1.88E-05
3.20E-08	1.89E-03	5.92E-04	1.99E-05
3.40E-08	2.01E-03	6.27E-04	2.11E-05
3.60E-08	2.13E-03	6.64E-04	2.24E-05
3.82E-08	2.25E-03	7.04E-04	2.37E-05
4.05E-08	2.39E-03	7.46E-04	2.51E-05
4.29E-08	2.53E-03	7.91E-04	2.66E-05
4.55E-08	2.68E-03	8.38E-04	2.82E-05
4.82E-08	2.84E-03	8.88E-04	2.99E-05
5.11E-08	3.01E-03	9.40E-04	3.16E-05
5.41E-08	3.19E-03	9.96E-04	3.35E-05

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
5.74E-08	3.38E-03	1.06E-03	3.55E-05
6.08E-08	3.58E-03	1.12E-03	3.76E-05
6.45E-08	3.79E-03	1.19E-03	3.99E-05
6.84E-08	4.02E-03	1.26E-03	4.22E-05
7.25E-08	4.25E-03	1.33E-03	4.47E-05
7.68E-08	4.51E-03	1.41E-03	4.74E-05
8.14E-08	4.77E-03	1.49E-03	5.02E-05
8.63E-08	5.06E-03	1.58E-03	5.32E-05
9.15E-08	5.36E-03	1.68E-03	5.63E-05
9.70E-08	5.67E-03	1.78E-03	5.97E-05
1.03E-07	6.01E-03	1.88E-03	6.32E-05
1.09E-07	6.37E-03	1.99E-03	6.69E-05
1.15E-07	6.74E-03	2.11E-03	7.09E-05
1.22E-07	7.14E-03	2.24E-03	7.51E-05
1.30E-07	7.56E-03	2.37E-03	7.95E-05
1.38E-07	8.01E-03	2.51E-03	8.42E-05
1.46E-07	8.48E-03	2.66E-03	8.92E-05
1.55E-07	8.98E-03	2.82E-03	9.45E-05
1.64E-07	9.51E-03	2.98E-03	1.00E-04
1.74E-07	1.01E-02	3.16E-03	1.06E-04
1.84E-07	1.07E-02	3.34E-03	1.12E-04
1.95E-07	1.13E-02	3.54E-03	1.19E-04
2.07E-07	1.20E-02	3.75E-03	1.26E-04
2.19E-07	1.27E-02	3.97E-03	1.33E-04
2.32E-07	1.34E-02	4.21E-03	1.41E-04
2.46E-07	1.42E-02	4.46E-03	1.49E-04
2.61E-07	1.50E-02	4.72E-03	1.58E-04
2.77E-07	1.59E-02	5.00E-03	1.67E-04
2.93E-07	1.68E-02	5.29E-03	1.77E-04
3.11E-07	1.78E-02	5.60E-03	1.87E-04
3.30E-07	1.89E-02	5.93E-03	1.98E-04
3.49E-07	2.00E-02	6.28E-03	2.10E-04
3.70E-07	2.11E-02	6.65E-03	2.22E-04
3.93E-07	2.24E-02	7.04E-03	2.35E-04
4.16E-07	2.37E-02	7.45E-03	2.49E-04
4.41E-07	2.51E-02	7.89E-03	2.63E-04

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.68E-07	2.65E-02	8.35E-03	2.79E-04
4.96E-07	2.81E-02	8.83E-03	2.95E-04
5.25E-07	2.97E-02	9.35E-03	3.12E-04
5.57E-07	3.14E-02	9.90E-03	3.30E-04
5.90E-07	3.32E-02	1.05E-02	3.49E-04
6.26E-07	3.51E-02	1.11E-02	3.69E-04
6.63E-07	3.72E-02	1.17E-02	3.91E-04
7.03E-07	3.93E-02	1.24E-02	4.13E-04
7.45E-07	4.16E-02	1.31E-02	4.37E-04
7.90E-07	4.40E-02	1.39E-02	4.62E-04
8.37E-07	4.65E-02	1.47E-02	4.89E-04
8.88E-07	4.92E-02	1.55E-02	5.17E-04
9.41E-07	5.20E-02	1.64E-02	5.47E-04
9.97E-07	5.50E-02	1.74E-02	5.78E-04
1.01E-06	5.57E-02	1.76E-02	5.86E-04
1.03E-06	5.65E-02	1.79E-02	5.94E-04
1.04E-06	5.73E-02	1.82E-02	6.03E-04
1.06E-06	5.82E-02	1.84E-02	6.11E-04
1.07E-06	5.90E-02	1.87E-02	6.20E-04
1.09E-06	5.98E-02	1.89E-02	6.29E-04
1.11E-06	6.07E-02	1.92E-02	6.38E-04
1.12E-06	6.15E-02	1.95E-02	6.47E-04
1.14E-06	6.24E-02	1.98E-02	6.56E-04
1.16E-06	6.33E-02	2.00E-02	6.65E-04
1.17E-06	6.42E-02	2.03E-02	6.75E-04
1.19E-06	6.51E-02	2.06E-02	6.84E-04
1.21E-06	6.60E-02	2.09E-02	6.94E-04
1.23E-06	6.69E-02	2.12E-02	7.04E-04
1.24E-06	6.79E-02	2.15E-02	7.13E-04
1.26E-06	6.88E-02	2.18E-02	7.24E-04
1.28E-06	6.98E-02	2.21E-02	7.34E-04
1.30E-06	7.08E-02	2.25E-02	7.44E-04
1.32E-06	7.18E-02	2.28E-02	7.55E-04
1.34E-06	7.28E-02	2.31E-02	7.65E-04
1.36E-06	7.38E-02	2.34E-02	7.76E-04
1.38E-06	7.49E-02	2.38E-02	7.87E-04

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.40E-06	7.59E-02	2.41E-02	7.98E-04
1.42E-06	7.70E-02	2.44E-02	8.09E-04
1.44E-06	7.81E-02	2.48E-02	8.21E-04
1.46E-06	7.92E-02	2.51E-02	8.32E-04
1.49E-06	8.03E-02	2.55E-02	8.44E-04
1.53E-06	8.25E-02	2.62E-02	8.68E-04
1.58E-06	8.49E-02	2.70E-02	8.92E-04
1.62E-06	8.73E-02	2.77E-02	9.17E-04
1.67E-06	8.97E-02	2.85E-02	9.43E-04
1.72E-06	9.23E-02	2.93E-02	9.70E-04
1.77E-06	9.48E-02	3.02E-02	9.97E-04
1.83E-06	9.75E-02	3.10E-02	1.02E-03
1.88E-06	1.00E-01	3.19E-02	1.05E-03
1.94E-06	1.03E-01	3.28E-02	1.08E-03
2.00E-06	1.06E-01	3.38E-02	1.11E-03
2.06E-06	1.09E-01	3.47E-02	1.14E-03
2.12E-06	1.12E-01	3.57E-02	1.18E-03
2.18E-06	1.15E-01	3.67E-02	1.21E-03
2.25E-06	1.18E-01	3.77E-02	1.24E-03
2.32E-06	1.22E-01	3.88E-02	1.28E-03
2.39E-06	1.25E-01	3.99E-02	1.31E-03
2.46E-06	1.28E-01	4.10E-02	1.35E-03
2.53E-06	1.32E-01	4.22E-02	1.39E-03
2.61E-06	1.36E-01	4.34E-02	1.43E-03
2.68E-06	1.39E-01	4.46E-02	1.47E-03
2.76E-06	1.43E-01	4.58E-02	1.51E-03
2.85E-06	1.47E-01	4.71E-02	1.55E-03
2.93E-06	1.51E-01	4.84E-02	1.59E-03
3.02E-06	1.55E-01	4.98E-02	1.63E-03
3.11E-06	1.60E-01	5.12E-02	1.68E-03
3.21E-06	1.64E-01	5.26E-02	1.73E-03
3.30E-06	1.69E-01	5.41E-02	1.77E-03
3.40E-06	1.73E-01	5.56E-02	1.82E-03
3.50E-06	1.78E-01	5.71E-02	1.87E-03
3.61E-06	1.83E-01	5.87E-02	1.92E-03
3.72E-06	1.88E-01	6.04E-02	1.97E-03

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.83E-06	1.93E-01	6.20E-02	2.03E-03
3.94E-06	1.98E-01	6.38E-02	2.08E-03
4.06E-06	2.04E-01	6.55E-02	2.14E-03
4.18E-06	2.09E-01	6.73E-02	2.20E-03
4.31E-06	2.15E-01	6.92E-02	2.26E-03
4.44E-06	2.21E-01	7.11E-02	2.32E-03
4.57E-06	2.27E-01	7.31E-02	2.38E-03
4.71E-06	2.33E-01	7.51E-02	2.45E-03
4.85E-06	2.39E-01	7.71E-02	2.51E-03
4.99E-06	2.45E-01	7.92E-02	2.58E-03
5.14E-06	2.52E-01	8.14E-02	2.65E-03
5.30E-06	2.59E-01	8.36E-02	2.72E-03
5.46E-06	2.66E-01	8.59E-02	2.79E-03
5.62E-06	2.73E-01	8.83E-02	2.87E-03
5.79E-06	2.80E-01	9.07E-02	2.94E-03
5.96E-06	2.87E-01	9.31E-02	3.02E-03
6.14E-06	2.95E-01	9.57E-02	3.10E-03
6.33E-06	3.03E-01	9.83E-02	3.18E-03
6.52E-06	3.11E-01	1.01E-01	3.27E-03
6.71E-06	3.19E-01	1.04E-01	3.35E-03
6.91E-06	3.28E-01	1.06E-01	3.44E-03
7.12E-06	3.36E-01	1.09E-01	3.53E-03
7.33E-06	3.45E-01	1.12E-01	3.63E-03
7.55E-06	3.54E-01	1.15E-01	3.72E-03
7.78E-06	3.63E-01	1.18E-01	3.82E-03
8.01E-06	3.73E-01	1.22E-01	3.92E-03
8.25E-06	3.83E-01	1.25E-01	4.02E-03
8.50E-06	3.93E-01	1.28E-01	4.12E-03
8.76E-06	4.03E-01	1.32E-01	4.23E-03
9.02E-06	4.13E-01	1.35E-01	4.34E-03
9.29E-06	4.24E-01	1.39E-01	4.45E-03
9.57E-06	4.35E-01	1.42E-01	4.57E-03
9.86E-06	4.46E-01	1.46E-01	4.69E-03
1.02E-05	4.58E-01	1.50E-01	4.81E-03
1.05E-05	4.69E-01	1.54E-01	4.93E-03
1.08E-05	4.81E-01	1.58E-01	5.06E-03

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.11E-05	4.94E-01	1.62E-01	5.19E-03
1.14E-05	5.06E-01	1.67E-01	5.32E-03
1.18E-05	5.19E-01	1.71E-01	5.45E-03
1.21E-05	5.32E-01	1.75E-01	5.59E-03
1.25E-05	5.46E-01	1.80E-01	5.74E-03
1.29E-05	5.60E-01	1.85E-01	5.88E-03
1.32E-05	5.74E-01	1.90E-01	6.03E-03
1.36E-05	5.88E-01	1.94E-01	6.18E-03
1.41E-05	6.03E-01	1.99E-01	6.34E-03
1.45E-05	6.18E-01	2.05E-01	6.49E-03
1.49E-05	6.34E-01	2.10E-01	6.66E-03
1.54E-05	6.49E-01	2.15E-01	6.82E-03
1.58E-05	6.66E-01	2.21E-01	6.99E-03
1.63E-05	6.82E-01	2.27E-01	7.17E-03
1.68E-05	6.99E-01	2.32E-01	7.34E-03
1.73E-05	7.16E-01	2.38E-01	7.53E-03
1.78E-05	7.34E-01	2.45E-01	7.71E-03
1.83E-05	7.52E-01	2.51E-01	7.90E-03
1.89E-05	7.71E-01	2.57E-01	8.09E-03
1.95E-05	7.89E-01	2.64E-01	8.29E-03
2.00E-05	8.09E-01	2.70E-01	8.50E-03
2.06E-05	8.29E-01	2.77E-01	8.70E-03
2.13E-05	8.49E-01	2.84E-01	8.91E-03
2.19E-05	8.69E-01	2.91E-01	9.13E-03
2.25E-05	8.90E-01	2.99E-01	9.35E-03
2.32E-05	9.12E-01	3.06E-01	9.58E-03
2.39E-05	9.34E-01	3.14E-01	9.81E-03
2.46E-05	9.56E-01	3.22E-01	1.00E-02
2.54E-05	9.79E-01	3.30E-01	1.03E-02
2.61E-05	1.00E+00	3.38E-01	1.05E-02
2.69E-05	1.03E+00	3.47E-01	1.08E-02
2.77E-05	1.05E+00	3.55E-01	1.10E-02
2.86E-05	1.08E+00	3.64E-01	1.13E-02
2.94E-05	1.10E+00	3.73E-01	1.16E-02
3.03E-05	1.13E+00	3.82E-01	1.18E-02
3.12E-05	1.15E+00	3.92E-01	1.21E-02

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.21E-05	1.18E+00	4.02E-01	1.24E-02
3.31E-05	1.21E+00	4.11E-01	1.27E-02
3.41E-05	1.24E+00	4.22E-01	1.30E-02
3.51E-05	1.27E+00	4.32E-01	1.33E-02
3.62E-05	1.30E+00	4.43E-01	1.36E-02
3.73E-05	1.33E+00	4.54E-01	1.39E-02
3.84E-05	1.36E+00	4.65E-01	1.43E-02
3.95E-05	1.39E+00	4.76E-01	1.46E-02
4.07E-05	1.42E+00	4.87E-01	1.49E-02
4.19E-05	1.45E+00	4.99E-01	1.53E-02
4.32E-05	1.49E+00	5.11E-01	1.56E-02
4.45E-05	1.52E+00	5.24E-01	1.60E-02
4.58E-05	1.56E+00	5.36E-01	1.63E-02
4.72E-05	1.59E+00	5.49E-01	1.67E-02
4.86E-05	1.63E+00	5.62E-01	1.71E-02
5.01E-05	1.66E+00	5.76E-01	1.75E-02
5.16E-05	1.70E+00	5.89E-01	1.79E-02
5.31E-05	1.74E+00	6.04E-01	1.83E-02
5.47E-05	1.78E+00	6.18E-01	1.87E-02
5.64E-05	1.82E+00	6.33E-01	1.91E-02
5.81E-05	1.86E+00	6.48E-01	1.95E-02
5.98E-05	1.90E+00	6.63E-01	2.00E-02
6.16E-05	1.94E+00	6.79E-01	2.04E-02
6.34E-05	1.99E+00	6.95E-01	2.09E-02
6.54E-05	2.03E+00	7.11E-01	2.13E-02
6.73E-05	2.08E+00	7.28E-01	2.18E-02
6.93E-05	2.12E+00	7.45E-01	2.23E-02
7.14E-05	2.17E+00	7.62E-01	2.28E-02
7.36E-05	2.22E+00	7.80E-01	2.33E-02
7.58E-05	2.26E+00	7.98E-01	2.38E-02
7.80E-05	2.31E+00	8.17E-01	2.43E-02
8.04E-05	2.36E+00	8.36E-01	2.48E-02
8.28E-05	2.42E+00	8.55E-01	2.54E-02
8.53E-05	2.47E+00	8.75E-01	2.59E-02
8.78E-05	2.52E+00	8.95E-01	2.65E-02
9.05E-05	2.58E+00	9.16E-01	2.70E-02

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
9.32E-05	2.63E+00	9.37E-01	2.76E-02
9.60E-05	2.69E+00	9.58E-01	2.82E-02
9.89E-05	2.75E+00	9.81E-01	2.88E-02
1.02E-04	2.81E+00	1.00E+00	2.95E-02
1.05E-04	2.87E+00	1.03E+00	3.01E-02
1.08E-04	2.93E+00	1.05E+00	3.07E-02
1.11E-04	2.99E+00	1.07E+00	3.14E-02
1.15E-04	3.05E+00	1.10E+00	3.20E-02
1.18E-04	3.12E+00	1.12E+00	3.27E-02
1.22E-04	3.18E+00	1.15E+00	3.34E-02
1.25E-04	3.25E+00	1.17E+00	3.41E-02
1.29E-04	3.32E+00	1.20E+00	3.48E-02
1.33E-04	3.39E+00	1.23E+00	3.55E-02
1.37E-04	3.46E+00	1.26E+00	3.63E-02
1.41E-04	3.53E+00	1.28E+00	3.70E-02
1.45E-04	3.60E+00	1.31E+00	3.78E-02
1.50E-04	3.68E+00	1.34E+00	3.86E-02
1.54E-04	3.75E+00	1.37E+00	3.94E-02
1.59E-04	3.83E+00	1.40E+00	4.02E-02
1.63E-04	3.91E+00	1.43E+00	4.10E-02
1.68E-04	3.99E+00	1.47E+00	4.19E-02
1.73E-04	4.07E+00	1.50E+00	4.27E-02
1.79E-04	4.16E+00	1.53E+00	4.36E-02
1.84E-04	4.24E+00	1.57E+00	4.45E-02
1.89E-04	4.33E+00	1.60E+00	4.55E-02
1.95E-04	4.42E+00	1.64E+00	4.64E-02
2.01E-04	4.51E+00	1.67E+00	4.73E-02
2.07E-04	4.60E+00	1.71E+00	4.83E-02
2.13E-04	4.69E+00	1.75E+00	4.93E-02
2.20E-04	4.79E+00	1.79E+00	5.03E-02
2.26E-04	4.89E+00	1.83E+00	5.13E-02
2.33E-04	4.99E+00	1.87E+00	5.23E-02
2.40E-04	5.09E+00	1.91E+00	5.34E-02
2.47E-04	5.19E+00	1.95E+00	5.45E-02
2.55E-04	5.29E+00	2.00E+00	5.56E-02
2.62E-04	5.40E+00	2.04E+00	5.67E-02

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
2.70E-04	5.51E+00	2.09E+00	5.78E-02
2.78E-04	5.62E+00	2.13E+00	5.90E-02
2.86E-04	5.73E+00	2.18E+00	6.01E-02
2.95E-04	5.85E+00	2.23E+00	6.13E-02
3.04E-04	5.96E+00	2.28E+00	6.26E-02
3.13E-04	6.08E+00	2.33E+00	6.38E-02
3.22E-04	6.20E+00	2.38E+00	6.51E-02
3.32E-04	6.32E+00	2.43E+00	6.63E-02
3.42E-04	6.45E+00	2.48E+00	6.76E-02
3.52E-04	6.57E+00	2.54E+00	6.90E-02
3.63E-04	6.70E+00	2.59E+00	7.03E-02
3.74E-04	6.84E+00	2.65E+00	7.17E-02
3.85E-04	6.97E+00	2.71E+00	7.32E-02
3.97E-04	7.11E+00	2.77E+00	7.46E-02
4.08E-04	7.25E+00	2.83E+00	7.61E-02
4.21E-04	7.39E+00	2.89E+00	7.76E-02
4.33E-04	7.54E+00	2.96E+00	7.91E-02
4.46E-04	7.68E+00	3.02E+00	8.06E-02
4.60E-04	7.83E+00	3.09E+00	8.22E-02
4.74E-04	7.99E+00	3.16E+00	8.38E-02
4.88E-04	8.15E+00	3.23E+00	8.55E-02
5.02E-04	8.30E+00	3.30E+00	8.71E-02
5.17E-04	8.47E+00	3.37E+00	8.88E-02
5.33E-04	8.63E+00	3.45E+00	9.06E-02
5.49E-04	8.80E+00	3.52E+00	9.23E-02
5.65E-04	8.97E+00	3.60E+00	9.41E-02
5.82E-04	9.14E+00	3.68E+00	9.59E-02
6.00E-04	9.32E+00	3.76E+00	9.78E-02
6.18E-04	9.50E+00	3.85E+00	9.97E-02
6.36E-04	9.68E+00	3.93E+00	1.02E-01
6.55E-04	9.87E+00	4.02E+00	1.04E-01
6.75E-04	1.01E+01	4.11E+00	1.06E-01
6.95E-04	1.03E+01	4.20E+00	1.08E-01
7.16E-04	1.05E+01	4.29E+00	1.10E-01
7.38E-04	1.07E+01	4.38E+00	1.12E-01
7.60E-04	1.09E+01	4.48E+00	1.14E-01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
7.83E-04	1.11E+01	4.58E+00	1.16E-01
8.06E-04	1.13E+01	4.68E+00	1.18E-01
8.30E-04	1.15E+01	4.78E+00	1.21E-01
8.55E-04	1.17E+01	4.89E+00	1.23E-01
8.81E-04	1.19E+01	5.00E+00	1.25E-01
9.07E-04	1.22E+01	5.11E+00	1.28E-01
9.21E-04	1.23E+01	5.16E+00	1.29E-01
9.35E-04	1.24E+01	5.22E+00	1.30E-01
9.49E-04	1.25E+01	5.28E+00	1.31E-01
9.63E-04	1.26E+01	5.34E+00	1.33E-01
9.69E-04	1.27E+01	5.36E+00	1.33E-01
9.77E-04	1.28E+01	5.40E+00	1.34E-01
9.84E-04	1.28E+01	5.42E+00	1.34E-01
9.91E-04	1.29E+01	5.45E+00	1.35E-01
9.98E-04	1.29E+01	5.48E+00	1.36E-01
1.01E-03	1.30E+01	5.51E+00	1.36E-01
1.02E-03	1.31E+01	5.58E+00	1.38E-13
1.04E-03	1.32E+01	5.64E+00	1.39E-01
1.05E-03	1.34E+01	5.70E+00	1.40E-01
1.07E-03	1.35E+01	5.76E+00	1.42E-01
1.08E-03	1.36E+01	5.82E+00	1.43E-01
1.10E-03	1.38E+01	5.89E+00	1.44E-01
1.12E-03	1.39E+01	5.95E+00	1.46E-01
1.13E-03	1.40E+01	6.02E+00	1.47E-01
1.15E-03	1.41E+01	6.09E+00	1.48E-01
1.17E-03	1.43E+01	6.15E+00	1.50E-01
1.18E-03	1.44E+01	6.22E+00	1.51E-01
1.20E-03	1.45E+01	6.29E+00	1.53E-01
1.22E-03	1.47E+01	6.36E+00	1.54E-01
1.24E-03	1.48E+01	6.43E+00	1.55E-01
1.26E-03	1.50E+01	6.50E+00	1.57E-01
1.27E-03	1.51E+01	6.57E+00	1.58E-01
1.29E-03	1.52E+01	6.64E+00	1.60E-01
1.31E-03	1.54E+01	6.72E+00	1.61E-01
1.33E-03	1.55E+01	6.79E+00	1.63E-01
1.35E-03	1.57E+01	6.87E+00	1.64E-01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.37E-03	1.58E+01	6.94E+00	1.66E-01
1.39E-03	1.60E+01	7.02E+00	1.68E-01
1.41E-03	1.61E+01	7.10E+00	1.69E-01
1.43E-03	1.63E+01	7.18E+00	1.71E-01
1.46E-03	1.64E+01	7.26E+00	1.72E-01
1.48E-03	1.66E+01	7.34E+00	1.74E-01
1.50E-03	1.67E+01	7.42E+00	1.76E-01
1.52E-03	1.69E+01	7.50E+00	1.77E-01
1.54E-03	1.71E+01	7.58E+00	1.79E-01
1.57E-03	1.72E+01	7.67E+00	1.81E-01
1.59E-03	1.75E+01	7.86E+00	1.84E-01
1.61E-03	1.80E+01	8.23E+00	1.89E-01
1.64E-03	1.83E+01	8.35E+00	1.92E-01
1.66E-03	1.85E+01	8.36E+00	1.94E-01
1.69E-03	1.87E+01	8.43E+00	1.96E-01
1.71E-03	1.90E+01	8.54E+00	2.00E-01
1.74E-03	1.90E+01	8.52E+00	1.99E-01
1.76E-03	1.86E+01	8.38E+00	1.95E-01
1.79E-03	1.87E+01	8.47E+00	1.96E-01
1.82E-03	1.89E+01	8.57E+00	1.98E-01
1.84E-03	1.91E+01	8.66E+00	2.00E-01
1.87E-03	1.93E+01	8.80E+00	2.03E-01
1.90E-03	1.98E+01	9.14E+00	2.07E-01
1.93E-03	2.02E+01	9.51E+00	2.12E-01
1.96E-03	2.03E+01	9.42E+00	2.13E-01
1.99E-03	2.05E+01	9.53E+00	2.15E-01
2.02E-03	2.09E+01	9.67E+00	2.19E-01
2.08E-03	2.10E+01	9.70E+00	2.20E-01
2.14E-03	2.09E+01	9.68E+00	2.20E-01
2.20E-03	2.13E+01	9.90E+00	2.24E-01
2.27E-03	2.17E+01	1.01E+01	2.28E-01
2.34E-03	2.21E+01	1.03E+01	2.32E-01
2.41E-03	2.26E+01	1.06E+01	2.37E-01
2.48E-03	2.30E+01	1.08E+01	2.41E-01
2.55E-03	2.34E+01	1.11E+01	2.45E-01
2.63E-03	2.38E+01	1.13E+01	2.50E-01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
2.71E-03	2.43E+01	1.16E+01	2.55E-01
2.79E-03	2.47E+01	1.18E+01	2.60E-01
2.87E-03	2.52E+01	1.21E+01	2.64E-01
2.96E-03	2.57E+01	1.24E+01	2.69E-01
3.05E-03	2.62E+01	1.26E+01	2.74E-01
3.14E-03	2.66E+01	1.29E+01	2.79E-01
3.23E-03	2.72E+01	1.33E+01	2.85E-01
3.33E-03	2.78E+01	1.36E+01	2.91E-01
3.43E-03	2.82E+01	1.38E+01	2.95E-01
3.53E-03	2.87E+01	1.41E+01	3.01E-01
3.64E-03	2.92E+01	1.45E+01	3.07E-01
3.75E-03	2.99E+01	1.49E+01	3.13E-01
3.81E-03	3.02E+01	1.51E+01	3.17E-01
3.86E-03	3.04E+01	1.52E+01	3.18E-01
3.98E-03	3.09E+01	1.54E+01	3.24E-01
4.10E-03	3.11E+01	1.55E+01	3.26E-01
4.22E-03	3.15E+01	1.58E+01	3.30E-01
4.35E-03	3.20E+01	1.61E+01	3.36E-01
4.48E-03	3.26E+01	1.65E+01	3.42E-01
4.61E-03	3.32E+01	1.69E+01	3.49E-01
4.75E-03	3.39E+01	1.73E+01	3.55E-01
4.89E-03	3.45E+01	1.77E+01	3.62E-01
5.04E-03	3.53E+01	1.83E+01	3.70E-01
5.19E-03	3.63E+01	1.91E+01	3.81E-01
5.35E-03	3.75E+01	1.96E+01	3.93E-01
5.51E-03	3.82E+01	2.01E+01	4.01E-01
5.67E-03	3.93E+01	2.08E+01	4.12E-01
5.84E-03	4.01E+01	2.13E+01	4.20E-01
5.93E-03	4.04E+01	2.15E+01	4.24E-01
6.02E-03	4.08E+01	2.18E+01	4.28E-01
6.20E-03	4.15E+01	2.22E+01	4.35E-01
6.38E-03	4.23E+01	2.28E+01	4.44E-01
6.57E-03	4.29E+01	2.31E+01	4.50E-01
6.77E-03	4.35E+01	2.35E+01	4.57E-01
6.98E-03	4.39E+01	2.39E+01	4.60E-01
7.18E-03	4.50E+01	2.47E+01	4.71E-01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
7.40E-03	4.58E+01	2.53E+01	4.80E-01
7.51E-03	4.63E+01	2.56E+01	4.85E-01
7.62E-03	4.68E+01	2.58E+01	4.90E-01
7.85E-03	4.76E+01	2.63E+01	4.99E-01
8.09E-03	4.83E+01	2.68E+01	5.06E-01
8.33E-03	4.91E+01	2.74E+01	5.15E-01
8.58E-03	5.00E+01	2.81E+01	5.24E-01
8.71E-03	5.05E+01	2.84E+01	5.29E-01
8.84E-03	5.09E+01	2.87E+01	5.34E-01
9.10E-03	5.19E+01	2.94E+01	5.44E-01
9.37E-03	5.28E+01	3.01E+01	5.54E-01
9.66E-03	5.38E+01	3.08E+01	5.64E-01
9.94E-03	5.48E+01	3.15E+01	5.75E-01
1.02E-02	5.58E+01	3.22E+01	5.85E-01
1.06E-02	5.68E+01	3.30E+01	5.96E-01
1.09E-02	5.79E+01	3.38E+01	6.07E-01
1.12E-02	5.91E+01	3.47E+01	6.20E-01
1.15E-02	6.03E+01	3.56E+01	6.32E-01
1.19E-02	6.14E+01	3.65E+01	6.44E-01
1.22E-02	6.24E+01	3.72E+01	6.54E-01
1.26E-02	6.37E+01	3.80E+01	6.67E-01
1.30E-02	6.50E+01	3.90E+01	6.82E-01
1.34E-02	6.61E+01	3.98E+01	6.93E-01
1.38E-02	6.74E+01	4.09E+01	7.07E-01
1.42E-02	6.88E+01	4.19E+01	7.21E-01
1.46E-02	7.02E+01	4.32E+01	7.36E-01
1.50E-02	7.15E+01	4.41E+01	7.49E-01
1.55E-02	7.28E+01	4.51E+01	7.63E-01
1.60E-02	7.42E+01	4.62E+01	7.78E-01
1.64E-02	7.54E+01	4.73E+01	7.91E-01
1.69E-02	7.69E+01	4.84E+01	8.06E-01
1.74E-02	7.82E+01	4.96E+01	8.20E-01
1.80E-02	7.96E+01	5.07E+01	8.34E-01
1.85E-02	8.10E+01	5.18E+01	8.49E-01
1.91E-02	8.24E+01	5.30E+01	8.64E-01
1.96E-02	8.45E+01	5.48E+01	8.86E-01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
2.02E-02	8.61E+01	5.60E+01	9.02E-01
2.08E-02	8.76E+01	5.73E+01	9.18E-01
2.14E-02	8.88E+01	5.84E+01	9.30E-01
2.21E-02	9.05E+01	5.98E+01	9.48E-01
2.28E-02	9.22E+01	6.13E+01	9.67E-01
2.34E-02	9.39E+01	6.28E+01	9.84E-01
2.41E-02	9.57E+01	6.43E+01	1.00E+00
2.49E-02	9.76E+01	6.60E+01	1.02E+00
2.56E-02	9.94E+01	6.76E+01	1.04E+00
2.64E-02	1.01E+02	6.93E+01	1.06E+00
2.72E-02	1.03E+02	7.10E+01	1.08E+00
2.80E-02	1.05E+02	7.26E+01	1.10E+00
2.88E-02	1.07E+02	7.44E+01	1.12E+00
2.97E-02	1.09E+02	7.62E+01	1.14E+00
3.06E-02	1.11E+02	7.80E+01	1.16E+00
3.15E-02	1.13E+02	7.99E+01	1.18E+00
3.24E-02	1.15E+02	8.19E+01	1.21E+00
3.34E-02	1.17E+02	8.39E+01	1.23E+00
3.44E-02	1.19E+02	8.60E+01	1.25E+00
3.54E-02	1.22E+02	8.81E+01	1.28E+00
3.65E-02	1.24E+02	9.03E+01	1.30E+00
3.76E-02	1.26E+02	9.26E+01	1.32E+00
3.87E-02	1.29E+02	9.49E+01	1.35E+00
3.99E-02	1.31E+02	9.73E+01	1.38E+00
4.11E-02	1.34E+02	9.97E+01	1.40E+00
4.23E-02	1.36E+02	1.02E+02	1.43E+00
4.36E-02	1.39E+02	1.05E+02	1.45E+00
4.49E-02	1.41E+02	1.07E+02	1.48E+00
4.63E-02	1.44E+02	1.10E+02	1.51E+00
4.76E-02	1.47E+02	1.13E+02	1.54E+00
4.91E-02	1.50E+02	1.16E+02	1.57E+00
5.05E-02	1.53E+02	1.19E+02	1.60E+00
5.21E-02	1.55E+02	1.22E+02	1.63E+00
5.36E-02	1.58E+02	1.24E+02	1.66E+00
5.52E-02	1.61E+02	1.28E+02	1.69E+00
5.69E-02	1.64E+02	1.31E+02	1.72E+00

	Nongestational 5–Year Peak Average		
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
5.86E-02	1.68E+02	1.35E+02	1.76E+00
6.03E-02	1.71E+02	1.38E+02	1.79E+00
6.22E-02	1.74E+02	1.41E+02	1.82E+00
6.40E-02	1.77E+02	1.44E+02	1.85E+00
6.59E-02	1.80E+02	1.48E+02	1.89E+00
6.79E-02	1.84E+02	1.52E+02	1.92E+00
7.00E-02	1.87E+02	1.56E+02	1.96E+00
7.21E-02	1.91E+02	1.60E+02	2.00E+00
7.42E-02	1.95E+02	1.64E+02	2.04E+00
7.64E-02	1.98E+02	1.68E+02	2.08E+00
7.87E-02	2.02E+02	1.73E+02	2.12E+00
8.11E-02	2.06E+02	1.77E+02	2.16E+00
8.35E-02	2.10E+02	1.82E+02	2.20E+00
8.60E-02	2.14E+02	1.87E+02	2.24E+00
8.86E-02	2.18E+02	1.92E+02	2.29E+00
9.13E-02	2.22E+02	1.96E+02	2.33E+00
9.40E-02	2.26E+02	2.01E+02	2.37E+00
9.68E-02	2.31E+02	2.07E+02	2.42E+00
9.97E-02	2.35E+02	2.12E+02	2.47E+00
1.03E-01	2.40E+02	2.18E+02	2.51E+00
1.06E-01	2.44E+02	2.23E+02	2.56E+00
1.09E-01	2.49E+02	2.29E+02	2.61E+00
1.12E-01	2.54E+02	2.35E+02	2.66E+00
1.16E-01	2.59E+02	2.41E+02	2.71E+00
1.19E-01	2.64E+02	2.48E+02	2.76E+00
1.23E-01	2.69E+02	2.54E+02	2.82E+00
1.26E-01	2.74E+02	2.60E+02	2.87E+00
1.30E-01	2.79E+02	2.67E+02	2.92E+00
1.34E-01	2.84E+02	2.74E+02	2.98E+00
1.38E-01	2.90E+02	2.81E+02	3.04E+00
1.42E-01	2.95E+02	2.89E+02	3.09E+00
1.46E-01	3.01E+02	2.96E+02	3.15E+00
1.51E-01	3.07E+02	3.04E+02	3.21E+00
1.55E-01	3.13E+02	3.12E+02	3.28E+00
1.60E-01	3.19E+02	3.20E+02	3.34E+00
1.65E-01	3.25E+02	3.29E+02	3.40E+00

	Nongestational 5–Year Peak Average		
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.70E-01	3.31E+02	3.37E+02	3.47E+00
1.75E-01	3.38E+02	3.46E+02	3.54E+00
1.80E-01	3.44E+02	3.55E+02	3.61E+00
1.86E-01	3.51E+02	3.65E+02	3.68E+00
1.91E-01	3.58E+02	3.75E+02	3.75E+00
1.97E-01	3.65E+02	3.85E+02	3.82E+00
2.03E-01	3.72E+02	3.95E+02	3.90E+00
2.09E-01	3.79E+02	4.05E+02	3.97E+00
2.15E-01	3.86E+02	4.16E+02	4.05E+00
2.22E-01	3.94E+02	4.27E+02	4.13E+00
2.28E-01	4.01E+02	4.39E+02	4.21E+00
2.35E-01	4.09E+02	4.50E+02	4.29E+00
2.42E-01	4.17E+02	4.62E+02	4.37E+00
2.49E-01	4.25E+02	4.74E+02	4.46E+00
2.57E-01	4.34E+02	4.87E+02	4.54E+00
2.65E-01	4.42E+02	5.00E+02	4.63E+00
2.72E-01	4.51E+02	5.14E+02	4.73E+00
2.81E-01	4.60E+02	5.28E+02	4.82E+00
2.89E-01	4.69E+02	5.42E+02	4.91E+00
2.98E-01	4.78E+02	5.56E+02	5.01E+00
3.07E-01	4.87E+02	5.71E+02	5.11E+00
3.16E-01	4.97E+02	5.87E+02	5.21E+00
3.25E-01	5.07E+02	6.03E+02	5.31E+00
3.35E-01	5.17E+02	6.19E+02	5.42E+00
3.45E-01	5.27E+02	6.36E+02	5.52E+00
3.56E-01	5.38E+02	6.53E+02	5.63E+00
3.66E-01	5.48E+02	6.71E+02	5.75E+00
3.77E-01	5.59E+02	6.89E+02	5.86E+00
3.89E-01	5.70E+02	7.08E+02	5.98E+00
4.00E-01	5.82E+02	7.27E+02	6.09E+00
4.12E-01	5.93E+02	7.47E+02	6.22E+00
4.25E-01	6.05E+02	7.67E+02	6.34E+00
4.37E-01	6.17E+02	7.88E+02	6.47E+00
4.50E-01	6.29E+02	8.10E+02	6.60E+00
4.64E-01	6.42E+02	8.32E+02	6.73E+00
4.78E-01	6.55E+02	8.55E+02	6.86E+00

	Nongestational 5–Year Peak Average		
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.92E-01	6.68E+02	8.78E+02	7.00E+00
5.07E-01	6.81E+02	9.02E+02	7.14E+00
5.22E-01	6.95E+02	9.26E+02	7.28E+00
5.38E-01	7.09E+02	9.52E+02	7.43E+00
5.54E-01	7.23E+02	9.78E+02	7.58E+00
5.71E-01	7.38E+02	1.01E+03	7.73E+00
5.88E-01	7.53E+02	1.03E+03	7.89E+00
6.05E-01	7.68E+02	1.06E+03	8.05E+00
6.23E-01	7.83E+02	1.09E+03	8.21E+00
6.42E-01	7.99E+02	1.12E+03	8.38E+00
6.61E-01	8.16E+02	1.15E+03	8.55E+00
6.81E-01	8.32E+02	1.18E+03	8.72E+00
7.02E-01	8.49E+02	1.22E+03	8.90E+00
7.23E-01	8.66E+02	1.25E+03	9.08E+00
7.44E-01	8.84E+02	1.28E+03	9.27E+00
7.67E-01	9.02E+02	1.32E+03	9.46E+00
7.90E-01	9.21E+02	1.36E+03	9.65E+00
8.13E-01	9.40E+02	1.39E+03	9.85E+00
8.38E-01	9.59E+02	1.43E+03	1.00E+01
8.63E-01	9.78E+02	1.47E+03	1.03E+01
8.89E-01	9.99E+02	1.51E+03	1.05E+01
9.16E-01	1.02E+03	1.56E+03	1.07E+01
9.43E-01	1.04E+03	1.60E+03	1.09E+01
9.71E-01	1.06E+03	1.64E+03	1.11E+01
1.00E+00	1.08E+03	1.69E+03	1.14E+01
1.03E+00	1.11E+03	1.74E+03	1.16E+01
1.06E+00	1.13E+03	1.79E+03	1.18E+01
1.09E+00	1.15E+03	1.84E+03	1.21E+01
1.13E+00	1.18E+03	1.89E+03	1.23E+01
1.16E+00	1.20E+03	1.94E+03	1.26E+01
1.19E+00	1.23E+03	1.99E+03	1.29E+01
1.23E+00	1.25E+03	2.05E+03	1.31E+01
1.27E+00	1.28E+03	2.11E+03	1.34E+01
1.31E+00	1.31E+03	2.17E+03	1.37E+01
1.34E+00	1.33E+03	2.23E+03	1.40E+01
1.38E+00	1.36E+03	2.29E+03	1.43E+01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.43E+00	1.39E+03	2.36E+03	1.46E+01
1.47E+00	1.42E+03	2.42E+03	1.49E+01
1.51E+00	1.45E+03	2.49E+03	1.52E+01
1.56E+00	1.48E+03	2.56E+03	1.55E+01
1.61E+00	1.51E+03	2.63E+03	1.59E+01
1.65E+00	1.55E+03	2.71E+03	1.62E+01
1.70E+00	1.58E+03	2.79E+03	1.66E+01
1.75E+00	1.61E+03	2.86E+03	1.69E+01
1.81E+00	1.65E+03	2.95E+03	1.73E+01
1.86E+00	1.68E+03	3.03E+03	1.77E+01
1.92E+00	1.72E+03	3.11E+03	1.80E+01
1.97E+00	1.76E+03	3.20E+03	1.84E+01
2.03E+00	1.80E+03	3.29E+03	1.88E+01
2.09E+00	1.84E+03	3.39E+03	1.92E+01
2.16E+00	1.88E+03	3.48E+03	1.97E+01
2.22E+00	1.92E+03	3.58E+03	2.01E+01
2.29E+00	1.96E+03	3.69E+03	2.05E+01
2.36E+00	2.00E+03	3.79E+03	2.10E+01
2.43E+00	2.05E+03	3.90E+03	2.14E+01
2.50E+00	2.09E+03	4.01E+03	2.19E+01
2.58E+00	2.14E+03	4.12E+03	2.24E+01
2.65E+00	2.19E+03	4.24E+03	2.29E+01
2.73E+00	2.23E+03	4.36E+03	2.34E+01
2.82E+00	2.28E+03	4.49E+03	2.39E+01
2.90E+00	2.33E+03	4.62E+03	2.45E+01
2.99E+00	2.39E+03	4.75E+03	2.50E+01
3.08E+00	2.44E+03	4.89E+03	2.56E+01
3.17E+00	2.50E+03	5.03E+03	2.62E+01
3.26E+00	2.55E+03	5.17E+03	2.67E+01
3.36E+00	2.61E+03	5.32E+03	2.74E+01
3.46E+00	2.67E+03	5.47E+03	2.80E+01
3.57E+00	2.73E+03	5.63E+03	2.86E+01
3.67E+00	2.79E+03	5.79E+03	2.93E+01
3.78E+00	2.86E+03	5.96E+03	2.99E+01
3.90E+00	2.92E+03	6.13E+03	3.06E+01
4.01E+00	2.99E+03	6.30E+03	3.13E+01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.13E+00	3.06E+03	6.49E+03	3.21E+01
4.26E+00	3.13E+03	6.67E+03	3.28E+01
4.39E+00	3.20E+03	6.87E+03	3.36E+01
4.52E+00	3.28E+03	7.06E+03	3.43E+01
4.65E+00	3.35E+03	7.27E+03	3.51E+01
4.79E+00	3.43E+03	7.48E+03	3.60E+01
4.94E+00	3.51E+03	7.69E+03	3.68E+01
5.08E+00	3.59E+03	7.92E+03	3.77E+01
5.24E+00	3.68E+03	8.15E+03	3.86E+01
5.39E+00	3.77E+03	8.38E+03	3.95E+01
5.56E+00	3.85E+03	8.62E+03	4.04E+01
5.72E+00	3.95E+03	8.87E+03	4.14E+01
5.89E+00	4.04E+03	9.13E+03	4.23E+01
6.07E+00	4.14E+03	9.40E+03	4.34E+01
6.25E+00	4.24E+03	9.67E+03	4.44E+01
6.44E+00	4.34E+03	9.95E+03	4.55E+01
6.63E+00	4.44E+03	1.02E+04	4.66E+01
6.83E+00	4.55E+03	1.05E+04	4.77E+01
7.04E+00	4.66E+03	1.08E+04	4.88E+01
7.25E+00	4.77E+03	1.12E+04	5.00E+01
7.47E+00	4.89E+03	1.15E+04	5.12E+01
7.69E+00	5.01E+03	1.18E+04	5.25E+01
7.92E+00	5.13E+03	1.22E+04	5.38E+01
8.16E+00	5.26E+03	1.25E+04	5.51E+01
8.40E+00	5.39E+03	1.29E+04	5.65E+01
8.66E+00	5.52E+03	1.33E+04	5.79E+01
8.92E+00	5.66E+03	1.36E+04	5.93E+01
9.18E+00	5.80E+03	1.40E+04	6.08E+01
9.46E+00	5.94E+03	1.44E+04	6.23E+01
9.74E+00	6.09E+03	1.49E+04	6.38E+01
1.00E+01	6.24E+03	1.53E+04	6.54E+01
1.06E+01	6.56E+03	1.62E+04	6.87E+01
1.13E+01	6.89E+03	1.71E+04	7.22E+01
1.20E+01	7.24E+03	1.81E+04	7.58E+01
1.27E+01	7.61E+03	1.92E+04	7.97E+01
1.34E+01	8.00E+03	2.03E+04	8.38E+01

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.42E+01	8.41E+03	2.15E+04	8.81E+01
1.51E+01	8.84E+03	2.28E+04	9.27E+01
1.60E+01	9.30E+03	2.41E+04	9.75E+01
1.70E+01	9.79E+03	2.55E+04	1.03E+02
1.80E+01	1.03E+04	2.70E+04	1.08E+02
1.90E+01	1.09E+04	2.86E+04	1.14E+02
2.02E+01	1.14E+04	3.03E+04	1.20E+02
2.14E+01	1.20E+04	3.21E+04	1.26E+02
2.27E+01	1.27E+04	3.39E+04	1.33E+02
2.40E+01	1.34E+04	3.59E+04	1.40E+02
2.55E+01	1.41E+04	3.80E+04	1.48E+02
2.70E+01	1.49E+04	4.03E+04	1.56E+02
2.86E+01	1.57E+04	4.26E+04	1.64E+02
3.04E+01	1.65E+04	4.52E+04	1.73E+02
3.22E+01	1.74E+04	4.78E+04	1.83E+02
3.41E+01	1.84E+04	5.06E+04	1.93E+02
3.62E+01	1.94E+04	5.36E+04	2.03E+02
3.83E+01	2.05E+04	5.67E+04	2.15E+02
4.06E+01	2.16E+04	6.00E+04	2.27E+02
4.31E+01	2.28E+04	6.36E+04	2.39E+02
4.57E+01	2.41E+04	6.73E+04	2.53E+02
4.84E+01	2.55E+04	7.12E+04	2.67E+02
5.13E+01	2.69E+04	7.54E+04	2.82E+02
5.44E+01	2.84E+04	7.98E+04	2.98E+02
5.76E+01	3.00E+04	8.45E+04	3.15E+02
6.11E+01	3.17E+04	8.94E+04	3.33E+02
6.48E+01	3.36E+04	9.46E+04	3.52E+02
6.86E+01	3.55E+04	1.00E+05	3.72E+02
7.28E+01	3.75E+04	1.06E+05	3.93E+02
7.71E+01	3.97E+04	1.12E+05	4.16E+02
8.18E+01	4.20E+04	1.19E+05	4.40E+02
8.67E+01	4.44E+04	1.25E+05	4.65E+02
9.19E+01	4.69E+04	1.33E+05	4.92E+02
9.74E+01	4.97E+04	1.40E+05	5.20E+02
1.03E+02	5.25E+04	1.49E+05	5.51E+02
1.09E+02	5.56E+04	1.57E+05	5.83E+02

Nongestational 5–Year Peak Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.16E+02	5.88E+04	1.66E+05	6.17E+02
1.23E+02	6.23E+04	1.76E+05	6.53E+02
1.30E+02	6.59E+04	1.86E+05	6.91E+02
1.38E+02	6.97E+04	1.96E+05	7.31E+02
1.46E+02	7.38E+04	2.07E+05	7.74E+02

E.4.3. Gestational

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.03E-09	2.89E-05	1.14E-05	3.05E-07
1.09E-09	3.07E-05	1.21E-05	3.23E-07
1.16E-09	3.25E-05	1.28E-05	3.42E-07
1.23E-09	3.45E-05	1.36E-05	3.63E-07
1.30E-09	3.65E-05	1.44E-05	3.89E-07
1.38E-09	3.87E-05	1.53E-05	4.07E-07
1.46E-09	4.11E-05	1.62E-05	4.31E-07
1.55E-09	4.35E-05	1.71E-05	4.54E-07
1.64E-09	4.61E-05	1.82E-05	4.81E-07
1.74E-09	4.88E-05	1.92E-05	5.14E-07
1.84E-09	5.18E-05	2.04E-05	5.45E-07
1.95E-09	5.49E-05	2.16E-05	5.78E-07
2.07E-09	5.82E-05	2.29E-05	6.13E-07
2.20E-09	6.17E-05	2.43E-05	6.49E-07
2.33E-09	6.53E-05	2.58E-05	6.88E-07
2.47E-09	6.93E-05	2.73E-05	7.30E-07
2.62E-09	7.34E-05	2.89E-05	7.73E-07
2.77E-09	7.79E-05	3.07E-05	8.18E-07
2.94E-09	8.25E-05	3.25E-05	8.69E-07
3.12E-09	8.74E-05	3.45E-05	9.21E-07
3.30E-09	9.27E-05	3.65E-05	9.76E-07
3.50E-09	9.83E-05	3.88E-05	1.03E-06
3.71E-09	1.04E-04	4.11E-05	1.09E-06
3.93E-09	1.10E-04	4.35E-05	1.16E-06
4.17E-09	1.17E-04	4.61E-05	1.23E-06
4.42E-09	1.24E-04	4.89E-05	1.31E-06
4.68E-09	1.31E-04	5.18E-05	1.38E-06
4.97E-09	1.39E-04	5.49E-05	1.47E-06
5.26E-09	1.48E-04	5.83E-05	1.55E-06
5.58E-09	1.57E-04	6.18E-05	1.65E-06
5.91E-09	1.66E-04	6.55E-05	1.73E-06
6.27E-09	1.76E-04	6.93E-05	1.85E-06
6.65E-09	1.86E-04	7.35E-05	1.96E-06
7.04E-09	1.98E-04	7.79E-05	2.08E-06
7.47E-09	2.09E-04	8.26E-05	2.21E-06

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
7.92E-09	2.22E-04	8.75E-05	2.34E-06
8.39E-09	2.35E-04	9.27E-05	2.48E-06
8.89E-09	2.49E-04	9.83E-05	2.63E-06
9.43E-09	2.64E-04	1.04E-04	2.78E-06
9.99E-09	2.80E-04	1.10E-04	2.95E-06
1.06E-08	2.97E-04	1.17E-04	3.14E-06
1.12E-08	3.15E-04	1.24E-04	3.31E-06
1.19E-08	3.34E-04	1.32E-04	3.52E-06
1.26E-08	3.54E-04	1.40E-04	3.70E-06
1.34E-08	3.75E-04	1.48E-04	3.95E-06
1.42E-08	3.97E-04	1.57E-04	4.18E-06
1.50E-08	4.21E-04	1.66E-04	4.43E-06
1.59E-08	4.47E-04	1.76E-04	4.70E-06
1.69E-08	4.73E-04	1.86E-04	4.98E-06
1.79E-08	5.01E-04	1.98E-04	5.28E-06
1.90E-08	5.31E-04	2.10E-04	5.59E-06
2.01E-08	5.63E-04	2.22E-04	5.93E-06
2.13E-08	5.97E-04	2.35E-04	6.28E-06
2.26E-08	6.33E-04	2.49E-04	6.66E-06
2.39E-08	6.71E-04	2.65E-04	7.03E-06
2.54E-08	7.11E-04	2.80E-04	7.48E-06
2.69E-08	7.53E-04	2.97E-04	7.93E-06
2.85E-08	7.98E-04	3.15E-04	8.40E-06
3.02E-08	8.46E-04	3.34E-04	8.91E-06
3.20E-08	8.97E-04	3.54E-04	9.44E-06
3.40E-08	9.50E-04	3.75E-04	1.00E-05
3.60E-08	1.01E-03	3.97E-04	1.06E-05
3.82E-08	1.07E-03	4.21E-04	1.12E-05
4.05E-08	1.13E-03	4.46E-04	1.19E-05
4.29E-08	1.20E-03	4.73E-04	1.26E-05
4.55E-08	1.27E-03	5.01E-04	1.34E-05
4.82E-08	1.35E-03	5.31E-04	1.42E-05
5.11E-08	1.43E-03	5.63E-04	1.50E-05
5.41E-08	1.51E-03	5.97E-04	1.59E-05
5.74E-08	1.60E-03	6.32E-04	1.69E-05
6.08E-08	1.70E-03	6.70E-04	1.79E-05
6.45E-08	1.80E-03	7.10E-04	1.90E-05

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
6.84E-08	1.91E-03	7.53E-04	2.01E-05
7.25E-08	2.02E-03	7.98E-04	2.13E-05
7.68E-08	2.14E-03	8.45E-04	2.26E-05
8.14E-08	2.27E-03	8.96E-04	2.39E-05
8.63E-08	2.41E-03	9.50E-04	2.53E-05
9.15E-08	2.55E-03	1.01E-03	2.68E-05
9.70E-08	2.70E-03	1.07E-03	2.85E-05
1.03E-07	2.86E-03	1.13E-03	3.01E-05
1.09E-07	3.03E-03	1.20E-03	3.19E-05
1.15E-07	3.22E-03	1.27E-03	3.39E-05
1.22E-07	3.41E-03	1.35E-03	3.59E-05
1.30E-07	3.61E-03	1.43E-03	3.80E-05
1.38E-07	3.83E-03	1.51E-03	4.03E-05
1.46E-07	4.05E-03	1.60E-03	4.27E-05
1.55E-07	4.30E-03	1.70E-03	4.52E-05
1.64E-07	4.55E-03	1.80E-03	4.79E-05
1.74E-07	4.82E-03	1.90E-03	5.08E-05
1.84E-07	5.11E-03	2.02E-03	5.38E-05
1.95E-07	5.41E-03	2.14E-03	5.70E-05
2.07E-07	5.74E-03	2.27E-03	6.04E-05
2.19E-07	6.08E-03	2.40E-03	6.40E-05
2.32E-07	6.44E-03	2.54E-03	6.78E-05
2.46E-07	6.82E-03	2.70E-03	7.18E-05
2.61E-07	7.23E-03	2.86E-03	7.61E-05
2.77E-07	7.66E-03	3.03E-03	8.06E-05
2.93E-07	8.11E-03	3.21E-03	8.54E-05
3.11E-07	8.60E-03	3.40E-03	9.05E-05
3.30E-07	9.11E-03	3.60E-03	9.58E-05
3.49E-07	9.65E-03	3.82E-03	1.02E-04
3.70E-07	1.02E-02	4.04E-03	1.08E-04
3.93E-07	1.08E-02	4.28E-03	1.14E-04
4.16E-07	1.15E-02	4.54E-03	1.21E-04
4.41E-07	1.21E-02	4.81E-03	1.28E-04
4.68E-07	1.29E-02	5.09E-03	1.35E-04
4.96E-07	1.36E-02	5.39E-03	1.43E-04
5.25E-07	1.44E-02	5.72E-03	1.52E-04
5.57E-07	1.53E-02	6.05E-03	1.61E-04

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
5.90E-07	1.62E-02	6.41E-03	1.70E-04
6.26E-07	1.72E-02	6.79E-03	1.81E-04
6.63E-07	1.82E-02	7.20E-03	1.91E-04
7.03E-07	1.92E-02	7.62E-03	2.02E-04
7.45E-07	2.04E-02	8.08E-03	2.14E-04
7.90E-07	2.16E-02	8.55E-03	2.27E-04
8.37E-07	2.29E-02	9.06E-03	2.40E-04
8.88E-07	2.42E-02	9.60E-03	2.55E-04
9.41E-07	2.56E-02	1.02E-02	2.70E-04
9.97E-07	2.71E-02	1.08E-02	2.86E-04
1.01E-06	2.75E-02	1.09E-02	2.90E-04
1.03E-06	2.79E-02	1.11E-02	2.94E-04
1.04E-06	2.83E-02	1.12E-02	2.98E-04
1.06E-06	2.88E-02	1.14E-02	3.03E-04
1.07E-06	2.92E-02	1.16E-02	3.07E-04
1.09E-06	2.96E-02	1.17E-02	3.11E-04
1.11E-06	3.00E-02	1.19E-02	3.16E-04
1.12E-06	3.05E-02	1.21E-02	3.21E-04
1.14E-06	3.09E-02	1.23E-02	3.25E-04
1.16E-06	3.14E-02	1.24E-02	3.30E-04
1.17E-06	3.18E-02	1.26E-02	3.35E-04
1.19E-06	3.23E-02	1.28E-02	3.40E-04
1.21E-06	3.27E-02	1.30E-02	3.45E-04
1.23E-06	3.32E-02	1.32E-02	3.50E-04
1.24E-06	3.37E-02	1.34E-02	3.55E-04
1.26E-06	3.42E-02	1.36E-02	3.60E-04
1.28E-06	3.47E-02	1.38E-02	3.65E-04
1.30E-06	3.52E-02	1.40E-02	3.71E-04
1.32E-06	3.57E-02	1.42E-02	3.76E-04
1.34E-06	3.62E-02	1.44E-02	3.81E-04
1.36E-06	3.68E-02	1.46E-02	3.87E-04
1.38E-06	3.73E-02	1.48E-02	3.93E-04
1.40E-06	3.78E-02	1.50E-02	3.98E-04
1.42E-06	3.84E-02	1.53E-02	4.04E-04
1.44E-06	3.89E-02	1.55E-02	4.10E-04
1.46E-06	3.95E-02	1.57E-02	4.16E-04
1.49E-06	4.01E-02	1.59E-02	4.22E-04

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.53E-06	4.13E-02	1.64E-02	4.34E-04
1.58E-06	4.25E-02	1.69E-02	4.47E-04
1.62E-06	4.37E-02	1.74E-02	4.60E-04
1.67E-06	4.50E-02	1.79E-02	4.73E-04
1.72E-06	4.63E-02	1.84E-02	4.87E-04
1.77E-06	4.77E-02	1.90E-02	5.02E-04
1.83E-06	4.91E-02	1.95E-02	5.16E-04
1.88E-06	5.05E-02	2.01E-02	5.31E-04
1.94E-06	5.20E-02	2.07E-02	5.47E-04
2.00E-06	5.35E-02	2.13E-02	5.63E-04
2.06E-06	5.50E-02	2.19E-02	5.79E-04
2.12E-06	5.66E-02	2.26E-02	5.96E-04
2.18E-06	5.83E-02	2.32E-02	6.13E-04
2.25E-06	6.00E-02	2.39E-02	6.31E-04
2.32E-06	6.17E-02	2.46E-02	6.50E-04
2.39E-06	6.35E-02	2.53E-02	6.68E-04
2.46E-06	6.54E-02	2.61E-02	6.88E-04
2.53E-06	6.73E-02	2.68E-02	7.08E-04
2.61E-06	6.92E-02	2.76E-02	7.28E-04
2.68E-06	7.12E-02	2.84E-02	7.49E-04
2.76E-06	7.33E-02	2.92E-02	7.71E-04
2.85E-06	7.54E-02	3.01E-02	7.94E-04
2.93E-06	7.76E-02	3.10E-02	8.17E-04
3.02E-06	7.98E-02	3.19E-02	8.40E-04
3.11E-06	8.22E-02	3.28E-02	8.64E-04
3.21E-06	8.45E-02	3.38E-02	8.89E-04
3.30E-06	8.70E-02	3.47E-02	9.15E-04
3.40E-06	8.95E-02	3.57E-02	9.42E-04
3.50E-06	9.21E-02	3.68E-02	9.69E-04
3.61E-06	9.47E-02	3.79E-02	9.97E-04
3.72E-06	9.74E-02	3.90E-02	1.03E-03
3.83E-06	1.00E-01	4.01E-02	1.05E-03
3.94E-06	1.03E-01	4.13E-02	1.09E-03
4.06E-06	1.06E-01	4.25E-02	1.12E-03
4.18E-06	1.09E-01	4.37E-02	1.15E-03
4.31E-06	1.12E-01	4.49E-02	1.18E-03
4.44E-06	1.15E-01	4.63E-02	1.22E-03

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.57E-06	1.19E-01	4.76E-02	1.25E-03
4.71E-06	1.22E-01	4.90E-02	1.29E-03
4.85E-06	1.26E-01	5.04E-02	1.32E-03
4.99E-06	1.29E-01	5.18E-02	1.36E-03
5.14E-06	1.33E-01	5.33E-02	1.40E-03
5.30E-06	1.37E-01	5.49E-02	1.44E-03
5.46E-06	1.41E-01	5.64E-02	1.48E-03
5.62E-06	1.45E-01	5.81E-02	1.52E-03
5.79E-06	1.49E-01	5.97E-02	1.57E-03
5.96E-06	1.53E-01	6.15E-02	1.61E-03
6.14E-06	1.57E-01	6.32E-02	1.66E-03
6.33E-06	1.62E-01	6.51E-02	1.70E-03
6.52E-06	1.66E-01	6.69E-02	1.75E-03
6.71E-06	1.71E-01	6.88E-02	1.80E-03
6.91E-06	1.76E-01	7.08E-02	1.85E-03
7.12E-06	1.81E-01	7.29E-02	1.90E-03
7.33E-06	1.86E-01	7.49E-02	1.96E-03
7.55E-06	1.91E-01	7.71E-02	2.01E-03
7.78E-06	1.97E-01	7.93E-02	2.07E-03
8.01E-06	2.02E-01	8.16E-02	2.13E-03
8.25E-06	2.08E-01	8.39E-02	2.19E-03
8.50E-06	2.14E-01	8.63E-02	2.25E-03
8.76E-06	2.20E-01	8.88E-02	2.31E-03
9.02E-06	2.26E-01	9.13E-02	2.38E-03
9.29E-06	2.33E-01	9.39E-02	2.45E-03
9.57E-06	2.39E-01	9.66E-02	2.51E-03
9.86E-06	2.46E-01	9.93E-02	2.59E-03
1.02E-05	2.53E-01	1.02E-01	2.66E-03
1.05E-05	2.60E-01	1.05E-01	2.73E-03
1.08E-05	2.67E-01	1.08E-01	2.81E-03
1.11E-05	2.74E-01	1.11E-01	2.89E-03
1.14E-05	2.82E-01	1.14E-01	2.97E-03
1.18E-05	2.90E-01	1.17E-01	3.05E-03
1.21E-05	2.98E-01	1.21E-01	3.13E-03
1.25E-05	3.06E-01	1.24E-01	3.22E-03
1.29E-05	3.15E-01	1.28E-01	3.31E-03
1.32E-05	3.23E-01	1.31E-01	3.40E-03

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.36E-05	3.32E-01	1.35E-01	3.50E-03
1.41E-05	3.42E-01	1.39E-01	3.59E-03
1.45E-05	3.51E-01	1.43E-01	3.69E-03
1.49E-05	3.61E-01	1.47E-01	3.79E-03
1.54E-05	3.71E-01	1.51E-01	3.90E-03
1.58E-05	3.81E-01	1.55E-01	4.01E-03
1.63E-05	3.91E-01	1.59E-01	4.12E-03
1.68E-05	4.02E-01	1.64E-01	4.23E-03
1.73E-05	4.13E-01	1.68E-01	4.34E-03
1.78E-05	4.24E-01	1.73E-01	4.46E-03
1.83E-05	4.36E-01	1.78E-01	4.59E-03
1.89E-05	4.48E-01	1.83E-01	4.71E-03
1.95E-05	4.60E-01	1.88E-01	4.84E-03
2.00E-05	4.73E-01	1.93E-01	4.97E-03
2.06E-05	4.85E-01	1.99E-01	5.11E-03
2.13E-05	4.99E-01	2.04E-01	5.24E-03
2.19E-05	5.12E-01	2.10E-01	5.39E-03
2.25E-05	5.26E-01	2.16E-01	5.53E-03
2.32E-05	5.40E-01	2.22E-01	5.68E-03
2.39E-05	5.55E-01	2.28E-01	5.83E-03
2.46E-05	5.70E-01	2.34E-01	5.99E-03
2.54E-05	5.85E-01	2.40E-01	6.15E-03
2.61E-05	6.01E-01	2.47E-01	6.32E-03
2.69E-05	6.17E-01	2.54E-01	6.49E-03
2.77E-05	6.33E-01	2.61E-01	6.66E-03
2.86E-05	6.50E-01	2.68E-01	6.84E-03
2.94E-05	6.68E-01	2.75E-01	7.02E-03
3.03E-05	6.85E-01	2.83E-01	7.21E-03
3.12E-05	7.04E-01	2.91E-01	7.40E-03
3.21E-05	7.22E-01	2.98E-01	7.60E-03
3.31E-05	7.41E-01	3.07E-01	7.80E-03
3.41E-05	7.61E-01	3.15E-01	8.00E-03
3.51E-05	7.81E-01	3.24E-01	8.21E-03
3.62E-05	8.02E-01	3.32E-01	8.43E-03
3.73E-05	8.24E-01	3.42E-01	8.66E-03
3.84E-05	8.46E-01	3.51E-01	8.89E-03
3.95E-05	8.68E-01	3.61E-01	9.12E-03

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.07E-05	8.91E-01	3.70E-01	9.36E-03
4.19E-05	9.14E-01	3.80E-01	9.61E-03
4.32E-05	9.38E-01	3.91E-01	9.86E-03
4.45E-05	9.62E-01	4.01E-01	1.01E-02
4.58E-05	9.87E-01	4.12E-01	1.04E-02
4.72E-05	1.01E+00	4.23E-01	1.07E-02
4.86E-05	1.04E+00	4.34E-01	1.09E-02
5.01E-05	1.07E+00	4.46E-01	1.12E-02
5.16E-05	1.09E+00	4.58E-01	1.15E-02
5.31E-05	1.12E+00	4.70E-01	1.18E-02
5.47E-05	1.15E+00	4.82E-01	1.21E-02
5.64E-05	1.18E+00	4.95E-01	1.24E-02
5.81E-05	1.21E+00	5.08E-01	1.27E-02
5.98E-05	1.24E+00	5.22E-01	1.30E-02
6.16E-05	1.27E+00	5.35E-01	1.34E-02
6.34E-05	1.30E+00	5.49E-01	1.37E-02
6.54E-05	1.34E+00	5.63E-01	1.40E-02
6.73E-05	1.37E+00	5.78E-01	1.44E-02
6.93E-05	1.40E+00	5.93E-01	1.48E-02
7.14E-05	1.44E+00	6.09E-01	1.51E-02
7.36E-05	1.48E+00	6.25E-01	1.55E-02
7.58E-05	1.51E+00	6.41E-01	1.59E-02
7.80E-05	1.55E+00	6.58E-01	1.63E-02
8.04E-05	1.59E+00	6.75E-01	1.67E-02
8.28E-05	1.63E+00	6.92E-01	1.71E-02
8.53E-05	1.67E+00	7.10E-01	1.75E-02
8.78E-05	1.71E+00	7.28E-01	1.80E-02
9.05E-05	1.75E+00	7.48E-01	1.84E-02
9.32E-05	1.80E+00	7.67E-01	1.89E-02
9.60E-05	1.84E+00	7.87E-01	1.94E-02
9.89E-05	1.89E+00	8.08E-01	1.98E-02
1.02E-04	1.94E+00	8.30E-01	2.03E-02
1.05E-04	1.98E+00	8.52E-01	2.09E-02
1.08E-04	2.03E+00	8.74E-01	2.14E-02
1.11E-04	2.08E+00	8.96E-01	2.19E-02
1.15E-04	2.13E+00	9.19E-01	2.24E-02
1.18E-04	2.18E+00	9.41E-01	2.29E-02

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.22E-04	2.23E+00	9.65E-01	2.35E-02
1.25E-04	2.29E+00	9.89E-01	2.40E-02
1.29E-04	2.34E+00	1.01E+00	2.46E-02
1.33E-04	2.40E+00	1.04E+00	2.52E-02
1.37E-04	2.46E+00	1.07E+00	2.58E-02
1.41E-04	2.51E+00	1.09E+00	2.64E-02
1.45E-04	2.57E+00	1.12E+00	2.71E-02
1.50E-04	2.64E+00	1.15E+00	2.77E-02
1.54E-04	2.70E+00	1.18E+00	2.83E-02
1.59E-04	2.76E+00	1.21E+00	2.90E-02
1.63E-04	2.83E+00	1.24E+00	2.97E-02
1.68E-04	2.89E+00	1.27E+00	3.04E-02
1.73E-04	2.96E+00	1.30E+00	3.11E-02
1.79E-04	3.04E+00	1.34E+00	3.19E-02
1.84E-04	3.12E+00	1.37E+00	3.27E-02
1.89E-04	3.19E+00	1.41E+00	3.35E-02
1.95E-04	3.25E+00	1.44E+00	3.42E-02
2.01E-04	3.34E+00	1.48E+00	3.51E-02
2.07E-04	3.42E+00	1.51E+00	3.59E-02
2.13E-04	3.50E+00	1.55E+00	3.68E-02
2.20E-04	3.58E+00	1.59E+00	3.77E-02
2.26E-04	3.67E+00	1.63E+00	3.85E-02
2.33E-04	3.75E+00	1.67E+00	3.94E-02
2.40E-04	3.84E+00	1.71E+00	4.04E-02
2.47E-04	3.93E+00	1.76E+00	4.13E-02
2.55E-04	4.02E+00	1.80E+00	4.22E-02
2.62E-04	4.11E+00	1.84E+00	4.32E-02
2.70E-04	4.21E+00	1.89E+00	4.42E-02
2.78E-04	4.32E+00	1.94E+00	4.53E-02
2.86E-04	4.41E+00	1.99E+00	4.63E-02
2.95E-04	4.50E+00	2.03E+00	4.73E-02
3.04E-04	4.60E+00	2.08E+00	4.84E-02
3.13E-04	4.70E+00	2.13E+00	4.94E-02
3.22E-04	4.81E+00	2.18E+00	5.05E-02
3.32E-04	4.92E+00	2.23E+00	5.16E-02
3.42E-04	5.02E+00	2.29E+00	5.28E-02
3.52E-04	5.13E+00	2.34E+00	5.39E-02

Gestational Average					Gestational Average					Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)		Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)		Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.63E-04	5.24E+00	2.40E+00	5.51E-02		9.77E-04	1.09E+01	5.33E+00	1.14E-01		1.64E-03	1.55E+01	7.99E+00	1.63E-01
3.74E-04	5.37E+00	2.46E+00	5.64E-02		9.84E-04	1.09E+01	5.36E+00	1.15E-01		1.66E-03	1.57E+01	8.09E+00	1.65E-01
3.85E-04	5.50E+00	2.52E+00	5.77E-02		9.91E-04	1.10E+01	5.39E+00	1.15E-01		1.69E-03	1.59E+01	8.18E+00	1.67E-01
3.97E-04	5.62E+00	2.58E+00	5.90E-02		9.98E-04	1.10E+01	5.42E+00	1.16E-01		1.71E-03	1.60E+01	8.28E+00	1.68E-01
4.08E-04	5.75E+00	2.65E+00	6.03E-02		1.01E-03	1.11E+01	5.46E+00	1.16E-01		1.74E-03	1.62E+01	8.37E+00	1.70E-01
4.21E-04	5.87E+00	2.71E+00	6.17E-02		1.02E-03	1.12E+01	5.52E+00	1.18E-01		1.76E-03	1.64E+01	8.47E+00	1.72E-01
4.33E-04	6.01E+00	2.78E+00	6.31E-02		1.04E-03	1.13E+01	5.58E+00	1.19E-01		1.79E-03	1.65E+01	8.57E+00	1.73E-01
4.46E-04	6.14E+00	2.85E+00	6.45E-02		1.05E-03	1.14E+01	5.65E+00	1.20E-01		1.82E-03	1.67E+01	8.67E+00	1.75E-01
4.60E-04	6.28E+00	2.91E+00	6.60E-02		1.07E-03	1.16E+01	5.72E+00	1.21E-01		1.84E-03	1.69E+01	8.77E+00	1.77E-01
4.74E-04	6.43E+00	2.99E+00	6.75E-02		1.08E-03	1.17E+01	5.78E+00	1.23E-01		1.87E-03	1.74E+01	9.10E+00	1.83E-01
4.88E-04	6.57E+00	3.06E+00	6.90E-02		1.10E-03	1.18E+01	5.85E+00	1.24E-01		1.90E-03	1.92E+01	1.02E+01	2.02E-01
5.02E-04	6.72E+00	3.14E+00	7.05E-02		1.12E-03	1.19E+01	5.92E+00	1.25E-01		1.93E-03	1.96E+01	1.04E+01	2.06E-01
5.17E-04	6.87E+00	3.21E+00	7.21E-02		1.13E-03	1.20E+01	5.99E+00	1.26E-01		1.96E-03	1.80E+01	9.44E+00	1.89E-01
5.33E-04	7.02E+00	3.29E+00	7.37E-02		1.15E-03	1.22E+01	6.06E+00	1.28E-01		1.99E-03	1.79E+01	9.41E+00	1.88E-01
5.49E-04	7.17E+00	3.37E+00	7.53E-02		1.17E-03	1.23E+01	6.13E+00	1.29E-01		2.02E-03	1.81E+01	9.49E+00	1.89E-01
5.65E-04	7.33E+00	3.45E+00	7.70E-02		1.18E-03	1.24E+01	6.20E+00	1.30E-01		2.08E-03	1.84E+01	9.67E+00	1.93E-01
5.82E-04	7.49E+00	3.53E+00	7.87E-02		1.20E-03	1.25E+01	6.27E+00	1.32E-01		2.14E-03	1.87E+01	9.88E+00	1.96E-01
6.00E-04	7.65E+00	3.62E+00	8.04E-02		1.22E-03	1.27E+01	6.34E+00	1.33E-01		2.20E-03	1.91E+01	1.01E+01	2.00E-01
6.18E-04	7.82E+00	3.71E+00	8.21E-02		1.24E-03	1.28E+01	6.42E+00	1.34E-01		2.27E-03	1.94E+01	1.03E+01	2.04E-01
6.36E-04	7.99E+00	3.79E+00	8.39E-02		1.26E-03	1.29E+01	6.49E+00	1.36E-01		2.34E-03	1.98E+01	1.06E+01	2.08E-01
6.55E-04	8.16E+00	3.89E+00	8.57E-02		1.27E-03	1.31E+01	6.57E+00	1.37E-01		2.41E-03	2.02E+01	1.08E+01	2.12E-01
6.75E-04	8.34E+00	3.98E+00	8.76E-02		1.29E-03	1.32E+01	6.64E+00	1.39E-01		2.48E-03	2.06E+01	1.11E+01	2.16E-01
6.95E-04	8.52E+00	4.07E+00	8.95E-02		1.31E-03	1.33E+01	6.72E+00	1.40E-01		2.55E-03	2.10E+01	1.13E+01	2.21E-01
7.16E-04	8.70E+00	4.17E+00	9.14E-02		1.33E-03	1.35E+01	6.80E+00	1.41E-01		2.63E-03	2.14E+01	1.16E+01	2.25E-01
7.38E-04	8.89E+00	4.27E+00	9.33E-02		1.35E-03	1.36E+01	6.88E+00	1.43E-01		2.71E-03	2.19E+01	1.18E+01	2.29E-01
7.60E-04	9.08E+00	4.37E+00	9.53E-02		1.37E-03	1.38E+01	6.96E+00	1.44E-01		2.79E-03	2.23E+01	1.21E+01	2.34E-01
7.83E-04	9.27E+00	4.47E+00	9.74E-02		1.39E-03	1.39E+01	7.04E+00	1.46E-01		2.87E-03	2.28E+01	1.24E+01	2.39E-01
8.06E-04	9.47E+00	4.58E+00	9.94E-02		1.41E-03	1.40E+01	7.12E+00	1.47E-01		2.96E-03	2.32E+01	1.27E+01	2.43E-01
8.30E-04	9.67E+00	4.69E+00	1.02E-01		1.43E-03	1.42E+01	7.21E+00	1.49E-01		3.05E-03	2.37E+01	1.30E+01	2.48E-01
8.55E-04	9.88E+00	4.80E+00	1.04E-01		1.46E-03	1.43E+01	7.29E+00	1.50E-01		3.14E-03	2.41E+01	1.33E+01	2.53E-01
8.81E-04	1.01E+01	4.91E+00	1.06E-01		1.48E-03	1.45E+01	7.37E+00	1.52E-01		3.23E-03	2.46E+01	1.36E+01	2.58E-01
9.07E-04	1.03E+01	5.03E+00	1.08E-01		1.50E-03	1.46E+01	7.46E+00	1.54E-01		3.33E-03	2.51E+01	1.39E+01	2.63E-01
9.21E-04	1.04E+01	5.09E+00	1.09E-01		1.52E-03	1.48E+01	7.55E+00	1.55E-01		3.43E-03	2.56E+01	1.42E+01	2.69E-01
9.35E-04	1.05E+01	5.15E+00	1.10E-01		1.54E-03	1.49E+01	7.63E+00	1.57E-01		3.53E-03	2.61E+01	1.46E+01	2.74E-01
9.49E-04	1.06E+01	5.21E+00	1.12E-01		1.57E-03	1.51E+01	7.72E+00	1.58E-01		3.64E-03	2.66E+01	1.49E+01	2.79E-01
9.63E-04	1.07E+01	5.27E+00	1.13E-01		1.59E-03	1.52E+01	7.81E+00	1.60E-01		3.75E-03	2.79E+01	1.57E+01	2.92E-01
9.69E-04	1.08E+01	5.30E+00	1.13E-01		1.61E-03	1.54E+01	7.90E+00	1.62E-01		3.81E-03	2.82E+01	1.59E+01	2.96E-01

	Gestational Average		
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.86E-03	2.69E+01	1.51E+01	2.83E-01
3.98E-03	2.73E+01	1.53E+01	2.87E-01
4.10E-03	2.78E+01	1.57E+01	2.91E-01
4.22E-03	2.83E+01	1.60E+01	2.97E-01
4.35E-03	2.88E+01	1.63E+01	3.02E-01
4.48E-03	2.94E+01	1.67E+01	3.08E-01
4.61E-03	2.99E+01	1.71E+01	3.14E-01
4.75E-03	3.05E+01	1.75E+01	3.20E-01
4.89E-03	3.11E+01	1.79E+01	3.26E-01
5.04E-03	3.30E+01	1.92E+01	3.47E-01
5.19E-03	3.41E+01	1.99E+01	3.57E-01
5.35E-03	3.48E+01	2.05E+01	3.65E-01
5.51E-03	3.56E+01	2.10E+01	3.73E-01
5.67E-03	3.63E+01	2.15E+01	3.81E-01
5.84E-03	3.70E+01	2.20E+01	3.88E-01
5.93E-03	3.74E+01	2.23E+01	3.92E-01
6.02E-03	3.78E+01	2.26E+01	3.96E-01
6.20E-03	3.85E+01	2.31E+01	4.04E-01
6.38E-03	3.93E+01	2.36E+01	4.12E-01
6.57E-03	4.01E+01	2.42E+01	4.20E-01
6.77E-03	4.08E+01	2.48E+01	4.28E-01
6.98E-03	4.16E+01	2.54E+01	4.37E-01
7.18E-03	4.25E+01	2.60E+01	4.45E-01
7.40E-03	4.33E+01	2.66E+01	4.54E-01
7.51E-03	4.37E+01	2.69E+01	4.58E-01
7.62E-03	4.35E+01	2.68E+01	4.57E-01
7.85E-03	4.42E+01	2.73E+01	4.64E-01
8.09E-03	4.50E+01	2.79E+01	4.72E-01
8.33E-03	4.59E+01	2.85E+01	4.81E-01
8.58E-03	4.68E+01	2.92E+01	4.90E-01
8.71E-03	4.72E+01	2.96E+01	4.95E-01
8.84E-03	4.77E+01	2.99E+01	5.00E-01
9.10E-03	4.86E+01	3.06E+01	5.10E-01
9.37E-03	4.95E+01	3.13E+01	5.19E-01
9.66E-03	5.05E+01	3.21E+01	5.29E-01
9.94E-03	5.15E+01	3.28E+01	5.40E-01
1.02E-02	5.25E+01	3.36E+01	5.50E-01

	Gestational Average		
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
1.06E-02	5.35E+01	3.44E+01	5.61E-01
1.09E-02	5.45E+01	3.52E+01	5.72E-01
1.12E-02	5.56E+01	3.61E+01	5.83E-01
1.15E-02	5.67E+01	3.69E+01	5.94E-01
1.19E-02	5.74E+01	3.75E+01	6.02E-01
1.22E-02	5.85E+01	3.84E+01	6.13E-01
1.26E-02	5.96E+01	3.93E+01	6.25E-01
1.30E-02	6.11E+01	4.05E+01	6.40E-01
1.34E-02	6.23E+01	4.15E+01	6.53E-01
1.38E-02	6.35E+01	4.25E+01	6.66E-01
1.42E-02	6.48E+01	4.36E+01	6.80E-01
1.46E-02	6.70E+01	4.55E+01	7.03E-01
1.50E-02	6.79E+01	4.62E+01	7.12E-01
1.55E-02	6.86E+01	4.68E+01	7.20E-01
1.60E-02	6.99E+01	4.79E+01	7.33E-01
1.64E-02	7.12E+01	4.90E+01	7.47E-01
1.69E-02	7.26E+01	5.02E+01	7.61E-01
1.74E-02	7.39E+01	5.14E+01	7.75E-01
1.80E-02	7.54E+01	5.27E+01	7.90E-01
1.85E-02	7.68E+01	5.40E+01	8.06E-01
1.91E-02	7.83E+01	5.53E+01	8.21E-01
1.96E-02	8.07E+01	5.74E+01	8.46E-01
2.02E-02	8.20E+01	5.86E+01	8.60E-01
2.08E-02	8.34E+01	5.98E+01	8.75E-01
2.14E-02	8.45E+01	6.08E+01	8.86E-01
2.21E-02	8.61E+01	6.23E+01	9.03E-01
2.28E-02	8.78E+01	6.38E+01	9.20E-01
2.34E-02	8.95E+01	6.54E+01	9.38E-01
2.41E-02	9.12E+01	6.70E+01	9.57E-01
2.49E-02	9.32E+01	6.88E+01	9.77E-01
2.56E-02	9.50E+01	7.05E+01	9.96E-01
2.64E-02	9.68E+01	7.22E+01	1.01E+00
2.72E-02	9.86E+01	7.40E+01	1.03E+00
2.80E-02	1.00E+02	7.58E+01	1.05E+00
2.88E-02	1.02E+02	7.76E+01	1.07E+00
2.97E-02	1.04E+02	7.95E+01	1.09E+00
3.06E-02	1.06E+02	8.13E+01	1.11E+00

	Gestational Average		
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
3.15E-02	1.08E+02	8.33E+01	1.13E+00
3.24E-02	1.10E+02	8.53E+01	1.16E+00
3.34E-02	1.12E+02	8.74E+01	1.18E+00
3.44E-02	1.15E+02	8.96E+01	1.20E+00
3.54E-02	1.17E+02	9.18E+01	1.22E+00
3.65E-02	1.19E+02	9.40E+01	1.25E+00
3.76E-02	1.21E+02	9.64E+01	1.27E+00
3.87E-02	1.24E+02	9.87E+01	1.30E+00
3.99E-02	1.26E+02	1.01E+02	1.32E+00
4.11E-02	1.28E+02	1.04E+02	1.35E+00
4.23E-02	1.31E+02	1.06E+02	1.37E+00
4.36E-02	1.33E+02	1.09E+02	1.40E+00
4.49E-02	1.36E+02	1.12E+02	1.42E+00
4.63E-02	1.38E+02	1.14E+02	1.45E+00
4.76E-02	1.41E+02	1.17E+02	1.48E+00
4.91E-02	1.44E+02	1.20E+02	1.51E+00
5.05E-02	1.47E+02	1.23E+02	1.54E+00
5.21E-02	1.49E+02	1.26E+02	1.57E+00
5.36E-02	1.52E+02	1.30E+02	1.60E+00
5.52E-02	1.55E+02	1.33E+02	1.63E+00
5.69E-02	1.59E+02	1.37E+02	1.66E+00
5.86E-02	1.62E+02	1.40E+02	1.70E+00
6.03E-02	1.64E+02	1.43E+02	1.72E+00
6.22E-02	1.67E+02	1.46E+02	1.75E+00
6.40E-02	1.70E+02	1.50E+02	1.78E+00
6.59E-02	1.73E+02	1.54E+02	1.82E+00
6.79E-02	1.77E+02	1.58E+02	1.86E+00
7.00E-02	1.81E+02	1.62E+02	1.89E+00
7.21E-02	1.84E+02	1.66E+02	1.93E+00
7.42E-02	1.88E+02	1.70E+02	1.97E+00
7.64E-02	1.91E+02	1.75E+02	2.01E+00
7.87E-02	1.95E+02	1.79E+02	2.05E+00
8.11E-02	1.99E+02	1.84E+02	2.08E+00
8.35E-02	2.03E+02	1.88E+02	2.12E+00
8.60E-02	2.06E+02	1.93E+02	2.16E+00
8.86E-02	2.10E+02	1.98E+02	2.21E+00
9.13E-02	2.14E+02	2.03E+02	2.25E+00

Gestational Average

Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
9.40E-02	2.19E+02	2.08E+02	2.29E+00
9.68E-02	2.23E+02	2.14E+02	2.34E+00
9.97E-02	2.28E+02	2.20E+02	2.39E+00
1.03E-01	2.32E+02	2.25E+02	2.43E+00
1.06E-01	2.37E+02	2.31E+02	2.48E+00
1.09E-01	2.41E+02	2.37E+02	2.53E+00
1.12E-01	2.46E+02	2.43E+02	2.58E+00
1.16E-01	2.51E+02	2.50E+02	2.63E+00
1.19E-01	2.55E+02	2.56E+02	2.68E+00
1.23E-01	2.60E+02	2.62E+02	2.72E+00
1.26E-01	2.65E+02	2.69E+02	2.78E+00
1.30E-01	2.70E+02	2.76E+02	2.83E+00
1.34E-01	2.75E+02	2.83E+02	2.89E+00
1.38E-01	2.81E+02	2.90E+02	2.94E+00
1.42E-01	2.86E+02	2.98E+02	3.00E+00
1.46E-01	2.92E+02	3.06E+02	3.06E+00
1.51E-01	2.97E+02	3.14E+02	3.12E+00
1.55E-01	3.03E+02	3.22E+02	3.18E+00
1.60E-01	3.09E+02	3.30E+02	3.24E+00
1.65E-01	3.15E+02	3.39E+02	3.30E+00
1.70E-01	3.21E+02	3.48E+02	3.37E+00
1.75E-01	3.27E+02	3.57E+02	3.43E+00
1.80E-01	3.34E+02	3.66E+02	3.50E+00
1.86E-01	3.40E+02	3.76E+02	3.57E+00
1.91E-01	3.47E+02	3.86E+02	3.64E+00
1.97E-01	3.54E+02	3.96E+02	3.71E+00
2.03E-01	3.61E+02	4.07E+02	3.78E+00
2.09E-01	3.68E+02	4.17E+02	3.85E+00
2.15E-01	3.75E+02	4.28E+02	3.93E+00
2.22E-01	3.82E+02	4.40E+02	4.01E+00
2.28E-01	3.90E+02	4.52E+02	4.09E+00
2.35E-01	3.98E+02	4.64E+02	4.17E+00
2.42E-01	4.05E+02	4.76E+02	4.25E+00
2.49E-01	4.13E+02	4.88E+02	4.33E+00
2.57E-01	4.21E+02	5.01E+02	4.42E+00
2.65E-01	4.30E+02	5.14E+02	4.50E+00
2.72E-01	4.38E+02	5.28E+02	4.59E+00

Gestational Average

Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
2.81E-01	4.47E+02	5.42E+02	4.68E+00
2.89E-01	4.56E+02	5.57E+02	4.78E+00
2.98E-01	4.65E+02	5.72E+02	4.87E+00
3.07E-01	4.74E+02	5.87E+02	4.97E+00
3.16E-01	4.83E+02	6.03E+02	5.06E+00
3.25E-01	4.93E+02	6.19E+02	5.16E+00
3.35E-01	5.02E+02	6.35E+02	5.26E+00
3.45E-01	5.12E+02	6.52E+02	5.37E+00
3.56E-01	5.23E+02	6.70E+02	5.48E+00
3.66E-01	5.33E+02	6.88E+02	5.59E+00
3.77E-01	5.44E+02	7.07E+02	5.70E+00
3.89E-01	5.55E+02	7.26E+02	5.81E+00
4.00E-01	5.65E+02	7.45E+02	5.93E+00
4.12E-01	5.77E+02	7.66E+02	6.05E+00
4.25E-01	5.89E+02	7.87E+02	6.17E+00
4.37E-01	6.00E+02	8.08E+02	6.29E+00
4.50E-01	6.12E+02	8.29E+02	6.42E+00
4.64E-01	6.25E+02	8.52E+02	6.55E+00
4.78E-01	6.37E+02	8.76E+02	6.68E+00
4.92E-01	6.50E+02	8.98E+02	6.81E+00
5.07E-01	6.63E+02	9.23E+02	6.95E+00
5.22E-01	6.76E+02	9.48E+02	7.09E+00
5.38E-01	6.90E+02	9.74E+02	7.23E+00
5.54E-01	7.04E+02	1.00E+03	7.38E+00
5.71E-01	7.18E+02	1.03E+03	7.53E+00
5.88E-01	7.32E+02	1.06E+03	7.68E+00
6.05E-01	7.47E+02	1.08E+03	7.83E+00
6.23E-01	7.62E+02	1.11E+03	7.99E+00
6.42E-01	7.78E+02	1.14E+03	8.15E+00
6.61E-01	7.94E+02	1.18E+03	8.32E+00
6.81E-01	8.10E+02	1.21E+03	8.49E+00
7.02E-01	8.26E+02	1.24E+03	8.66E+00
7.23E-01	8.43E+02	1.28E+03	8.84E+00
7.44E-01	8.61E+02	1.31E+03	9.02E+00
7.67E-01	8.78E+02	1.35E+03	9.21E+00
7.90E-01	8.96E+02	1.38E+03	9.40E+00
8.13E-01	9.15E+02	1.42E+03	9.59E+00

Gestational Average

Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
8.38E-01	9.33E+02	1.46E+03	9.79E+00
8.63E-01	9.53E+02	1.50E+03	9.99E+00
8.89E-01	9.72E+02	1.54E+03	1.02E+01
9.16E-01	9.93E+02	1.59E+03	1.04E+01
9.43E-01	1.01E+03	1.63E+03	1.06E+01
9.71E-01	1.03E+03	1.68E+03	1.08E+01
1.00E+00	1.06E+03	1.72E+03	1.11E+01
1.03E+00	1.08E+03	1.77E+03	1.13E+01
1.06E+00	1.10E+03	1.82E+03	1.15E+01
1.09E+00	1.12E+03	1.87E+03	1.18E+01
1.13E+00	1.15E+03	1.92E+03	1.20E+01
1.16E+00	1.17E+03	1.98E+03	1.23E+01
1.19E+00	1.20E+03	2.03E+03	1.25E+01
1.23E+00	1.22E+03	2.09E+03	1.28E+01
1.27E+00	1.25E+03	2.15E+03	1.31E+01
1.31E+00	1.27E+03	2.21E+03	1.33E+01
1.34E+00	1.30E+03	2.27E+03	1.36E+01
1.38E+00	1.33E+03	2.33E+03	1.39E+01
1.43E+00	1.35E+03	2.40E+03	1.42E+01
1.47E+00	1.38E+03	2.46E+03	1.45E+01
1.51E+00	1.41E+03	2.53E+03	1.48E+01
1.56E+00	1.44E+03	2.60E+03	1.51E+01
1.61E+00	1.47E+03	2.68E+03	1.55E+01
1.65E+00	1.51E+03	2.75E+03	1.58E+01
1.70E+00	1.54E+03	2.83E+03	1.61E+01
1.75E+00	1.57E+03	2.91E+03	1.65E+01
1.81E+00	1.61E+03	2.99E+03	1.68E+01
1.86E+00	1.64E+03	3.08E+03	1.72E+01
1.92E+00	1.68E+03	3.16E+03	1.76E+01
1.97E+00	1.71E+03	3.25E+03	1.79E+01
2.03E+00	1.75E+03	3.34E+03	1.83E+01
2.09E+00	1.79E+03	3.44E+03	1.87E+01
2.16E+00	1.83E+03	3.54E+03	1.91E+01
2.22E+00	1.87E+03	3.64E+03	1.96E+01
2.29E+00	1.91E+03	3.74E+03	2.00E+01
2.36E+00	1.95E+03	3.85E+03	2.04E+01
2.43E+00	1.99E+03	3.95E+03	2.09E+01

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
2.50E+00	2.04E+03	4.07E+03	2.13E+01
2.58E+00	2.08E+03	4.18E+03	2.18E+01
2.65E+00	2.13E+03	4.30E+03	2.23E+01
2.73E+00	2.17E+03	4.42E+03	2.28E+01
2.82E+00	2.22E+03	4.55E+03	2.33E+01
2.90E+00	2.27E+03	4.68E+03	2.38E+01
2.99E+00	2.32E+03	4.81E+03	2.44E+01
3.08E+00	2.38E+03	4.95E+03	2.49E+01
3.17E+00	2.43E+03	5.09E+03	2.55E+01
3.26E+00	2.48E+03	5.24E+03	2.60E+01
3.36E+00	2.54E+03	5.39E+03	2.66E+01
3.46E+00	2.60E+03	5.54E+03	2.72E+01
3.57E+00	2.66E+03	5.70E+03	2.79E+01
3.67E+00	2.72E+03	5.86E+03	2.85E+01
3.78E+00	2.78E+03	6.03E+03	2.91E+01
3.90E+00	2.84E+03	6.20E+03	2.98E+01
4.01E+00	2.91E+03	6.38E+03	3.05E+01
4.13E+00	2.98E+03	6.56E+03	3.12E+01
4.26E+00	3.04E+03	6.75E+03	3.19E+01
4.39E+00	3.12E+03	6.95E+03	3.27E+01
4.52E+00	3.19E+03	7.15E+03	3.34E+01
4.65E+00	3.26E+03	7.35E+03	3.42E+01
4.79E+00	3.34E+03	7.56E+03	3.50E+01
4.94E+00	3.42E+03	7.78E+03	3.58E+01
5.08E+00	3.50E+03	8.01E+03	3.66E+01
5.24E+00	3.58E+03	8.24E+03	3.75E+01
5.39E+00	3.66E+03	8.47E+03	3.84E+01
5.56E+00	3.75E+03	8.72E+03	3.93E+01
5.72E+00	3.84E+03	8.97E+03	4.02E+01
5.89E+00	3.93E+03	9.23E+03	4.12E+01
6.07E+00	4.02E+03	9.50E+03	4.22E+01
6.25E+00	4.12E+03	9.77E+03	4.32E+01
6.44E+00	4.22E+03	1.01E+04	4.42E+01
6.63E+00	4.32E+03	1.03E+04	4.53E+01
6.83E+00	4.42E+03	1.06E+04	4.64E+01
7.04E+00	4.53E+03	1.10E+04	4.75E+01
7.25E+00	4.64E+03	1.13E+04	4.86E+01

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
7.47E+00	4.75E+03	1.16E+04	4.98E+01
7.69E+00	4.87E+03	1.19E+04	5.10E+01
7.92E+00	4.99E+03	1.23E+04	5.23E+01
8.16E+00	5.11E+03	1.26E+04	5.36E+01
8.40E+00	5.24E+03	1.30E+04	5.49E+01
8.66E+00	5.37E+03	1.34E+04	5.62E+01
8.92E+00	5.50E+03	1.38E+04	5.76E+01
9.18E+00	5.63E+03	1.42E+04	5.91E+01
9.46E+00	5.77E+03	1.46E+04	6.05E+01
9.74E+00	5.92E+03	1.50E+04	6.20E+01
1.00E+01	6.07E+03	1.54E+04	6.36E+01
1.06E+01	6.37E+03	1.63E+04	6.68E+01
1.13E+01	6.69E+03	1.73E+04	7.01E+01
1.20E+01	7.03E+03	1.83E+04	7.37E+01
1.27E+01	7.39E+03	1.94E+04	7.74E+01
1.34E+01	7.76E+03	2.05E+04	8.14E+01
1.42E+01	8.16E+03	2.17E+04	8.56E+01
1.51E+01	8.59E+03	2.30E+04	9.00E+01
1.60E+01	9.03E+03	2.43E+04	9.47E+01
1.70E+01	9.50E+03	2.57E+04	9.96E+01
1.80E+01	1.00E+04	2.72E+04	1.05E+02
1.90E+01	1.05E+04	2.88E+04	1.10E+02
2.02E+01	1.11E+04	3.05E+04	1.16E+02
2.14E+01	1.17E+04	3.23E+04	1.22E+02
2.27E+01	1.23E+04	3.42E+04	1.29E+02
2.40E+01	1.30E+04	3.62E+04	1.36E+02
2.55E+01	1.37E+04	3.83E+04	1.43E+02
2.70E+01	1.44E+04	4.06E+04	1.51E+02
2.86E+01	1.52E+04	4.30E+04	1.59E+02
3.04E+01	1.60E+04	4.55E+04	1.68E+02
3.22E+01	1.69E+04	4.82E+04	1.77E+02
3.41E+01	1.78E+04	5.10E+04	1.87E+02
3.62E+01	1.88E+04	5.40E+04	1.97E+02
3.83E+01	1.99E+04	5.71E+04	2.08E+02
4.06E+01	2.10E+04	6.05E+04	2.20E+02
4.31E+01	2.21E+04	6.40E+04	2.32E+02
4.57E+01	2.34E+04	6.78E+04	2.45E+02

Gestational Average			
Intake (ng/kg-day)	Fat (ng/kg)	Body Burden (ng/kg)	Blood (ng/kg)
4.84E+01	2.47E+04	7.18E+04	2.59E+02
5.13E+01	2.61E+04	7.60E+04	2.73E+02
5.44E+01	2.75E+04	8.04E+04	2.89E+02
5.76E+01	2.91E+04	8.51E+04	3.05E+02
6.11E+01	3.08E+04	9.01E+04	3.22E+02
6.48E+01	3.25E+04	9.53E+04	3.41E+02
6.86E+01	3.44E+04	1.01E+05	3.60E+02
7.28E+01	3.63E+04	1.07E+05	3.81E+02
7.71E+01	3.84E+04	1.13E+05	4.03E+02
8.18E+01	4.06E+04	1.20E+05	4.26E+02
8.67E+01	4.30E+04	1.26E+05	4.51E+02
9.19E+01	4.55E+04	1.34E+05	4.77E+02
9.74E+01	4.81E+04	1.42E+05	5.04E+02
1.03E+02	5.09E+04	1.50E+05	5.33E+02
1.09E+02	5.38E+04	1.58E+05	5.64E+02
1.16E+02	5.70E+04	1.68E+05	5.97E+02
1.23E+02	6.03E+04	1.77E+05	6.32E+02
1.30E+02	6.38E+04	1.87E+05	6.69E+02
1.38E+02	6.76E+04	1.98E+05	7.08E+02
1.46E+02	7.15E+04	2.09E+05	7.50E+02

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APPENDIX F

Epidemiological Kinetic Modeling

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NOTICE

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APPENDIX F. EPIDEMIOLOGICAL KINETIC MODELING

F.1. DERIVATION OF BACKGROUND CONCENTRATION

Background intakes for the Seveso cohort were estimated from information from two separate studies. The details of the modeling and the estimated background intakes are described in this section.

F.1.1. Needham et al. (1998)

F.1.1.1. *Summary of Modeling Approach*

Needham et al. (1998)reported lipid adjusted serum concentrations in 11 pools of individuals in the non-ABR region near the site of the Seveso TCDD accident in July, 1976. The individuals in this region did not suffer exposure from the event and represent a control population in the study. There were 4−10 individuals per pool, and the median LASC concentration across the pools was reported by the study authors to be 15 ppt.

All subjects in the pooled samples were above age 25, but no further details about age are given in the study. Mocarelli et al. (1991) reported details about 10 subjects in the non-ABR region at the time of serum sample collection in 1976. The oldest individual in this sample was 46. In the absence of other information, this age was used as an upper bound, suggesting a median age (between 25 and 46) of approximately 35 years old.

The Emond model is not coded to allow the background intake to vary in time. Thus, it was assumed that the background intake remained constant over the lifetime of the individual. The Emond model was used to determine the chronic daily intake which gives a terminal concentration of 15 ppt at the age of 35 for both women and men. The background intake was then rounded to the nearest 1E−05 ng/kg-day.

F.1.1.2. *Input for Continuous Exposure to Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 306600. % AGE AT MEASUREMENT (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
```

```
BCK_TIME_ON  = 0. % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 306600. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 306600. % AGE AT MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.       % NO BACKGROUND EXPOSURE (0 NG/KG/DAY)

% CONTINUOUS EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 3.5E-4 % MALES

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ
```

F.1.1.3. *Needham et al. ([1998](#)) Results*

Table F-1. Estimated Background Intakes for Needham et al. ([1998](#))

Average age at measurement (years)	Measured LASC (ppt)	Continuous intake matching measured LASC (ng/kg/day)
35	15	3.5E−04 (males)
		3.9E−04 (females)

F.1.2. Eskenazi et al. ([2004](#))

F.1.2.1. *Summary of Modeling Approach*

Eskenazi et al. ([2004](#)) reported TCDD levels in pooled samples from individuals living in

zone non-ABR in 1976. Table 3 in that study reports mean TCDD for three different age groups.

As an alternative background intake for endpoints measured in children compared with the

Needham background, the 0−12 age group was used to determine chronic intakes using the

Emond model. The two pooled sample results were averaged to give a target TCDD level of

40.5 ppt. It was assumed that both males and females had this average concentration. The

Emond model was run until the chronic intake gave an average LASC of 40.5 when averaged

between ages 0 and 12. The background intake was then rounded to the

nearest 1E−05 ng/kg-day.

F.1.2.2. *Input for Continuous Exposure to Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 105120. % UPPER AGE RANGE IN SAMPLE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 105120. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 105120. % UPPER AGE RANGE IN SAMPLE (HOURS)
MSTOTBCKGR   = 0.      % NO BACKGROUND EXPOSURE (0 NG/KG/DAY)

% CONTINUOUS EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 4.22E-3 % MALES

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
mean(_cbsngkgliadj)
```

F.1.2.3. *Eskenazi et al. (2004) Results*

Table F-2. Estimated Background Intakes for Eskenazi et al. (2004)

Average age at measurement (years)	Measured LASC (ppt)	Continuous intake matching measured LASC (ng/kg-day)
0−12	40.5	4.22E−03 (males)
		4.29E−03 (females)

F.2. KINETIC MODELING OF EPIDEMIOLOGICAL STUDIES CONSIDERED FOR RfD

F.2.1. Baccarelli et al. (2008)

F.2.1.1. *Input for Exposure During Pregnancy*

```
% EXPOSURE PARAMETERS
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 401190. % LENGTH OF CRITICAL WINDOW (HOURS)
```

```
DAY_CYCLE     = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON   = 401190. % AGE AT BEGINNING OF BACKGROUND EXPOSURE (HOURS)
BCK_TIME_OFF  = 401190. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
CONCEPTION_T  = 262800. % AGE AT CONCEPTION (HOURS)
TIMELIMIT     = 269184. % AGE AT END OF PREGNANCY (HOURS)
TRANSTIME_ON  = 264312. % AGE AT MOTHER-FETUS EXCHANGE (HOURS)
MSTOTBCKGR    = 0.      % NO BACKGROUND EXPOSURE (0 NG/KG/DAY)

% CONTINUOUS EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 0.021 % MATCHING MATERNAL LASC OF 235 NG/KG
```

F.2.1.2. *Baccarelli et al. ([2008](#)) Results*

Table F-3. Estimated continuous intake corresponding to maternal serum concentration

Variable	Value	Notes
Infant b-TSH	5 μU/mL	BMR
Maternal lipid adjusted serum	235 ng/kg	From Figure 2A
Intake	0.020 ng/kg-day	From Emond model; pregnancy at 30 years

TSH = thyroid stimulating hormone; BMR = benchmark response.

F.2.2. Mocarelli et al. ([2008](#))

F.2.2.1. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5.
CINT = 1.
EXP_TIME_ON  = 54312.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 54335.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 58692.  % AGE AT LASC MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.00035 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)

% EVENT EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 8.2   % 1ST QUARTILE
      % 22.5  % 2ND QUARTILE
      % 78.4  % 3RD QUARTILE
      % 231.9 % 4TH QUARTILE

% HUMAN VARIABLE PARAMETERS
```

```
1   MALE   = 1.
2   FEMALE = 0.
3   Y0     = 0. % AGE AT BEGINNING OF SIMULATION
4
5   % POST-PROCESSING
6   start @nocallback
7   CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==58524):length(_t)))
8
9
```

F.2.2.2. *Input for Exposure from Event to End of Critical Window*

```
11  % MODEL PARAMETERS
12  output @clear
13  prepare @clear T CBSNGKGLIADJ CBNGKG
14
15  % EXPOSURE PARAMETERS
16  MAXT = 0.5.
17  CINT = 1.
18  EXP_TIME_ON  = 54312.  % AGE AT EXPOSURE (HOURS)
19  EXP_TIME_OFF = 54335.  % AGE AT END OF EXPOSURE (HOURS)
20  DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
21  BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
22  BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
23  TIMELIMIT    = 87600.  % LENGTH OF CRITICAL WINDOW (HOURS)
24  MSTOTBCKGR   = 0.00035 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)
25
26  % EVENT EXPOSURE DOSE (NG/KG/DAY)
27  MSTOT = 8.2   % 1ST QUARTILE
28        % 22.5  % 2ND QUARTILE
29        % 78.4  % 3RD QUARTILE
30        % 231.9 % 4TH QUARTILE
31
32  % HUMAN VARIABLE PARAMETERS
33  MALE   = 1.
34  FEMALE = 0.
35  Y0     = 0. % AGE AT BEGINNING OF SIMULATION
36
37  % POST-PROCESSING
38  start @nocallback
39  meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
40  meanCBSNGKGLIADJ
41  maxCBSNGKGLIADJ=max(_cbsngkgliadj);
42  maxCBSNGKGLIADJ
43
44
```

F.2.2.3. *Input for Continuous Exposure over Critical Window*

```
46  % MODEL PARAMETERS
47  output @clear
48  prepare @clear T CBSNGKGLIADJ CBNGKG
49
50  % EXPOSURE PARAMETERS
51  MAXT = 0.5.
52  CINT = 1.
53  EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
54  EXP_TIME_OFF = 87601.  % LENGTH OF CRITICAL WINDOW (HOURS)
55  DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
```

```
1  BCK_TIME_ON  = 0.       % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
2  BCK_TIME_OFF = 613200.  % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
3  TIMELIMIT    = 87600.   % LENGTH OF CRITICAL WINDOW (HOURS)
4  MSTOTBCKGR   = 0.       % NO BACKGROUND EXPOSURE (0 NG/KG/DAY)
5
6  % CONTINUOUS EXPOSURE DOSE (NG/KG/DAY)
7  MSTOT = 7.97E-3 % 1ST QUARTILE - MATCHING MEAN
8        % 2.08E-2 % 2ND QUARTILE - MATCHING MEAN
9        % 7.21E-2 % 3RD QUARTILE - MATCHING MEAN
10       % 2.12E-1 % 4TH QUARTILE - MATCHING MEAN
11       % 3.21E-2 % 1ST QUARTILE - MATCHING MAX
12       % 1.41E-1 % 2ND QUARTILE - MATCHING MAX
13       % 8.73E-1 % 3RD QUARTILE - MATCHING MAX
14       % 3.89E+0 % 4TH QUARTILE - MATCHING MAX
15
16 % HUMAN VARIABLE PARAMETERS
17 MALE   = 1.
18 FEMALE = 0.
19 Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION
20
21 % POST-PROCESSING
22 start @nocallback
23 meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
24 maxCBSNGKGLIADJ=max(_cbsngkgliadj);
25
26
```

F.2.2.4. *Mocarelli ([2008](#)) Results*

Table F-4. Matching peak and average after pulse to chronic intake for Mocarelli et al. ([2008](#))

Subject modeled	Quartile	Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	Average of continuous intake rates (ng/kg-day)
									TEQ
Needham background									
Male	1st	68	8.2	57.7	7.97E−03	249.0	3.21E−02	2.01E−02	2.32E−02
Male	2nd	142	22.5	116.8	2.08E−02	668.7	1.41E−01	8.08E−02	8.39E−02
Male	3rd	345	78.4	276.7	7.21E−02	2288.7	8.73E−01	4.73E−01	4.76E−01
Male	4th	733	231.9	579.4	2.12E−01	6658.9	3.89E+00	2.05E+00	2.06E+00

LASC = lipid adjusted serum concentration.

F.2.3. Alaluusua et al. ([2004](#))

F.2.3.1. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 21900.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 21923.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 26280.  % AGE AT LASC MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.00035 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)

% EVENT EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 10.9   % 1ST TERTILE - MALE
      % 10.4   % 1ST TERTILE - FEMALE
      % 105.9  % 2ND TERTILE - MALE
      % 102.3  % 2ND TERTILE - FEMALE
      % 3419.2 % 3RD TERTILE - MALE
      % 4266.1 % 3RD TERTILE - FEMALE

% HUMAN VARIABLE PARAMETERS
MALE  = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==26112):length(_t)))
```

F.2.3.2. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 21900.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 21923.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 43800.  % LENGTH OF CRITICAL WINDOW (HOURS)
MSTOTBCKGR   = 0.00035 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)

% EVENT EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 10.9   % 1ST TERTILE - MALE
      % 10.4   % 1ST TERTILE - FEMALE
```

```
        % 105.9  % 2ND TERTILE - MALE
        % 102.3  % 2ND TERTILE - FEMALE
        % 3419.2 % 3RD TERTILE - MALE
        % 4266.1 % 3RD TERTILE - FEMALE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
meanCBSNGKGLIADJ
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
maxCBSNGKGLIADJ
```

F.2.3.3. *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 43801.  % LENGTH OF CRITICAL WINDOW (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 43800.  % LENGTH OF CRITICAL WINDOW (HOURS)
MSTOTBCKGR   = 0.      % NO BACKGROUND EXPOSURE (0 NG/KG/DAY)

% CONTINUOUS EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 1.62E-2 % 1ST TERTILE - MALE   - MATCHING MEAN
      % 1.51E-2 % 1ST TERTILE - FEMALE - MATCHING MEAN
      % 1.53E-1 % 2ND TERTILE - MALE   - MATCHING MEAN
      % 1.44E-1 % 2ND TERTILE - FEMALE - MATCHING MEAN
      % 4.94E+0 % 3RD TERTILE - MALE   - MATCHING MEAN
      % 4.68E+0 % 3RD TERTILE - FEMALE - MATCHING MEAN
      % 6.95E-2 % 1ST TERTILE - MALE   - MATCHING MAX
      % 6.15E-2 % 1ST TERTILE - FEMALE - MATCHING MAX
      % 1.72E+0 % 2ND TERTILE - MALE   - MATCHING MAX
      % 1.58E+0 % 2ND TERTILE - FEMALE - MATCHING MAX
      % 1.14E+2 % 3RD TERTILE - MALE   - MATCHING MAX
      % 1.08E+2 % 3RD TERTILE - FEMALE - MATCHING MAX

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
```

```
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
```

F.2.3.4. *Alaluusua et al. ([2004](#)) Results*

Table F-5. Matching peak and average after pulse to chronic intake for Alaluusua et al. ([2004](#))

| Subject modeled | Tertile | TCDD Only | | | | | | | | TEQ |
		Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	Average of male and female continuous intake rates (ng/kg-day)	Average of continuous intake rates (ng/kg-day)
Needham Background										
Male	1st	72.1	10.9	61.8	1.62E−02	286.7	6.95E−02	4.28E−02	4.06E−02	4.39E−02
Female			10.4	62.1	1.51E−02	271.2	6.15E−02	3.83E−02		
Male	2nd	375.4	105.9	316.3	1.53E−01	2626.9	1.72E+00	9.34E−01	8.97E-01	9.01E-01
Female			102.3	318.1	1.44E−01	2536.8	1.58E+00	8.60E−01		
Male	3rd	4266.1	3419.2	3559.0	4.94E+00	79877.5	1.14E+02	5.95E+01	5.79E+01	5.79E+01
Female			4266.1	3581.9	4.68E+00	78251.9	1.08E+02	5.64E+01		

LASC = lipid adjusted serum concentration.

F.2.4. Eskanazi et al. ([2002](#))

F.2.4.1. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 58692.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 58715.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 63072.  % AGE AT LASC MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)

% EVENT EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 5.4    % 28-DAY   EC GROUP
       % 2684.8 % Over 1000 ppt GROUP
```

```
1
2    % HUMAN VARIABLE PARAMETERS
3    MALE   = 0.
4    FEMALE = 1.
5    Y0     = 0. % AGE AT BEGINNING OF SIMULATION
6
7    % POST-PROCESSING
8    start @nocallback
9    CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==62904):length(_t)))
10
11
```

F.2.4.2. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
13   % MODEL PARAMETERS
14   output @clear
15   prepare @clear T CBSNGKGLIADJ CBNGKG
16
17   % EXPOSURE PARAMETERS
18   MAXT = 0.5
19   CINT = 1.
20   EXP_TIME_ON  = 58692.  % AGE AT EXPOSURE (HOURS)
21   EXP_TIME_OFF = 58715.  % AGE AT END OF EXPOSURE (HOURS)
22   DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
23   BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
24   BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
25   TIMELIMIT    = 113880. % LENGTH OF CRITICAL WINDOW (HOURS)
26   MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)
27
28   % EVENT EXPOSURE DOSE (NG/KG/DAY)
29   MSTOT = 5.4    % 28-DAY   EC GROUP
30         % 2684.8 % Over 1000 ppt GROUP
31
32   % HUMAN VARIABLE PARAMETERS
33   MALE   = 0.
34   FEMALE = 1.
35   Y0     = 0. % AGE AT BEGINNING OF SIMULATION
36
37   % POST-PROCESSING
38   start @nocallback
39   meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
40   meanCBSNGKGLIADJ
41   maxCBSNGKGLIADJ=max(_cbsngkgliadj);
42   maxCBSNGKGLIADJ
43
44
```

F.2.4.3. *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
46   % MODEL PARAMETERS
47   output @clear
48   prepare @clear T CBSNGKGLIADJ CBNGKG
49
50   % EXPOSURE PARAMETERS
51   MAXT = 0.5
52   CINT = 1.
53   EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
54   EXP_TIME_OFF = 113881. % LENGTH OF CRITICAL WINDOW (HOURS)
55   DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
```

```
1  BCK_TIME_ON  = 0.        % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
2  BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
3  TIMELIMIT    = 113880. % LENGTH OF CRITICAL WINDOW (HOURS)
4  MSTOTBCKGR   = 0.        % NO BACKGROUND EXPOSURE (0 NG/KG/DAY)
5
6  % CONTINUOUS EXPOSURE DOSE (NG/KG/DAY)
7  MSTOT = 3.64E-3 % 28-DAY   EC EXPOSURE GROUP - MATCHING MEAN
8          % 1.51E+0 % Over 1000 ppt EXPOSURE GROUP - MATCHING MEAN
9          % 1.68E-2 % 28-DAY   EC EXPOSURE GROUP - MATCHING MAX
10         % 6.06E+1 % Over 1000 ppt EXPOSURE GROUP - MATCHING MAX
11
12 % HUMAN VARIABLE PARAMETERS
13 MALE   = 1.
14 FEMALE = 0.
15 Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION
16
17 % POST-PROCESSING
18 start @nocallback
19 meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
20 maxCBSNGKGLIADJ=max(_cbsngkgliadj);
21
22
```

23 **F.2.4.4. *Eskenazi et al. ([2002](#)) Results***

24

25

26 **Table F-6. Matching peak and average after pulse to chronic intake for**
27 **Eskenazi et al. ([2002](#))**

28

		TCDD Only							TEQ
Subject modeled	Exposure group	Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	Average of continuous intake rates (ng/kg-day)
Needham background									
Female	28-day EC	50	5.4	37.3	3.64E-03	166.9	1.68E−02	1.02E−02	1.37E−02
Female	Over 1,000 ppt	4,060	2684.8	2548.8	1.51E+00	74597.2	6.06E+01	3.11E+01	3.11E+01

29
30 LASC = lipid adjusted serum concentration; EC = estrous cycle.

F.3. KINETIC MODELING OF EPIDEMIOLOGICAL STUDIES FOR SENSITIVITY ANALYSIS

F.3.1. Alaluusua et al. (2004)

F.3.1.1. *Summary of Modeling Approach*

For the sensitivity analysis, modeling for Alaluusua et al. (2004) (detailed in Section 4.2.3.3) was repeated using alternative male and female background intakes estimated from Eskenazi et al. (2004) for children aged 0−12 as described in Section F.1.2. EPA used the Emond human PBPK model to estimate continuous daily oral TCDD intakes for each exposure tertile from corresponding measured LASC values estimated by calculating the geometric mean of the tertile ranges provided by Alaluusua et al. (2004). Serum levels were measured within one year of the incident; in the absence of further specific information about measurement lag, a lag time of 6 months between the event and the measurement was assumed. This value was then used to model the associated peak and mean LASC from time of the event (average age 2.5 years) to the end of the critical window (5 years). Continuous daily intakes matching the peak and mean LASC were determined by modeling exposure from birth to the end of the critical exposure window. Male and female estimates were modeled separately and then averaged to give a single continuous intake estimate for each exposure tertile.

As part of the sensitivity analysis, total TEQ intake was estimated by adding the background intake of all other dioxin-like compounds (DLCs) to the calculated TCDD intake. For the modeling approach used for derivation of the RfD using the Needham et al. (1998) background value, total background TEQ intake was estimated to be ten times the background TCDD (see Section 4.5.3). Thus, the additive background DLC intake was calculated to be nine times the background TCDD intake. This additive background DLC factor was then added to the modeled TCDD intake values to estimate total TEQ intakes. Additive factors were calculated for both males (3.15×10^{-3} ng/kg-day) and females (3.51×10^{-3} ng/kg-day).

For the modeling approach using the Eskenazi et al. (2004) background value, total TEQ intake was estimated from TEQ and TCDD intakes provided in the study in Table 3. The study TCDD concentration was first subtracted from the study TEQ concentration to calculate the additive DLC concentration. Because new toxic equivalency factors (TEFs) were published in 2005, this additive DLC concentration was multiplied by a factor of 0.7 to account for the difference between the current TEFs and those used by Eskenazi et al.(2004). This preliminary additive DLC concentration was added to the study TCDD concentration to calculate a total TEQ

1 concentration. EPA then used the Emond human PBPK model to find a continuous intake

2 producing the total TEQ concentration from birth to age 12. The estimated Eskenazi et al.

3 (2004) background TCDD intake was subtracted from this modeled total TEQ background intake

4 to provide an additive DLC background intake. This additive factor was then applied to the

5 modeled TCDD concentrations of each exposure tertile. Additive factors were calculated for

6 both males (9.08×10^{-3} ng/kg-day) and females (9.11×10^{-3} ng/kg-day).

7
8
9 **Table F-7. Model inputs derived from study details for Alaluusua et al.**
10 **(2004)**
11

Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Critical exposure window (years)
2.5	0.5	2.5	5

12
13 LASC = lipid adjusted serum concentration.
14
15

16 **F.3.1.2. *Input for Exposure from Event to LASC Measurement***

```
17 % MODEL PARAMETERS
18 output @clear
19 prepare @clear T CBSNGKGLIADJ CBNGKG
20
21 % EXPOSURE PARAMETERS
22 MAXT = 0.5
23 CINT = 1.
24 EXP_TIME_ON  = 21900.  % AGE AT EXPOSURE (HOURS)
25 EXP_TIME_OFF = 21923.  % AGE AT END OF EXPOSURE (HOURS)
26 DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
27 BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
28 BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
29 TIMELIMIT    = 26280.  % AGE AT LASC MEASUREMENT (HOURS)
30 MSTOTBCKGR   = 0.00422 % ESKENAZI BACKGROUND EXPOSURE DOSE (NG/KG/DAY)
31
32 % EVENT EXPOSURE DOSE (NG/KG/DAY)
33 MSTOT = 8.2    % 1ST TERTILE - MALE
34       % 7.5    % 1ST TERTILE - FEMALE
35       % 103.1  % 2ND TERTILE - MALE
36       % 99.4   % 2ND TERTILE - FEMALE
37       % 3416.5 % 3RD TERTILE - MALE
38       % 3343.3 % 3RD TERTILE - FEMALE
39
40 % HUMAN VARIABLE PARAMETERS
41 MALE   = 1.
42 FEMALE = 0.
43 Y0     = 0. % AGE AT BEGINNING OF SIMULATION
44
```

```
% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==26112):length(_t)))
```

F.3.1.3. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 21900.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 21923.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 43800.  % LENGTH OF CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.00422 % ESKENAZI BACKGROUND EXPOSURE DOSE (NG/KG/DAY)

% EVENT EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 8.2    % 1ST TERTILE - MALE
      % 7.5    % 1ST TERTILE - FEMALE
      % 103.1  % 2ND TERTILE - MALE
      % 99.4   % 2ND TERTILE - FEMALE
      % 3416.5 % 3RD TERTILE - MALE
      % 3343.3 % 3RD TERTILE - FEMALE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
meanCBSNGKGLIADJ
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
maxCBSNGKGLIADJ
```

F.3.1.4. *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 43801.  % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
```

```
1   TIMELIMIT   = 43800.  % LENGTH OF CRITICAL EXPOSURE WINDOW (HOURS)
2   MSTOTBCKGR  = 0.       % NO BACKGROUND EXPOSURE (0 NG/KG/DAY)
3
4   % CONTINUOUS EXPOSURE DOSE (NG/KG/DAY)
5   MSTOT = 1.81E-2 % 1ST TERTILE - MALE   - MATCHING MEAN
6         % 1.69E-2 % 1ST TERTILE - FEMALE - MATCHING MEAN
7         % 1.56E-1 % 2ND TERTILE - MALE   - MATCHING MEAN
8         % 1.46E-1 % 2ND TERTILE - FEMALE - MATCHING MEAN
9         % 4.94E+0 % 3RD TERTILE - MALE   - MATCHING MEAN
10        % 4.68E+0 % 3RD TERTILE - FEMALE - MATCHING MEAN
11        % 4.70E-2 % 1ST TERTILE - MALE   - MATCHING MAX
12        % 4.04E-2 % 1ST TERTILE - FEMALE - MATCHING MAX
13        % 1.58E+0 % 2ND TERTILE - MALE   - MATCHING MAX
14        % 1.45E+0 % 2ND TERTILE - FEMALE - MATCHING MAX
15        % 1.13E+2 % 3RD TERTILE - MALE   - MATCHING MAX
16        % 1.07E+2 % 3RD TERTILE - FEMALE - MATCHING MAX
17
18  % HUMAN VARIABLE PARAMETERS
19  MALE   = 1.
20  FEMALE = 0.
21  Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION
22
23  % POST-PROCESSING
24  start @nocallback
25  meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
26  maxCBSNGKGLIADJ=max(_cbsngkgliadj);
27
28
29
```

F.3.1.5. *Alaluusua et al. (2004) Results*

**Table F-8. Matching peak and average after pulse to chronic intake for
Alaluusua et al. (2004) using alternate background value**

Subject modeled	Tertile	Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	Average of male and female continuous intake rates (ng/kg-day)	TEQ — Average of male and female continuous intake rates (ng/kg-day)
Eskenazi background										
Male	1st	72.1	8.2	67.5	1.81E−02	218.4	4.70E−02	3.25E−02	3.06E−02	3.97E−02
Female			7.5	68.0	1.69E−02	203.0	4.04E−02	2.87E−02		
Male	2nd	375.4	103.1	319.4	1.56E−01	2479.1	1.58E+00	8.68E−01	8.32E−01	8.41E−01
Female			99.4	321.2	1.46E−01	2390.4	1.45E+00	7.97E−01		
Male	3rd	4266.1	3416.5	3560.0	4.94E+00	79502.9	1.13E+02	5.92E+01	5.76E+01	5.76E+01
Female			3343.3	3582.9	4.68E+00	77847.7	1.07E+02	5.61E+01		

LASC = lipid adjusted serum concentration.

F.3.2. Baccarelli et al. (2008)

F.3.2.1. *Summary of Modeling Approach*

For the sensitivity analysis, total TEQ intakes were estimated. For Baccarelli et al.

(2008), total TEQ exposure was obtained from Figure 2-D by digitizing the figure and finding

the TEQ concentration on the regression line associated with a b-TSH of 5 µU/mL (489 ppt).

Modeling was then repeated as described in Section F.3.1.1 to determine the continuous daily

intake associated with this concentration.

F.3.2.2. *Baccarelli et al. (2008) Results*

Table F-9. Estimated continuous intake corresponding to maternal serum concentration for TEQ

Variable	Value	Notes
Infant b-TSH	5 μU/mL	BMR
Maternal lipid adjusted serum TEQ	489 ng/kg	From Figure 2D
Intake	0.059 ng/kg-day	From Emond model; pregnancy at 30 years

TSH = thyroid stimulating hormone; BMR = benchmark response.

F.3.3. Eskenazi et al. (2002)

F.3.3.1. *Summary of Modeling Approach*

For the sensitivity analysis, modeling for Eskenazi et al. (2002) (detailed in Section 4.2.3.4) was repeated using the female background intake estimated from Eskenazi et al. (2004) (see Section F.1.2). Modeling was carried out for the mid and high exposure tertiles as described in Section F.3.1.1 using this alternative background value. The measured LASC of the lowest exposure tertile was lower than the estimated background exposure; thus, for this tertile, the Emond human PBPK model was used to find the chronic intake over the critical exposure window (13 years) which matched the measured concentration.

As part of the sensitivity analysis, the total TEQ intakes were estimated. For the mid and high tertiles, this was done by adding the Eskenazi et al. (2004) female background DLC intake to the calculated TCDD intake as discussed in Section F.3.1.1. Total TEQ intake was estimated for the lowest tertile assuming that TEQ intake is equal to ten times the modeled TCDD intake.

Table F-10. Model inputs derived from study details for Eskenazi et al. (2002)

Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Critical exposure window (years)
6.7	0.5	6.7	13

LASC = lipid adjusted serum concentration.

F.3.3.2. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 58692.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 58715.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 63072.  % AGE AT LASC MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.00422 % ESKENAZI BACKGROUND EXPOSURE DOSE (NG/KG/DAY)

% EVENT EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 2679.4  % Over 1000 ppt GROUP

% HUMAN VARIABLE PARAMETERS
MALE   = 0.
FEMALE = 1.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==62904):length(_t)))
```

F.3.3.3. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 58692.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 58715.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 113880. % LENGTH OF CRITICAL WINDOW (HOURS)
MSTOTBCKGR   = 0.00422 % ESKENAZI BACKGROUND EXPOSURE DOSE (NG/KG/DAY)

% EVENT EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 2679.4  % Over 1000 ppt GROUP

% HUMAN VARIABLE PARAMETERS
MALE   = 0.
FEMALE = 1.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
```

```
1   meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
2   meanCBSNGKGLIADJ
3   maxCBSNGKGLIADJ=max(_cbsngkgliadj);
4   maxCBSNGKGLIADJ
5
6
```

7   **F.3.3.4.** *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
8    output @clear
9    prepare @clear T CBSNGKGLIADJ CBNGKG
10
11   % EXPOSURE PARAMETERS
12   MAXT = 0.5
13   CINT = 1.
14   EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
15   EXP_TIME_OFF = 113881. % LENGTH OF CRITICAL WINDOW (HOURS)
16   DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
17   BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
18   BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
19   TIMELIMIT    = 113880. % LENGTH OF CRITICAL WINDOW (HOURS)
20   MSTOTBCKGR   = 0.      % NO BACKGROUND EXPOSURE (0 NG/KG/DAY)
21
22   % CONTINUOUS EXPOSURE DOSE (NG/KG/DAY)
23   MSTOT = 3.08E-3 % 28-DAY   EC EXPOSURE GROUP
24         % 1.52E+0 % Over 1000 ppt EXPOSURE GROUP - MATCHING MEAN
25         % 6.00E+1 % Over 1000 ppt EXPOSURE GROUP - MATCHING MAX
26
27   % HUMAN VARIABLE PARAMETERS
28   MALE   = 1.
29   FEMALE = 0.
30   Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION
31
32   % POST-PROCESSING
33   start @nocallback
34   meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
35   maxCBSNGKGLIADJ=max(_cbsngkgliadj);
36
```

2
3
4   **Table F-11. Matching peak and average after pulse to chronic intake for**
5   **Eskenazi et al. (2002) using alternate background value**
6

Subject modeled	Exposure group	TCDD Only							TEQ
		Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC/ measured concentration (if LASC below background) (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	Average of continuous intake rates (ng/kg-day)
Eskenazi background									
Female	28-day EC	50	Below background				3.08E−03	3.08E−03	3.08E−02
Female	Over 1000 ppt	4060	2679.4	2552.8	1.52E+00	73933.1	6.00E+01	3.08E+01	3.08E+01

7
8   LASC = lipid adjusted serum concentration.
9
10
11   **F.3.4. Eskenazi et al. (2005)**

12   **F.3.4.1.** *Summary of Modeling Approach*

13   Eskenazi et al. (2005) investigated the association of TCDD exposure and age at

14   menopause in women who were premenopausal in 1976 and living near Seveso, Italy. Study

15   authors divided TCDD exposures into quintiles for analysis (reported in Table 3). Because the

16   dose-response trend is not clear, it was difficult to determine a NOAEL and LOAEL for this

17   study, and all quintiles were modeled. Measured LASC values for the second, third, and fourth

18   quintiles were estimated by calculating the geometric means of the quintile ranges rounded to the

19   nearest tenth. No range was specified for the first quintile (defined as ≤20.4 ppt) and fifth

20   quintile (defined as >300 ppt). Instead, for the first quintile, measured LASC was estimated by

21   dividing the upper bound of the exposure range by 2 to give an estimate of 10.2 ppt. For the fifth

22   quintile, the lower bound of the exposure range was used as the measured LASC estimate.

23   The mean age at time of the incident was not reported by Eskenazi et al.(2005). Thus, the

24   age at incident was approximated by subtracting the lag between event and interview (21 years)

25   from the mean age at menopause (56.6, Table 1) to get an approximate mean age at incident of

1   35.6 years old. A critical susceptibility window for this endpoint could not be determined.

2   Because women are susceptible to ovarian function effects until menopause, an assumed critical

3   exposure window of 50 years was assigned for the sensitivity analysis. Serum levels were

4   measured within one year of the incident, and an LASC measurement lag time of 0.5 years was

5   assumed. Modeling was carried out as detailed in Section F.3.1.1 for the second, third, fourth,

6   and fifth quintiles using the background intake estimated from Needham et al. (1998) (see

7   Section F.1.1). The measured LASC of the first quintile was lower than the estimated Needham

8   et al. (1998) background exposure; thus, for this quintile, the Emond human PBPK model was

9   used to find the intake over the assumed critical exposure window which matched the measured

10 LASC value.

11   As part of the sensitivity analysis, total TEQ intakes were estimated for the second, third,

12 fourth, and fifth quintiles by adding the Needham et al. (1998) background DLC intake to the

13 modeled TCDD intake as discussed in Section F.3.1.1. Total TEQ intake for the first quintile

14 was estimated assuming that total TEQ intake is equal to ten times the modeled TCDD intake.

15
16
17   **Table F-12. Model inputs derived from study details for Eskenazi et al.**
18   **(2005)**
19

	Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Assumed critical exposure window (years)
	35.6	0.5	13.6	50

20
21 LASC = lipid adjusted serum concentration.
22
23
24 **F.3.4.2. *Input for Exposure from Event to LASC Measurement***
25 % MODEL PARAMETERS
26 output @clear
27 prepare @clear T CBSNGKGLIADJ CBNGKG
28
29 % EXPOSURE PARAMETERS
30 MAXT = 0.5
31 CINT = 1.
32 EXP_TIME_ON = 311856. % AGE AT EXPOSURE (HOURS)
33 EXP_TIME_OFF = 311879. % AGE AT END OF EXPOSURE (HOURS)
34 DAY_CYCLE   = 24.   % LENGTH OF DAY (HOURS/DAY)
35 BCK_TIME_ON = 0.   % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
36 BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
37 TIMELIMIT   = 316236. % AGE AT LASC MEASUREMENT (HOURS)
38 MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)

```
1
2   % EVENT EXPOSURE DOSE (NG/KG/DAY)
3   MSTOT = 2.1  % 2ND QUINTILE
4         % 5.5  % 3RD QUINTILE
5         % 13.8 % 4TH QUINTILE
6         % 23.4 % 5TH QUINTILE
7
8   % HUMAN VARIABLE PARAMETERS
9   MALE   = 1.
10  FEMALE = 0.
11  Y0     = 0. % AGE AT BEGINNING OF SIMULATION
12
13  % POST-PROCESSING
14  start @nocallback
15  CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==316068):length(_t)))
16
17
```

18 **F.3.4.3.** *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
19  % MODEL PARAMETERS
20  output @clear
21  prepare @clear T CBSNGKGLIADJ CBNGKG
22
23  % EXPOSURE PARAMETERS
24  MAXT = 0.5
25  CINT = 1.
26  EXP_TIME_ON  = 311856. % AGE AT EXPOSURE (HOURS)
27  EXP_TIME_OFF = 311879. % AGE AT END OF EXPOSURE (HOURS)
28  DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
29  BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
30  BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
31  TIMELIMIT    = 438000. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
32  MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)
33
34  % EVENT EXPOSURE DOSE (NG/KG/DAY)
35  MSTOT = 2.1  % 2ND QUINTILE
36        % 5.5  % 3RD QUINTILE
37        % 13.8 % 4TH QUINTILE
38        % 23.4 % 5TH QUINTILE
39
40  % HUMAN VARIABLE PARAMETERS
41  MALE   = 1.
42  FEMALE = 0.
43  Y0     = 0. % AGE AT BEGINNING OF SIMULATION
44
45  % POST-PROCESSING
46  start @nocallback
47  meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
48  meanCBSNGKGLIADJ
49  maxCBSNGKGLIADJ=max(_cbsngkgliadj);
50  maxCBSNGKGLIADJ
51
52
```

53 **F.3.4.4.** *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
54  % MODEL PARAMETERS
55  output @clear
```

```
 1    prepare @clear T CBSNGKGLIADJ CBNGKG
 2
 3    % EXPOSURE PARAMETERS
 4    MAXT = 0.5
 5    CINT = 1.
 6    EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
 7    EXP_TIME_OFF = 438001. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
 8    DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
 9    BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
10    BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
11    TIMELIMIT    = 438000. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
12    MSTOTBCKGR   = 0.      % NO BACKGROUND EXPOSURE (0 NG/KG/DAY)
13
14    % CONTINUOUS EXPOSURE DOSE (NG/KG/DAY)
15    MSTOT = 1.04E-3 % 2ND QUINTILE - MATCHING MEAN
16          % 1.73E-3 % 3RD QUINTILE - MATCHING MEAN
17          % 3.44E-3 % 4TH QUINTILE - MATCHING MEAN
18          % 5.47E-3 % 5TH QUINTILE - MATCHING MEAN
19          % 3.42E-3 % 2ND QUINTILE - MATCHING MAX
20          % 1.29E-2 % 3RD QUINTILE - MATCHING MAX
21          % 5.16E-2 % 4TH QUINTILE - MATCHING MAX
22          % 1.15E-1 % 5TH QUINTILE - MATCHING MAX
23
24    % HUMAN VARIABLE PARAMETERS
25    MALE   = 1.
26    FEMALE = 0.
27    Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION
28
29    % POST-PROCESSING
30    start @nocallback
31    meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
32    maxCBSNGKGLIADJ=max(_cbsngkgliadj);
33
34
```

F.3.4.5. *Eskenazi et al. (2005) Results*

Table F-13. Matching peak and average after pulse to chronic intake for
Eskenazi et al. (2005)

Subject modeled	Quintile	TCDD only							TEQ
		Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC/ measured concentration (if LASC below background) (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	Average of continuous intake rates (ng/kg-day)
Female	1st	10.2	LASC below background				1.57E−04	1.57E−04	1.57E-−03
Female	2nd	26.4	2.1	25.9	1.04E−03	89.4	3.42E−03	2.23E−03	5.74E−03
Female	3rd	43.1	5.5	37.7	1.73E−03	209.4	1.29E−02	7.31E−03	1.08E−02
Female	4th	80.0	13.8	62.1	3.44E−03	506.1	5.16E−02	2.75E−02	3.10E−02
Female	5th	118.0	23.4	85.9	5.47E−03	848.3	1.15E−01	6.02E−02	6.37E−02

LASC = lipid adjusted serum concentration.

F.3.5. Mocarelli et al. (2000)

F.3.5.1. *Summary of Modeling Approach*

Mocarelli et al. (2000) examined sex ratio of offspring born to parents exposed to dioxin in Seveso, Italy. Sex and age at exposure were also tested as factors possibly affecting sex ratio. Because no difference in sex ratio was observed in groups in which only the mothers were exposed to TCDD, only male exposures were modeled. Because the authors conducted this statistical test using a dichotomous exposure variable (exposed vs. unexposed or <15 ppt), and because there is no clear dose-response trend in sex ratios of offspring and father's TCDD concentrations, a NOAEL and LOAEL were difficult to establish for this study. All quintiles (reported in Table 2) of fathers' exposure were modeled using the Emond human PBPK model. Measured LASC values for all quintiles were estimated by calculating the geometric mean of the quintile ranges reported in Table 2 in the study.

1   Average ages at conception for various year ranges were provided in the study in Table 5.

2   From these ages, a population-weighted average age at conception of 31.0 and average age at the

3   time of exposure in 1976 of 20.5 were calculated. No critical susceptibility window could be

4   determined for this study; however, an assumed critical exposure window of 31.0 years was

5   assumed to match the average age at time of conception. Modeling was carried out as detailed in

6   Section F.3.1.1 using the background intake estimated from Needham et al. (1998) (see

7   Section F.1.1) with the exception that a 5-year response surface was used to find continuous

8   intakes matching the modeled peak and mean LASC values, as detailed in Section F.3.5.1.

9   As part of the sensitivity analysis, total TEQ intakes were estimated for all tertiles by

10   adding the Needham et al. (1998) background DLC intake to the modeled TCDD intake as

11   discussed in Section F.3.1.1.

12
13
14   **Table F-14. Model inputs derived from study details for Mocarelli et al.**
15   **(2000)**
16

	Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Assumed critical exposure window (years)
	20.5	0.5	20	31.0

17
18   LASC = lipid adjusted serum concentration.
19
20
21   **F.3.5.2. *Input for Exposure from Event to LASC Measurement***

```
22   % MODEL PARAMETERS
23   output @clear
24   prepare @clear T CBSNGKGLIADJ CBNGKG
25
26   % EXPOSURE PARAMETERS
27   MAXT = 0.5
28   CINT = 1.
29   EXP_TIME_ON  = 179580. % AGE AT EXPOSURE (HOURS)
30   EXP_TIME_OFF = 179603. % AGE AT END OF EXPOSURE (HOURS)
31   DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
32   BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
33   BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
34   TIMELIMIT    = 183960. % AGE AT LASC MEASUREMENT (HOURS)
35   MSTOTBCKGR   = 0.00035 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)
36
37   % EVENT EXPOSURE DOSE (NG/KG/DAY)
38   MSTOT = 1.2   % 1ST QUINTILE
39         % 4.2   % 2ND QUINTILE
40         % 11.0  % 3RD QUINTILE
```

```
      % 30.2   % 4TH QUINTILE
      % 1420.0 % 5TH QUINTILE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==183792):length(_t)))
```

F.3.5.3. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 179580. % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 179603. % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 271560. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.00035 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)

% EVENT EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 1.2     % 1ST QUINTILE
      % 4.2     % 2ND QUINTILE
      % 11.0    % 3RD QUINTILE
      % 30.2    % 4TH QUINTILE
      % 1420.0 % 5TH QUINTILE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
meanCBSNGKGLIADJ
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
maxCBSNGKGLIADJ
```

1 **F.3.5.4.** *Mocarelli et al. (2000) Results*

2
3
4   **Table F-15. Matching peak and average after pulse to 5-year average**
5   **response surface for Mocarelli et al. (2000)**
6

Subject modeled	Quintile	TCDD only							TEQ
		Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	5-Year response surface matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	5-Year response surface matching peak LASC (ng/kg-day)	Average of 5-Year response surface values (ng/kg-day)	Average of 5-Year response surface values (ng/kg-day)
Male	1st	21.7	1.2	19.0	2.82E−04	52.4	1.35E−03	8.17E−04	3.97E−03
Male	2nd	44	4.2	33.0	6.56E−04	160.0	7.93E−03	4.30E−03	7.45E−03
Male	3rd	84.8	11.0	46.9	1.58E−03	397.3	3.41E−02	1.78E−02	2.10E−02
Male	4th	176.5	30.2	112.4	4.69E−03	1072.0	1.62E−01	8.31E−02	8.63E−02
Male	5th	2723.7	1420.0	1485.2	2.66E−01	48470.7	2.63E+01	1.33E+01	1.33E+01

7
8 LASC = lipid adjusted serum concentration.
9
10
11 **F.3.6. Mocarelli et al. (2008)**

12 **F.3.6.1.** *Summary of Modeling Approach*

13   For the sensitivity analysis, modeling for Mocarelli et al. (2008) (detailed in

14 Section 4.2.3.2) was repeated using the male background intake estimated from Eskenazi et al.

15 (2004) (see Section F.1.2) for children aged 0–12. Modeling was carried out as described in

16 Section F.3.1.1 using this alternative background value.

17   As part of the sensitivity analysis, total TEQ intakes were estimated for all quartiles by

18 adding the Eskenazi et al. (2004) background DLC intake to the modeled TCDD intake as

19 discussed in Section F.3.1.1.

20

Table F-16. Model inputs derived from study details for Mocarelli et al. (2008)

Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Critical exposure window (years)
6.2	0.5	3.8	10

LASC = lipid adjusted serum concentration.

F.3.6.2. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 54312.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 54335.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 58692.  % AGE AT LASC MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.00422 % ESKENAZI BACKGROUND EXPOSURE DOSE (NG/KG/DAY)

% EVENT EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 3.4   % 1ST QUARTILE
      % 17.7  % 2ND QUARTILE
      % 73.6  % 3RD QUARTILE
      % 227.1 % 4TH QUARTILE

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==58524):length(_t)))
```

F.3.6.3. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 54312.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 54335.  % AGE AT END OF EXPOSURE (HOURS)
```

```
1   DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
2   BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
3   BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
4   TIMELIMIT    = 87600.  % LENGTH OF CRITICAL EXPOSURE WINDOW (HOURS)
5   MSTOTBCKGR   = 0.00422 % ESKENAZI BACKGROUND EXPOSURE DOSE (NG/KG/DAY)
6
7   % EVENT EXPOSURE DOSE (NG/KG/DAY)
8   MSTOT = 3.4   % 1ST QUARTILE
9         % 17.7  % 2ND QUARTILE
10        % 73.6  % 3RD QUARTILE
11        % 227.1 % 4TH QUARTILE
12
13  % HUMAN VARIABLE PARAMETERS
14  MALE   = 1.
15  FEMALE = 0.
16  Y0     = 0. % AGE AT BEGINNING OF SIMULATION
17
18  % POST-PROCESSING
19  start @nocallback
20  meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
21  meanCBSNGKGLIADJ
22  maxCBSNGKGLIADJ=max(_cbsngkgliadj);
23  maxCBSNGKGLIADJ
24
25
```

26 **F.3.6.4.** *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
27  % MODEL PARAMETERS
28  output @clear
29  prepare @clear T CBSNGKGLIADJ CBNGKG
30
31  % EXPOSURE PARAMETERS
32  MAXT = 0.5
33  CINT = 1.
34  EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
35  EXP_TIME_OFF = 87601.  % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
36  DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
37  BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
38  BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
39  TIMELIMIT    = 87600.  % LENGTH OF CRITICAL EXPOSURE WINDOW (HOURS)
40  MSTOTBCKGR   = 0.      % NO BACKGROUND EXPOSURE (0 NG/KG/DAY)
41
42  % CONTINUOUS EXPOSURE DOSE (NG/KG/DAY)
43  MSTOT = 1.03E-2 % 1ST QUARTILE - MATCHING MEAN
44        % 2.32E-2 % 2ND QUARTILE - MATCHING MEAN
45        % 7.47E-2 % 3RD QUARTILE - MATCHING MEAN
46        % 2.15E-1 % 4TH QUARTILE - MATCHING MEAN
47        % 1.34E-2 % 1ST QUARTILE - MATCHING MAX
48        % 1.02E-1 % 2ND QUARTILE - MATCHING MAX
49        % 7.70E-1 % 3RD QUARTILE - MATCHING MAX
50        % 3.67E+0 % 4TH QUARTILE - MATCHING MAX
51
52  % HUMAN VARIABLE PARAMETERS
53  MALE   = 1.
54  FEMALE = 0.
55  Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION
56
```

```
% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
```

F.3.6.5. *Mocarelli et al. ([2008](#)) Results*

Table F-17. Matching peak and average after pulse to chronic intake for Mocarelli et al. ([2008](#)) using alternate background value

Subject modeled	Quartile	TCDD only							TEQ
		Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	Average of continuous intake rates (ng/kg-day)
Eskenazi background									
Male	1st	68	3.4	69.7	1.03E−02	137.7	1.34E−02	1.18E−02	2.09E−02
Male	2nd	142	17.7	126.3	2.32E−02	538.8	1.02E−01	6.24E−02	7.14E−02
Male	3rd	345	73.6	283.4	7.47E−02	2100.3	7.70E−01	4.23E−01	4.32E−01
Male	4th	733	227.1	584.2	2.15E−01	6373.9	3.67E+00	1.94E+00	1.95E+00

LASC = lipid adjusted serum concentration.

F.3.7. Mocarelli et al. ([2011](#))

F.3.7.1. *Summary of Modeling Approach*

Mocarelli et al. ([2011](#)) examined sperm effects in boys who experienced perinatal TCDD exposure during the Seveso event in 1976. Study authors used a model based on 1st-order kinetics to extrapolate the measured LASC concentrations to the concentration at conception. For consistency with all other exposure estimates, EPA did not use the study authors' exposure estimates and instead used the Emond human PBPK model to estimate concentrations at conception. The median measured LASC for mothers who breastfed was provided in the study (reported in Table 2) and was selected as a LOAEL. Measured LASC of the comparison group was assumed equal to the value reported in Eskenazi et al. ([2004](#)) (average of 10.4 ppt) for the 20−40 age group.

1   An average age of 24.8 years old at the time of the incident was reported in the study text

2   in the Materials and Methods section. Two mean ages-at-conception were evaluated by

3   EPA: 30 and 45 years old. Serum levels were measured within one year of the incident, and an

4   LASC measurement lag time of 0.5 years was assumed. Modeling was carried out for the

5   exposure group that breastfed as detailed in Section F.3.1.1 using the background intake

6   estimated from Needham et al. (1998) (see Section F.1.1). Continuous daily intakes were found

7   for both evaluated ages-at-conception. Because the measured LASC of the comparison group

8   was assumed to be at background, for this group the Emond human PBPK model was used to

9   find the intake which matched the Eskenazi et al. (2004) age-adjusted average concentration for

10   ages 20 to 40.

11   As part of the sensitivity analysis, total TEQ intakes were estimated for the exposure

12   group that breastfed by adding the Needham et al. (1998) background DLC intake to the modeled

13   TCDD intake as discussed in Section F.3.1.1. Total TEQ intake for the comparison group was

14   estimated assuming that total TEQ intake is equal to ten times the modeled TCDD intake.

15

16

17   **Table F-18. Model inputs derived from study details for Mocarelli et al.**
18   **(2011)**
19

	Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Assumed critical exposure window (years)
	24.8	0.5	5.2, 20.2	30, 45

20
21   LASC = lipid adjusted serum concentration.
22

23

24   **F.3.7.2. *Input for Exposure from Event to LASC Measurement***

```
25   % MODEL PARAMETERS
26   output @clear
27   prepare @clear T CBSNGKGLIADJ CBNGKG
28
29   % EXPOSURE PARAMETERS
30   MAXT = 0.5
31   CINT = 1.
32   EXP_TIME_ON  = 217248. % AGE AT EXPOSURE (HOURS)
33   EXP_TIME_OFF = 217249. % AGE AT END OF EXPOSURE (HOURS)
34   DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
35   BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
36   BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
37   TIMELIMIT    = 221628. % AGE AT LASC MEASUREMENT (HOURS)
```

```
1  MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)
2
3  % EVENT EXPOSURE DOSE (NG/KG/DAY)
4  MSTOT = 6.4 % BREASTFEEDING GROUP
5
6  % HUMAN VARIABLE PARAMETERS
7  MALE   = 1.
8  FEMALE = 0.
9  Y0     = 0. % AGE AT BEGINNING OF SIMULATION
10
11 % POST-PROCESSING
12 start @nocallback
13 CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==58524):length(_t)))
14
15
```

F.3.7.3. *Input for Exposure from Event to the Study-Average Age at Conception*

```
17 % MODEL PARAMETERS
18 output @clear
19 prepare @clear T CBSNGKGLIADJ CBNGKG
20
21 % EXPOSURE PARAMETERS
22 MAXT = 0.5
23 CINT = 1.
24 EXP_TIME_ON  = 217248. % AGE AT EXPOSURE (HOURS)
25 EXP_TIME_OFF = 217249. % AGE AT END OF EXPOSURE (HOURS)
26 DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
27 BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
28 BCK_TIME_OFF = 438000. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
29 TIMELIMIT    = 247032. % REPORTED AGE AT CONCEPTION (HOURS)
30 MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)
31
32 % EVENT EXPOSURE DOSE (NG/KG/DAY)
33 MSTOT = 6.4 % BREASTFEEDING GROUP
34
35 MALE   = 0.
36 FEMALE = 1.
37 Y0     = 0. % AGE AT BEGINNING OF SIMULATION
38
39 % POST-PROCESSING
40 start @nocallback
41 meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
42 meanCBSNGKGLIADJ
43 maxCBSNGKGLIADJ=max(_cbsngkgliadj);
44 maxCBSNGKGLIADJ
45
46
```

F.3.7.4. *Input for Continuous Exposure until Age at Conception for General Population*

```
48 % MODEL PARAMETERS
49 output @clear
50 prepare @clear T CBSNGKGLIADJ CBNGKG
51
52 % EXPOSURE PARAMETERS
53 CINT = 1
54 MAXT  = 0.5
55 EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
```

```
EXP_TIME_OFF = 262801. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
             % 394201.
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 262800. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
             % 394200.
MSTOTBCKGR   = 0.      % NO BACKGROUND EXPOSURE (0 NG/KG/DAY)

% CONTINUOUS EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 2.90E-4 % COMPARISON GROUP    - AGE 30 AT CONCEPTION - MATCHING MEAN
      % 1.85E-4 % COMPARISON GROUP    - AGE 45 AT CONCEPTION - MATCHING MEAN
      % 1.64E-3 % BREASTFEEDING GROUP - AGE 30 AT CONCEPTION - MATCHING MEAN
      % 1.14E-3 % BREASTFEEDING GROUP - AGE 45 AT CONCEPTION - MATCHING MEAN

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
```

F.3.7.5. *Mocarelli et al. ([2011](#)) Results*

Table F-19. Matching concentration at conception for the study population to chronic intake for the general population for Mocarelli et al. ([2011](#))

Subject modeled	Exposure group	General population age at conception	TCDD only				TEQ
			Measured LASC (ng/kg)	Event dose (ng/kg)	Terminal LASC at conception (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Continuous intake matching average LASC (ng/kg-day)
Female	Comparison	30	10.4	LASC at background		2.90E−04	2.90E−03
Female		45				1.85E−04	1.85E−03
Female	Breastfed	30	46.8	6.357	40.2	1.64E−03	5.15E−03
Female		45				1.14E−03	4.65E−03

LASC = lipid adjusted serum concentration.

1 **F.3.8. Warner et al. ([2004](#))**

2 **F.3.8.1.** *Summary of Modeling Approach*

3   Warner et al. ([2004](#)) studied age at onset of menarche in women who were premenarcheal

4 in 1976 at the time of first exposure. Study authors divided exposure groups into quartiles, and

5 further divided the first quartile into "low" and "high" exposure groups (reported in Table 3).

6 Measured LASC values for high exposure first quartile, second quartile, and third quartile were

7 estimated by calculating the geometric means of the quartile ranges rounded to the nearest tenth.

8 No range was specified for the low exposure first quartile (defined as ≤20 ppt) and fourth

9 quartile (defined as >300 ppt). Instead, for the lowest exposure group, measured LASC was

10 estimated by dividing the upper bound of the exposure range by 2 to give an estimate of 10 ppt.

11 For the highest exposure group, the lower bound of the exposure range was used as the measured

12 LASC estimate.

13   The average age of the subjects on July 10, 1976 was reported to be 6.9 years in the text

14 in the Results section. The critical susceptibility window for this endpoint could not be

15 determined; however, an assumed critical exposure window of 12.8 was established for modeling

16 purposes based on the age at menarche (12.8 ± 1.6 years) reported by Warner et al. ([2004](#)).

17 Serum levels were measured within one year of the incident, therefore an LASC measurement

18 lag time of 0.5 years was assumed. Modeling was carried out as detailed in Section F.3.3.1 for

19 all exposure groups using the background intake estimated from Needham et al. ([1998](#)) (see

20 Section F.1.1) and for the second, third, and fourth quartiles using the alternative background

21 intake value estimated from Eskenazi et al. ([2004](#)) (see Section F.1.2). The measured LASC of

22 the two lowest exposure groups were lower than the estimated Eskenazi et al. ([2004](#)) background

23 exposure; thus, for these exposure groups, the Emond human PBPK model was used to find the

24 intake over the assumed critical exposure window which matched the measured concentrations.

25   As part of the sensitivity analysis, total TEQ intakes were estimated for all exposure

26 groups modeled with the Needham et al. ([1998](#)) background intake and for the second, third, and

27 fourth quartiles modeled with the Eskenazi et al. ([2004](#)) background exposure by adding the

28 background DLC intake to the calculated TCDD intakes of each exposure group as discussed in

29 Section F.3.3.1 using the Eskenazi et al. ([2004](#)) female additive background DLC factor. Total

30 TEQ was estimated for the two lowest exposure groups modeled with the Eskenazi et al. ([2004](#))

background exposure assuming that total TEQ intake was equal to ten times the modeled TCDD intake.

Table F-20. Model inputs derived from study details for Warner et al. (2004)

Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Assumed critical exposure window (years)
6.9	0.5	5.9	12.8

LASC = lipid adjusted serum concentration.

F.3.8.2. *Input for Exposure from Event to LASC Measurement*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 60444.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 60467.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 64824.  % AGE AT LASC MEASUREMENT (HOURS)
MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)
             % 0.00429 % ESKENAZI BACKGROUND EXPOSURE DOSE (NG/KG/DAY)

% EVENT EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 0.3  % 1ST QUARTILE LOW - NEEDHAM BACKGROUND
      % 3.0  % 1ST QUARTILE HIGH - NEEDHAM BACKGROUND
      % 11.9 % 2ND QUARTILE - NEEDHAM BACKGROUND
      % 37.9 % 3RD QUARTILE - NEEDHAM BACKGROUND
      % 64.8 % 4TH QUARTILE - NEEDHAM BACKGROUND
      % 6.4  % 2ND QUARTILE - ESKENAZI BACKGROUND
      % 32.5 % 3RD QUARTILE - ESKENAZI BACKGROUND
      % 59.3 % 4TH QUARTILE - ESKENAZI BACKGROUND

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==64656):length(_t)))
```

F.3.8.3. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 60444.  % AGE AT EXPOSURE (HOURS)
EXP_TIME_OFF = 60467.  % AGE AT END OF EXPOSURE (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 112128. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)
             % 0.00429 % ESKENAZI BACKGROUND EXPOSURE DOSE (NG/KG/DAY)

% EVENT EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 0.3  % 1ST QUARTILE LOW - NEEDHAM BACKGROUND
      % 3.0  % 1ST QUARTILE HIGH - NEEDHAM BACKGROUND
      % 11.9 % 2ND QUARTILE - NEEDHAM BACKGROUND
      % 37.9 % 3RD QUARTILE - NEEDHAM BACKGROUND
      % 64.8 % 4TH QUARTILE - NEEDHAM BACKGROUND
      % 6.4  % 2ND QUARTILE - ESKENAZI BACKGROUND
      % 32.5 % 3RD QUARTILE - ESKENAZI BACKGROUND
      % 59.3 % 4TH QUARTILE - ESKENAZI BACKGROUND

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % AGE AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
meanCBSNGKGLIADJ
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
maxCBSNGKGLIADJ
```

F.3.8.4. *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.      % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 112129. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 112128. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.      % NO BACKGROUND EXPOSURE (0 NG/KG/DAY)
```

```
% CONTINUOUS EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 7.46E-4. % 1ST QUARTILE LOW - NEEDHAM  BACKGROUND - MATCHING MEAN
      % 2.40E-3. % 1ST QUARTILE HIGH - NEEDHAM  BACKGROUND - MATCHING MEAN
      % 7.79E-3. % 2ND QUARTILE - NEEDHAM  BACKGROUND - MATCHING MEAN
      % 2.31E-2. % 3RD QUARTILE - NEEDHAM  BACKGROUND - MATCHING MEAN
      % 3.94E-2. % 4TH QUARTILE - NEEDHAM  BACKGROUND - MATCHING MEAN
      % 1.06E-2. % 2ND QUARTILE - ESKENAZI BACKGROUND - MATCHING MEAN
      % 2.61E-2. % 3RD QUARTILE - ESKENAZI BACKGROUND - MATCHING MEAN
      % 4.24E-2. % 4TH QUARTILE - ESKENAZI BACKGROUND - MATCHING MEAN
      % 6.81E-4  % 1ST QUARTILE LOW - NEEDHAM  BACKGROUND - MATCHING MAX
      % 8.09E-3  % 1ST QUARTILE HIGH - NEEDHAM  BACKGROUND - MATCHING MAX
      % 5.12E-2  % 2ND QUARTILE - NEEDHAM  BACKGROUND - MATCHING MAX
      % 2.78E-1  % 3RD QUARTILE - NEEDHAM  BACKGROUND - MATCHING MAX
      % 6.04E-1  % 4TH QUARTILE - NEEDHAM  BACKGROUND - MATCHING MAX
      % 2.66E-2  % 2ND QUARTILE - ESKENAZI BACKGROUND - MATCHING MAX
      % 2.21E-1  % 3RD QUARTILE - ESKENAZI BACKGROUND - MATCHING MAX
      % 5.17E-1  % 4TH QUARTILE - ESKENAZI BACKGROUND - MATCHING MAX

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
maxCBSNGKGLIADJ=max(_cbsngkgliadj);
```

F.3.8.5. *Warner et al. (2004) Results*

Table F-21. Matching peak and average after pulse to chronic intake for Warner et al. (2004)

Subject modeled	Quartile	Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC/ measured concentration (if LASC below background) (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	TEQ Average of continuous intake rates (ng/kg-day)
Needham background									
Female	1st (low)	10.0	0.3	10.4	7.46E−04	15.2	6.81E−04	7.14E−04	4.22E−03
Female	1st (high)	33.5	3.0	26.7	2.40E−03	97.7	8.09E−03	5.25E−03	8.76E−03
Female	2nd	88.6	11.9	64.5	7.79E−03	357.1	5.12E−02	2.95E−02	3.30E−02
Female	3rd	205.2	37.9	143.5	2.31E−02	1119.0	2.78E−01	1.50E−01	1.54E−01
Female	4th	300.0	64.8	207.2	3.94E−02	1896.6	6.04E−01	3.22E−01	3.25E−01
Eskenazi background									
Female	1st (low)	10.0	LASC below background				4.09E−04	4.09E−04	4.09E−03
Female	1st (high)	33.5	LASC below background				1.86E−03	1.86E−03	1.86E−02
Female	2nd	88.6	6.4	80.9	1.06E−02	228.2	2.66E−02	1.86E−02	2.77E−02
Female	3rd	205.2	32.5	156.2	2.61E−02	958.9	2.21E−01	1.23E−01	1.33E−01
Female	4th	300.0	59.3	218.2	4.24E−02	1708.9	5.17E−01	2.80E−01	2.89E−01

LASC = lipid adjusted serum concentration.

F.3.9. Warner et al. (2007)

F.3.9.1. *Summary of Modeling Approach*

Warner et al. (2007) examined ovarian function in women residents of Seveso, Italy in 1996−1998, approximately 21 years after the incident. For analysis of ovulation status, authors divided the exposure range into quartile groups (reported in Table 3). Measured LASC values for the second and third quartiles were estimated by calculating the geometric mean of the quartile ranges rounded to the nearest tenth of a ppt. No range was specified for the first quartile

1 (defined as ≤20 ppt) and fourth quartile (defined as >212 ppt). For the first quartile, the upper

2 end of the exposure range was divided by two to give an estimate of 10 ppt. For the fourth

3 quartile, the lower bound of the exposure group was used as the measured LASC estimate.

4   Warner et al., (2007) reported the average age of women at the time of the interviews

5 (1996−1998) to be 31.3 years old in the text in the Results section. Because interviews took

6 place on average 21 years after the incident, average age at the time of the incident was estimated

7 to be 10 years old. Serum values were collected within a year of the incident, and an LASC

8 measurement lag time of 0.5 years was assumed. A critical susceptibility window for this

9 endpoint could not be determined. Because women are susceptible to ovarian function effects

10 until menopause, an assumed critical exposure window of 50 years was assigned as a

11 conservative estimate for the sensitivity analysis. Modeling was carried out as detailed in

12 Section F.3.1.1 using the background intake estimated from Needham et al. (1998) (see

13 Section F.1.1).

14   As part of the sensitivity analysis, the intake when including DLCs was estimated by

15 adding the background DLC intake to the calculated TCDD intake as discussed in

16 Section F.3.3.1 using the Needham et al. (1998) female additive background DLC factor.

17
18
19 **Table F-22. Model inputs derived from study details for Warner et al. (2007)**
20

Average age at event (years)	Time lag between exposure and LASC measurement (years)	Time lag between exposure and effect (years)	Assumed critical exposure window (years)
10	0.5	21	50

21
22 LASC = lipid adjusted serum concentration.
23
24
25 **F.3.9.2. *Input for Exposure from Event to LASC Measurement***

```
26  % MODEL PARAMETERS
27  output @clear
28  prepare @clear T CBSNGKGLIADJ CBNGKG
29
30  % EXPOSURE PARAMETERS
31  MAXT = 0.5
32  CINT = 1.
33  EXP_TIME_ON  = 87600.  % AGE AT EXPOSURE (HOURS)
34  EXP_TIME_OFF = 87623.  % AGE AT END OF EXPOSURE (HOURS)
35  DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
36  BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
```

```
1   BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
2   TIMELIMIT    = 91980.  % AGE AT LASC MEASUREMENT (HOURS)
3   MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)
4
5   % EVENT EXPOSURE DOSE (NG/KG/DAY)
6   MSTOT = 0.1   % 1ST QUARTILE
7         % 3.7   % 2ND QUARTILE
8         % 127.8 % 3RD QUARTILE
9         % 212.0 % 4TH QUARTILE
10
11  % HUMAN VARIABLE PARAMETERS
12  MALE   = 1.
13  FEMALE = 0.
14  Y0     = 0. % AGE AT BEGINNING OF SIMULATION
15
16  % POST-PROCESSING
17  start @nocallback
18  CBSNGKGLIADJ_oneday=mean(_cbsngkgliadj(find(_t==91812):length(_t)))
19
20
```

21 ### F.3.9.3. *Input for Exposure from Event to the End of the Assumed Critical Exposure Window*

```
22  % MODEL PARAMETERS
23  output @clear
24  prepare @clear T CBSNGKGLIADJ CBNGKG
25
26  % EXPOSURE PARAMETERS
27  MAXT = 0.5
28  CINT = 1.
29  EXP_TIME_ON  = 87600.  % AGE AT EXPOSURE (HOURS)
30  EXP_TIME_OFF = 87623.  % AGE AT END OF EXPOSURE (HOURS)
31  DAY_CYCLE    = 24.     % LENGTH OF DAY (HOURS/DAY)
32  BCK_TIME_ON  = 0.      % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
33  BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
34  TIMELIMIT    = 438000. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
35  MSTOTBCKGR   = 0.00039 % NEEDHAM BACKGROUND EXPOSURE DOSE (NG/KG/DAY)
36
37  % EVENT EXPOSURE DOSE (NG/KG/DAY)
38  MSTOT = 0.1   % 1ST QUARTILE
39        % 3.7   % 2ND QUARTILE
40        % 127.8 % 3RD QUARTILE
41        % 212.0 % 4TH QUARTILE
42
43  % HUMAN VARIABLE PARAMETERS
44  MALE   = 1.
45  FEMALE = 0.
46  Y0     = 0. % AGE AT BEGINNING OF SIMULATION
47
48  % POST-PROCESSING
49  start @nocallback
50  meanCBSNGKGLIADJ=mean(_cbsngkgliadj(find(_t==EXP_TIME_ON):length(_t)));
51  meanCBSNGKGLIADJ
52  maxCBSNGKGLIADJ=max(_cbsngkgliadj);
53  maxCBSNGKGLIADJ
54
55
56
```

F.3.9.4. *Input for Continuous Exposure over Assumed Critical Exposure Window*

```
% MODEL PARAMETERS
output @clear
prepare @clear T CBSNGKGLIADJ CBNGKG

% EXPOSURE PARAMETERS
MAXT = 0.5
CINT = 1.
EXP_TIME_ON  = 0.        % CONTINUOUS EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
EXP_TIME_OFF = 438001. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
DAY_CYCLE    = 24.      % LENGTH OF DAY (HOURS/DAY)
BCK_TIME_ON  = 0.       % BACKGROUND EXPOSURE BEGINS AT BIRTH (AGE 0 HOURS)
BCK_TIME_OFF = 613200. % AGE AT END OF BACKGROUND EXPOSURE (HOURS)
TIMELIMIT    = 438000. % LENGTH OF ASSUMED CRITICAL EXPOSURE WINDOW (HOURS)
MSTOTBCKGR   = 0.       % NO BACKGROUND EXPOSURE (0 NG/KG/DAY)

% CONTINUOUS EXPOSURE DOSE (NG/KG/DAY)
MSTOT = 4.75E-4 % 1ST QUARTILE - MATCHING MEAN
      % 7.74E-4 % 2ND QUARTILE - MATCHING MEAN
      % 1.84E-3 % 3RD QUARTILE - MATCHING MEAN
      % 3.00E-3 % 4TH QUARTILE - MATCHING MEAN
      % 3.93E-4 % 1ST QUARTILE - MATCHING MAX
      % 5.63E-3 % 2ND QUARTILE - MATCHING MAX
      % 7.02E-2 % 3RD QUARTILE - MATCHING MAX
      % 2.04E-1 % 4TH QUARTILE - MATCHING MAX

% HUMAN VARIABLE PARAMETERS
MALE   = 1.
FEMALE = 0.
Y0     = 0. % 0 YEARS OLD AT BEGINNING OF SIMULATION

% POST-PROCESSING
start @nocallback
meanCBSNGKGLIADJ=mean(_cbsngkgliadj);
maxCBSNGKGLIADJ=max(_cbsngkgliadj);

```

2
3
4   **Table F-23. Matching peak and average after pulse to chronic intake for**
5   **Warner et al. ([2007](#))**
6

Subject modeled	Quartile	TCDD only							TEQ
		Measured LASC (ng/kg)	Event dose (ng/kg)	Average LASC after pulse dose (ng/kg)	Continuous intake matching average LASC (ng/kg-day)	Peak LASC after pulse dose (ng/kg)	Continuous intake matching peak LASC (ng/kg-day)	Average of continuous intake rates (ng/kg-day)	Average of continuous intake rates (ng/kg-day)
Needham background									
Female	1st	10.0	0.1	14.1	4.75E−04	20.4	3.93E−04	4.34E−04	3.94E−03
Female	2nd	39.3	3.7	20.7	7.74E−04	125.6	5.63E−03	3.20E−03	6.71E−03
Female	3rd	127.8	19.5	39.4	1.84E−03	616.7	7.02E−02	3.60E−02	3.95E−02
Female	4th	212.0	39.4	56.3	3.00E−03	1229.7	2.04E−01	1.04E−01	1.07E−01

7
8   LASC = lipid adjusted serum concentration.
9
10
11   **F.4. REFERENCES**

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APPENDIX G

Noncancer Benchmark Dose Modeling

November 2011

NOTICE

THIS DOCUMENT IS AN AGENCY/INTERAGENCY REVIEW DRAFT. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

CONTENTS—APPENDIX G: Noncancer Benchmark Dose Modeling

CONTENTS (continued)

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C<small>ONTENTS</small> **(continued)**

</div>

APPENDIX G.   NONCANCER BENCHMARK DOSE MODELING

G.1. BENCHMARK DOSE SOFTWARE (BMDS) INPUT TABLES

G.1.1. Amin et al. (2000)

Endpoint[c]	Administered dose (ng/kg-day)		
	0	**25[a]**	**100**
	Internal dose (ng/kg blood)[b]		
	0	**3.38**	**10.57**
	(*n* = 10)	(*n* = 10)	(*n* = 10)
Saccharin consumed, female rats (0.25%) (mL saccharin solution/100 g body weight)[c]	31.67 ± 6.53	24.60 ± 3.79	10.70 ± 1.68
Saccharin consumed, female rats (0.50%) (mL saccharin solution/100 g body weight)[c]	22.40 ± 5.05	11.38 ± 2.42	4.54 ± 1.05
Saccharin preference ratio, female rats (0.25%) (ratio of saccharin solution consumed to total fluid consumed)[d]	82.14 ± 4.22	58.12 ± 10.71	54.87 ± 6.17
Saccharin preference ratio, female rats (0.50%) (ratio of saccharin solution consumed to total fluid consumed)[d]	72.73 ± 7.79	44.48 ± 10.39	33.77 ± 7.79

[a] Lowest-observed-adverse-effect level (LOAEL) identified.
[b] From the Emond physiologically based pharmacokinetic (PBPK) model described in Section 3.3.
[c] Values are the mean ± standard error (SE). Data obtained from Figure 2 in Amin et al. (2000).
[d] Values are the ratio ± SE. Data obtained from Figure 3 in Amin et al. (2000).

G.1.2. Bell et al. (2007)

Endpoint	Administered dose (ng/kg-day)			
	0	**2.4[a]**	**8**	**46**
	Internal dose (ng/kg blood)[b]			
	0	**2.20**	**5.14**	**18.41**
	(*n* = 30)	(*n* = 30)	(*n* = 30)	(*n* = 30)
Proportion of male rat pups that had not undergone balano-preputial separation on PND 49[c]	1/30 (3%)	5/30 (17%)	6/30 (20%)	15/30 (50%)

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Data obtained from Figure 2 in Bell et al. (2007).

PND = postnatal day.

G.1.3. Cantoni et al. ([1981])

Endpoint	Administered dose (ng/kg-day)			
	0	**1.43**[a]	**14.3**	**143**
	Internal dose (ng/kg blood)[b]			
	0	**1.85**	**8.84**	**50.05**
	(*n* = 4)	(*n* = 4)	(*n* = 3)	(*n* = 3)
Urinary coproporphyrins in female rats (µg coproporphyrin methyl ester/24 hr) at 3 months[c]	0.74 ± 0.17	1.81 ± 0.42[d]	2.73 ± 0.75[e]	3.00 ± 1.30[e]
Urinary porphyrins in rats (nmol/24 hr) after 45 weeks[c]	2.27 ± 0.49	5.55 ± 0.85[d]	7.62 ± 1.79[d]	196.89 ± 63.14[e]

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SE. Data for urinary coproporphyrins and urinary porphyrins obtained from Figure 1 and Table 1, respectively, in Cantoni et al. ([1981]).
[d] Statistically significant as compared to control ($p < 0.05$).
[e] Statistically significant as compared to control ($p < 0.01$).

2
3
4 ### G.1.4. Crofton et al. ([2005])

Endpoint	Administered dose (ng/kg-day)									
	0	**0.1**	**3**	**10**	**30**[a]	**100**[b]	**300**	**1,000**	**3,000**	**10,000**
	Internal dose (ng/kg blood)[c]									
	0	**0.02**	**0.49**	**1.38**	**3.46**	**9.26**	**23.07**	**65.65**	**180.90**	**583.48**
	(*n* = 14)	(*n* = 6)	(*n* = 12)	(*n* = 6)	(*n* = 6)	(*n* = 6)	(*n* = 6)	(*n* = 6)	(*n* = 6)	(*n* = 4)
Serum T4 in female rats (% control)[d]	100.00 ± 15.44	96.27 ± 14.98	98.57 ± 18.11	99.76 ± 19.04	93.32 ± 12.11	70.94 ± 12.74	62.52 ± 14.75	52.68 ± 22.73	54.66 ± 19.71	49.15 ± 11.15

[a] No-observed-adverse-effect level (NOAEL) identified.
[b] LOAEL identified.
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the mean ± SD. Data were obtained from a Crofton et al. ([2005]) supplemental file, available at http://ehp.niehs.nih.gov/docs/2005/8195/supplemental.pdf.

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G.1.5.   DeCaprio et al. (1986)

Endpoint	Administered dose (ng/kg-day)				
	0	**0.12**	**0.61**[a]	**4.9**[b]	**26**
	Internal dose (ng/kg blood) [c]				
	NM	**NM**	**NM**	**NM**	**NM**
	(*n* = 10)	(*n* = 10)	(*n* = 11)	(*n* = 10)	(*n* = 4)
Absolute kidney weight (g), males[d]	5.49 ± 0.17	5.14 ± 0.12	4.71 ± 0.12	4.3 ± 0.15[f]	-
Absolute thymus weight (g), males[d]	0.56 ± 0.050	0.45 ± 0.022	0.44 ± 0.034	0.35 ± 0.167[g]	-
Body weight (g), males[e]	713 ± 15	682 ± 16	651 ± 19	603 ± 20[f]	433 ± 38[h]
Relative brain weight, males[d]	0.54 ± 0.015	0.56 ± 0.016	0.6 ± 0.016	0.65 ± 0.016[f]	-
Relative liver weight, males[d]	4.54 ± 0.23	4.1 ± 0.14	5.36 ± 0.61	5.63 ± 0.29[f]	-
Relative thymus weight, males[d]	0.078 ± 0.006	0.066 ± 0.003	0.068 ± 0.004	0.06 ± 0.003[f]	-

Endpoint	Administered dose (ng/kg-day)				
	0	**0.12**	**0.68**	**4.86**	**31**
	Internal dose (ng/kg blood)[c]				
	0	**NM**	**NM**	**NM**	**NM**
	(*n* = 8)	(*n* = 10)	(*n* = 9)	(*n* = 10)	(*n* = 4)
Body weight (g), females[e]	602 ± 12	583 ± 22	570 ± 22	531 ± 14[f]	351 ± 49[h]
Relative liver weight, females[d]	4.3 ± 0.26	4.49 ± 0.35	4.27 ± 0.16	5.54 ± 0.43[f]	-

[a] NOAEL identified.
[b] LOAEL identified.
[c] Internal dose not calculated using the Emond PBPK (guinea pigs).
[d] Organ weight data in guinea pigs obtained from Table 2 of DeCaprio et al. (1986). Values are the mean $\pm$ SE.
Relative organs weights were calculated as organ weight (g)/body weight (g) $\times$ 100.
[e] Body weight data in guinea pigs obtained from Table 1 of DeCaprio et al. (1986). Values are the mean $\pm$ SE.
[f] Statistically significant as compared to control ($p < 0.05$).
[g] Statistically significant as compared to control ($p < 0.01$).
[h] Statistically significant as compared to control ($p < 0.001$).

NM = not modeled.

1 **G.1.6. Franc et al. ([2001](#))**

Endpoint	Administered dose (ng/kg-day)			
	0	**10[a]**	**30[b]**	**100**
	Internal dose (ng/kg blood) [c]			
	0	**6.59**	**14.48**	**36.43**
	(*n* = 8)	(*n* = 8)	(*n* = 8)	(*n* = 8)
S-D rats, relative liver weight[d]	100.0 ± 5.0	108.1 ± 6.0[e]	116.8 ± 9.2[e]	155.3 ± 10.9[e]
L-E rats, relative liver weight[d]	100.0 ± 3.5	106.3 ± 6.3	116.8 ± 3.2[e]	122.2 ± 7.0[e]
S-D rats, relative thymus weight[d]	100.2 ± 29.4	91.2 ± 17.0	51.4 ± 15.4[e]	22.8 ± 10.6[e]
L-E rats, relative thymus weight[d]	103.4 ± 19.3	95.4 ± 24.9	38.7 ± 17.0[e]	35.0 ± 27.6[e]
H/W rats, relative thymus weight[d]	101.2 ± 12.7	97.5 ± 11.7.0	71.0 ± 8.5[e]	49.3 ± 15.4[e]

[a] NOAEL identified.
[b] LOAEL identified.
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the mean ± SE. Data obtained from Figure 5 in Franc et al. ([2001](#)).
[e] Statistically significant as compared to control ($p < 0.05$).

H/W = Han/Wistar; L-E = Long-Evans; S-D = Sprague-Dawley.

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4 **G.1.7. Hojo et al. ([2002](#))**

Endpoint	Administered dose (ng/kg-day)			
	0	**20[a]**	**60**	**180**
	Internal dose (ng/kg blood)[b]			
	0	**1.62**	**4.17**	**10.70**
	(*n* = 5)	(*n* = 5)	(*n* = 6)	(*n* = 5)
DRL reinforcements/min, rat litters[c]	−0.814 ± 0.45	−0.364 ± 0.82	0.374 ± 0.54	−0.163 ± 0.44
DRL responses/min, rat litters[c]	18.44 ± 7.99	−0.99 ± 10.96	−4.52 ± 7.19	−0.41 ± 15.23

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] DRL = differential reinforcement of low rate. Values are the mean ± SD. Data obtained from Table 5 in Hojo et al. ([2002](#)).

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1 **G.1.8.   Kattainen et al. ([2001](#))**

Endpoint	Administered dose (ng/kg-day)				
	0	**30**[a]	**100**	**300**	**1,000**
	Internal dose (ng/kg blood)[b]				
	0	**2.23**	**6.25**	**16.08**	**46.86**
	(*n* = 16)	(*n* = 17)	(*n* = 15)	(*n* = 12)	(*n* = 19)
3rd molar mesio-distal length in female rat offspring (molar development) (mm)[c]	1.86 ± 0.017	1.58 ± 0.045[d]	1.6 ± 0.069[d]	1.5 ± 0.064[d]	1.35 ± 0.118[d]
Proportion of female rat offspring without 3rd molar eruption on PND 35[e]	1/16 (10%)	3/17 (20%)	4/15 (30%)	6/12 (50%)[d]	13/19 (70%)[d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SE. Data were obtained from Figure 3 in Kattainen et al. ([2001](#)).
[d] Statistically significant as compared to control ($p < 0.05$).
[e] Data were obtained from Figure 2 in Kattainen et al. ([2001](#)).

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4 **G.1.9.   Keller et al. ([2008a](#); [2008b](#); [2007](#))**

Endpoint	Administered dose (ng/kg-day)			
	0	**10**[a]	**100**	**1,000**
	Internal dose (ng/kg blood)[b]			
	0	**0.54**	**4.29**	**34.06**
Frequency of missing 3rd mandibular molars in CBA J mice[c]	0/29 (0%)	2/23 (10%)	6/29 (20%)	30/30 (100%)

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Data obtained from Table 1 in Keller et al. ([2007](#)).

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G.1.10. Kociba et al. ([1978](#))

Endpoint	Administered dose (ng/kg-day)			
	0	**1[a]**	**10[b]**	**100**
	Internal dose (ng/kg blood) [c]			
	0	**1.55**	**7.15**	**38.56**
	(*n* = 5)	**(*n* = 5)**	**(*n* = 5)**	**(*n* = 5)**
Urinary coproporphyrin (µg/48 h), female rats[d]	9.8 ± 1.3	8.6 ± 2	16.4 ± 4.7 [e]	17.4 ± 4[e]
µg uroporphyrin per mg creatinine, female rats[d]	0.157 ± 0.05	0.143 ± 0.037	0.181 ± 0.053	0.296 ± 0.074 [e]

[a] NOAEL identified.
[b] LOAEL identified.
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the mean ± SD. Data obtained from Table 2 in Kociba et al. ([1978](#)).
[e] Statistically significant as compared to control ($p < 0.05$).

G.1.11. Kuchiiwa et al. ([2002](#))

Endpoint	Administered Dose (ng/kg-day)		
	0	**0.7[a]**	**70**
	Internal Dose (ng/kg blood)[b]		
	0	**0.26**	**9.12**
	(*n* = 6)	**(*n* = 6)**	**(*n* = 6)**
Immunoreactive neurons in dorsalis, males[c]	237.1 ± 29.0	136.6 ± 22.4[d]	86.0 ± 13.2[d,e]
Immunoreactive neurons in medianus, males[c]	91.1 ± 12.2	33.3 ± 4.55[d]	23.1 ± 8.10[d,e]
Immunoreactive neurons in B9, males[c]	152.1 ± 16.0	46.8 ± 12.1[d]	19.6 ± 15.2[d,e]
Immunoreactive neurons in magnus, males[c]	43.61 ± 3.40	19.82 ± 10.20[d]	11.10 ± 3.88[d,e]

[a] LOAEL identified.
[b] From the Emond PRPK model described in Section 3.3.
[c] Values are the mean ± SD. Data obtained from Figure 2 in Kuchiiwa et al. ([2002](#)).
[d] Statistically significant as compared to control ($p < 0.01$).
[e] Dose dropped from BMD modeling

G.1.12. Latchoumycandane and Mathur ([2002](#))

Endpoint	Administered dose (ng/kg-day)			
	0	**1**[a]	**10**	**100**
	Internal dose (ng/kg blood)[b]			
	0	**0.78**	**4.65**	**27.27**
	(*n* = 6)	(*n* = 6)	(*n* = 6)	(*n* = 6)
Daily sperm production (×10⁶) in adult male rats (mg)[c]	22.19 ± 2.67	15.67 ± 2.65[d]	13.65 ± 2.19[d]	13.1 ± 3.16[d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SD. Data obtained from Table 1 in Latchoumycandane and Mathur ([2002](#)).
[d] Statistically significant as compared to control ($p < 0.05$).

G.1.13. Li et al. ([1997](#))

Endpoint	Administered dose (ng/kg-day)									
	0	**3**[a]	**10**[b]	**30**	**100**	**300**	**1,000**	**3,000**	**10,000**	**30,000**
	Internal dose (ng/kg blood)[c]									
	0	**0.27**	**0.80**	**2.1**	**5.87**	**15**	**43.33**	**119.94**	**385.96**	**1,171.90**
	(*n* = 10)	(*n* = 10)	(*n* = 10)	(*n* = 10)	(*n* = 10)	(*n* = 10)	(*n* = 10)	(*n* = 10)	(*n* = 10)	(*n* = 10)
Serum FSH (ng/mL) in female rats[d]	23.86 ± 9.38	22.16 ± 15.34	85.23 ± 29.83	73.30 ± 15.34	126.14 ± 50.28	132.10 ± 36.65	116.76 ± 16.19	304.26 ± 48.58	346.88 ± 47.73	455.11 ± 90.34

[a] NOAEL identified.
[b] LOAEL identified.
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the mean ± SE. Data obtained from Figure 3 in Li et al. ([1997](#)).

FSH = follicle stimulatin hormone.

1 **G.1.14. Li et al. (2006)**

Endpoint	Administered dose (ng/kg-day)			
	0	**2[a]**	**50**	**100**
	Internal dose (ng/kg blood)[b]			
	0	**0.16**	**2.84**	**5.12**
	(*n* = 10)	(*n* = 10)	(*n* = 10)	(*n* = 10)
Serum estradiol/(pg·mL)$^{-1}$ in female mice (1~3d)[c]	10.17 ± 3.85	19.91 ± 6.31	24.72 ± 4.60	18.09 ± 5.57
Serum progesterone (ng·mL)$^{-1}$ in female mice (1~3d)[c]	61.74 ± 3.51	30.56 ± 12.80[d]	16.93 ± 10.53	11.36 ± 13.83

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SE. Data obtained from Figures 3 (estradiol) and 4 (progesterone) in Li et al. (2006).
[d] Statistically significant as compared to control ($p < 0.01$).

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4 **G.1.15. Markowski et al. (2001)**

Endpoint	Administered dose (ng/kg-day)			
	0	**20[a]**	**60**	**180**
	Internal dose (ng/kg blood)[b]			
	0	**1.56**	**4.03**	**10.32**
	(*n* = 7)	(*n* = 4)	(*n* = 6)	(*n* = 7)
FR10 earned run opportunities, adult female offspring[c]	13.29 ± 8.65	11.25 ± 5.56	5.75 ± 3.53	7 ± 6.01
FR2 total revolutions, adult female offspring[c]	119.29 ± 69.9	108.5 ± 61	56.5 ± 31.21	68.14 ± 33.23
FR5 earned run opportunities, adult female offspring[c]	26.14 ± 12.28	23.5 ± 7.04	12.8 ± 6.17	13.14 ± 7.14

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SD. Data obtained from Table 3 in Markowski et al. (2001).

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1   G.1.16. Miettinen et al. ([2006](#))

Endpoint	Administered dose (ng/kg-day)				
	0	**30[a]**	**100**	**300**	**1,000**
	Internal dose (ng/kg blood)[b]				
	0	**2.22**	**6.23**	**16.01**	**46.64**
	(*n* = 42)	(*n* = 29)	(*n* = 15)	(*n* = 24)	(*n* = 32)
Cariogenic lesions in rat pups[c]	25/42 (60%)	23/29 (79%)[d]	19/25 (76%)	20/24 (83%)[d]	29/32 (91%)[d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Data obtained from Table 2 in Miettinen et al. ([2006](#)).
[d] Statistically significant as compared to control ($p < 0.05$).

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4   G.1.17. National Toxicology Program ([1982](#))

Endpoint	Administered dose (ng/kg-day)			
	0	**1.43[a]**	**7.14**	**71.4**
	Internal dose (ng/kg blood)[b]			
	0	**0.77**	**2.27**	**11.24**
	(*n* = 73)	(*n* = 49)	(*n* = 49)	(*n* = 50)
Numbers of male mice with toxic hepatitis[c]	1/73 (1.4%)	5/49 (10%)	3/49 (6.1%)	44/50 (88%)

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Data obtained from Table 11 in NTP ([1982](#)).

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1   **G.1.18. National Toxicology Program ([2006](#))**

Endpoint[c]	Administered dose (ng/kg-day)					
	0	**2.14[a]**	**7.14**	**15.7**	**32.9**	**71.4**
	Internal dose (ng/kg blood)[b]					
	0	**2.56**	**5.69**	**9.79**	**16.57**	**29.70**
	(*n* = 10)	(*n* = 10)	(*n* = 10)	(*n* = 10)	(*n* = 10)	(*n* = 10)
Gingival squamous hyperplasia	1/53 (2%)	7/54 (13%)[d]	14/53 (26%)[e]	13/53 (25%)[e]	15/53 (28%)[e]	16/53 (30%)[e]
Liver, hepatocyte hypertrophy	0/53 (0%)	19/54 (40%)[e]	19/53 (40%)[c]	42/53 (80%)[e]	41/53 (80%)[e]	52/53 (100%)[e]
Heart, cardiomyopathy	10/53 (19%)	12/54 (22%)	22/53[e] (42%)	25/52[e] (48%)	32/53[e] (60%)	36/52[e] (69%)
Liver, eosinophilic focus, multiple	3/53 (6%)	8/54 (15%)	14/53 (26%)	17/53 (32%)	22/53 (42%)	42/53 (79%)
Liver, fatty change, diffuse	0/53 (0%)	2/54 (4%)	12/53[e] (23%)	17/53[e] (32%)	30/53[e] (57%)	48/53[e] (91%)
Liver, necrosis	1/53 (2%)	4/54 (7%)	4/53 (8%)	8/53[d] (15%)	10/53[e] (19%)	17/53[e] (32%)
Liver, pigmentation	4/53 (8%)	9/54 (17%)	34/53[e] (64%)	48/53[e] (91%)	52/53[e] (98%)	53/53[e] (100%)
Liver, toxic hepatopathy	0/53 (0%)	2/54 (4%)	8/53 (15%)	30/53 (57%)	45/50 (85%)	53/53 (100%)
Oval cell hyperplasia	0/53 (0%)	4/54 (10%)[d]	3/53 (10%)	20/53 (40%)[e]	38/53 (70%)[d]	53/53 (100%)[e]
Lung, alveolar to bronchiolar epithelial metaplasia (Alveolar epithelium, metaplasia, bronchiolar)	2/53 (4%)	19/54[e] (35%)	33/53[e] (62%)	35/52[e] (67%)	45/53[e] (85%)	46/52[e] (89%)

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Data are for female rats in 2-year gavage study. Data for all endpoints obtained from Table A5b in NTP ([2006](#)).
[d] Statistically significant as compared to control ($p < 0.05$).
[e] Statistically significant as compared to control ($p < 0.01$).

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1   **G.1.19. Ohsako et al. (2001)**

	Administered dose (ng/kg-day)				
	0	**12.5[a]**	**50[b]**	**200**	**800**
	Internal dose (ng/kg blood)[c]				
	0	**1.04**	**3.47**	**11.36**	**38.42**
Endpoint	(*n* = 12)	(*n* = 10)	(*n* = 10)	(*n* = 10)	(*n* = 12)
Anogenital distance (mm) in male rat offspring, PND120[d]	28.91 ± 0.90	27.94 ± 0.79	25.17 ± 1.02[e]	26.01 ± 0.90[f]	23.80 ± 0.45[e]

[a] NOAEL for selected endpoint.
[b] LOAEL for selected endpoint.
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the mean ± SE. Data obtained from Figure 7 in Ohsako et al. (2001).
[e] Statistically significant as compared to control ($p < 0.01$).
[f] Statistically significant as compared to control ($p < 0.05$).

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4   **G.1.20. Sewall et al. (1995)**

	Administered dose (ng/kg-day)				
	0	**3.5**	**10.7[a]**	**35[b]**	**125**
	Internal dose (ng/kg blood)[c]				
	0	**3.29**	**7.11**	**16.63**	**44.66**
Endpoint	(*n* = 9)	(*n* = 9)	(*n* = 9)	(*n* = 9)	(*n* = 9)
Serum levels of T4 (nmol/L), saline non noninitiated[d]	30.70 ± 1.55	27.88 ± 2.39	25.90 ± 2.27	23.56 ± 1.79[e]	18.40 ± 1.37[e]

[a] NOAEL for selected endpoint.
[b] LOAEL for selected endpoint.
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the mean ± SE. Data obtained from Figure 1 in Sewall et al. (1995).
[e] Statistically significant as compared to control ($p < 0.05$).

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1   **G.1.21. Shi et al. ([2007])**

Endpoint	Administered dose (ng/kg-day)				
	0	**0.143[a]**	**0.714[b]**	**7.14**	**28.6**
	Internal dose (ng/kg blood)[c]				
	0	**0.34**	**1.07**	**5.23**	**13.91**
	(*n* = 10)	(*n* = 10)	(*n* = 10)	(*n* = 10)	(*n* = 10)
Serum estradiol—17β at proestrus 9 in female rats at 9 mo. of age (pg/mL)[d]	102.86 ± 13.10	86.19 ± 6.19	63.33 ± 9.29[e]	48.1 ± 5.95[e]	38.57 ± 7.14[e]

[a] NOAEL identified.
[b] LOAEL identified.
[c] From the Emond PBPK model described in Section 3.3.
[d] Values are the mean ± SE. Data obtained from Figure 4 in Shi et al. ([2007]).
[e] Statistically significant as compared to control (*p* < 0.05).

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4   **G.1.22. Smialowicz et al. ([2008])**

Endpoint	Administered dose (ng/kg-day)				
	0	**1.07[a]**	**10.7**	**107**	**321**
	Internal dose (ng/kg blood)[b]				
	0	**0.44**	**2.46**	**13.40**	**31.65**
	(*n* = 15)	(*n* = 14)	(*n* = 15)	(*n* = 15)	(*n* = 8)
PFC per 10^6 cells in female mice[c]	1,491 ± 716	1,129 ± 171[d]	945 ± 516[d]	677 ± 465[d]	161 ± 117[d]
PFC × 10^4 per spleen in female mice[c]	27.8 ± 13.4	21 ± 13.6[d]	17.6 ± 9.4[d]	12.6 ± 8.7[d]	3.0 ± 3.1[d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SD. Data obtained from Table 4 in Smialowicz et al. ([2008]).
[d] Statistically significant as compared to control (*p* < 0.05).

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1 **G.1.23. Smith et al. ([1976](#))**

Endpoint	Administered Dose (ng/kg-day)					
	0	**1**	**10**	**100[a]**	**1,000[b]**	**3,000**
	Internal Dose (ng/kg blood)[c]					
	0	**0.12**	**1.01**	**7.11**	**50.59**	**138.07**
Cleft palate in pups[d]	0/34 (0%)	2/41 (4.9%)	0/19 (0%)	1/17 (5.9%)	4/19 (21%)[e]	10/14 (71%)[e]

[a] NOAEL identified
[b] LOAEL identified
[c] From the Emond PRPK model described in Section 3.3.
[d] Values are the incidence and number of litter groups. Data obtained from Table 3 in Smith et al. ([1976](#)).
[e] Statistically significant as compared to control ($p < 0.01$).

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4 **G.1.24. Sparschu et al. ([1971](#))**

Endpoint	Administered Dose (ng/kg-day)				
	0	**30[a]**	**125[b]**	**500**	**2,000**
	Internal Dose (ng/kg blood)[c]				
	0	**5.09**	**16.28**	**52.87**	**188.26**
	(*n* = 117)	(*n* = 55)	(*n* = 66)	(*n* = 39)	(*n* = 3)
Body weight of male fetuses[d]	4.03 ± 0.37	4.14 ± 0.26	3.85 ± 0.35[e]	3.86 ± 0.61[e]	2.72 ± 0.25[e]
	(*n* = 129)	(*n* = 60)	(*n* = 58)	(*n* = 54)	(*n* = 4)
Body weight of female fetuses[d]	3.89 ± 0.39	3.98 ± 0.35	3.71 ± 0.37[e]	3.78 ± 0.54[e]	2.69 ± 0.19[e]

[a] NOAEL identified
[b] LOAEL identified
[c] From the Emond PRPK model described in Section 3.3.
[d] Values are the mean ± SD. Data obtained from Table 4 in Sparschu et al. ([1971](#)).
[e] Statistically significant as compared to control ($p < 0.05$).

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7 **G.1.25. Toth et al. ([1979](#))**

Endpoint	Administered dose (ng/kg-day)			
	0	**1[a]**	**100**	**1,000**
	Internal dose (ng/kg blood)[b]			
	0	**0.57**	**14.21**	**91.21**
	(*n* =38)	(*n* = 44)	(*n* = 44)	(*n* = 43)
Number with amyloidosis plus skin	0/38 (0%)	5/44 (11%)	10/44 (23%)	17/43 (40%)

lesions in mice[c]			
Number with skin lesions in mice[c]	0/38 (0%)	5/44 (11%)	13/44 (30%)	25/43 (58%)

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Data obtained from Table 2 in Toth et al. (1979).

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3 **G.1.26. van Birgelen et al. (1995)**

Endpoint	Administered dose (ng/kg-day)					
	0	14[a]	26	47	320	1,024
	Internal dose (ng/kg blood)[b]					
	0	7.20	11.76	18.09	86.41	250.16
	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)
Hepatic retinol (mg/g liver) in female rats[c]	14.9 ± 3.1	8.4 ± 1.2^d	8.2 ± 0.8^d	5.1 ± 0.3^d	2.2 ± 0.3^d	0.6 ± 0.2^d
Hepatic retinol palmitate (mg/g liver) in female rats[c]	472 ± 96	94 ± 24^d	107 ± 27^d	74 ± 14^d	22 ± 8^d	3 ± 1^d
Plasma FT4 (pmol/L) in female rats[c]	23.4 ± 1.1	24.5 ± 2.0	22.4 ± 1.0	19.3 ± 3.3	16.3 ± 1.5^d	10.3 ± 1.7^d
Plasma TT4 (nmol/L) in female rats[c]	40.9 ± 2.4	41.4 ± 1.9	41.4 ± 2.3	32.3 ± 2.6^d	33.6 ± 2.2^d	25.5 ± 2.7^d

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SE. Data obtained from Table 3 in van Birgelen et al. (1995).
[d] Statistically significant as compared to control ($p < 0.05$).

FT4 = free thyroxine; TT4 = total thyroxine.

4
5

G.1.27. White et al. ([1986])

Endpoint	Administered dose (ng/kg-day)						
	0	**10[a]**	**50**	**100**	**500**	**1,000**	**2,000**
	Internal dose (ng/kg blood)[b]						
	0	**1.09**	**4.08**	**7.14**	**26.81**	**48.72**	**90.56**
	(*n* = 8)	(*n* = 8)	(*n* = 8)	(*n* = 8)	(*n* = 8)	(*n* = 8)	(*n* = 8)
CH50 (U/mL) in female mice[c]	91 ± 5	54 ± 3[d]	63 ± 4[d]	56 ± 9[d]	41 ± 6[d]	32 ± 6[d]	17 ± 6[d]

[a] LOAEL identified.
[b] From the Emond PBPK model described in Section 3.3.
[c] Values are the mean ± SE. Data obtained from Table 1 in White et al. ([1986]).
[d] Statistically significant as compared to control ($p < 0.05$).

G.2. ALTERNATE DOSE: WHOLE BLOOD BMDS RESULTS

G.2.1. Amin et al. ([2000]): 0.25% Saccharin Consumed, Female

G.2.1.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Linear[b]	**1**	**0.551**	**179.214**	**9.147E+00**	**6.094E+00**	
Polynomial, 2-degree	1	0.551	179.214	9.147E+00	6.094E+00	
Power	1	0.551	179.214	9.147E+00	6.094E+00	power bound hit (power = 1)
Power, unrestricted[c]	0	N/A	180.858	8.367E+00	3.419E+00	unrestricted (power = 0.736)

[a] Nonconstant variance model selected ($p = 0.0005$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.1.2. *Output for Selected Model: Linear*

Amin et al. ([2000]): 0.25% Saccharin Consumed, Female

```
  ==================================================================
       Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
       Input Data File: C:\1\Blood\1_Amin_2000_25_SC_Linear_1.(d)
       Gnuplot Plotting File:  C:\1\Blood\1_Amin_2000_25_SC_Linear_1.plt
                                 Mon Feb 08 10:44:22 2010
  ==================================================================

  -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
```

```
     The form of the response function is:

     Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


     Dependent variable = Mean
     Independent variable = Dose
     Signs of the polynomial coefficients are not restricted
     The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

     Total number of dose groups = 3
     Total number of records with missing values = 0
     Maximum number of iterations = 250
     Relative Function Convergence has been set to: 1e-008
     Parameter Convergence has been set to: 1e-008




                      Default Initial Parameter Values
                              lalpha =      5.29482
                                 rho =            0
                              beta_0 =      31.5112
                              beta_1 =     -1.97726



          Asymptotic Correlation Matrix of Parameter Estimates

                     lalpha          rho       beta_0       beta_1

       lalpha            1        -0.99       -0.029        0.044

          rho        -0.99            1        0.026        -0.04

       beta_0       -0.029        0.026            1        -0.94

       beta_1        0.044        -0.04        -0.94            1




                              Parameter Estimates


                                                         95.0% Wald
Confidence Interval
         Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha         -2.54215          1.65048           -5.77702
0.692726
            rho          2.40985         0.541771            1.34799
3.4717
         beta_0          31.2644           4.1929            23.0464
39.4823
         beta_1          -1.9414         0.436071           -2.79609
-1.08672
```

```
     Table of Data and Estimated Values of Interest

 Dose        N    Obs Mean      Est Mean   Obs Std Dev   Est Std Dev   Scaled
Res.
------      ---   --------      --------   -----------   -----------   ---------
-

    0        10      31.7         31.3         20.6          17.8        0.0727
3.378       10      24.6         24.7          12           13.4       -0.0264
10.57       10      10.7         10.8         5.33          4.91       -0.0362




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

           Model      Log(likelihood)   # Param's       AIC
            A1          -92.841935          4        193.683870
            A2          -85.255316          6        182.510632
            A3          -85.429148          5        180.858295
         fitted         -85.606998          4        179.213995
            R           -98.136607          2        200.273213


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test     -2*log(Likelihood Ratio)  Test df        p-value

   Test 1            25.7626             4            <.0001
   Test 2            15.1732             2          0.0005072
   Test 3            0.347663            1            0.5554
```

```
   Test 4                 0.3557          1          0.5509


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data


The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here


The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data



              Benchmark Dose Computation


Specified effect =              1


Risk Type       =    Estimated standard deviations from the control mean


Confidence level =        0.95


          BMD =        9.14709



          BMDL =       6.09414
```

G.2.1.3. *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

10:44 02/08 2010

4 **G.2.1.4.** *Output for Additional Model Presented: Power, Unrestricted*

5 Amin et al. (2000): 0.25% Saccharin Consumed, Female

```
6
7
8     ==========================================================================
9          Power Model. (Version: 2.15;  Date: 04/07/2008)
10         Input Data File: C:\1\Blood\1_Amin_2000_25_SC_Pwr_U_1.(d)
11         Gnuplot Plotting File:  C:\1\Blood\1_Amin_2000_25_SC_Pwr_U_1.plt
12                                      Mon Feb 08 10:44:22 2010
13    ==========================================================================
14
15    -
16  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18    The form of the response function is:
19
20    Y[dose] = control + slope * dose^power
21
22
23    Dependent variable = Mean
```

```
Independent variable = Dose
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                   Default Initial Parameter Values
                         lalpha =       5.29482
                            rho =             0
                        control =       31.6727
                          slope =       -2.2195
                          power =      0.952715


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho       control        slope        power

   lalpha             1        -0.99          0.34        -0.17       -0.061

      rho         -0.99            1         -0.42         0.19        0.068

  control          0.34        -0.42             1        -0.72        -0.56

    slope         -0.17         0.19         -0.72            1         0.97

    power        -0.061        0.068         -0.56         0.97            1




                              Parameter Estimates


                                                          95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          lalpha        -2.48291          2.08669              -6.57274
1.60693
             rho         2.38455         0.692047               1.02817
3.74094
         control           32.99          5.40754               22.3914
43.5886
           slope        -3.91099          3.83883               -11.435
3.61299
           power        0.735877         0.350669             0.0485775
1.42318




    Table of Data and Estimated Values of Interest
```

```
 Dose        N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------      ---   --------     --------   -----------  -----------   ---------
-


    0       10      31.7          33         20.6         18.7        -0.223
3.378       10      24.6         23.4         12          12.4         0.302
10.57       10      10.7         10.8        5.33         4.94        -0.08

Warning: Likelihood for fitted model larger than the Likelihood for model
A3.




Model Descriptions for likelihoods calculated


Model A1:        Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
         Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:        Yi = Mu + e(i)
         Var{e(i)} = Sigma^2



                   Likelihoods of Interest

          Model      Log(likelihood)   # Param's      AIC
           A1          -92.841935           4      193.683870
           A2          -85.255316           6      182.510632
           A3          -85.429148           5      180.858295
         fitted        -85.429148           5      180.858295
           R           -98.136607           2      200.273213



                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                   Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1           25.7626             4           <.0001
  Test 2           15.1732             2          0.0005072
```

```
   Test 3               0.347663           1           0.5554
   Test 4              -8.2423e-013        0             NA
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-
Square
     test for fit is not valid

                  Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

            BMD = 8.36678

            BMDL = 3.41906

G.2.1.5. *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

10:44 02/08 2010

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4 **G.2.2. Amin et al. (2000): 0.25% Saccharin Preference Ratio, Female**

5 **G.2.2.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 p-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Linear[b]	**1**	**0.002**	**227.807**	**1.162E+01**	**5.572E+00**	
Polynomial, 2-degree	1	0.002	227.807	1.162E+01	5.572E+00	
Power	1	0.002	227.807	1.162E+01	5.572E+00	power bound hit (power = 1)

[a] Nonconstant variance model selected ($p = 0.0135$).
[b] Best-fitting model, BMDS output presented in this appendix.

6
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8

G.2.2.2.   *Output for Selected Model: Linear*

Amin et al. (2000): 0.25% Saccharin Preference Ratio, Female

```
====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\Blood\2_Amin_2000_25_SP_Linear_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\2_Amin_2000_25_SP_Linear_1.plt
                                        Mon Feb 08 10:44:49 2010
====================================================================

 -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                          lalpha =      6.34368
                             rho =            0
                          beta_0 =      75.4888
                          beta_1 =     -2.24733



        Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho        beta_0       beta_1

    lalpha             1           -1          0.22        -0.31

       rho            -1            1         -0.22         0.31

    beta_0          0.22        -0.22            1         -0.77

    beta_1         -0.31         0.31         -0.77            1




                         Parameter Estimates
```

         Variable   Estimate   Std. Err.   Lower Conf. Limit
Upper Conf. Limit
         lalpha   3.00523   9.2122   -15.0503
21.0608
           rho   0.797764   2.21138   -3.53646
5.13199
         beta_0   75.1087   6.74312   61.8924
88.3249
         beta_1   -2.16469   1.00825   -4.14082
-0.188553

     Table of Data and Estimated Values of Interest

 Dose   N   Obs Mean   Est Mean   Obs Std Dev   Est Std Dev   Scaled
Res.
 ------   --- --------   --------   -----------   -----------   ---------
-

    0   10   82.1   75.1   13.3   25.2   0.884
3.378   10   58.1   67.8   33.9   24.2   -1.27
10.57   10   54.9   52.2   19.5   21.8   0.383

 Model Descriptions for likelihoods calculated

 Model A1:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model R: Yi = Mu + e(i)
          Var{e(i)} = Sigma^2

                   Likelihoods of Interest

          Model   Log(likelihood)   # Param's   AIC
          A1   -108.574798   4   225.149597
          A2   -104.269377   6   220.538754
          A3   -105.147952   5   220.295903
        fitted   -109.903705   4   227.807410
          R   -112.382522   2   228.765045

                  Explanation of Tests

```
   Test 1:  Do responses and/or variances differ among Dose levels?
            (A2 vs. R)
   Test 2:  Are Variances Homogeneous? (A1 vs A2)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)
   Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
   (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)


                    Tests of Interest


    Test    -2*log(Likelihood Ratio)  Test df       p-value


    Test 1              16.2263           4         0.00273
    Test 2              8.61084           2         0.0135
    Test 3              1.75715           1          0.185
    Test 4              9.51151           1         0.002042


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model



                  Benchmark Dose Computation

Specified effect =              1

Risk Type       =     Estimated standard deviations from the control mean

Confidence level =        0.95

          BMD =        11.6241


          BMDL =       5.57215
```

1 **G.2.2.3.** *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

10:44 02/08 2010

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4 **G.2.3.** **Amin et al. (2000): 0.50% Saccharin Consumed, Female**

5 **G.2.3.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ² *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Linear[b]	**1**	**0.060**	**158.591**	**1.016E+01**	**6.567E+00**	
Polynomial, 2-degree	1	0.060	158.591	1.016E+01	6.567E+00	
Power	1	0.060	158.591	1.016E+01	6.567E+00	power bound hit (power = 1)
Power, unrestricted[c]	0	N/A	157.060	6.567E+00	1.155E+00	unrestricted (power = 0.396)

[a] Nonconstant variance model selected (p = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

6
7

G.2.3.2. *Output for Selected Model: Linear*

Amin et al. (2000): 0.50% Saccharin Consumed, Female

```
 ====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\Blood\3_Amin_2000_50_SC_Linear_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\3_Amin_2000_50_SC_Linear_1.plt
                                      Mon Feb 08 10:45:20 2010
 ====================================================================

 -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                          lalpha =      4.68512
                             rho =            0
                          beta_0 =      20.0631
                          beta_1 =     -1.57142



        Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho       beta_0       beta_1

    lalpha             1        -0.96        0.019      -0.0016

       rho         -0.96            1       -0.031        0.015

    beta_0         0.019       -0.031            1        -0.96

    beta_1       -0.0016        0.015        -0.96            1




                          Parameter Estimates
```

```
                                                      95.0% Wald
Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha         -0.982115         0.982262            -2.90731
0.943084
            rho          2.11808          0.401166            1.33181
2.90435
         beta_0          18.6171          3.1782              12.3879
24.8462
         beta_1         -1.33226          0.322037            -1.96344
-0.70108




     Table of Data and Estimated Values of Interest

 Dose       N     Obs Mean      Est Mean    Obs Std Dev   Est Std Dev    Scaled
Res.
 ------     ---   --------      --------    -----------   -----------   ---------
-

    0      10      22.4          18.6           16           13.5          0.873
3.378     10      11.4          14.1          7.66          10.1         -0.856
10.57     10      4.54          4.54          3.33          3.04         -0.00339




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                  Likelihoods of Interest

          Model    Log(likelihood)    # Param's      AIC
           A1         -83.696404          4        175.392808
           A2         -73.511830          6        159.023660
           A3         -73.530233          5        157.060467
         fitted       -75.295363          4        158.590726
           R          -90.294746          2        184.589492



                  Explanation of Tests
```

```
Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)


                    Tests of Interest


   Test     -2*log(Likelihood Ratio)  Test df        p-value


   Test 1              33.5658           4            <.0001
   Test 2              20.3691           2            <.0001
   Test 3            0.0368066           1            0.8479
   Test 4              3.53026           1            0.06026
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different
model


```
                  Benchmark Dose Computation

Specified effect =             1

Risk Type        =      Estimated standard deviations from the control mean

Confidence level =         0.95

          BMD =          10.1633


          BMDL =         6.56742
```

G.2.3.3. *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

10:45 02/08 2010

G.2.3.4. *Output for Additional Model Presented: Power, Unrestricted*

Amin et al. (2000): 0.50% Saccharin Consumed, Female

```
============================================================
       Power Model. (Version: 2.15;  Date: 04/07/2008)
       Input Data File: C:\1\Blood\3_Amin_2000_50_SC_Pwr_U_1.(d)
       Gnuplot Plotting File:  C:\1\Blood\3_Amin_2000_50_SC_Pwr_U_1.plt
                                        Mon Feb 08 10:45:20 2010
============================================================

 -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
```

```
Independent variable = Dose
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          lalpha =        4.68512
                             rho =              0
                         control =        22.3564
                           slope =       -6.53901
                           power =       0.425213


          Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha         rho       control        slope         power

     lalpha            1       -0.96          0.34        -0.31        -0.15

        rho        -0.96           1         -0.47         0.36         0.15

    control         0.34       -0.47             1        -0.81        -0.52

      slope        -0.31        0.36         -0.81            1         0.92

      power        -0.15        0.15         -0.52         0.92            1




                             Parameter Estimates


                                                        95.0% Wald
Confidence Interval
        Variable       Estimate       Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          lalpha      -0.708629           1.298            -3.25267
1.83541
             rho       1.96142        0.529653            0.923323
2.99953
         control       22.6293         4.48416             13.8405
31.4181
           slope      -7.10123         4.04394            -15.0272
0.824743
           power      0.395571        0.168677           0.0649698
0.726173




    Table of Data and Estimated Values of Interest
```

```
 Dose        N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------      ---   --------    --------   -----------  -----------   ---------
-

    0       10      22.4         22.6          16           15       -0.0577
3.378       10      11.4         11.1        7.66         7.46        0.105
10.57       10      4.54         4.58        3.33         3.12       -0.0475

Degrees of freedom for Test A3 vs fitted <= 0




 Model Descriptions for likelihoods calculated


 Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:          Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

            Model      Log(likelihood)   # Param's       AIC
            A1          -83.696404           4       175.392808
            A2          -73.511830           6       159.023660
            A3          -73.530233           5       157.060467
         fitted         -73.530233           5       157.060467
            R           -90.294746           2       184.589492


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test     -2*log(Likelihood Ratio)   Test df        p-value

   Test 1              33.5658            4           <.0001
   Test 2              20.3691            2           <.0001
   Test 3            0.0368066            1           0.8479
```

```
   Test 4                      0            0                NA
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-
Square
     test for fit is not valid

                 Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

            BMD = 6.56719

            BMDL = 1.15476

1   **G.2.3.5.** *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

10:45 02/08 2010

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4   **G.2.4.   Amin et al. (2000): 0.50% Saccharin Preference Ratio, Female**

5   **G.2.4.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Linear[b]	**1**	**0.135**	**234.250**	**8.144E+00**	**5.105E+00**	
Polynomial, 2-degree	1	0.135	234.250	8.144E+00	5.105E+00	
Power	1	0.135	234.250	8.144E+00	5.105E+00	power bound hit (power = 1)
Power, unrestricted[c]	0	N/A	234.020	2.598E+00	1.057E−14	unrestricted (power = 0.282)

[a] Constant variance model selected ($p = 0.5593$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

6
7

G.2.4.2. *Output for Selected Model: Linear*

Amin et al. (2000): 0.50% Saccharin Preference Ratio, Female

```
====================================================================
      Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
      Input Data File: C:\1\Blood\4_Amin_2000_50_SP_LinearCV_1.(d)
      Gnuplot Plotting File:  C:\1\Blood\4_Amin_2000_50_SP_LinearCV_1.plt
                                        Mon Feb 08 10:45:50 2010
====================================================================

 -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




                  Default Initial Parameter Values
                          alpha =      764.602
                            rho =            0    Specified
                         beta_0 =      65.8627
                         beta_1 =     -3.34297



          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha        beta_0         beta_1

     alpha            1       2.6e-008       2.1e-009

    beta_0      2.6e-008            1          -0.73

    beta_1      2.1e-009         -0.73             1

```

```
                              Parameter Estimates


                                                        95.0% Wald
Confidence Interval
        Variable         Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
           alpha          741.255         191.391               366.135
1116.38
          beta_0          65.8627         7.22524               51.7015
80.0239
          beta_1         -3.34297         1.12815              -5.55412
-1.13183




     Table of Data and Estimated Values of Interest

 Dose        N     Obs Mean      Est Mean    Obs Std Dev   Est Std Dev    Scaled
Res.
 ------      ---   --------      --------    -----------   -----------   ---------
-

    0        10      72.7          65.9          24.6          27.2         0.797
3.378        10      44.5          54.6          32.9          27.2         -1.17
10.57        10      33.8          30.5          24.6          27.2         0.375




 Model Descriptions for likelihoods calculated


 Model A1:         Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2

 Model A2:         Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma(i)^2

 Model A3:         Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:         Yi = Mu + e(i)
         Var{e(i)} = Sigma^2


                     Likelihoods of Interest


         Model      Log(likelihood)   # Param's       AIC
          A1         -113.009921          4        234.019841
          A2         -112.428886          6        236.857773
          A3         -113.009921          4        234.019841
        fitted       -114.125184          3        234.250368
          R          -117.976057          2        239.952114
```

```
                    Explanation of Tests

  Test 1:  Do responses and/or variances differ among Dose levels?
           (A2 vs. R)
  Test 2:  Are Variances Homogeneous? (A1 vs A2)
  Test 3:  Are variances adequately modeled? (A2 vs. A3)
  Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
  (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                       Tests of Interest

    Test    -2*log(Likelihood Ratio)  Test df       p-value

    Test 1             11.0943            4          0.02552
    Test 2             1.16207            2          0.5593
    Test 3             1.16207            2          0.5593
    Test 4             2.23053            1          0.1353

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data



                 Benchmark Dose Computation

Specified effect =              1

Risk Type         =     Estimated standard deviations from the control mean

Confidence level =         0.95

           BMD =        8.14425


           BMDL =       5.10523
```

G.2.4.3. *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

10:45 02/08 2010

4 **G.2.4.4.** *Output for Additional Model Presented: Power, Unrestricted*

5 Amin et al. (2000): 0.50% Saccharin Preference Ratio, Female

```
       ====================================================================
       Power Model. (Version: 2.15;   Date: 04/07/2008)
       Input Data File: C:\1\Blood\4_Amin_2000_50_SP_PwrCV_U_1.(d)
       Gnuplot Plotting File:  C:\1\Blood\4_Amin_2000_50_SP_PwrCV_U_1.plt
                                        Mon Feb 08 10:45:50 2010
       ====================================================================

   -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
```

```
   Independent variable = Dose
   rho is set to 0
   The power is not restricted
   A constant variance model is fit

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                          alpha =       764.602
                            rho =             0    Specified
                        control =       72.7273
                          slope =      -20.0402
                          power =      0.281985


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                  alpha        control         slope          power

      alpha           1      -1.2e-009      -1.2e-009      -2.2e-010

    control   -1.2e-009              1          -0.51          -0.22

      slope   -1.2e-009          -0.51              1           0.92

      power   -2.2e-010          -0.22           0.92              1




                            Parameter Estimates


                                                        95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
          alpha         688.142          177.677                  339.9
1036.38
        control         72.7273          8.29543                56.4686
88.986
          slope        -20.0402          15.0576               -49.5526
9.47219
          power        0.281985         0.325861               -0.35669
0.920661
```

```
      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean      Est Mean    Obs Std Dev   Est Std Dev    Scaled
Res.
------     ---   --------      --------    -----------   -----------    ---------
-

    0      10      72.7          72.7         24.6          26.2        4.67e-009
3.378      10      44.5          44.5         32.9          26.2        1.52e-008
10.57      10      33.8          33.8         24.6          26.2        1.77e-008


 Warning: Likelihood for fitted model larger than the Likelihood for model
A3.




 Model Descriptions for likelihoods calculated


 Model A1:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:          Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
            A1          -113.009921          4        234.019841
            A2          -112.428886          6        236.857773
            A3          -113.009921          4        234.019841
          fitted        -113.009921          4        234.019841
            R           -117.976057          2        239.952114


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value
```

```
    Test 1              11.0943           4              0.02552
    Test 2              1.16207           2              0.5593
    Test 3              1.16207           2              0.5593
    Test 4           -2.84217e-014        0                 NA
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-
Square
     test for fit is not valid

                   Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

            BMD = 2.59831

           BMDL = 1.05661e-014


```

1    **G.2.4.5.** *Figure for Additional Model Presented: Power, Unrestricted*



Power Model with 0.95 Confidence Level

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1    **G.2.5.   Bell et al. ([2007](#)): Balano-Preputial Separation, Postnatal Day (PND) 49**

2    **G.2.5.1.** *Summary Table of BMDS Modeling Results*

| Model | Degrees of freedom | $\chi^2$ p-value | AIC | BMD (ng/kg) | BMDL (ng/kg) | Notes |
|---|---|---|---|---|---|---|
| Gamma | 2 | 0.684 | 112.136 | 2.867E+00 | 1.943E+00 | power bound hit (power = 1) |
| Logistic | 2 | 0.342 | 113.915 | 6.159E+00 | 4.746E+00 | negative intercept (intercept = −2.246) |
| **Log-logistic[a]** | **2** | **0.777** | **111.908** | **2.246E+00** | **1.394E+00** | **slope bound hit (slope = 1)** |
| Log-probit | 2 | 0.269 | 114.254 | 5.322E+00 | 3.512E+00 | slope bound hit (slope = 1) |
| Multistage, 3-degree | 2 | 0.684 | 112.136 | 2.867E+00 | 1.943E+00 | final ß = 0 |
| Probit | 2 | 0.367 | 113.713 | 5.715E+00 | 4.422E+00 | |
| Weibull | 2 | 0.684 | 112.136 | 2.867E+00 | 1.943E+00 | power bound hit (power = 1) |
| Gamma, unrestricted | 1 | 0.566 | 113.746 | 1.862E+00 | 1.829E−01 | unrestricted (power = 0.741) |
| Log-logistic, unrestricted[b] | 1 | 0.501 | 113.871 | 1.998E+00 | 2.795E−01 | unrestricted (slope = 0.93) |
| Log-probit, unrestricted | 1 | 0.456 | 113.977 | 2.038E+00 | 3.250E−01 | unrestricted (slope = 0.54) |
| Weibull, unrestricted | 1 | 0.551 | 113.771 | 1.914E+00 | 2.346E−01 | unrestricted (power = 0.795) |

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

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5    **G.2.5.2.** *Output for Selected Model: Log-Logistic*

6    Bell et al. ([2007](#)): Balano-Preputial Separation, PND 49
7
8
```
9   ==
10   Logistic Model. (Version: 2.12; Date: 05/16/2008)
11   Input Data File: C:\1\Blood\5_Bell_2007_BPS_LogLogistic_1.(d)
12   Gnuplot Plotting File: C:\1\Blood\5_Bell_2007_BPS_LogLogistic_1.plt
13   Mon Feb 08 10:46:18 2010
14   ==
15
16   0
17   ~~~~~~
18
19   The form of the probability function is:
20
21   P[response] = background+(1-background)/[1+EXP(-intercept-
22   slope*Log(dose))]
23
24
25   Dependent variable = DichEff
26   Independent variable = Dose
```

```
   Slope parameter is restricted as slope >= 1


   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




   User has chosen the log transformed model


                  Default Initial Parameter Values
                      background =    0.0333333
                       intercept =     -2.99896
                           slope =          1



           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

               background    intercept

background            1        -0.49

 intercept         -0.49           1




                              Parameter Estimates

                                                  95.0% Wald
Confidence Interval
      Variable         Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
     background        0.038005            *                 *
*
      intercept        -3.00658            *                 *
*
         slope              1              *                 *
*

* - Indicates that this value is not calculated.




                         Analysis of Deviance Table

      Model        Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -53.7077         4
    Fitted model       -53.954          2       0.492596      2
0.7817
```

```
Reduced model        -63.9797          1        20.544        3
0.0001309

          AIC:          111.908


                        Goodness   of   Fit
                                                        Scaled
     Dose     Est._Prob.    Expected    Observed    Size    Residual
   -------------------------------------------------------------------
    0.0000     0.0380         1.140      1.000        30     -0.134
    2.2040     0.1326         3.977      5.000        30      0.551
    5.1378     0.2329         6.988      6.000        30     -0.427
   18.4110     0.4965        14.895     15.000        30      0.038

 Chi^2 = 0.50     d.f. = 2        P-value = 0.7769


    Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

          BMD =       2.24647
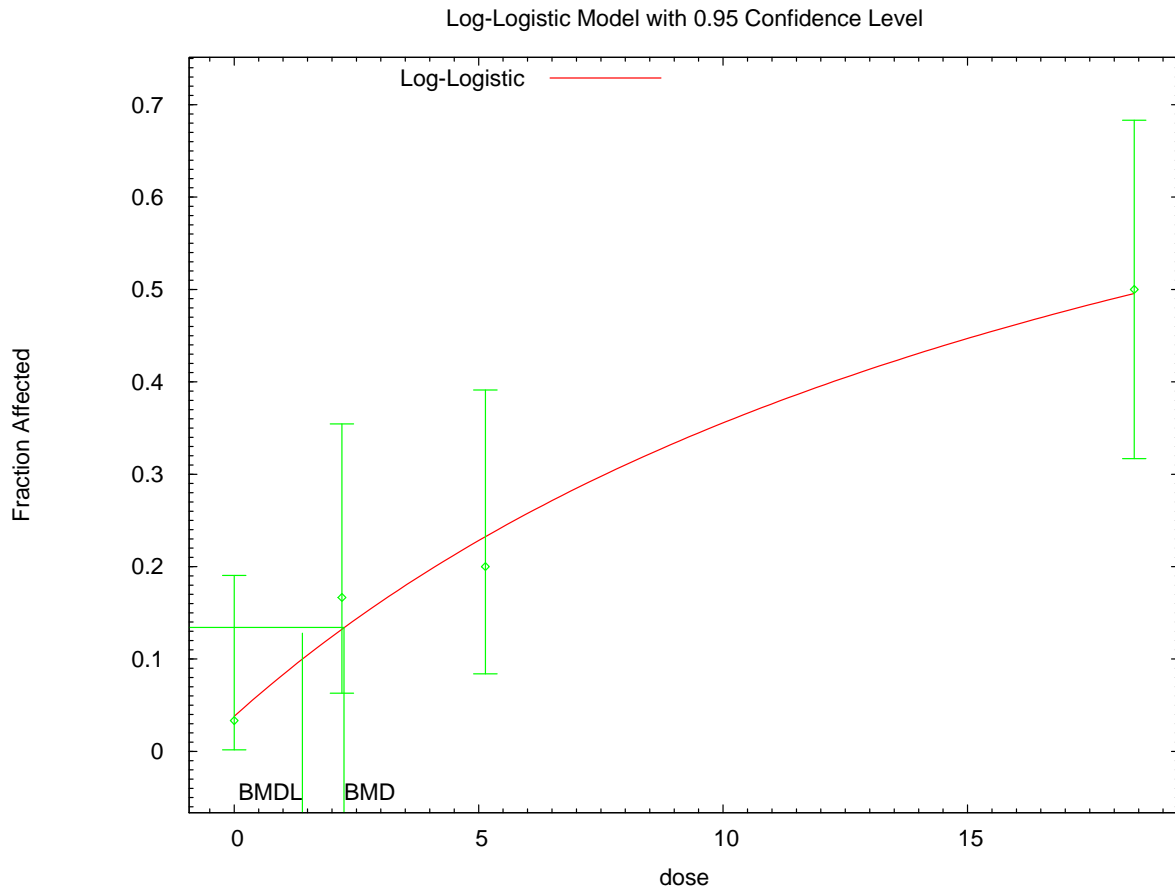
          BMDL =      1.39385
```

1   **G.2.5.3.** *Figure for Selected Model: Log-Logistic*

Log-Logistic Model with 0.95 Confidence Level

10:46 02/08 2010

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3
4   **G.2.5.4.** *Output for Additional Model Presented: Log-Logistic, Unrestricted*

5   Bell et al. ([2007](#)): Balano-Preputial Separation, PND 49

6
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8
```
      ====================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\5_Bell_2007_BPS_LogLogistic_U_1.(d)
         Gnuplot Plotting File:
   C:\1\Blood\5_Bell_2007_BPS_LogLogistic_U_1.plt
                                        Mon Feb 08 10:46:18 2010
      ====================================================================

   0
   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

      The form of the probability function is:

      P[response] = background+(1-background)/[1+EXP(-intercept-
   slope*Log(dose))]
```
23

```
    Dependent variable = DichEff
    Independent variable = Dose
    Slope parameter is not restricted

    Total number of observations = 4
    Total number of records with missing values = 0
    Maximum number of iterations = 250
    Relative Function Convergence has been set to: 1e-008
    Parameter Convergence has been set to: 1e-008




    User has chosen the log transformed model


                    Default Initial Parameter Values
                       background =    0.0333333
                        intercept =     -2.68464
                            slope =     0.858398


          Asymptotic Correlation Matrix of Parameter Estimates

                  background      intercept          slope

 background              1          -0.48           0.35

  intercept          -0.48              1          -0.94

     slope           0.35          -0.94              1




                             Parameter Estimates

                                                  95.0% Wald
Confidence Interval
      Variable         Estimate        Std. Err.       Lower Conf. Limit
Upper Conf. Limit
     background       0.0353402              *                   *
*
      intercept        -2.84051              *                   *
*
         slope        0.929645              *                   *
*

* - Indicates that this value is not calculated.




                         Analysis of Deviance Table

     Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
    Full model        -53.7077         4
   Fitted model       -53.9354         3       0.455534       1
0.4997
```

```
Reduced model          -63.9797          1          20.544          3
0.0001309

          AIC:          113.871


                         Goodness  of  Fit
                                                          Scaled
     Dose      Est._Prob.     Expected     Observed     Size     Residual
    -------------------------------------------------------------------------
     0.0000     0.0353          1.060        1.000          30       -0.060
     2.2040     0.1400          4.201        5.000          30        0.420
     5.1378     0.2389          7.166        6.000          30       -0.499
    18.4110     0.4858         14.573       15.000          30        0.156

 Chi^2 = 0.45     d.f. = 1          P-value = 0.5005


    Benchmark Dose Computation

Specified effect =          0.1

Risk Type        =      Extra risk

Confidence level =          0.95

          BMD =      1.99765

          BMDL =     0.279534
```

1   **G.2.5.5.   *Figure for Additional Model Presented: Log-Logistic, Unrestricted***

Log-Logistic Model with 0.95 Confidence Level

10:46 02/08 2010

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G.2.6. Cantoni et al. ([1981](#)): Urinary Coproporhyrins, 3 Months

G.2.6.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.003	32.882	3.209E+01	1.567E+01	
Exponential (M3)	2	0.003	32.882	3.209E+01	1.567E+01	power hit bound (*d* = 1)
Exponential (M4)[b]	**1**	**0.486**	**23.459**	**5.339E−01**	**1.803E−01**	
Exponential (M5)	1	0.486	23.459	5.339E−01	1.803E−01	power hit bound (*d* = 1)
Hill	1	0.788	23.047	4.333E−01	error	*n* lower bound hit (*n* = 1)
Linear	2	0.005	31.595	1.464E+01	2.753E+00	
Polynomial, 3-degree	2	0.005	31.595	1.464E+01	2.753E+00	
Power	2	0.005	31.595	1.464E+01	2.753E+00	power bound hit (power = 1)
Power, unrestricted[c]	1	0.610	23.235	2.766E−02	2.031E−05	unrestricted (power = 0.304)
Hill, unrestricted	0	N/A	24.974	2.602E−01	error	unrestricted (*n* = 0.739)

[a] Nonconstant variance model selected (*p* = 0.0039).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.6.2. *Output for Selected Model: Exponential (M4)*

Cantoni et al. ([1981](#)): Urinary Coproporhyrins, 3 Months

```
      ====================================================================
           Exponential Model. (Version: 1.61;  Date: 7/24/2009)
           Input Data File: C:\1\Blood\6_Cantoni_1981_UriCopro_Exp_1.(d)
           Gnuplot Plotting File:
                                         Mon Feb 08 10:46:46 2010
      ====================================================================

  Figure1-UrinaryCoproporphyrin_3months
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
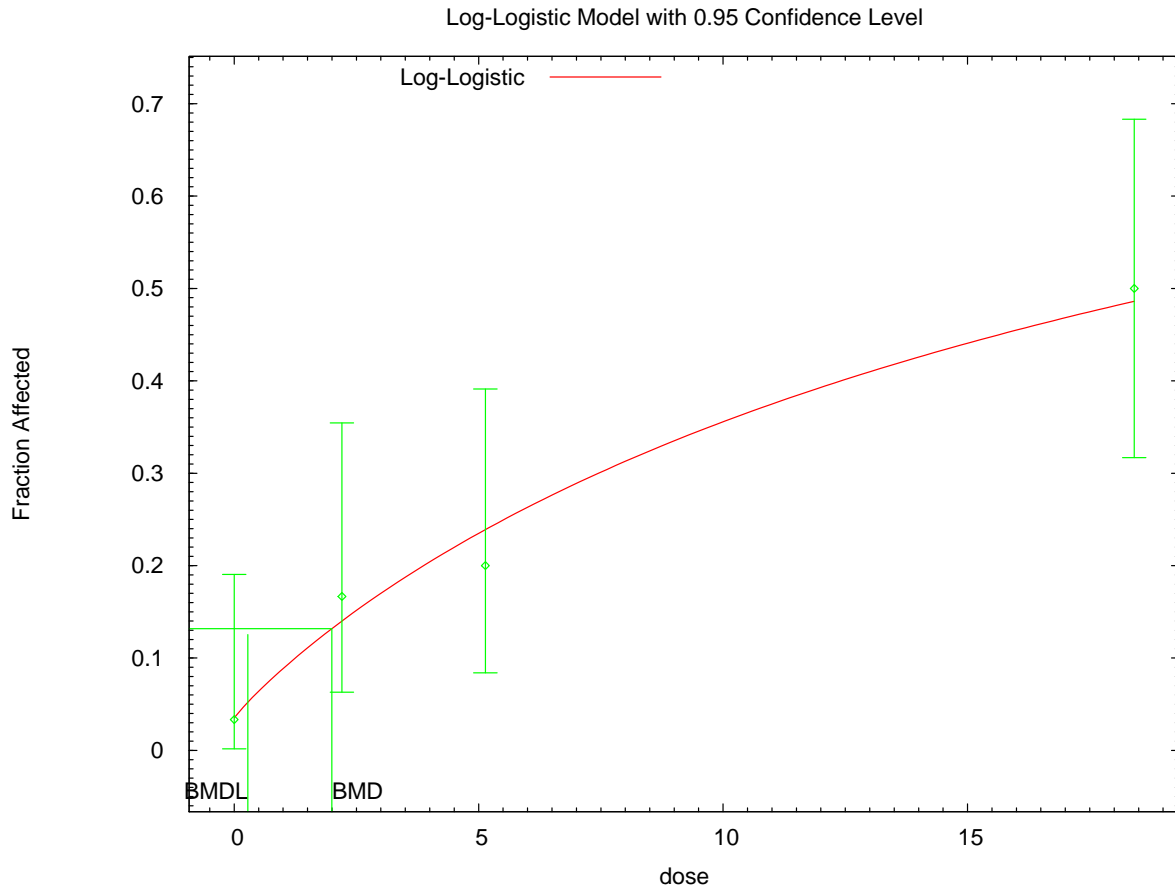
   The form of the response function by Model:
      Model 2:    Y[dose] = a * exp{sign * b * dose}
      Model 3:    Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:    Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:    Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
```

```
Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                    Initial Parameter Values

                    Variable           Model 4
                    --------           --------
                     lnalpha          -1.50063
                        rho           2.60979
                          a          0.704303
                          b         0.0604961
                          c           4.47268
                          d                 1



                    Parameter Estimates

                    Variable           Model 4
                    --------           -------
                     lnalpha          -1.75302
                        rho            2.6322
                          a          0.761218
                          b          0.241561
                          c           4.15597
                          d                 1


        Table of Stats From Input Data

   Dose      N        Obs Mean      Obs Std Dev
   -----    ---      ----------    -------------
      0      4        0.7414         0.3475
  1.847      4         1.807         0.8341
  8.839      4         2.734          1.506
  50.05      4             3            2.6



             Estimated Values of Interest

    Dose      Est Mean       Est Std    Scaled Residual
   ------    ----------     ---------   ----------------
```

```
        0              0.7612           0.2907              -0.1366
     1.847             1.626            0.7892               0.4588
     8.839             2.88             1.674               -0.1743
    50.05              3.164            1.895               -0.1725




   Other models for which likelihoods are calculated:

      Model A1:        Yij = Mu(i) + e(ij)
                  Var{e(ij)} = Sigma^2

      Model A2:        Yij = Mu(i) + e(ij)
                  Var{e(ij)} = Sigma(i)^2

      Model A3:        Yij = Mu(i) + e(ij)
                  Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

      Model  R:        Yij = Mu + e(i)
                  Var{e(ij)} = Sigma^2


                           Likelihoods of Interest

                   Model      Log(likelihood)      DF          AIC
                   -------    ----------------     ----     ------------
                     A1         -12.90166           5        35.80333
                     A2          -6.203643          8        28.40729
                     A3          -6.487204          6        24.97441
                      R         -15.73713           2        35.47427
                      4          -6.729737          5        23.45947



   Additive constant for all log-likelihoods =      -14.7.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                           Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 6a: Does Model 4 fit the data? (A3 vs 4)



                           Tests of Interest

     Test          -2*log(Likelihood Ratio)          D. F.           p-value
    --------       ------------------------          ------      --------------
     Test 1                  19.07                      6            0.004052
     Test 2                  13.4                       3            0.003854
     Test 3                  0.5671                     2            0.7531
     Test 6a                 0.4851                     1            0.4861
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose
levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous
variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled
variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems
to adequately describe the data.

Benchmark Dose Computations:

   Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

   Confidence Level = 0.950000

                BMD =   0.533855

               BMDL =   0.180293

G.2.6.3. *Figure for Selected Model: Exponential (M4)*

Exponential Model 4 with 0.95 Confidence Level

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G.2.6.4. *Output for Additional Model Presented: Power, Unrestricted*

Cantoni et al. (1981): Urinary Coproporhyrins, 3 Months

```
   ====================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\Blood\6_Cantoni_1981_UriCopro_Pwr_U_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\6_Cantoni_1981_UriCopro_Pwr_U_1.plt
                                    Mon Feb 08 10:46:47 2010
   ====================================================================
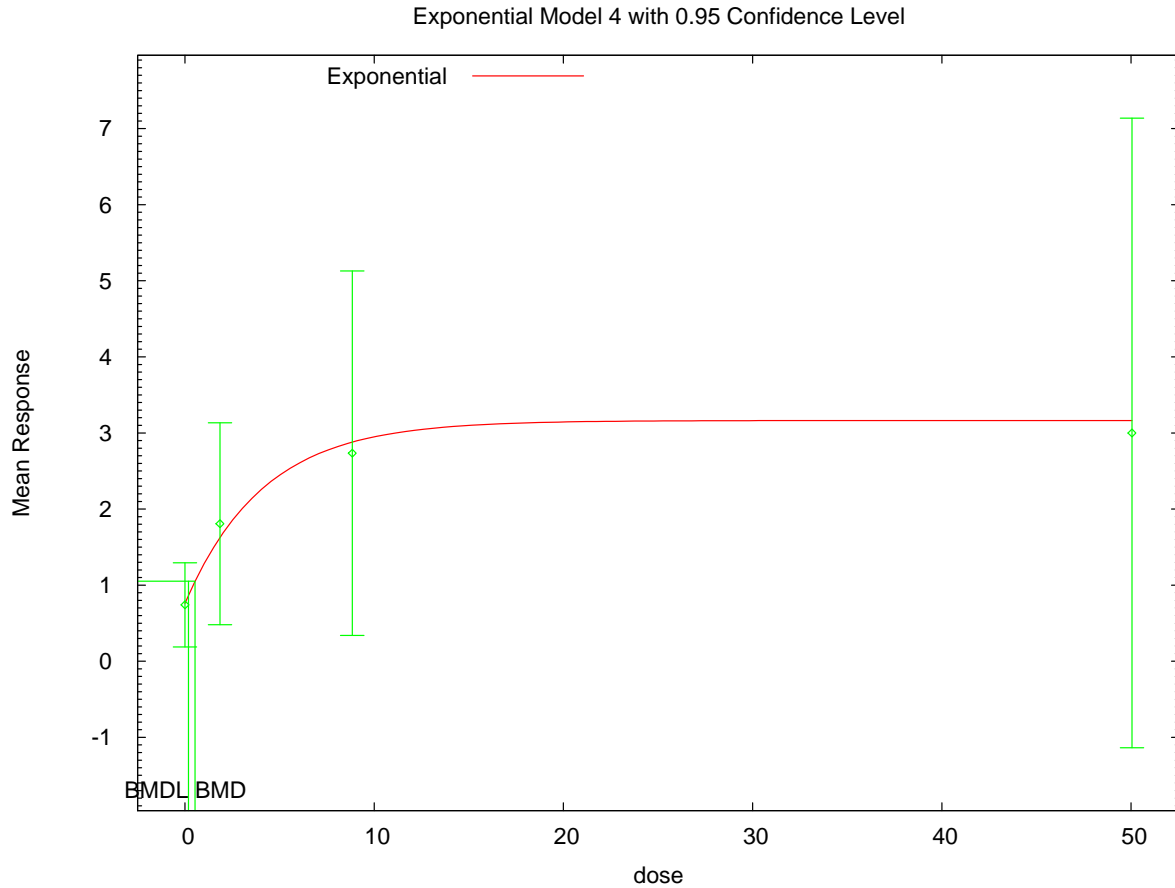
 Figure1-UrinaryCoproporphyrin_3months
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function is:

    Y[dose] = control + slope * dose^power
```

```
Dependent variable = Mean
Independent variable = Dose
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                         lalpha =        0.90039
                            rho =              0
                        control =       0.741372
                          slope =        0.93685
                          power =       0.224904


        Asymptotic Correlation Matrix of Parameter Estimates

                lalpha          rho        control         slope          power

   lalpha            1        -0.62          -0.53        -0.036          0.024

      rho        -0.62            1           0.43          -0.2          -0.16

  control        -0.53         0.43              1         -0.28          0.086

    slope       -0.036         -0.2          -0.28             1          -0.77

    power        0.024        -0.16          0.086         -0.77              1




                            Parameter Estimates

                                                      95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
         lalpha         -1.78125        0.617807             -2.99213
-0.570373
            rho          2.64332        0.744946              1.18325
4.10338
        control          0.75678        0.139979              0.482426
1.03113
          slope         0.845767        0.324854              0.209065
1.48247
          power         0.304211        0.135053             0.0395119
0.568909




     Table of Data and Estimated Values of Interest
```

```
 Dose        N    Obs Mean    Est Mean   Obs Std Dev   Est Std Dev   Scaled
Res.
------       ---   --------    --------   -----------   -----------   ---------
-

    0        4     0.741       0.757       0.348         0.284        -0.109
1.847        4     1.81        1.78        0.834         0.877         0.0705
8.839        4     2.73        2.4         1.51          1.3           0.515
50.05        4     3           3.54        2.6           2.18         -0.493
```

Model Descriptions for likelihoods calculated

Model A1:   Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2

Model A2:   Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma(i)^2

Model A3:   Yij = Mu(i) + e(ij)
         Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model R: Yi = Mu + e(i)
         Var{e(i)} = Sigma^2

                    Likelihoods of Interest

           Model   Log(likelihood)   # Param's   AIC
           A1   -12.901663   5   35.803325
           A2   -6.203643   8   28.407287
           A3   -6.487204   6   24.974409
        fitted   -6.617347   5   23.234694
           R   -15.737135   2   35.474269

                    Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

  Test   -2*log(Likelihood Ratio)   Test df   p-value

  Test 1   19.067   6   0.004052
  Test 2   13.396   3   0.003854
  Test 3   0.567122   2   0.7531
```

```
   Test 4                0.260285          1          0.6099
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

                  Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

              BMD = 0.0276599

              BMDL = 2.03143e-005

1   **G.2.6.5.**   *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

10:46 02/08 2010

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1 **G.2.7.   Cantoni et al. ([1981](#)): Urinary Porphyrins**

2 **G.2.7.1.   *Summary Table of BMDS Modeling Results***

Model[a]	Degrees of freedom	χ^2 p-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)[b]	2	<0.001	55.465	3.760E+00	2.762E+00	
Exponential (M3)	2	<0.001	55.465	3.760E+00	2.762E+00	power hit bound ($d = 1$)
Exponential (M4)	1	<0.0001	59.187	2.484E−01	1.448E−01	
Exponential (M5)	0	N/A	61.084	2.878E−01	1.461E−01	
Hill	0	N/A	62.199	6.233E+00	3.341E+00	
Linear	2	<0.001	57.187	2.484E−01	1.448E−01	
Polynomial, 3-degree	1	<0.0001	10.000	error	error	
Power	1	<0.0001	59.084	2.878E−01	1.461E−01	

[a] Nonconstant variance model selected (p = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.

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5 **G.2.7.2.   *Output for Selected Model: Exponential (M2)***

6 Cantoni et al. ([1981](#)): Urinary Porphyrins

```
   ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\7_Cantoni_1981_UriPor_Exp_1.(d)
        Gnuplot Plotting File:
                                        Mon Feb 08 10:47:24 2010
   ======================================================================

 Table 1, dose converted to ng per kg per day
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
     Model 2:    Y[dose] = a * exp{sign * b * dose}
     Model 3:    Y[dose] = a * exp{sign * (b * dose)^d}
     Model 4:    Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 5:    Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

     Model 2 is nested within Models 3 and 4.
     Model 3 is nested within Model 5.
     Model 4 is nested within Model 5.


     Dependent variable = Mean
```

```
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                    Initial Parameter Values

                  Variable          Model 2
                  --------          --------
                   lnalpha            -3.57509
                       rho             2.23456
                         a             3.36453
                         b           0.0819801
                         c                   0
                         d                   1




                    Parameter Estimates

                  Variable          Model 2
                  --------          -------
                   lnalpha          -1.85879
                       rho           1.82273
                         a           3.57896
                         b         0.0803347
                         c                 0
                         d                 1



          Table of Stats From Input Data

   Dose      N        Obs Mean     Obs Std Dev
   -----    ---       ----------   -------------
       0     4         2.27           0.49
   1.847     4         5.55           0.85
   8.839     3         7.62           1.79
   50.05     3        196.9          63.14



          Estimated Values of Interest

   Dose      Est Mean      Est Std      Scaled Residual
   ------    ----------    ---------    ----------------
       0       3.579         1.262          -2.074
   1.847       4.152         1.445           1.936
   8.839        7.28          2.41          0.2441
   50.05       199.5         49.25         -0.09069
```

```
   Other models for which likelihoods are calculated:

     Model A1:        Yij = Mu(i) + e(ij)
               Var{e(ij)} = Sigma^2

     Model A2:        Yij = Mu(i) + e(ij)
               Var{e(ij)} = Sigma(i)^2

     Model A3:        Yij = Mu(i) + e(ij)
               Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

     Model  R:        Yij = Mu + e(i)
               Var{e(ij)} = Sigma^2


                          Likelihoods of Interest

                 Model      Log(likelihood)     DF        AIC
                 -------    ----------------    ----    ------------
                   A1         -51.42175          5       112.8435
                   A2         -15.31211          8       46.62422
                   A3         -15.66963          6       43.33925
                    R         -68.75058          2       141.5012
                    2         -23.73254          4       55.46509


   Additive constant for all log-likelihoods =     -12.87.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                           Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)
   Test 4:  Does Model 2 fit the data? (A3 vs. 2)



                           Tests of Interest

    Test          -2*log(Likelihood Ratio)        D. F.        p-value
    --------      ------------------------        ------      --------------
    Test 1                  106.9                   6         < 0.0001
    Test 2                  72.22                   3         < 0.0001
    Test 3                  0.715                   2           0.6994
    Test 4                  16.13                   2          0.000315


   The p-value for Test 1 is less than .05.  There appears to be a
   difference between response and/or variances among the dose
   levels, it seems appropriate to model the data.
```

The p-value for Test 2 is less than .1. A non-homogeneous
variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled
variance appears to be appropriate here.

The p-value for Test 4 is less than .1. Model 2 may not adequately
describe the data; you may want to consider another model.

Benchmark Dose Computations:

Specified Effect = 1.000000

        Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

              BMD =   3.75968

              BMDL =   2.76247

G.2.7.3. *Figure for Selected Model: Exponential (M2)*

Exponential Model 2 with 0.95 Confidence Level

10:47 02/08 2010

1 **G.2.8.   Crofton et al. ([2005](#)): Serum, T4**

2 **G.2.8.1.   *Summary Table of BMDS Modeling Results***

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	8	<0.0001	516.356	1.144E+02	6.239E+01	
Exponential (M3)	8	<0.0001	516.356	1.144E+02	6.239E+01	power hit bound (*d* = 1)
Exponential (M4)[b]	**7**	**0.942**	**476.449**	**5.190E+00**	**3.029E+00**	
Exponential (M5)	6	0.912	478.234	5.757E+00	3.094E+00	
Hill	6	0.972	477.450	5.724E+00	3.024E+00	
Linear	8	<0.0001	522.460	2.406E+02	1.761E+02	
Polynomial, 8-degree	8	<0.0001	522.460	2.406E+02	1.761E+02	
Power	8	<0.0001	522.460	2.406E+02	1.761E+02	power bound hit (power = 1)
Power, unrestricted	7	0.018	491.101	2.449E+00	3.307E−01	unrestricted (power = 0.243)

[a] Constant variance model selected (*p* = 0.7647).
[b] Best-fitting model, BMDS output presented in this appendix.

3
4
5 **G.2.8.2.   *Output for Selected Model: Exponential (M4)***

6 Crofton et al. ([2005](#)): Serum, T4
7
8
```
9    =====================================================================
10           Exponential Model. (Version: 1.61;  Date: 7/24/2009)
11           Input Data File: C:\1\Blood\8_Crofton_2005_T4_ExpCV_1.(d)
12           Gnuplot Plotting File:
13                                       Mon Feb 08 10:48:04 2010
14    =====================================================================
15
16    0
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the response function by Model:
20         Model 2:     Y[dose] = a * exp{sign * b * dose}
21         Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
22         Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
23         Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
24
25      Note: Y[dose] is the median response for exposure = dose;
26            sign = +1 for increasing trend in data;
27            sign = -1 for decreasing trend.
28
29         Model 2 is nested within Models 3 and 4.
30         Model 3 is nested within Model 5.
31         Model 4 is nested within Model 5.
32
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.


Total number of dose groups = 10
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


MLE solution provided: Exact


                      Initial Parameter Values

                  Variable           Model 4
                  --------           --------
                   lnalpha                  5.47437
                      rho(S)                       0
                       a                   104.999
                       b                 0.00641895
                       c                   0.445764
                       d                         1


   (S) = Specified




                      Parameter Estimates

                  Variable           Model 4
                  --------           -------
                   lnalpha                  5.50623
                      rho                        0
                       a                   100.332
                       b                  0.076678
                       c                  0.523626
                       d                         1



          Table of Stats From Input Data

    Dose        N        Obs Mean      Obs Std Dev
    -----      ---      ----------     -------------
        0       14           100        15.44
   0.0202        6         96.27        14.98
   0.4882       12         98.57        18.11
   1.384         6         99.76        19.04
   3.455         6         93.32        12.11
   9.257         6         70.94        12.74
  23.07          6         62.52        14.75
  65.65          6         52.68        22.73
 180.9           6         54.66        19.71
```

```
        583.5        4           49.15          11.15


                    Estimated Values of Interest

      Dose        Est Mean       Est Std      Scaled Residual
     ------      ----------     ---------     ----------------
         0          100.3         15.69          -0.07952
    0.0202          100.3         15.69          -0.6231
    0.4882          98.58         15.69          -0.000744
     1.384          95.52         15.69           0.6614
     3.455          89.21         15.69           0.6422
     9.257          76.04         15.69          -0.7962
     23.07          60.69         15.69           0.2854
     65.65          52.85         15.69          -0.02621
     180.9          52.54         15.69           0.3319
     583.5          52.54         15.69          -0.4323




  Other models for which likelihoods are calculated:

     Model A1:         Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma^2

     Model A2:         Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma(i)^2

     Model A3:         Yij = Mu(i) + e(ij)
                 Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

     Model  R:         Yij = Mu + e(i)
                 Var{e(ij)} = Sigma^2



                         Likelihoods of Interest

               Model      Log(likelihood)       DF          AIC
               -------    ----------------      ----     ------------
                 A1          -233.0774           11        488.1549
                 A2          -230.2028           20        500.4056
                 A3          -233.0774           11        488.1549
                  R          -268.4038            2        540.8076
                  4          -234.2243            4        476.4486



   Additive constant for all log-likelihoods =     -66.16.  This constant
  added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                         Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
  R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
```

```
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                         Tests of Interest

   Test           -2*log(Likelihood Ratio)      D. F.        p-value
 --------         ------------------------      ------      --------------
   Test 1                          76.4           18         < 0.0001
   Test 2                         5.749            9           0.7647
   Test 3                         5.749            9           0.7647
  Test 6a                         2.294            7           0.9418


   The p-value for Test 1 is less than .05.  There appears to be a
   difference between response and/or variances among the dose
   levels, it seems appropriate to model the data.

   The p-value for Test 2 is greater than .1.  A homogeneous
   variance model appears to be appropriate here.

   The p-value for Test 3 is greater than .1.  The modeled
   variance appears to be appropriate here.

   The p-value for Test 6a is greater than .1.  Model 4 seems
   to adequately describe the data.


Benchmark Dose Computations:

   Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

   Confidence Level = 0.950000

             BMD =       5.18983

             BMDL =       3.02894
```

1　**G.2.8.3.** *Figure for Selected Model: Exponential (M4)*

Exponential Model 4 with 0.95 Confidence Level

10:48 02/08 2010

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G.2.9.   Franc et al. (2001): Sprague-Dawley (S-D) Rats, Relative Liver Weight

2   **G.2.9.1. *Summary Table of BMDS Modeling Results***

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.968	234.369	7.800E+00	6.040E+00	
Exponential (M3)	1	0.880	236.327	9.201E+00	6.051E+00	
Exponential (M4)	1	0.580	236.610	6.365E+00	4.512E+00	
Exponential (M5)	0	N/A	238.346	9.474E+00	4.425E+00	
Hill	0	N/A	238.346	9.479E+00	3.004E+00	
Linear	2	0.858	234.610	6.365E+00	4.512E+00	
Polynomial, 3-degree	1	0.935	236.311	8.946E+00	4.598E+00	
Power[b]	1	0.839	236.346	9.474E+00	4.587E+00	

[a] Constant variance model selected (*p* = 0.107).
[b] Best-fitting model, BMDS output presented in this appendix.

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4
5   **G.2.9.2. *Output for Selected Model: Power***

6   Franc et al. (2001): S-D Rats, Relative Liver Weight
7
```
8    ======================================================================
9         Power Model. (Version: 2.15;  Date: 04/07/2008)
10        Input Data File: C:\1\Blood\88_Franc_2001_SD_RelLivWt_PowerCV_1.(d)
11        Gnuplot Plotting File:
12   C:\1\Blood\88_Franc_2001_SD_RelLivWt_PowerCV_1.plt
13                                      Thu Apr 15 11:46:32 2010
14    ======================================================================
15
16   Figure 5, SD rats, relative liver weight
17   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the response function is:
20
21     Y[dose] = control + slope * dose^power
22
23
24     Dependent variable = Mean
25     Independent variable = Dose
26     rho is set to 0
27     The power is restricted to be greater than or equal to 1
28     A constant variance model is fit
29
30     Total number of dose groups = 4
31     Total number of records with missing values = 0
32     Maximum number of iterations = 250
33     Relative Function Convergence has been set to: 1e-008
34     Parameter Convergence has been set to: 1e-008
```

```
                      Default Initial Parameter Values
                            alpha =      527.447
                              rho =            0   Specified
                          control =          100
                            slope =     0.947018
                            power =      1.13144


              Asymptotic Correlation Matrix of Parameter Estimates

              ( *** The model parameter(s)  -rho
                    have been estimated at a boundary point, or have been
specified by the user,
                    and do not appear in the correlation matrix )

                        alpha       control        slope        power

        alpha              1    -6.3e-009     5.4e-009    -4.7e-009

      control     -6.3e-009            1        -0.74         0.71

        slope      5.4e-009        -0.74            1           -1

        power     -4.7e-009         0.71           -1            1




                              Parameter Estimates

                                                         95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          462.113          115.528              235.682
688.544
        control          100.494          7.31114              86.1645
114.824
          slope         0.593276          1.31535             -1.98476
3.17131
          power          1.25841         0.597816             0.086712
2.43011




      Table of Data and Estimated Values of Interest

  Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
 ------     ---   --------     --------   -----------  -----------   ---------
-

     0       8        100          100            14         21.5      -0.065
 6.587      8        108          107          16.9         21.5       0.158
 14.48      8        117          118          25.9         21.5      -0.109
```

```
36.43      8        155         155         30.9        21.5        0.0157




 Model Descriptions for likelihoods calculated


 Model A1:          Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:          Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:          Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:          Yi = Mu + e(i)
           Var{e(i)} = Sigma^2



                   Likelihoods of Interest

           Model      Log(likelihood)    # Param's       AIC
            A1         -114.152281            5       238.304562
            A2         -111.103649            8       238.207299
            A3         -114.152281            5       238.304562
         fitted        -114.172940            4       236.345880
            R          -125.052064            2       254.104127



                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                   Tests of Interest

   Test     -2*log(Likelihood Ratio)  Test df        p-value

   Test 1            27.8968            6            <.0001
   Test 2            6.09726            3             0.107
   Test 3            6.09726            3             0.107
   Test 4            0.0413179          1             0.8389


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data


The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here
```

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

                    Benchmark Dose Computation

Specified effect =   0.1

Risk Type   =   Relative risk

Confidence level =   0.95

              BMD = 9.47408

              BMDL = 4.5873

G.2.9.3. *Figure for Selected Model: Power*

Power Model with 0.95 Confidence Level

11:46 04/15 2010

G.2.10. Franc et al. ([2001](#)): Long-Evans (L-E) Rats, Relative Liver Weight

G.2.10.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.441	208.974	1.708E+01	1.098E+01	
Exponential (M3)	2	0.441	208.974	1.708E+01	1.098E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.785	209.408	7.997E+00	2.601E+00	
Exponential (M5)	1	0.785	209.408	7.997E+00	2.601E+00	power hit bound (*d* = 1)
Hill[b]	1	0.829	209.381	7.725E+00	1.225E+00	*n* lower bound hit (*n* = 1)
Linear	2	0.499	208.725	1.570E+01	9.619E+00	
Polynomial, 3-degree	1	<0.0001	10.000	8.604E+00	error	
Power	2	0.499	208.725	1.570E+01	9.619E+00	power bound hit (power = 1)
Hill, unrestricted[c]	0	N/A	211.337	7.217E+00	1.147E+00	unrestricted (*n* = 0.545)
Power, unrestricted	1	0.965	209.336	7.193E+00	error	unrestricted (power = 0.524)

[a] Nonconstant variance model selected (*p* = 0.0632).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.10.2. *Output for Selected Model: Hill*

Franc et al. ([2001](#)): L-E Rats, Relative Liver Weight

```
    =====================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\89_Franc_2001_LE_RelLivWt_Hill_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\89_Franc_2001_LE_RelLivWt_Hill_1.plt
                                    Thu Apr 15 11:48:44 2010
    =====================================================================

 Figure 5, L-E rats, relative liver weight
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 4
```

```
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          lalpha =      5.41581
                             rho =            0
                       intercept =          100
                               v =       22.225
                               n =     0.443155
                               k =       18.746



        Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -n
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                   lalpha          rho      intercept             v             k

     lalpha            1           -1        -0.21          0.33          0.18

        rho           -1            1         0.21         -0.33         -0.18

  intercept        -0.21         0.21            1         0.028          0.35

          v         0.33        -0.33        0.028             1          0.91

          k         0.18        -0.18         0.35          0.91             1




                               Parameter Estimates

                                                    95.0% Wald
Confidence Interval
        Variable       Estimate       Std. Err.    Lower Conf. Limit
Upper Conf. Limit
         lalpha       -17.2754         17.3066          -51.1957
16.6449
            rho        4.77884         3.67625          -2.42648
11.9842
      intercept        99.5348         3.61286           92.4538
106.616
              v        36.3963         24.1862          -11.0079
83.8004
              n              1              NA
              k        20.5223         28.2566          -34.8596
75.9042

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
```

```
       has no standard error.



       Table of Data and Estimated Values of Interest

  Dose        N    Obs Mean     Est Mean    Obs Std Dev   Est Std Dev    Scaled
 Res.
 ------       ---  --------     --------    -----------   -----------   ---------
 -

    0        8       100        99.5          10           10.5         0.125
6.584        8       106        108          17.9          12.9        -0.455
14.47        8       117        115          8.97          14.8         0.426
36.41        8       122        123          19.9          17.4        -0.0954



 Model Descriptions for likelihoods calculated


  Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

  Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                   Likelihoods of Interest

          Model      Log(likelihood)   # Param's     AIC
           A1         -100.516456          5       211.032912
           A2          -96.870820          8       209.741641
           A3          -99.666984          6       211.333969
         fitted        -99.690373          5       209.380746
           R          -105.717087          2       215.434174



                 Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                      Tests of Interest
```

```
     Test    -2*log(Likelihood Ratio)  Test df        p-value

     Test 1              17.6925          6          0.007048
     Test 2              7.29127          3          0.06317
     Test 3              5.59233          2          0.06104
     Test 4            0.0467774          1           0.8288
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1. You may want to consider a
different variance model

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

          Benchmark Dose Computation

Specified effect =   0.1

Risk Type   =   Relative risk

Confidence level =   0.95

          BMD =   7.72492

          BMDL =   1.22451

1 **G.2.10.3.** *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

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2
3
4 **G.2.10.4.** *Output for Additional Model Presented: Hill, Unrestricted*

5 Franc et al. (2001): L-E Rats, Relative Liver Weight

6
7
8
```
       ====================================================================
9         Hill Model. (Version: 2.14;  Date: 06/26/2008)
10        Input Data File: C:\1\Blood\89_Franc_2001_LE_RelLivWt_Hill_U_1.(d)
11        Gnuplot Plotting File:
12 C:\1\Blood\89_Franc_2001_LE_RelLivWt_Hill_U_1.plt
13                                      Thu Apr 15 11:48:50 2010
14       ====================================================================
15
16  Figure 5, L-E rats, relative liver weight
17 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19    The form of the response function is:
20
21    Y[dose] = intercept + v*dose^n/(k^n + dose^n)
22
23
```

```
Dependent variable = Mean
Independent variable = Dose
Power parameter is not restricted
The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          lalpha =      5.41581
                             rho =            0
                       intercept =          100
                               v =       22.225
                               n =     0.443155
                               k =       18.746


          Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha         rho    intercept           v           n
k

     lalpha           1          -1       -0.22       -0.14        0.24
-0.15

        rho          -1           1        0.22        0.14       -0.24
0.15

  intercept       -0.22        0.22           1       0.022        0.11
0.013

          v       -0.14        0.14       0.022           1        -0.9
1

          n        0.24       -0.24        0.11        -0.9           1
-0.92

          k       -0.15        0.15       0.013           1       -0.92
1




                              Parameter Estimates


                                                       95.0% Wald
Confidence Interval
       Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
        lalpha        -19.2405            18.21            -54.9315
16.4505
           rho         5.19575          3.86861            -2.38657
12.7781
```

```
     intercept          99.5348           3.51796              92.6398
106.43
               v         440.285           13708.5             -26427.9
27308.5
               n         0.544741          0.730981            -0.887956
1.97744
               k         7266.27           485402              -944104
958637




    Table of Data and Estimated Values of Interest

 Dose       N     Obs Mean      Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
 ------     ---   --------      --------   -----------  -----------   ---------
-

    0       8      100          99.5          10          10.3         0.128
6.584       8      106          109          17.9          13         -0.589
14.47       8      117          114          8.97         14.6         0.558
36.41       8      122          123          19.9         17.8        -0.0957

Degrees of freedom for Test A3 vs fitted <= 0




 Model Descriptions for likelihoods calculated


 Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                  Likelihoods of Interest

          Model     Log(likelihood)   # Param's      AIC
           A1        -100.516456          5       211.032912
           A2        -96.870820           8       209.741641
           A3        -99.666984           6       211.333969
         fitted      -99.668321           6       211.336641
           R         -105.717087          2       215.434174



              Explanation of Tests
```

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)


                    Tests of Interest


  Test     -2*log(Likelihood Ratio)  Test df       p-value

  Test 1             17.6925            6          0.007048
  Test 2             7.29127            3          0.06317
  Test 3             5.59233            2          0.06104
  Test 4           0.00267242           0             NA


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data


The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate


The p-value for Test 3 is less than .1.  You may want to consider a
different variance model


NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid



         Benchmark Dose Computation

Specified effect =          0.1

Risk Type        =      Relative risk

Confidence level =          0.95

          BMD =        7.21718

          BMDL =       1.14742
```

1 **G.2.10.5.** *Figure for Additional Model Presented: Hill, Unrestricted*

Hill Model with 0.95 Confidence Level

11:48 04/15 2010

2
3
4

G.2.11. Franc et al. ([2001](#)): S-D Rats, Relative Thymus Weight

G.2.11.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 p-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.814	285.107	2.478E+00	1.535E+00	
Exponential (M3)	1	0.016	292.452	3.173E+01	1.007E+00	
Exponential (M4)[b]	1	0.720	286.825	1.878E+00	9.221E−01	
Exponential (M5)	0	N/A	288.696	3.296E+00	9.365E−01	
Hill	0	N/A	288.696	3.625E+00	6.199E−01	
Linear	2	0.404	286.508	4.783E+00	3.893E+00	
Polynomial, 3-degree[c]	2	0.404	286.508	4.783E+00	3.893E+00	
Power	2	0.404	286.508	4.783E+00	3.893E+00	power bound hit (power = 1)
Power, unrestricted	1	0.483	287.189	6.795E−01	3.271E−03	unrestricted (power = 0.515)

[a] Nonconstant variance model selected (p = 0.0320).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.11.2. *Output for Selected Model: Exponential (M4)*

Franc et al. ([2001](#)): S-D Rats, Relative Thymus Weight

```
  =======================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\Blood\91_Franc_2001_SD_RelThyWt_Exp_1.(d)
         Gnuplot Plotting File:
                                       Thu Apr 15 11:51:19 2010
  =======================================================================

 Figure 5, SD rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                    Initial Parameter Values

                    Variable          Model 4
                    --------          --------
                     lnalpha           3.35464
                        rho           1.08199
                          a               105
                          b         0.0569979
                          c          0.108531
                          d                 1




                     Parameter Estimates

                    Variable          Model 4
                    --------          -------
                     lnalpha            2.4312
                        rho           1.28672
                          a           110.959
                          b         0.0663498
                          c          0.146486
                          d                 1


         Table of Stats From Input Data

    Dose      N         Obs Mean      Obs Std Dev
    -----     ---       ----------    -------------
       0       8           100           83.2
    6.587      8          91.17          47.97
    14.48      8          51.41          43.48
    36.43      8          22.79          29.98



             Estimated Values of Interest

     Dose       Est Mean       Est Std     Scaled Residual
    ------     ----------     ---------    ----------------
       0           111          69.78          -0.4442
```

```
      6.587          77.43          55.36            0.7019
      14.48          52.49          43.11           -0.0709
      36.43           24.7          26.54           -0.2031




   Other models for which likelihoods are calculated:

      Model A1:          Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma^2

      Model A2:          Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma(i)^2

      Model A3:          Yij = Mu(i) + e(ij)
                 Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

      Model  R:          Yij = Mu + e(i)
                 Var{e(ij)} = Sigma^2


                         Likelihoods of Interest

                    Model      Log(likelihood)     DF        AIC
                    -------    ----------------    ----    ------------
                      A1         -141.9834           5       293.9669
                      A2         -137.5818           8       291.1637
                      A3         -138.3482           6       288.6964
                       R         -146.9973           2       297.9946
                       4         -138.4123           5       286.8245


   Additive constant for all log-likelihoods =     -29.41.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                         Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 6a: Does Model 4 fit the data? (A3 vs 4)



                         Tests of Interest

     Test         -2*log(Likelihood Ratio)        D. F.        p-value
    --------      ------------------------        ------     --------------
     Test 1                          18.83           6          0.004459
     Test 2                          8.803           3          0.03203
     Test 3                          1.533           2          0.4647
    Test 6a                         0.1282           1          0.7203
```

```
 1
 2      The p-value for Test 1 is less than .05.  There appears to be a
 3      difference between response and/or variances among the dose
 4      levels, it seems appropriate to model the data.
 5
 6      The p-value for Test 2 is less than .1.  A non-homogeneous
 7      variance model appears to be appropriate.
 8
 9      The p-value for Test 3 is greater than .1.  The modeled
10      variance appears to be appropriate here.
11
12      The p-value for Test 6a is greater than .1.  Model 4 seems
13      to adequately describe the data.
14
15
16   Benchmark Dose Computations:
17
18      Specified Effect = 0.100000
19
20            Risk Type = Relative deviation
21
22      Confidence Level = 0.950000
23
24                  BMD =     1.87814
25
26                 BMDL =     0.922136
27
```

1 **G.2.11.3.** *Figure for Selected Model: Exponential (M4)*

Exponential_beta Model 4 with 0.95 Confidence Level

11:51 04/15 2010

2
3
4 **G.2.11.4.** *Output for Additional Model Presented: Polynomial, 3-degree*

5 Franc et al. (2001): S-D Rats, Relative Thymus Weight

6
7
```
8    =====================================================================
9         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
10        Input Data File: C:\1\Blood\91_Franc_2001_SD_RelThyWt_Poly_1.(d)
11        Gnuplot Plotting File:
12   C:\1\Blood\91_Franc_2001_SD_RelThyWt_Poly_1.plt
13                                      Thu Apr 15 11:51:20 2010
14   =====================================================================
15
16   Figure 5, SD rats, relative thymus weight
17   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19      The form of the response function is:
20
21      Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
22
23
```

```
Dependent variable = Mean
Independent variable = Dose
The polynomial coefficients are restricted to be negative
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          lalpha =        8.0075
                             rho =             0
                          beta_0 =           100
                          beta_1 =             0
                          beta_2 =     -0.475283
                          beta_3 =             0




            Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -beta_2    -beta_3
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                    lalpha          rho         beta_0         beta_1

       lalpha            1        -0.99          0.018         0.0095

          rho        -0.99            1         -0.022        -0.0024

       beta_0        0.018       -0.022              1          -0.87

       beta_1       0.0095      -0.0024          -0.87              1




                              Parameter Estimates


                                                      95.0% Wald
Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
        lalpha          2.8315          1.71297           -0.525852
6.18885
           rho         1.19884         0.416889            0.381756
2.01593
        beta_0         94.5944         14.6685             65.8446
123.344
        beta_1        -1.97776        0.509904            -2.97715
-0.978362
        beta_2               0              NA
        beta_3               0              NA
```

```
NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.



     Table of Data and Estimated Values of Interest

 Dose        N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
 Res.
 ------      ---  --------     --------   -----------  -----------   ---------
 -

     0        8       100         94.6         83.2           63       0.243
 6.587        8      91.2         81.6           48         57.6       0.471
 14.48        8      51.4           66         43.5         50.7      -0.811
 36.43        8      22.8         22.5           30         26.7      0.0269



 Model Descriptions for likelihoods calculated


 Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                    Likelihoods of Interest

           Model      Log(likelihood)    # Param's      AIC
            A1         -141.983433            5      293.966865
            A2         -137.581833            8      291.163667
            A3         -138.348184            6      288.696368
         fitted        -139.254163            4      286.508326
            R          -146.997301            2      297.994602



                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

```
                        Tests of Interest

    Test    -2*log(Likelihood Ratio)  Test df        p-value

    Test 1              18.8309           6          0.004459
    Test 2               8.8032           3           0.03203
    Test 3               1.5327           2            0.4647
    Test 4               1.81196          2            0.4041


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data



                 Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Relative risk

Confidence level =           0.95

             BMD =       4.78292


             BMDL =        3.8932
```

1   **G.2.11.5.** *Figure for Additional Model Presented: Polynomial, 3-degree*

Polynomial Model with 0.95 Confidence Level

11:51 04/15 2010

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1 **G.2.12. Franc et al. ([2001](#)): Long-Evans (L-E) Rats, Relative Thymus Weight**

2 **G.2.12.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.440	301.449	2.726E+00	1.212E+00	
Exponential (M3)	2	0.440	301.449	2.726E+00	1.212E+00	power hit bound ($d = 1$)
Exponential (M4)[b]	1	0.227	303.266	2.084E+00	5.926E−01	
Exponential (M5)	0	N/A	303.805	7.859E+00	9.801E−01	
Hill	0	N/A	303.805	7.480E+00	7.512E−01	
Linear	2	0.304	302.186	5.045E+00	3.349E+00	
Polynomial, 3-degree	2	0.304	302.186	5.045E+00	3.349E+00	
Power	2	0.304	302.186	5.045E+00	3.349E+00	power bound hit (power = 1)
Power, unrestricted	1	0.168	303.710	1.374E+00	9.032E−09	unrestricted (power = 0.601)

[a] Constant variance model selected ($p = 0.5063$).
[b] Best-fitting model, BMDS output presented in this appendix.

3
4
5 **G.2.12.2.** *Output for Selected Model: Exponential (M4)*

6 Franc et al. ([2001](#)): L-E Rats, Relative Thymus Weight
7
```
8   =====================================================================
9          Exponential Model. (Version: 1.61;  Date: 7/24/2009)
10         Input Data File: C:\1\Blood\92_Franc_2001_LE_RelThyWt_ExpCV_1.(d)
11         Gnuplot Plotting File:
12                                     Thu Apr 15 11:53:37 2010
13  =====================================================================
14
15  Figure 5, L-E rats, relative thymus weight
16 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18    The form of the response function by Model:
19       Model 2:     Y[dose] = a * exp{sign * b * dose}
20       Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
21       Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
22       Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
23
24     Note: Y[dose] is the median response for exposure = dose;
25           sign = +1 for increasing trend in data;
26           sign = -1 for decreasing trend.
27
28       Model 2 is nested within Models 3 and 4.
29       Model 3 is nested within Model 5.
30       Model 4 is nested within Model 5.
31
32
```

```
1    Dependent variable = Mean
2    Independent variable = Dose
3    Data are assumed to be distributed: normally
4    Variance Model: exp(lnalpha +rho *ln(Y[dose]))
5    rho is set to 0.
6    A constant variance model is fit.
7
8    Total number of dose groups = 4
9    Total number of records with missing values = 0
10   Maximum number of iterations = 250
11   Relative Function Convergence has been set to: 1e-008
12   Parameter Convergence has been set to: 1e-008
13
14   MLE solution provided: Exact
15
16
17                  Initial Parameter Values
18
19                  Variable          Model 4
20                  --------          --------
21                    lnalpha            8.1814
22                     rho(S)                 0
23                        a               105
24                        b         0.0506168
25                        c          0.166582
26                        d                 1
27
28      (S) = Specified
29
30
31
32                   Parameter Estimates
33
34                  Variable          Model 4
35                  --------          -------
36                    lnalpha           8.22706
37                       rho                 0
38                        a           105.977
39                        b         0.0660042
40                        c          0.221786
41                        d                 1
42
43
44          Table of Stats From Input Data
45
46     Dose      N         Obs Mean      Obs Std Dev
47     -----    ---        ----------    -------------
48         0     8             100        54.72
49     6.584     8           95.41        70.46
50     14.47     8           38.69        47.97
51     36.41     8           34.98        77.96
52
53
54          Estimated Values of Interest
55
56      Dose      Est Mean      Est Std     Scaled Residual
57     ------    ----------    ---------    ----------------
```

```
      0              106          61.16          -0.2764
   6.584           76.91         61.16           0.8555
  14.47            55.24         61.16          -0.765
  36.41            30.96         61.16           0.186




    Other models for which likelihoods are calculated:

       Model A1:         Yij = Mu(i) + e(ij)
                  Var{e(ij)} = Sigma^2

       Model A2:         Yij = Mu(i) + e(ij)
                  Var{e(ij)} = Sigma(i)^2

       Model A3:         Yij = Mu(i) + e(ij)
                  Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

       Model  R:         Yij = Mu + e(i)
                  Var{e(ij)} = Sigma^2


                          Likelihoods of Interest

                  Model      Log(likelihood)      DF         AIC
                  -------    ----------------      ----    ------------
                    A1         -146.9024            5        303.8049
                    A2         -145.7361            8        307.4723
                    A3         -146.9024            5        303.8049
                     R         -150.6049            2        305.2098
                     4         -147.6329            4        303.2658


    Additive constant for all log-likelihoods =      -29.41.  This constant
added to the
    above values gives the log-likelihood including the term that does not
    depend on the model parameters.



                          Explanation of Tests

    Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
    Test 2:  Are Variances Homogeneous? (A2 vs. A1)
    Test 3:  Are variances adequately modeled? (A2 vs. A3)

    Test 6a: Does Model 4 fit the data? (A3 vs 4)



                          Tests of Interest

     Test          -2*log(Likelihood Ratio)          D. F.          p-value
    --------       ------------------------          ------       --------------
     Test 1                  9.738                      6             0.1362
     Test 2                  2.333                      3             0.5063
     Test 3                  2.333                      3             0.5063
     Test 6a                 1.461                      1             0.2268
```

```
The p-value for Test 1 is greater than .05.  There may not be a
diffence between responses and/or variances among the dose levels
Modelling the data with a dose/response curve may not be appropriate.

The p-value for Test 2 is greater than .1.  A homogeneous
variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1.  The modeled
variance appears to be appropriate here.

The p-value for Test 6a is greater than .1.  Model 4 seems
to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 0.100000

        Risk Type = Relative deviation

  Confidence Level = 0.950000

             BMD =      2.08379

            BMDL =      0.592601
```

1   **G.2.12.3.** *Figure for Selected Model: Exponential (M4)*

Exponential_beta Model 4 with 0.95 Confidence Level

11:53 04/15 2010

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G.2.13. Franc et al. (2001): Han/Wistar (H/W) Rats, Relative Thymus Weight

2 ### G.2.13.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)[b]	2	0.698	261.646	5.094E+00	3.132E+00	
Exponential (M3)	1	0.407	263.616	5.944E+00	3.140E+00	
Exponential (M4)	1	0.396	263.646	5.063E+00	1.864E+00	
Exponential (M5)	0	N/A	264.927	9.945E+00	2.127E+00	
Hill	0	N/A	264.927	9.638E+00	1.853E+00	
Linear	2	0.645	261.804	6.874E+00	5.006E+00	
Polynomial, 3-degree	2	0.645	261.804	6.874E+00	5.006E+00	
Power	2	0.645	261.804	6.874E+00	5.006E+00	power bound hit (power = 1)
Power, unrestricted	1	0.363	263.755	5.487E+00	2.573E−01	unrestricted (power = 0.881)

[a] Constant variance model selected ($p = 0.4331$).
[b] Best-fitting model, BMDS output presented in this appendix.

3
4
5 ### G.2.13.2. *Output for Selected Model: Exponential (M2)*

6 Franc et al. (2001): H/W Rats, Relative Thymus Weight
7
8
```
 9   =====================================================================
10          Exponential Model. (Version: 1.61;  Date: 7/24/2009)
11          Input Data File: C:\1\Blood\93_Franc_2001_HW_RelThyWt_ExpCV_1.(d)
12          Gnuplot Plotting File:
13                                       Thu Apr 15 11:55:55 2010
14   =====================================================================
15
16  Figure 5, H/W rats, relative thymus weight
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19    The form of the response function by Model:
20       Model 2:     Y[dose] = a * exp{sign * b * dose}
21       Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
22       Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
23       Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
24
25     Note: Y[dose] is the median response for exposure = dose;
26          sign = +1 for increasing trend in data;
27          sign = -1 for decreasing trend.
28
29       Model 2 is nested within Models 3 and 4.
30       Model 3 is nested within Model 5.
31       Model 4 is nested within Model 5.
32
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.


Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


MLE solution provided: Exact



                  Initial Parameter Values

                  Variable          Model 2
                  --------          --------
                    lnalpha              6.96647
                       rho(S)                  0
                         a             56.9433
                         b           0.0204806
                         c                   0
                         d                   1


   (S) = Specified




                  Parameter Estimates

                  Variable          Model 2
                  --------          -------
                    lnalpha              6.98895
                       rho                   0
                         a             103.047
                         b           0.0206828
                         c                   0
                         d                   1



        Table of Stats From Input Data

   Dose      N         Obs Mean    Obs Std Dev
   -----     ---       ----------   -------------
       0      8            100      35.98
   6.588      8          97.53      32.98
   14.48      8          71.02      23.99
   36.44      8          49.29      43.48



             Estimated Values of Interest

     Dose      Est Mean       Est Std    Scaled Residual
```

```
    ------       ----------      ---------      ----------------
       0             103           32.93            -0.2617
     6.588          89.92          32.93             0.6532
    14.48           76.38          32.93            -0.4596
    36.44           48.49          32.93             0.06871




Other models for which likelihoods are calculated:

   Model A1:        Yij = Mu(i) + e(ij)
               Var{e(ij)} = Sigma^2

   Model A2:        Yij = Mu(i) + e(ij)
               Var{e(ij)} = Sigma(i)^2

   Model A3:        Yij = Mu(i) + e(ij)
               Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

   Model  R:        Yij = Mu + e(i)
               Var{e(ij)} = Sigma^2


                        Likelihoods of Interest

                Model      Log(likelihood)      DF         AIC
                -------    -----------------    ----    ------------
                 A1         -127.4636            5       264.9271
                 A2         -126.0925            8        268.185
                 A3         -127.4636            5       264.9271
                  R         -132.935             2        269.87
                  2         -127.8231            3       261.6463


   Additive constant for all log-likelihoods =     -29.41.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.


                        Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)
   Test 4:  Does Model 2 fit the data? (A3 vs. 2)


                        Tests of Interest

    Test          -2*log(Likelihood Ratio)          D. F.          p-value
   --------       ------------------------          ------       --------------
    Test 1                  13.69                      6            0.03336
    Test 2                  2.742                      3            0.4331
    Test 3                  2.742                      3            0.4331
    Test 4                  0.7192                     2            0.698
```

```
 1
 2
 3       The p-value for Test 1 is less than .05.  There appears to be a
 4       difference between response and/or variances among the dose
 5       levels, it seems appropriate to model the data.
 6
 7       The p-value for Test 2 is greater than .1.  A homogeneous
 8       variance model appears to be appropriate here.
 9
10       The p-value for Test 3 is greater than .1.  The modeled
11       variance appears to be appropriate here.
12
13       The p-value for Test 4 is greater than .1.  Model 2 seems
14       to adequately describe the data.
15
16
17    Benchmark Dose Computations:
18
19       Specified Effect = 0.100000
20
21             Risk Type = Relative deviation
22
23       Confidence Level = 0.950000
24
25                   BMD =      5.09411
26
27                  BMDL =      3.13214
28
```

Exponential_beta Model 2 with 0.95 Confidence Level

11:55 04/15 2010

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G.2.14. Hojo et al. ([2002](#)): DRL Reinforce per Minute

G.2.14.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Hill	1	0.101	4.465	1.667E+00	6.209E−08	*n* upper bound hit (*n* = 18)
Linear	2	0.009	9.124	1.352E+01	6.020E+00	
Polynomial, 3-degree	2	0.009	9.124	1.352E+01	6.020E+00	
Power	2	0.009	9.124	1.352E+01	6.020E+00	power bound hit (power = 1)
Power, unrestricted	1	0.025	6.780	2.428E−01	1.070E−14	unrestricted (power = 0.103)
Exponential (M2)	2	0.007	9.612	1.623E+01	8.673E+00	
Exponential (M3)	2	0.007	9.612	1.623E+01	8.673E+00	power hit bound (*d* = 1)
Exponential (M4)[b]	**1**	**0.054**	**5.488**	**1.316E+00**	**2.367E−03**	
Exponential (M5)	0	N/A	6.465	1.728E+00	9.452E−03	

[a] Constant variance model selected (*p* = 0.4321).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.14.2. *Output for Selected Model: Exponential (M4)*

Hojo et al. ([2002](#)): DRL Reinforce Per Minute

```
 =====================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\21_Hojo_2002_DRLrein_ExpCV_1.(d)
        Gnuplot Plotting File:
                                    Mon Feb 08 10:49:08 2010
 =====================================================================

 Table 5, values adjusted by a constant to allow exponential model
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.


Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


MLE solution provided: Exact


                    Initial Parameter Values

                    Variable          Model 4
                    --------          --------
                      lnalpha          -1.29672
                         rho(S)                0
                           a            0.0817
                           b            0.15642
                           c            16.3733
                           d                  1


   (S) = Specified




                    Parameter Estimates

                    Variable          Model 4
                    --------          -------
                      lnalpha          -1.11961
                         rho                  0
                           a          0.0547452
                           b           0.708154
                           c             18.214
                           d                  1



         Table of Stats From Input Data

   Dose       N        Obs Mean      Obs Std Dev
   -----      ---      ----------    -------------
       0       5        0.086         0.448
   1.625       5        0.536         0.821
   4.169       6        1.274          0.54
    10.7       5        0.737         0.443



              Estimated Values of Interest

     Dose      Est Mean       Est Std     Scaled Residual
```

```
      ------      ----------      ---------      ----------------
          0        0.05475        0.5713             0.1223
      1.625        0.6989         0.5713            -0.6375
      4.169        0.9479         0.5713             1.398
       10.7        0.9966         0.5713            -1.016




  Other models for which likelihoods are calculated:

    Model A1:          Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma^2

    Model A2:          Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma(i)^2

    Model A3:          Yij = Mu(i) + e(ij)
                 Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

    Model  R:          Yij = Mu + e(i)
                 Var{e(ij)} = Sigma^2



                          Likelihoods of Interest

                  Model      Log(likelihood)      DF        AIC
                  -------    -----------------    ----    ------------
                    A1          3.11555             5        3.7689
                    A2          4.489557            8        7.020886
                    A3          3.11555             5        3.7689
                     R         -2.435087            2        8.870174
                     4          1.255891            4        5.488219



   Additive constant for all log-likelihoods =       -19.3.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                          Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 6a: Does Model 4 fit the data? (A3 vs 4)



                          Tests of Interest

    Test           -2*log(Likelihood Ratio)        D. F.        p-value
    --------       ------------------------        ------      --------------
    Test 1                   13.85                    6          0.03137
    Test 2                   2.748                    3          0.4321
    Test 3                   2.748                    3          0.4321
```

```
Test 6a                              3.719          1              0.05379


   The p-value for Test 1 is less than .05.  There appears to be a
   difference between response and/or variances among the dose
   levels, it seems appropriate to model the data.

   The p-value for Test 2 is greater than .1.  A homogeneous
   variance model appears to be appropriate here.

   The p-value for Test 3 is greater than .1.  The modeled
   variance appears to be appropriate here.

   The p-value for Test 6a is less than .1.  Model 4 may not adequately
   describe the data; you may want to consider another model.


Benchmark Dose Computations:

   Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

   Confidence Level = 0.950000

                BMD =      1.31616

               BMDL =   0.00236664
```

1 **G.2.14.3.** *Figure for Selected Model: Exponential (M4)*

Exponential Model 4 with 0.95 Confidence Level

10:49 02/08 2010

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1 **G.2.15. Hojo et al. ([2002](#)): DRL Response per Minute**

2 **G.2.15.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Hill	0	N/A	126.353	1.373E+00	1.070E−14	
Linear	2	0.006	132.243	1.064E+01	5.340E+00	
Polynomial, 3-degree	2	0.006	132.243	1.064E+01	5.340E+00	
Power	2	0.006	132.243	1.064E+01	5.340E+00	power bound hit (power = 1)
Power, unrestricted	2	0.741	122.455	1.070E+03	error	unrestricted (power = 0)
Exponential (M2)	2	0.570	122.980	5.027E−01	error	
Exponential (M3)	2	0.570	122.980	5.027E−01	error	power hit bound (*d* = 1)
Exponential (M4)[b]	**1**	**0.477**	**124.360**	**3.813E−01**	**1.553E−02**	
Exponential (M5)	0	N/A	126.353	8.430E−01	2.221E−02	

[a] Constant variance model selected (*p* = 0.3004).
[b] Best-fitting model, BMDS output presented in this appendix.

3
4
5 **G.2.15.2.** *Output for Selected Model: Exponential (M4)*

6 Hojo et al. ([2002](#)): DRL Response Per Minute
7
8
```
9    =====================================================================
10          Exponential Model. (Version: 1.61;  Date: 7/24/2009)
11          Input Data File: C:\1\Blood\23_Hojo_2002_DRLresp_ExpCV_1.(d)
12          Gnuplot Plotting File:
13                                      Mon Feb 08 10:50:10 2010
14    =====================================================================
15
16  Table 5, values adjusted by a constant to allow exponential model
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19    The form of the response function by Model:
20       Model 2:     Y[dose] = a * exp{sign * b * dose}
21       Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
22       Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
23       Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
24
25     Note: Y[dose] is the median response for exposure = dose;
26           sign = +1 for increasing trend in data;
27           sign = -1 for decreasing trend.
28
29       Model 2 is nested within Models 3 and 4.
30       Model 3 is nested within Model 5.
31       Model 4 is nested within Model 5.
32
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                    Initial Parameter Values

                    Variable          Model 4
                    --------          --------
                     lnalpha              4.51689
                        rho(S)                  0
                         a              24.6362
                         b              0.379327
                         c              0.0184785
                         d                    1


   (S) = Specified




                    Parameter Estimates

                    Variable          Model 4
                    --------          -------
                     lnalpha              4.54096
                        rho                   0
                         a              23.4674
                         b              1.61185
                         c              0.101317
                         d                    1



        Table of Stats From Input Data

    Dose       N       Obs Mean      Obs Std Dev
    -----     ---     ----------    -------------
        0       5       23.46         7.986
    1.625       5        4.013        10.96
    4.169       6        0.478         7.194
     10.7       5        4.594        15.23



                Estimated Values of Interest

     Dose      Est Mean       Est Std     Scaled Residual
```

```
   ------        ----------      ---------      ----------------
       0             23.47          9.684           -0.001008
   1.625             3.915          9.684            0.02265
   4.169             2.403          9.684           -0.4869
    10.7             2.378          9.684            0.5118




Other models for which likelihoods are calculated:

   Model A1:          Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma^2

   Model A2:          Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

   Model A3:          Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

   Model  R:          Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2



                        Likelihoods of Interest

                 Model      Log(likelihood)      DF        AIC
                 -------    -----------------    ----    ------------
                   A1         -57.92733           5       125.8547
                   A2         -56.09669           8       128.1934
                   A3         -57.92733           5       125.8547
                    R         -64.49611           2       132.9922
                    4         -58.1801            4       124.3602



   Additive constant for all log-likelihoods =      -19.3.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                        Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 6a: Does Model 4 fit the data? (A3 vs 4)



                        Tests of Interest

   Test          -2*log(Likelihood Ratio)         D. F.          p-value
   --------      ------------------------        ------       --------------
   Test 1                     16.8                  6              0.01005
   Test 2                     3.661                 3              0.3004
   Test 3                     3.661                 3              0.3004
```

```
   Test 6a                          0.5056            1             0.4771


     The p-value for Test 1 is less than .05.  There appears to be a
     difference between response and/or variances among the dose
     levels, it seems appropriate to model the data.

     The p-value for Test 2 is greater than .1.  A homogeneous
     variance model appears to be appropriate here.

     The p-value for Test 3 is greater than .1.  The modeled
     variance appears to be appropriate here.

     The p-value for Test 6a is greater than .1.  Model 4 seems
     to adequately describe the data.


  Benchmark Dose Computations:

    Specified Effect = 1.000000

           Risk Type = Estimated standard deviations from control

    Confidence Level = 0.950000

                 BMD =    0.381347

                BMDL =    0.0155267
```

1 **G.2.15.3.** *Figure for Selected Model: Exponential (M4)*

Exponential Model 4 with 0.95 Confidence Level

10:50 02/08 2010

2
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1 **G.2.16. Kattainen et al. ([2001](#)): 3rd Molar Eruption, Female**

2 **G.2.16.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Logistic	3	0.360	88.508	9.223E+00	6.671E+00	
Log-logistic[a]	**3**	**0.982**	**85.227**	**2.399E+00**	**1.328E+00**	**slope bound hit (slope = 1)**
Log-probit	3	0.522	87.424	7.346E+00	4.561E+00	slope bound hit (slope = 1)
Probit	3	0.379	88.352	8.802E+00	6.549E+00	
Multistage, 4-degree	3	0.781	86.155	4.042E+00	2.626E+00	final ß = 0
Log-logistic, unrestricted[b]	2	0.949	87.162	1.931E+00	1.840E−01	unrestricted (slope = 0.91)
Log-probit, unrestricted	2	0.941	87.181	2.075E+00	2.395E−01	unrestricted (slope = 0.549)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

3
4

5 **G.2.16.2.** *Output for Selected Model: Log-Logistic*

6 Kattainen et al. ([2001](#)): 3rd Molar Eruption, Female
7

```
8
9   ====================================================================
10         Logistic Model. (Version: 2.12; Date: 05/16/2008)
11         Input Data File: C:\1\Blood\24_Katt_2001_Erup_LogLogistic_BMR1.(d)
12         Gnuplot Plotting File:
13  C:\1\Blood\24_Katt_2001_Erup_LogLogistic_BMR1.plt
14                                   Mon Feb 08 10:50:39 2010
15   ====================================================================
16
17   Figure 2
18  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
19
20     The form of the probability function is:
21
22     P[response] = background+(1-background)/[1+EXP(-intercept-
23  slope*Log(dose))]
24
25
26     Dependent variable = DichEff
27     Independent variable = Dose
28     Slope parameter is restricted as slope >= 1
29
30     Total number of observations = 5
31     Total number of records with missing values = 0
32     Maximum number of iterations = 250
33     Relative Function Convergence has been set to: 1e-008
34     Parameter Convergence has been set to: 1e-008
35
```

User has chosen the log transformed model


```
                    Default Initial Parameter Values
                       background =       0.0625
                        intercept =    -3.07535
                           slope =           1
```


          Asymptotic Correlation Matrix of Parameter Estimates

          (*** The model parameter(s) -slope
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix)

```
              background      intercept

background             1          -0.53

 intercept         -0.53              1
```


                               Parameter Estimates

                                                       95.0% Wald
Confidence Interval
      Variable   Estimate   Std. Err.   Lower Conf. Limit
Upper Conf. Limit
     background   0.0699339   *   *
*
       intercept   -3.07219   *   *
*
         slope   1   *   *
*

* - Indicates that this value is not calculated.

                          Analysis of Deviance Table

      Model   Log(likelihood) # Param's Deviance Test d.f.   P-value
     Full model   -40.5286   5
    Fitted model   -40.6137   2   0.170195   3
0.9823
    Reduced model   -50.7341   1   20.411   4
0.0004142

          AIC: 85.2274

                               Goodness of Fit
                                                              Scaled
```

```
      Dose      Est._Prob.    Expected    Observed     Size      Residual
     -------------------------------------------------------------------
      0.0000     0.0699        1.119       1.000        16        -0.117
      2.2297     0.1570        2.669       3.000        17         0.221
      6.2523     0.2788        4.182       4.000        15        -0.105
     16.0824     0.4670        5.604       6.000        12         0.229
     46.8576     0.7066       13.426      13.000        19        -0.215


 Chi^2 = 0.17      d.f. = 3        P-value = 0.9820



   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =       Extra risk

Confidence level =            0.95

          BMD =        2.39879

          BMDL =       1.32815
```

1   **G.2.16.3.** *Figure for Selected Model: Log-Logistic*

Log-Logistic Model with 0.95 Confidence Level

10:50 02/08 2010

2
3
4   **G.2.16.4.** *Output for Additional Model Presented: Log-Logistic, Unrestricted*

5   Kattainen et al. (2001): 3rd Molar Eruption, Female

6
7
```
8    ========================================================================
9           Logistic Model. (Version: 2.12; Date: 05/16/2008)
10          Input Data File: C:\1\Blood\24_Katt_2001_Erup_LogLogistic_U_BMR1.(d)
11          Gnuplot Plotting File:
12   C:\1\Blood\24_Katt_2001_Erup_LogLogistic_U_BMR1.plt
13                                     Mon Feb 08 10:50:40 2010
14   ========================================================================
15
16    Figure 2
17   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19      The form of the probability function is:
20
21      P[response] = background+(1-background)/[1+EXP(-intercept-
22   slope*Log(dose))]
23
```

```
Dependent variable = DichEff
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


              Default Initial Parameter Values
                  background =       0.0625
                   intercept =      -2.7659
                       slope =    0.901885


        Asymptotic Correlation Matrix of Parameter Estimates

             background     intercept        slope

background            1         -0.52         0.38

 intercept        -0.52             1         -0.94

    slope         0.38         -0.94             1



                         Parameter Estimates

                                               95.0% Wald
Confidence Interval
      Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
    background       0.0630045             *                *
*
     intercept       -2.79616             *                *
*
         slope       0.910333             *                *
*

* - Indicates that this value is not calculated.




                      Analysis of Deviance Table

      Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model       -40.5286          5
    Fitted model       -40.5811          3     0.105049      2
0.9488
```

```
   Reduced model          -50.7341          1          20.411        4
0.0004142

          AIC:          87.1622


                              Goodness  of  Fit
                                                              Scaled
     Dose      Est._Prob.    Expected    Observed    Size    Residual
    -------------------------------------------------------------------
    0.0000      0.0630        1.008       1.000        16     -0.008
    2.2297      0.1683        2.862       3.000        17      0.090
    6.2523      0.2922        4.383       4.000        15     -0.217
   16.0824      0.4692        5.631       6.000        12      0.214
   46.8576      0.6903       13.116      13.000        19     -0.058

 Chi^2 = 0.10     d.f. = 2       P-value = 0.9491


    Benchmark Dose Computation

Specified effect =          0.1

Risk Type        =       Extra risk

Confidence level =          0.95

          BMD =        1.93079

          BMDL =       0.18403
```

1   **G.2.16.5.** *Figure for Additional Model Presented: Log-Logistic, Unrestricted*

Log-Logistic Model with 0.95 Confidence Level

10:50 02/08 2010

2
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1 **G.2.17. Kattainen et al. ([2001](#)): 3rd Molar Length, Female**

2 **G.2.17.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	3	<0.0001	−124.866	1.669E+01	9.933E+00	
Exponential (M3)	3	<0.0001	−124.866	1.669E+01	9.933E+00	power hit bound ($d = 1$)
Exponential (M4)	2	0.002	−147.120	4.237E−01	2.530E−01	
Exponential (M5)	2	0.002	−147.120	4.237E−01	2.530E−01	power hit bound ($d = 1$)
Hill[b]	**2**	**0.022**	**−152.239**	**3.132E−01**	**1.679E−01**	***n* lower bound hit ($n = 1$)**
Linear	3	<0.0001	−124.024	1.982E+01	1.277E+01	
Polynomial, 4-degree	3	<0.0001	−124.024	1.982E+01	1.277E+01	
Power	3	<0.0001	−124.024	1.982E+01	1.277E+01	power bound hit (power = 1)
Hill, unrestricted[c]	1	<0.0001	−130.856	1.215E−02	error	unrestricted ($n = 13.042$)
Power, unrestricted	2	0.263	−157.201	1.964E−03	8.002E−06	unrestricted (power = 0.195)

[a] Nonconstant variance model selected ($p = <0.0001$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

3
4

5 **G.2.17.2.** *Output for Selected Model: Hill*

6 Kattainen et al. ([2001](#)): 3rd Molar Length, Female
7
8

```
9    ====================================================================
10         Hill Model. (Version: 2.14;  Date: 06/26/2008)
11         Input Data File: C:\1\Blood\25_Katt_2001_Length_Hill_1.(d)
12         Gnuplot Plotting File:  C:\1\Blood\25_Katt_2001_Length_Hill_1.plt
13                                     Mon Feb 08 10:51:09 2010
14    ====================================================================
15
16   Figure 3 female only
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the response function is:
20
21     Y[dose] = intercept + v*dose^n/(k^n + dose^n)
22
23
24     Dependent variable = Mean
25     Independent variable = Dose
26     Power parameter restricted to be greater than 1
27     The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))
28
29     Total number of dose groups = 5
30     Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                           lalpha =     -2.37155
                              rho =            0
                        intercept =      1.85591
                                v =    -0.507874
                                n =     0.845932
                                k =      2.03129



            Asymptotic Correlation Matrix of Parameter Estimates


            ( *** The model parameter(s)  -n
                    have been estimated at a boundary point, or have been
specified by the user,
                    and do not appear in the correlation matrix )

                    lalpha         rho    intercept            v            k

    lalpha               1       -0.98       -0.16         0.84        -0.38

       rho           -0.98           1         0.2        -0.79          0.4

 intercept           -0.16         0.2           1         -0.3        -0.11

         v            0.84       -0.79        -0.3            1        -0.52

         k           -0.38         0.4       -0.11        -0.52            1




                              Parameter Estimates


                                                        95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
         lalpha         3.31084            1.404            0.559057
6.06262
            rho        -14.2657          2.62739            -19.4153
-9.11612
      intercept         1.85483        0.0159477             1.82357
1.88609
              v        -0.453667       0.0620227            -0.575229
-0.332105
              n               1               NA
              k         1.91219         0.624785             0.687636
3.13675

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

```
      Table of Data and Estimated Values of Interest

  Dose        N    Obs Mean    Est Mean   Obs Std Dev   Est Std Dev   Scaled
Res.
 ------       ---  --------    --------   -----------   -----------   ---------
-

     0        16     1.86        1.85       0.0661        0.0639        0.0674
  2.23        17     1.58        1.61       0.185         0.175        -0.789
 6.252        15      1.6        1.51       0.265          0.28         1.22
 16.08        12      1.5        1.45       0.221         0.371         0.51
 46.86        19     1.35        1.42       0.515         0.431        -0.716



Model Descriptions for likelihoods calculated


Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                  Likelihoods of Interest

          Model      Log(likelihood)    # Param's        AIC
           A1           56.758717            6        -101.517434
           A2           85.856450           10        -151.712901
           A3           84.934314            7        -155.868628
         fitted         81.119648            5        -152.239295
           R            45.373551            2         -86.747101


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest
```

```
    Test    -2*log(Likelihood Ratio)  Test df         p-value

    Test 1             80.9658          8             <.0001
    Test 2             58.1955          4             <.0001
    Test 3             1.84427          3             0.6053
    Test 4             7.62933          2             0.02205
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different
model

          Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

           BMD =   0.313211

           BMDL =   0.167922

G.2.17.3. *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

10:51 02/08 2010

G.2.17.4. *Output for Additional Model Presented: Hill, Unrestricted*

Kattainen et al. (2001): 3rd Molar Length, Female

```
     =======================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\1\Blood\25_Katt_2001_Length_Hill_U_1.(d)
          Gnuplot Plotting File:  C:\1\Blood\25_Katt_2001_Length_Hill_U_1.plt
                                        Mon Feb 08 10:51:09 2010
     =======================================================================

  Figure 3 female only
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function is:

    Y[dose] = intercept + v*dose^n/(k^n + dose^n)


    Dependent variable = Mean
```

```
Independent variable = Dose
Power parameter is not restricted
The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                  Default Initial Parameter Values
                        lalpha =     -2.37155
                           rho =            0
                     intercept =      1.85591
                             v =    -0.507874
                             n =     0.845932
                             k =      2.03129


          Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho    intercept             v             n
k

     lalpha            1        -0.98        -0.16          0.84       1.4e-016
3.3e-017

        rho        -0.98            1         0.22         -0.77      -2.2e-016
-5.1e-017

  intercept        -0.16         0.22            1         -0.35         6e-017
1.4e-017

          v         0.84        -0.77        -0.35             1      -2.6e-016
-6.2e-017

          n     1.4e-016     -2.2e-016        6e-017     -2.6e-016             1
1

          k     3.3e-017     -5.1e-017      1.4e-017     -6.2e-017             1
1




                           Parameter Estimates

                                                     95.0% Wald
Confidence Interval
       Variable       Estimate       Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha        4.25154          1.5913               1.13265
7.37044
            rho       -15.7639         2.90127              -21.4503
-10.0776
```

```
   intercept            1.85591          0.0160104                1.82453
1.88729
              v           -0.357293          0.0463784              -0.448193
-0.266393
              n            13.0417          4.64308e+013          -9.10027e+013
9.10027e+013
              k           0.0136512         2.57737e+011          -5.05155e+011
5.05155e+011




    Table of Data and Estimated Values of Interest

 Dose        N     Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
 Res.
 ------      ---   --------     --------   ----------   ----------   ---------
 -

    0        16      1.86         1.86       0.0661        0.064      2.09e-009
  2.23       17      1.58         1.5        0.185         0.345        0.937
 6.252       15      1.6          1.5        0.265         0.345        1.09
 16.08       12      1.5          1.5        0.221         0.345        0.0534
 46.86       19      1.35         1.5        0.515         0.345        -1.9




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                  Likelihoods of Interest

         Model      Log(likelihood)    # Param's      AIC
          A1          56.758717            6       -101.517434
          A2          85.856450           10       -151.712901
          A3          84.934314            7       -155.868628
        fitted        71.427978            6       -130.855955
          R           45.373551            2        -86.747101


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
```

```
           (A2 vs. R)
  Test 2:  Are Variances Homogeneous? (A1 vs A2)
  Test 3:  Are variances adequately modeled? (A2 vs. A3)
  Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
  (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)


                     Tests of Interest


    Test    -2*log(Likelihood Ratio)  Test df        p-value


    Test 1            80.9658          8              <.0001
    Test 2            58.1955          4              <.0001
    Test 3            1.84427          3              0.6053
    Test 4            27.0127          1              <.0001


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data


The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here


The p-value for Test 4 is less than .1.  You may want to try a different
model



          Benchmark Dose Computation


Specified effect =             1


Risk Type        =     Estimated standard deviations from the control mean


Confidence level =         0.95


            BMD =        0.012148



BMDL computation failed.
```

1 **G.2.17.5.** *Figure for Additional Model Presented: Hill, Unrestricted*

Hill Model

10:51 02/08 2010

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G.2.18. Keller et al. (2007): Missing Mandibular Molars, CBA J

2 **G.2.18.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	1	0.105	52.510	3.342E+00	8.986E−01	
Logistic	2	0.335	49.984	3.069E+00	2.212E+00	
Log-logistic	1	0.105	52.524	4.009E+00	2.411E+00	
Log-probit	1	0.105	52.524	3.845E+00	2.421E+00	
Multistage, 1-degree[a]	**3**	**0.255**	**50.425**	**1.091E+00**	**7.624E−01**	
Multistage, 2-degree	1	0.122	51.391	1.916E+00	9.654E−01	
Multistage, 3-degree	1	0.150	50.853	1.713E+00	9.584E−01	
Probit	2	0.342	49.904	2.927E+00	2.053E+00	
Weibull	1	0.108	52.219	2.744E+00	9.350E−01	

[a] Best-fitting model, BMDS output presented in this appendix.

3
4
5 **G.2.18.2.** *Output for Selected Model: Multistage, 1-Degree*

6 Keller et al. (2007): Missing Mandibular Molars, CBA J
7
8
9
```
     =====================================================================
10        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
11        Input Data File: C:\1\Blood\26_Keller_2007_Molars_Multi1_1.(d)
12        Gnuplot Plotting File:  C:\1\Blood\26_Keller_2007_Molars_Multi1_1.plt
13                                   Mon Feb 08 10:51:47 2010
14     =====================================================================
15
16   Table 1 using mandibular molars only
17   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the probability function is:
20
21     P[response] = background + (1-background)*[1-EXP(
22                   -beta1*dose^1)]
23
24     The parameter betas are restricted to be positive
25
26
27     Dependent variable = DichEff
28     Independent variable = Dose
29
30   Total number of observations = 4
31   Total number of records with missing values = 0
32   Total number of parameters in model = 2
33   Total number of specified parameters = 0
```

```
Degree of polynomial = 1


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                       Background =          0
                         Beta(1) = 3.03988e+018



          Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -Background
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                  Beta(1)


    Beta(1)              1




                              Parameter Estimates

                                                  95.0% Wald
Confidence Interval
        Variable          Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
      Background               0               *                *
*
        Beta(1)        0.096571             *                *
*

* - Indicates that this value is not calculated.




                      Analysis of Deviance Table

      Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -21.5798        4
    Fitted model      -24.2126        1       5.26564        3
0.1533
  Reduced model         -71.326        1       99.4926        3        <.0001

        AIC:         50.4251



                          Goodness  of  Fit

                                                            Scaled
      Dose      Est._Prob.   Expected   Observed    Size      Residual
   -------------------------------------------------------------------------
```

```
   0.0000      0.0000          0.000      0.000         29        0.000
   0.5374      0.0506          1.163      2.000         23        0.796
   4.2881      0.3391          9.833      6.000         29       -1.504
  34.0560      0.9627         28.881     30.000         30        1.078


 Chi^2 = 4.06      d.f. = 3         P-value = 0.2554



   Benchmark Dose Computation

Specified effect =              0.1

Risk Type        =      Extra risk

Confidence level =              0.95

          BMD =        1.09102

         BMDL =       0.762404

         BMDU =        1.56496

Taken together, (0.762404, 1.56496) is a 90     % two-sided confidence
interval for the BMD
```

1 **G.2.18.3.** *Figure for Selected Model: Multistage, 1-Degree*

Multistage Model with 0.95 Confidence Level

10:51 02/08 2010

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4 **G.2.19. Kociba et al. ([1978](#)): Urinary Coproporphyrin, Females**

5 **G.2.19.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 p-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	<0.0001	82.975	2.378E+01	1.340E+01	
Exponential (M3)	2	<0.0001	82.975	2.378E+01	1.340E+01	power hit bound (d = 1)
Exponential (M4)[b]	**1**	**0.006**	**73.823**	**1.566E+00**	**7.180E−01**	
Exponential (M5)	0	N/A	69.047	6.225E+00	1.586E+00	
Hill	0	N/A	69.047	5.473E+00	error	
Linear	2	<0.001	82.233	1.790E+01	3.862E+00	
Polynomial, 3-degree	2	<0.001	82.233	1.790E+01	3.862E+00	
Power	2	<0.001	82.233	1.790E+01	3.862E+00	power bound hit (power = 1)
Power, unrestricted	1	<0.001	78.691	1.148E+00	8.984E−09	unrestricted (power = 0.416)

[a] Nonconstant variance model selected (p = 0.0298).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.19.2. *Output for Selected Model: Exponential (M4)*

Kociba et al. (1978): Urinary Coproporphyrin, Females

```
==================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\29_Kociba_1978_Copro_Exp_1.(d)
        Gnuplot Plotting File:
                                        Mon Feb 08 10:52:47 2010
==================================================================
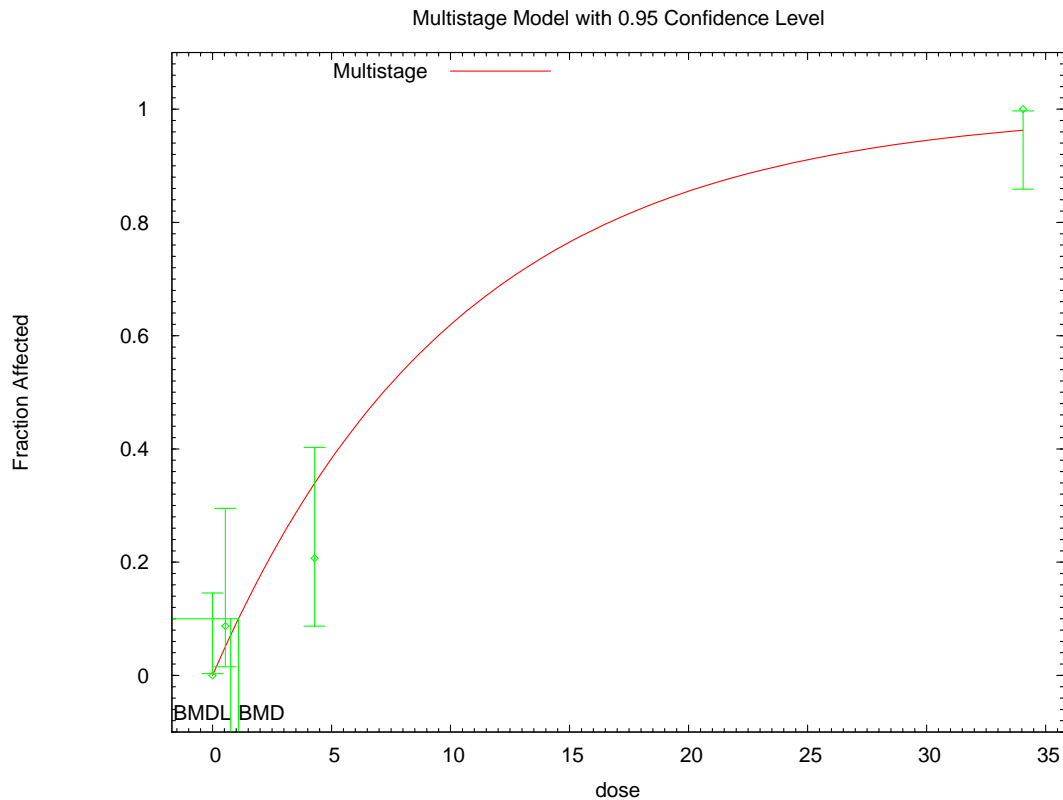
Table2-UrinaryCoproporphyrin
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the response function by Model:
     Model 2:    Y[dose] = a * exp{sign * b * dose}
     Model 3:    Y[dose] = a * exp{sign * (b * dose)^d}
     Model 4:    Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 5:    Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

   Note: Y[dose] is the median response for exposure = dose;
         sign = +1 for increasing trend in data;
         sign = -1 for decreasing trend.

     Model 2 is nested within Models 3 and 4.
     Model 3 is nested within Model 5.
     Model 4 is nested within Model 5.


  Dependent variable = Mean
  Independent variable = Dose
  Data are assumed to be distributed: normally
  Variance Model: exp(lnalpha +rho *ln(Y[dose]))
  The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

  Total number of dose groups = 4
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

  MLE solution provided: Exact



                 Initial Parameter Values

                 Variable           Model 4
                 --------           --------
                  lnalpha           -5.58269
                      rho            2.98472
                        a               8.17
                        b          0.0692478
                        c            2.23623
                        d                  1


```

```
                    Parameter Estimates

            Variable          Model 4
            --------          -------
            lnalpha          -4.90852
               rho            2.80743
                 a            8.91071
                 b            0.15304
                 c            1.97526
                 d                  1


            Table of Stats From Input Data

    Dose      N       Obs Mean      Obs Std Dev
    -----    ---     ----------    -------------
       0      5          9.8            1.3
    1.547     5          8.6             2
    7.155     5         16.4            4.7
    38.56     5         17.4             4



            Estimated Values of Interest

    Dose      Est Mean      Est Std     Scaled Residual
    ------   ----------    ---------    ----------------
       0        8.911        1.852           1.074
    1.547      10.74         2.407          -1.991
    7.155      14.69         3.736           1.021
    38.56      17.58         4.805          -0.08246



Other models for which likelihoods are calculated:

   Model A1:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma^2

   Model A2:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma(i)^2

   Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

   Model  R:        Yij = Mu + e(i)
            Var{e(ij)} = Sigma^2



                    Likelihoods of Interest

            Model     Log(likelihood)     DF        AIC
            -------   ----------------    ----    -----------
              A1        -31.69739          5       73.39478
              A2        -27.21541          8       70.43081
              A3        -28.16434          6       68.32868
               R        -41.73188          2       87.46376
```

```
                                4        -31.91136              5        73.82272


    Additive constant for all log-likelihoods =      -18.38.   This constant
added to the
    above values gives the log-likelihood including the term that does not
    depend on the model parameters.



                            Explanation of Tests

    Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
    Test 2:  Are Variances Homogeneous? (A2 vs. A1)
    Test 3:  Are variances adequately modeled? (A2 vs. A3)

    Test 6a: Does Model 4 fit the data? (A3 vs 4)



                            Tests of Interest

      Test           -2*log(Likelihood Ratio)        D. F.          p-value
    --------         ------------------------       ------       --------------
     Test 1                     29.03                  6            < 0.0001
     Test 2                     8.964                  3             0.02977
     Test 3                     1.898                  2             0.3872
    Test 6a                     7.494                  1             0.00619


    The p-value for Test 1 is less than .05.  There appears to be a
    difference between response and/or variances among the dose
    levels, it seems appropriate to model the data.

    The p-value for Test 2 is less than .1.  A non-homogeneous
    variance model appears to be appropriate.

    The p-value for Test 3 is greater than .1.  The modeled
    variance appears to be appropriate here.

    The p-value for Test 6a is less than .1.  Model 4 may not adequately
    describe the data; you may want to consider another model.


Benchmark Dose Computations:

    Specified Effect = 1.000000

           Risk Type = Estimated standard deviations from control

    Confidence Level = 0.950000

              BMD =      1.56562

             BMDL =      0.718033
```

1 **G.2.19.3.** *Figure for Selected Model: Exponential (M4)*

Exponential Model 4 with 0.95 Confidence Level

10:52 02/08 2010

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4 **G.2.20. Kociba et al. ([1978](#)): Uroporphyrin per Creatinine, Female**

5 **G.2.20.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 p-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.755	−93.828	1.641E+01	1.259E+01	
Exponential (M3)	2	0.755	−93.828	1.641E+01	1.259E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.499	−91.935	1.216E+01	3.958E+00	
Exponential (M5)	0	N/A	−90.190	7.542E+00	4.128E+00	
Hill	0	N/A	−90.190	7.607E+00	3.966E+00	
Linear[b]	**2**	**0.793**	**−93.928**	**1.306E+01**	**9.287E+00**	
Polynomial, 3-degree	2	0.793	−93.928	1.306E+01	9.287E+00	
Power	1	0.497	−91.928	1.326E+01	9.287E+00	

[a] Constant variance model selected (*p* = 0.4919).
[b] Best-fitting model, BMDS output presented in this appendix.

6

G.2.20.2. *Output for Selected Model: Linear*

Kociba et al. ([1978](#)): Uroporphyrin per Creatinine, Female

```
 ====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\Blood\28_Kociba_1978_Uropor_LinearCV_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\28_Kociba_1978_Uropor_LinearCV_1.plt
                                       Mon Feb 08 10:52:17 2010
 ====================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          alpha =    0.0030385
                            rho =           0    Specified
                         beta_0 =     0.149139
                         beta_1 =   0.00381789


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                    alpha        beta_0        beta_1

     alpha              1     1.9e-009     -2.6e-009

    beta_0     1.9e-009            1          -0.6

    beta_1    -2.6e-009         -0.6            1
```

```
                              Parameter Estimates


                                                      95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha       0.00248773      0.000786688        0.000945846
0.00402961
         beta_0         0.149139        0.0139684           0.121761
0.176517
         beta_1       0.00381789      0.000711776         0.00242284
0.00521295




     Table of Data and Estimated Values of Interest

 Dose        N     Obs Mean      Est Mean    Obs Std Dev   Est Std Dev   Scaled
Res.
 ------      ---    --------      --------    -----------   -----------   ---------
-

     0       5       0.157         0.149         0.05         0.0499        0.352
1.547       5       0.143         0.155         0.037        0.0499        -0.54
7.155       5       0.181         0.176         0.053        0.0499        0.204
38.56       5       0.296         0.296         0.074        0.0499       -0.0161




 Model Descriptions for likelihoods calculated



 Model A1:        Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:        Yi = Mu + e(i)
         Var{e(i)} = Sigma^2



                     Likelihoods of Interest

            Model      Log(likelihood)   # Param's       AIC
             A1          50.195349           5        -90.390697
             A2          51.400051           8        -86.800103
             A3          50.195349           5        -90.390697
           fitted        49.963863           3        -93.927727
              R          41.049755           2        -78.099510
```

```
                        Explanation of Tests

   Test 1:  Do responses and/or variances differ among Dose levels?
            (A2 vs. R)
   Test 2:  Are Variances Homogeneous? (A1 vs A2)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)
   Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
   (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                        Tests of Interest

     Test    -2*log(Likelihood Ratio)  Test df        p-value

     Test 1              20.7006           6           0.002076
     Test 2              2.40941           3            0.4919
     Test 3              2.40941           3            0.4919
     Test 4              0.46297           2            0.7934

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data



                Benchmark Dose Computation

Specified effect =              1

Risk Type        =      Estimated standard deviations from the control mean

Confidence level =          0.95

          BMD =          13.064


          BMDL =         9.28715
```

1   **G.2.20.3.** *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

10:52 02/08 2010

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4   **G.2.21. Kuchiiwa et al. ([2002](#)): Immunoreactive Neurons in Dorsalis, Males**

5   **G.2.21.1.** *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	0	N/A [c]	93.91	6.044E−02	4.270E−02	

[a] Constant variance model selected ($p = 0.530$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] *p*-value could not be calculated because there were no available degrees of freedom.

6
7

1 **G.2.21.2.** *Output for Selected Model: Linear*

```
=======================================================================
          Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
          Input Data File:
C:\USEPA\BMDS21\1\79_Kuchiiwa_2002_dors_blood_dd_LinearCV_1.(d)
          Gnuplot Plotting File:
C:\USEPA\BMDS21\1\79_Kuchiiwa_2002_dors_blood_dd_LinearCV_1.plt
                                         Tue Aug 16 13:54:37 2011
 =======================================================================
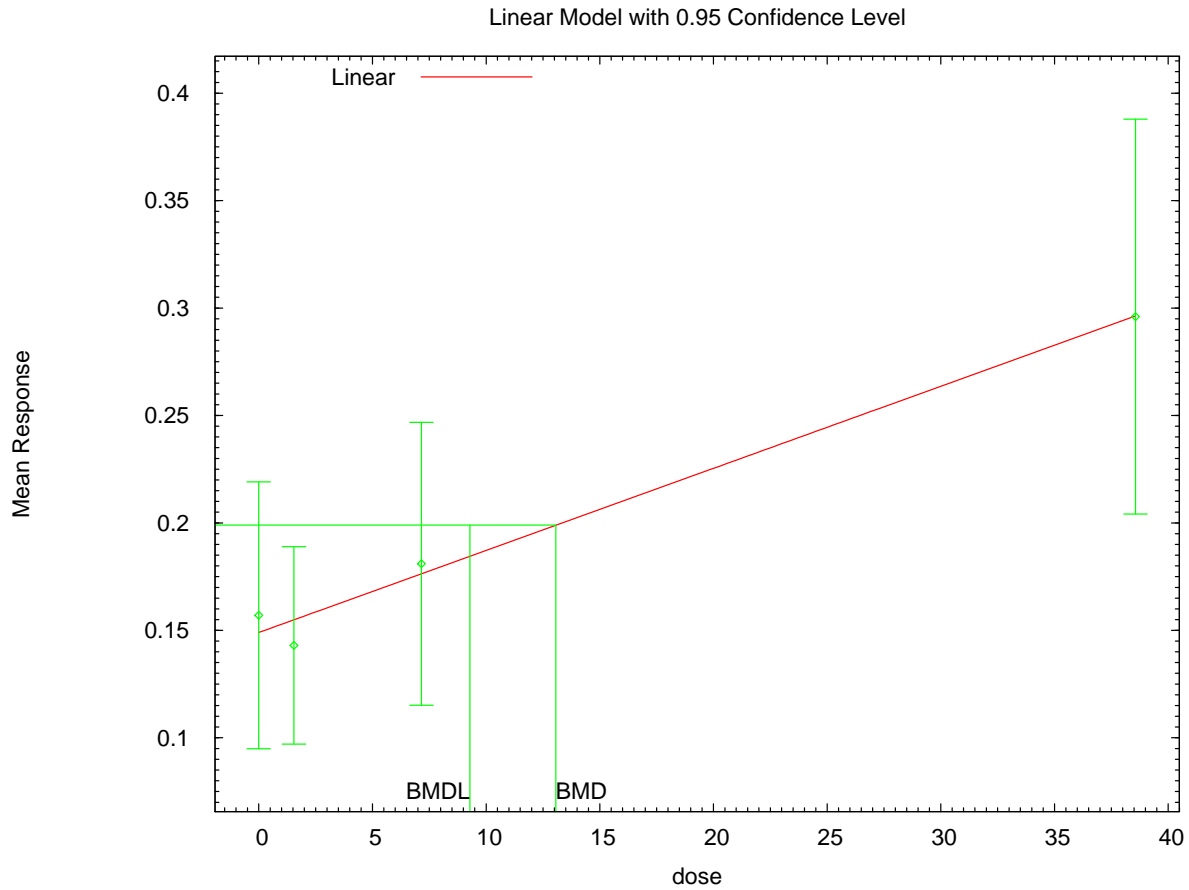
 number_labeled_cells_dorsalis_TWAblooddose
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 2
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                     Default Initial Parameter Values
                           alpha =      670.324
                             rho =            0   Specified
                          beta_0 =      237.097
                          beta_1 =     -391.046



          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                   alpha        beta_0         beta_1

     alpha             1    -4.2e-008      2.3e-008

    beta_0    -4.2e-008            1         -0.71

    beta_1     2.3e-008        -0.71             1
```

```
                              Parameter Estimates


                                                    95.0% Wald
Confidence Interval
       Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         alpha         558.603         228.049            111.636
1005.57
        beta_0         237.097         9.64886            218.186
256.008
        beta_1        -391.046         53.0749           -495.071
-287.021




     Table of Data and Estimated Values of Interest

 Dose       N     Obs Mean     Est Mean    Obs Std Dev  Est Std Dev   Scaled
Res.
 ------     ---   --------     --------    -----------  -----------   ---------
-

    0        6       237          237           29          23.6      1.03e-007
0.2571      6       137          137          22.4         23.6      2.15e-008

Degrees of freedom for Test A3 vs fitted <= 0




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

          Model    Log(likelihood)   # Param's      AIC
           A1        -43.952634           3       93.905267
           A2        -43.755407           4       95.510815
           A3        -43.952634           3       93.905267
         fitted      -43.952634           3       93.905267
           R         -54.206960           2      112.413921
```

```
                    Explanation of Tests

  Test 1:  Do responses and/or variances differ among Dose levels?
           (A2 vs. R)
  Test 2:  Are Variances Homogeneous? (A1 vs A2)
  Test 3:  Are variances adequately modeled? (A2 vs. A3)
  Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
  (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

    Test     -2*log(Likelihood Ratio)  Test df        p-value

    Test 1             20.9031            2            <.0001
    Test 2             0.394453           1             0.53
    Test 3             0.394453           1             0.53
    Test 4        8.81073e-013            0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


              Benchmark Dose Computation

Specified effect =              1

Risk Type        =      Estimated standard deviations from the control mean

Confidence level =         0.95

          BMD =      0.0604398


          BMDL =      0.0427028
```

1   **G.2.21.3.** *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

13:54 08/16 2011

2
3
4   **G.2.22. Kuchiiwa et al. (2002): Immunoreactive Neurons in Medianus, Males**

5   **G.2.22.1.** *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	0	N/A [c]	65.97	4.928E−02	3.227E−02	

[a] Modeled variance model selected (*p* = 0.025).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] *p*-value could not be calculated because there were no available degrees of freedom.

6
7
8   **G.2.22.2.** *Output for Selected Model: Linear*

9   ```
     ===
10   Polynomial Model. (Version: 2.13; Date: 04/08/2008)
11   Input Data File:
12   C:\USEPA\BMDS21\1\80_Kuchiiwa_2002_med_blood_dd_Linear_1.(d)
     ```

```
       Gnuplot Plotting File:
C:\USEPA\BMDS21\1\80_Kuchiiwa_2002_med_blood_dd_Linear_1.plt
                                    Tue Aug 16 13:55:40 2011
 ====================================================================

 number_labeled_cells_medianus_TWAblooddose
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 2
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                         lalpha =      4.43247
                            rho =            0
                         beta_0 =      91.1157
                         beta_1 =     -225.014



           Asymptotic Correlation Matrix of Parameter Estimates

                   lalpha           rho        beta_0        beta_1

     lalpha             1         -0.99      2.7e-009     -1.9e-009

        rho         -0.99             1       -3e-009      2.2e-009

     beta_0      2.7e-009       -3e-009             1         -0.94

     beta_1     -1.9e-009      2.2e-009         -0.94             1




                              Parameter Estimates


                                                        95.0% Wald
Confidence Interval
        Variable         Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
        lalpha         -3.97249          3.27352            -10.3885
2.44349
           rho          1.9468         0.810306            0.358628
3.53497
```

```
          beta_0              91.1157              4.52665              82.2436
99.9878
          beta_1              -225.014             18.8038              -261.869
-188.16



     Table of Data and Estimated Values of Interest

  Dose       N     Obs Mean      Est Mean    Obs Std Dev  Est Std Dev   Scaled
 Res.
 ------     ---    --------      --------    -----------  -----------   ---------
 -

     0       6       91.1          91.1          12.1         11.1      4.41e-009
 0.2571     6       33.3          33.3          4.55         4.16      -4.19e-009

Degrees of freedom for Test A2 vs A3 <= 0

 Warning: Likelihood for fitted model larger than the Likelihood for model
 A3.




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                    Likelihoods of Interest

          Model       Log(likelihood)    # Param's       AIC
           A1          -31.500916            3         69.001832
           A2          -28.985335            4         65.970670
           A3          -28.985335            4         65.970670
         fitted        -28.985335            4         65.970670
           R           -46.859574            2         97.719148



                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
```

```
   Test 3:  Are variances adequately modeled? (A2 vs. A3)
   Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
   (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                       Tests of Interest

     Test    -2*log(Likelihood Ratio)  Test df        p-value

     Test 1              35.7485             2           <.0001
     Test 2              5.03116             1           0.0249
     Test 3          2.47269e-012            0             NA
     Test 4         -2.47269e-012            0             NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

NA - Degrees of freedom for Test 3 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


                Benchmark Dose Computation

Specified effect =              1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =         0.95

            BMD =      0.0492768

           BMDL =       0.032269
```

1   **G.2.22.3.** *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

13:55 08/16 2011

2
3
4   **G.2.23. Kuchiiwa et al. (2002): Immunoreactive Neurons in B9, Males**

5   **G.2.23.1.** *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	**0**	**N/A [c]**	**86.12**	**4.172E−02**	**3.015E−02**	

[a] Constant variance model selected ($p = 0.504$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] *p*-value could not be calculated because there were no available degrees of freedom.

6
7
8   **G.2.23.2.** *Output for Selected Model: Linear*

9   ```
==
10   Polynomial Model. (Version: 2.13; Date: 04/08/2008)
11   Input Data File:
12   C:\USEPA\BMDS21\1\81_Kuchiiwa_2002_b9_blood_dd_LinearCV_1.(d)
```

```
     Gnuplot Plotting File:
C:\USEPA\BMDS21\1\81_Kuchiiwa_2002_b9_blood_dd_LinearCV_1.plt
                                    Tue Aug 16 13:57:44 2011
 =====================================================================


 number_labeled_cells_b9_TWAblooddose
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~


   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 2
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




                   Default Initial Parameter Values
                          alpha =      350.225
                            rho =            0   Specified
                         beta_0 =      152.086
                         beta_1 =     -409.531



          Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -rho
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                    alpha        beta_0        beta_1

     alpha              1     2.2e-007     -2.5e-007

    beta_0      2.2e-007            1          -0.71

    beta_1     -2.5e-007         -0.71            1




                             Parameter Estimates


                                                  95.0% Wald
Confidence Interval
        Variable         Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
```

```
         alpha            291.854            119.149              58.3265
525.381
         beta_0           152.086              6.9744            138.416
165.756
         beta_1          -409.531             38.3637           -484.722
-334.339




    Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
 ------     ---  --------    --------    -----------  -----------   ---------
-

    0       6      152         152           16          17.1       -5.3e-007
0.2571      6      46.8        46.8          21.1        17.1        3.27e-007

Degrees of freedom for Test A3 vs fitted <= 0




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                    Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1         -40.057520           3        86.115041
             A2         -39.834453           4        87.668907
             A3         -40.057520           3        86.115041
          fitted        -40.057520           3        86.115041
             R          -54.163617           2       112.327234



                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
```

```
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                   Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              28.6583          2           <.0001
  Test 2              0.446134         1           0.5042
  Test 3              0.446134         1           0.5042
  Test 4           1.87583e-012        0             NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


               Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

          BMD =      0.0417154

          BMDL =     0.0301486
```

G.2.23.3. *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

2
3
4 **G.2.24. Kuchiiwa et al. (2002): Immunoreactive Neurons in Magnus, Males**

5 **G.2.24.1.** *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	0	N/A [c]	60.36	3.354E−02	2.048E−02	

[a] Modeled variance model selected ($p = 0.013$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] *p*-value could not be calculated because there were no available degrees of freedom.

6
7
8 **G.2.24.2.** *Output for Selected Model: Linear*

9
10
```
==================================================================
      Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
```

```
        Input Data File:
C:\USEPA\BMDS21\1\82_Kuchiiwa_2002_mag_blood_dd_Linear_1.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\1\82_Kuchiiwa_2002_mag_blood_dd_Linear_1.plt
                                     Tue Aug 16 13:56:37 2011
 ======================================================================

 number_labeled_cells_magnus_TWAblooddose
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~


   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 2
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




                   Default Initial Parameter Values
                         lalpha =       4.05645
                            rho =             0
                         beta_0 =       43.6123
                         beta_1 =      -92.5263



         Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha           rho        beta_0        beta_1

    lalpha             1         -0.99      4.1e-009     -5.6e-008

       rho         -0.99             1     -4.6e-009      5.3e-008

    beta_0      4.1e-009     -4.6e-009             1         -0.32

    beta_1     -5.6e-008      5.3e-008         -0.32             1




                              Parameter Estimates


                                                      95.0% Wald
Confidence Interval
        Variable         Estimate         Std. Err.      Lower Conf. Limit
Upper Conf. Limit
         lalpha          12.7854           3.52508               5.87638
19.6944
```

```
           rho          -2.78668              1.03556              -4.81635
-0.757015
          beta_0          43.6123              1.26679              41.1294
46.0952
          beta_1         -92.5263              15.5809             -123.064
-61.9882




     Table of Data and Estimated Values of Interest

 Dose        N    Obs Mean      Est Mean    Obs Std Dev  Est Std Dev   Scaled
Res.
------      ---   --------      --------    -----------  -----------   ---------
-

    0        6      43.6          43.6          3.4          3.1      1.13e-008
0.2571       6      19.8          19.8         10.2         9.31      1.88e-008

Degrees of freedom for Test A2 vs A3 <= 0

Degrees of freedom for Test A3 vs fitted <= 0




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                    Likelihoods of Interest

          Model      Log(likelihood)   # Param's      AIC
           A1         -29.244768          3        64.489536
           A2         -26.179929          4        60.359859
           A3         -26.179929          4        60.359859
         fitted       -26.179929          4        60.359859
            R         -37.469939          2        78.939878



                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
```

```
   Test 2:  Are Variances Homogeneous? (A1 vs A2)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)
   Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
   (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)


                       Tests of Interest


     Test    -2*log(Likelihood Ratio)  Test df        p-value


     Test 1                22.58          2            <.0001
     Test 2             6.12968           1           0.01329
     Test 3         7.10543e-015          0              NA
     Test 4                    0          0              NA


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data


The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate


NA - Degrees of freedom for Test 3 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid



                Benchmark Dose Computation


Specified effect =             1


Risk Type       =     Estimated standard deviations from the control mean


Confidence level =         0.95


           BMD =      0.0335363


          BMDL =       0.020483
```

1   **G.2.24.3.** *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

13:56 08/16 2011

2
3

1 **G.2.25. Latchoumycandane and Mathur ([2002](#)): Sperm Production**

2 **G.2.25.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	<0.0001	93.831	1.739E+01	9.432E+00	
Exponential (M3)	2	<0.0001	93.831	1.739E+01	9.432E+00	power hit bound (*d* = 1)
Exponential (M4)	1	0.700	75.261	1.912E−01	7.976E−02	
Exponential (M5)	0	N/A	77.263	2.925E−01	7.970E−02	
Hill[b]	**1**	**0.962**	**75.115**	**1.171E−01**	**1.324E−02**	***n* lower bound hit (*n* = 1)**
Linear	2	<0.0001	94.250	1.995E+01	1.212E+01	
Polynomial, 3-degree	2	<0.0001	94.250	1.995E+01	1.212E+01	
Power	2	<0.0001	94.250	1.995E+01	1.212E+01	power bound hit (power = 1)
Hill, unrestricted[c]	0	N/A	77.113	9.955E−02	1.228E−09	unrestricted (*n* = 0.916)
Power, unrestricted	1	0.501	75.566	6.921E−06	6.921E−06	unrestricted (power = 0.087)

[a] Constant variance model selected (*p* = 0.8506).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

3
4

5 **G.2.25.2.** *Output for Selected Model: Hill*

6 Latchoumycandane and Mathur ([2002](#)): Sperm Production
7
8
```
9    =====================================================================
10          Hill Model. (Version: 2.14;  Date: 06/26/2008)
11          Input Data File: C:\1\Blood\30_Latch_2002_Sperm_HillCV_1.(d)
12          Gnuplot Plotting File:  C:\1\Blood\30_Latch_2002_Sperm_HillCV_1.plt
13                                   Mon Feb 08 10:53:26 2010
14    =====================================================================
15
16    (x10^6) Table 1 without Vitamin E
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the response function is:
20
21     Y[dose] = intercept + v*dose^n/(k^n + dose^n)
22
23
24     Dependent variable = Mean
25     Independent variable = Dose
26     rho is set to 0
27     Power parameter restricted to be greater than 1
28     A constant variance model is fit
29
30     Total number of dose groups = 4
```

```
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          alpha =      7.23328
                            rho =            0    Specified
                      intercept =        22.19
                              v =        -9.09
                              n =      1.93059
                              k =     0.546864



          Asymptotic Correlation Matrix of Parameter Estimates


          ( *** The model parameter(s)  -rho     -n
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha    intercept           v            k

     alpha            1    -2.2e-009    -3.7e-008    -5.9e-009

 intercept    -2.2e-009           1        -0.76        -0.23

         v    -3.7e-008        -0.76           1        -0.24

         k    -5.9e-009        -0.23        -0.24            1




                              Parameter Estimates


                                                   95.0% Wald
Confidence Interval
       Variable        Estimate       Std. Err.    Lower Conf. Limit
Upper Conf. Limit
          alpha         6.0283         1.74022            2.61753
9.43907
       intercept       22.1894         1.00236            20.2248
24.154
             v         -9.16715        1.30966           -11.734
-6.60026
             n                1              NA
             k         0.320198        0.220443          -0.111862
0.752259


NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.



```

```
      Table of Data and Estimated Values of Interest

 Dose        N    Obs Mean     Est Mean    Obs Std Dev   Est Std Dev   Scaled
Res.
------      ---   --------     --------    -----------   -----------   ---------
-

    0        6      22.2         22.2         2.67          2.46        0.000631
0.7845       6      15.7         15.7         2.65          2.46        -0.00931
4.651        6      13.7         13.6         2.19          2.46        0.0372
27.27        6      13.1         13.1         3.16          2.46        -0.0285




 Model Descriptions for likelihoods calculated


 Model A1:          Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma^2

 Model A2:          Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma(i)^2

 Model A3:          Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:          Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                    Likelihoods of Interest

            Model     Log(likelihood)   # Param's      AIC
             A1          -33.556444          5        77.112888
             A2          -33.158811          8        82.317623
             A3          -33.556444          5        77.112888
           fitted        -33.557588          4        75.115176
             R           -47.392394          2        98.784788


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)   Test df        p-value

   Test 1           28.4672              6            <.0001
   Test 2           0.795266             3            0.8506
```

```
   Test 3              0.795266         3         0.8506
   Test 4              0.00228746       1         0.9619


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data


The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here



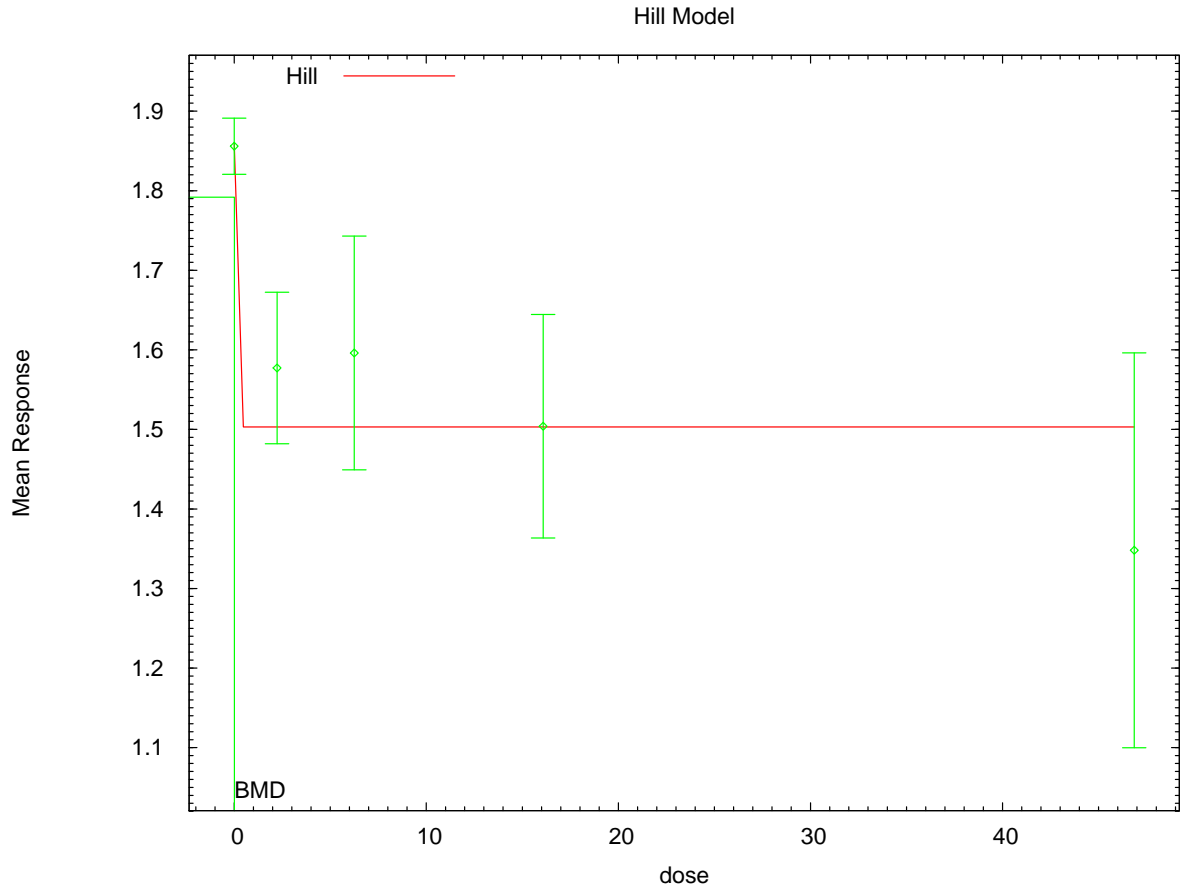The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data



          Benchmark Dose Computation

Specified effect =              1

Risk Type        =       Estimated standard deviations from the control mean

Confidence level =          0.95

           BMD =       0.117131

          BMDL =     0.0132353
```

1 **G.2.25.3.** *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

10:53 02/08 2010

2
3
4 **G.2.25.4.** *Output for Additional Model Presented: Hill, Unrestricted*

5 Latchoumycandane and Mathur ([2002](#)): Sperm Production

6
7
```
8  ========================================================================
9         Hill Model. (Version: 2.14;  Date: 06/26/2008)
10        Input Data File: C:\1\Blood\30_Latch_2002_Sperm_HillCV_U_1.(d)
11        Gnuplot Plotting File:  C:\1\Blood\30_Latch_2002_Sperm_HillCV_U_1.plt
12                                       Mon Feb 08 10:53:26 2010
13 ========================================================================
14
15 (x10^6) Table 1 without Vitamin E
16 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18    The form of the response function is:
19
20    Y[dose] = intercept + v*dose^n/(k^n + dose^n)
21
22
23    Dependent variable = Mean
24    Independent variable = Dose
25    rho is set to 0
```

```
Power parameter is not restricted
A constant variance model is fit


Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          alpha =        7.23328
                            rho =              0    Specified
                      intercept =          22.19
                              v =          -9.09
                              n =        1.93059
                              k =       0.546864



            Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                 alpha      intercept          v              n              k

     alpha           1      -9.8e-009     1.6e-007       1.6e-007       1.2e-007

 intercept   -9.8e-009              1          -0.5         -0.015          -0.13

         v    1.6e-007           -0.5             1           0.76           0.56

         n    1.6e-007         -0.015          0.76              1           0.86

         k    1.2e-007          -0.13          0.56           0.86              1




                              Parameter Estimates


                                                       95.0% Wald
Confidence Interval
      Variable         Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
         alpha          6.02773          1.74006              2.61728
9.43818
      intercept           22.19          1.00231              20.2255
24.1545
              v        -9.23667          2.03204             -13.2194
-5.25394
              n        0.916265          1.66287             -2.34291
4.17544
              k        0.301742         0.440535            -0.561692
1.16518
```

G-160   DRAFT – DO NOT CITE OR QUOTE

```
      Table of Data and Estimated Values of Interest

 Dose        N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
 ------      ---  --------     --------   -----------  -----------   ---------
 -

    0        6     22.2         22.2        2.67         2.46        3.4e-008
0.7845       6     15.7         15.7        2.65         2.46       -1.51e-007
4.651        6     13.7         13.6        2.19         2.46        2.62e-007
27.27        6     13.1         13.1        3.16         2.46       -5.45e-007

Degrees of freedom for Test A3 vs fitted <= 0



 Model Descriptions for likelihoods calculated


 Model A1:          Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:          Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:          Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:          Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                    Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1          -33.556444          5        77.112888
            A2          -33.158811          8        82.317623
            A3          -33.556444          5        77.112888
         fitted         -33.556444          5        77.112888
            R           -47.392394          2        98.784788


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest
```

```
     Test      -2*log(Likelihood Ratio)  Test df         p-value

     Test 1               28.4672          6             <.0001
     Test 2              0.795266          3             0.8506
     Test 3              0.795266          3             0.8506
     Test 4          6.96332e-013          0                NA
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-
Square
     test for fit is not valid

         Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

            BMD =   0.0995543

            BMDL =   1.22818e-009

1 **G.2.25.5.** *Figure for Additional Model Presented: Hill, Unrestricted*

Hill Model with 0.95 Confidence Level

10:53 02/08 2010

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1 **G.2.26. Li et al. ([1997](#)): Follicle-Stimulating Hormone (FSH)**

2 **G.2.26.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	8	<0.0001	1,095.292	5.222E+02	4.121E+02	
Exponential (M3)	8	<0.0001	1,095.292	5.222E+02	4.121E+02	power hit bound (*d* = 1)
Exponential (M4)	7	<0.0001	1,059.480	3.432E+01	9.930E+00	
Exponential (M5)	6	<0.0001	1,066.195	1.019E+02	8.583E−01	
Hill	7	<0.0001	1,056.459	5.423E+00	error	*n* lower bound hit (*n* = 1)
Linear	8	<0.0001	1,077.695	2.003E+02	1.357E+02	
Polynomial, 8-degree	9	<0.0001	1,155.670	error	1.916E+02	
Power[b]	**8**	**<0.0001**	**1,077.695**	**2.003E+02**	**1.357E+02**	**power bound hit (power = 1)**
Hill, unrestricted	6	0.001	1,039.481	2.204E−01	error	unrestricted (*n* = 0.32)
Power, unrestricted[c]	7	0.002	1,037.474	1.963E−01	2.484E−02	unrestricted (power = 0.305)

[a] Nonconstant variance model selected (*p* = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

3
4
5 **G.2.26.2.** *Output for Selected Model: Power*

6 Li et al. ([1997](#)): FSH
7
8
9
```
      =======================================================================
10           Power Model. (Version: 2.15;  Date: 04/07/2008)
11           Input Data File: C:\1\Blood\72_Li_1997_FSH_Pwr_1.(d)
12           Gnuplot Plotting File:  C:\1\Blood\72_Li_1997_FSH_Pwr_1.plt
13                                     Mon Feb 08 13:36:35 2010
14      =======================================================================
15
16  Figure 3: FSH in female S-D rats 24hr after dosing, 22 day old rats
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the response function is:
20
21     Y[dose] = control + slope * dose^power
22
23
24     Dependent variable = Mean
25     Independent variable = Dose
26     The power is restricted to be greater than or equal to 1
27     The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
28
29     Total number of dose groups = 10
30     Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                   Default Initial Parameter Values
                        lalpha =        9.8191
                           rho =             0
                       control =       22.1591
                         slope =        52.284
                         power =       0.294106



          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -power
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                 lalpha          rho        control         slope

     lalpha           1        -0.99        -0.29        -0.033

        rho       -0.99            1          0.2         0.033

    control       -0.29          0.2            1         -0.36

      slope      -0.033        0.033        -0.36             1




                           Parameter Estimates

                                                      95.0% Wald
Confidence Interval
        Variable       Estimate       Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          lalpha        3.50054           1.225          1.09958
5.9015
             rho        1.27087        0.241869         0.796814
1.74492
         control        87.4348         12.9347          62.0833
112.786
           slope       0.492306       0.0919718         0.312044
0.672567
           power              1              NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.




     Table of Data and Estimated Values of Interest
```

```
  Dose        N   Obs Mean     Est Mean   Obs Std Dev   Est Std Dev   Scaled
Res.
------      ---   --------     --------   -----------   -----------   ---------
-


     0      10     23.9          87.4         29.6          98.6        -2.04
0.266      10     22.2          87.6         48.5          98.7        -2.1
0.7988     10     85.2          87.8         94.3          98.9        -0.0832
2.097      10     73.3          88.5         48.5          99.4        -0.483
5.867      10      126          90.3          159           101        1.12
   15      10      132          94.8          116           104        1.14
43.33      10      117           109         51.2           113        0.223
119.9      10      304           146          154           137        3.65
  386      10      347           277          151           205        1.07
 1172      10      455           664          286           358        -1.85




Model Descriptions for likelihoods calculated


Model A1:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:          Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                   Likelihoods of Interest


           Model      Log(likelihood)    # Param's      AIC
            A1         -535.687163            11      1093.374327
            A2         -496.367061            20      1032.734122
            A3         -502.709623            12      1029.419246
         fitted        -534.847518             4      1077.695035
            R          -574.835246             2      1153.670492



                   Explanation of Tests


Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)


                   Tests of Interest
```

```
     Test    -2*log(Likelihood Ratio)  Test df         p-value

     Test 1              156.936          18            <.0001
     Test 2              78.6402          9             <.0001
     Test 3              12.6851          8             0.1232
     Test 4              64.2758          8             <.0001
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different
model

                   Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

              BMD = 200.314

             BMDL = 135.673

G.2.26.3. *Figure for Selected Model: Power*

Power Model with 0.95 Confidence Level

13:36 02/08 2010

G.2.26.4. *Output for Additional Model Presented: Power, Unrestricted*

Li et al. (1997): FSH

```
  =====================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\Blood\72_Li_1997_FSH_Pwr_U_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\72_Li_1997_FSH_Pwr_U_1.plt
                                       Mon Feb 08 13:36:46 2010
  =====================================================================

 Figure 3: FSH in female S-D rats 24hr after dosing, 22 day old rats
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function is:

    Y[dose] = control + slope * dose^power


    Dependent variable = Mean
    Independent variable = Dose
```

```
     The power is not restricted
     The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

     Total number of dose groups = 10
     Total number of records with missing values = 0
     Maximum number of iterations = 250
     Relative Function Convergence has been set to: 1e-008
     Parameter Convergence has been set to: 1e-008



                     Default Initial Parameter Values
                           lalpha =        9.8191
                              rho =             0
                          control =       22.1591
                            slope =        52.284
                            power =      0.294106


          Asymptotic Correlation Matrix of Parameter Estimates

                    lalpha          rho        control        slope         power

       lalpha            1        -0.99        -0.69        -0.06         0.26

          rho        -0.99            1         0.65       0.0089        -0.23

      control        -0.69         0.65            1        -0.23        0.029

        slope        -0.06       0.0089        -0.23            1        -0.85

        power         0.26        -0.23        0.029        -0.85            1




                              Parameter Estimates


                                                        95.0% Wald
Confidence Interval
        Variable       Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          lalpha        3.67487         1.12134              1.47708
5.87265
             rho        1.17882        0.221526             0.744632
1.613
         control        15.8201         6.87715              2.34113
29.299
           slope         52.528         9.46821              33.9706
71.0853
           power       0.304867       0.0336805             0.238855
0.37088




     Table of Data and Estimated Values of Interest
```

```
 Dose        N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------      ---   --------     --------   -----------  -----------   ---------
-


    0        10     23.9         15.8        29.6          32          0.795
0.266        10     22.2         50.9        48.5         63.7        -1.43
0.7988       10     85.2         64.9        94.3         73.5         0.876
2.097        10     73.3         81.7        48.5         84.1        -0.314
5.867        10     126          106         159          98.1         0.652
15           10     132          136         116          114        -0.102
43.33        10     117          182         51.2         135        -1.52
119.9        10     304          242         154          160         1.24
386          10     347          339         151          195         0.134
1172         10     455          469         286          236        -0.182
```

Model Descriptions for likelihoods calculated

Model A1:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model R: Yi = Mu + e(i)
          Var{e(i)} = Sigma^2

                    Likelihoods of Interest

          Model   Log(likelihood)   # Param's   AIC
           A1   -535.687163   11   1093.374327
           A2   -496.367061   20   1032.734122
           A3   -502.709623   12   1029.419246
         fitted   -513.737215   5   1037.474431
           R   -574.835246   2   1153.670492

                    Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest
```

```
   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              156.936           18           <.0001
   Test 2              78.6402            9           <.0001
   Test 3              12.6851            8           0.1232
   Test 4              22.0552            7           0.002485
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different
model

                 Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

            BMD = 0.196278

            BMDL = 0.0248364

1 **G.2.26.5.** *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

13:36 02/08 2010

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G.2.27. Li et al. ([2006](#)): Estradiol, 3-Day

2 **G.2.27.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.156	269.027	1.416E+01	5.544E+00	
Exponential (M3)	2	0.156	269.027	1.416E+01	5.544E+00	power hit bound ($d = 1$)
Exponential (M4)	1	0.341	268.212	error	error	
Exponential (M5)	0	N/A	270.212	error	error	
Hill	0	N/A	270.212	error	error	
Linear[b]	**2**	**0.162**	**268.952**	**1.606E+01**	**5.379E+00**	
Polynomial, 3-degree	2	0.162	268.952	1.606E+01	5.379E+00	
Power	2	0.162	268.952	1.606E+01	5.379E+00	power bound hit (power = 1)
Hill, unrestricted	0	N/A	270.265	9.273E+12	9.273E+12	unrestricted ($n = 0.03$)
Power, unrestricted	1	0.328	268.265	9.455E+10	error	unrestricted (power = 0.015)

[a] Constant variance model selected ($p = 0.4372$).
[b] Best-fitting model, BMDS output presented in this appendix.

3
4

5 **G.2.27.2.** *Output for Selected Model: Linear*

6 Li et al. ([2006](#)): Estradiol, 3-Day
7
8
```
9     =======================================================================
10           Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
11           Input Data File: C:\1\Blood\31_Li_2006_Estra_LinearCV_1.(d)
12           Gnuplot Plotting File:  C:\1\Blood\31_Li_2006_Estra_LinearCV_1.plt
13                                     Mon Feb 08 10:54:00 2010
14     =======================================================================
15
16   Figure 3, 3-day estradiol
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the response function is:
20
21     Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
22
23
24     Dependent variable = Mean
25     Independent variable = Dose
26     rho is set to 0
27     Signs of the polynomial coefficients are not restricted
28     A constant variance model is fit
29
30     Total number of dose groups = 4
31     Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                      Default Initial Parameter Values
                             alpha =       267.211
                               rho =             0    Specified
                            beta_0 =       16.1705
                            beta_1 =        1.0106



              Asymptotic Correlation Matrix of Parameter Estimates

              ( *** The model parameter(s)  -rho
                    have been estimated at a boundary point, or have been
specified by the user,
                    and do not appear in the correlation matrix )

                      alpha         beta_0          beta_1

        alpha             1       2.1e-012         5e-014

      beta_0      2.1e-012              1           -0.69

      beta_1        5e-014          -0.69               1




                              Parameter Estimates


                                                     95.0% Wald
Confidence Interval
         Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
            alpha         263.435         58.9057            147.981
378.888
           beta_0         16.1705         3.55949            9.19407
23.147
           beta_1          1.0106          1.2148           -1.37037
3.39156




      Table of Data and Estimated Values of Interest

  Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
 ------     ---   --------     --------   -----------  -----------   --------
-

     0      10      10.2         16.2         12.2         16.2        -1.17
0.1588    10      19.9         16.3          20          16.2         0.697
2.839     10      24.7          19          14.6         16.2         1.11
5.124     10      18.1         21.3         17.6         16.2        -0.635
```

```
Model Descriptions for likelihoods calculated


Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                   Likelihoods of Interest

          Model     Log(likelihood)    # Param's      AIC
           A1        -129.653527            5       269.307054
           A2        -128.294657            8       272.589314
           A3        -129.653527            5       269.307054
         fitted      -131.476097            3       268.952193
           R         -131.819169            2       267.638338



                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                   Tests of Interest

  Test     -2*log(Likelihood Ratio)  Test df        p-value

  Test 1            7.04902            6             0.3163
  Test 2            2.71774            3             0.4372
  Test 3            2.71774            3             0.4372
  Test 4            3.64514            2             0.1616

The p-value for Test 1 is greater than .05.  There may not be a
diffence between responses and/or variances among the dose levels
Modelling the data with a dose/response curve may not be appropriate


The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here



The p-value for Test 3 is greater than .1.  The modeled variance appears
```

to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

                 Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

          BMD =   16.0605

          BMDL =   5.37895

G.2.27.3. *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

10:54 02/08 2010

G.2.28. Li et al. (2006): Progesterone, 3-Day

G.2.28.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ² *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	<0.001	329.928	2.619E+00	error	
Exponential (M3)	2	0.001	328.101	1.340E−01	error	power hit bound (*d* = 1)
Exponential (M4)	1	0.384	315.734	1.074E−02	6.633E−03	
Exponential (M5)	0	N/A	317.734	4.301E−02	4.272E−03	
Hill[b]	**1**	**0.386**	**315.728**	**9.461E−04**	**8.006E−11**	***n* lower bound hit (*n* = 1)**
Linear	2	<0.001	330.729	3.891E+00	2.626E+00	
Polynomial, 3-degree	2	<0.001	330.729	3.891E+00	2.626E+00	
Power	2	<0.001	330.729	3.891E+00	2.626E+00	power bound hit (power = 1)
Power, unrestricted	1	0.404	315.673	2.812E−59	2.812E−59	unrestricted (power = 0.01)

[a] Nonconstant variance model selected ($p = 0.0013$).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.28.2. *Output for Selected Model: Hill*

Li et al. (2006): Progesterone, 3-Day

```
   ==================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File: C:\1\Blood\32_Li_2006_Progest_Hill_1.(d)
          Gnuplot Plotting File:  C:\1\Blood\32_Li_2006_Progest_Hill_1.plt
                                         Wed Feb 10 10:57:14 2010
   ==================================================================

 Figure 4, 3-day progesterone
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
```

```
Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                          lalpha =      7.08699
                             rho =            0
                       intercept =      61.7404
                               v =     -50.3835
                               n =      1.47286
                               k =     0.128302



            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -n
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                  lalpha          rho    intercept            v            k

      lalpha           1        -0.99       -0.093         0.82         0.22

         rho       -0.99            1         0.12        -0.79         -0.2

   intercept      -0.093         0.12            1        -0.43        0.014

           v        0.82        -0.79        -0.43            1        0.035

           k        0.22         -0.2        0.014        0.035            1




                              Parameter Estimates


                                                     95.0% Wald
Confidence Interval
       Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
       lalpha          14.0902          3.36095             7.50284
20.6775
          rho         -2.27438         0.861553              -3.963
-0.585772
    intercept          61.7488           3.3373             55.2078
68.2898
            v         -42.1007          7.70852            -57.2091
-26.9922
            n                1               NA
            k       0.00282851         0.020619           -0.037584
0.0432411

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

```
     Table of Data and Estimated Values of Interest

 Dose        N     Obs Mean      Est Mean    Obs Std Dev   Est Std Dev    Scaled
Res.
------      ---   --------      --------    -----------   -----------   ---------
-

    0       10      61.7          61.7          11.1          10.6       -0.00251
0.1588      10      30.6          20.4          40.5          37.2        0.865
2.839       10      16.9          19.7          33.3          38.7       -0.225
5.124       10      11.4          19.7          43.7          38.8       -0.678
```

Model Descriptions for likelihoods calculated


```
Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2
```

Likelihoods of Interest

```
          Model      Log(likelihood)   # Param's      AIC
           A1         -159.632675          5       329.265349
           A2         -151.812765          8       319.625529
           A3         -152.488175          6       316.976349
         fitted       -152.863841          5       315.727683
           R          -165.698875          2       335.397750
```

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

```
  Test     -2*log(Likelihood Ratio)   Test df        p-value

  Test 1            27.7722              6          0.0001037
```

```
   Test 2              15.6398          3          0.001344
   Test 3              1.35082          2          0.5089
   Test 4              0.751333         1          0.3861
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
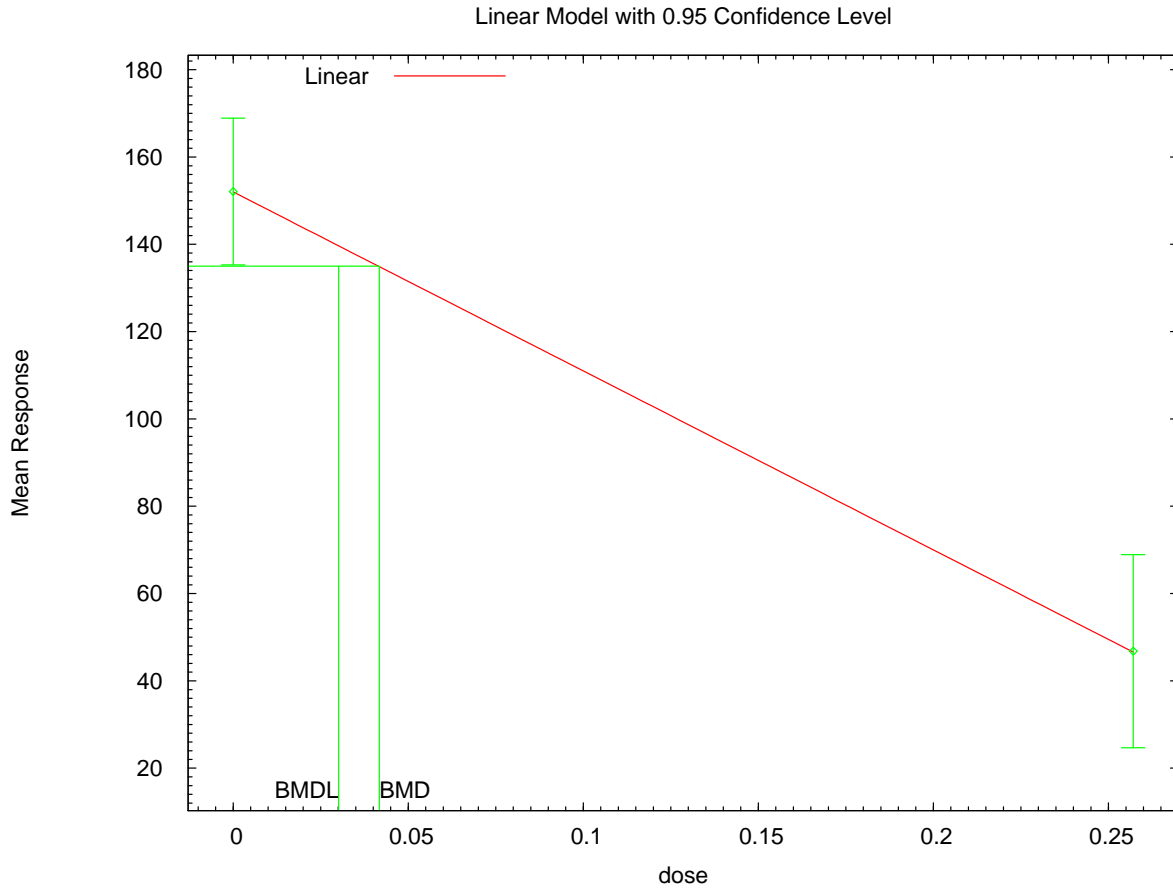model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

        Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

          BMD =   0.000946102

         BMDL = 8.00639e-011

1   **G.2.28.3.** *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

10:57 02/10 2010

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G.2.29. Markowski et al. ([2001](#)): FR10 Run Opportunities

G.2.29.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)[b]	**2**	**0.304**	**117.150**	**8.570E+00**	**2.887E+00**	
Exponential (M3)	2	0.304	117.150	8.570E+00	2.887E+00	power hit bound (*d* = 1)
Exponential (M4)	1	0.371	117.570	3.452E+00	1.299E−02	
Exponential (M5)	0	N/A	118.918	2.315E+00	1.391E−02	
Hill	0	N/A	118.918	1.801E+00	1.274E−09	
Linear	2	0.226	117.744	1.106E+01	5.741E+00	
Polynomial, 3-degree	2	0.226	117.744	1.106E+01	5.741E+00	
Power	2	0.226	117.744	1.106E+01	5.741E+00	power bound hit (power = 1)
Power, unrestricted	1	0.239	118.158	5.768E+00	1.032E−14	unrestricted (power = 0.276)

[a] Constant variance model selected (*p* = 0.1719).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.29.2. *Output for Selected Model: Exponential (M2)*

Markowski et al. ([2001](#)): FR10 Run Opportunities


```
=====================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\Blood\33_Mark_2001_FR10opp_ExpCV_1.(d)
        Gnuplot Plotting File:
                                      Mon Feb 08 10:55:13 2010
=====================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.


Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


MLE solution provided: Exact



                    Initial Parameter Values

                  Variable          Model 2
                  --------          --------
                    lnalpha            3.5321
                        rho(S)              0
                          a          6.77975
                          b        0.0581937
                          c                0
                          d                1


   (S) = Specified




                    Parameter Estimates

                  Variable          Model 2
                  --------          -------
                    lnalpha          3.63127
                        rho                0
                          a          12.2901
                          b        0.0808832
                          c                0
                          d                1



         Table of Stats From Input Data

    Dose      N        Obs Mean     Obs Std Dev
    -----    ---      ----------    -------------
        0     7        13.29           8.65
    1.557     4        11.25           5.56
     4.03     6         5.75           3.53
    10.32     7            7           6.01



                 Estimated Values of Interest

     Dose      Est Mean      Est Std     Scaled Residual
```

```
     ------      ----------      ---------      ----------------
         0          12.29          6.145             0.4305
     1.557          10.84          6.145             0.1347
      4.03          8.871          6.145            -1.244
     10.32          5.335          6.145             0.717




   Other models for which likelihoods are calculated:

      Model A1:         Yij = Mu(i) + e(ij)
                   Var{e(ij)} = Sigma^2

      Model A2:         Yij = Mu(i) + e(ij)
                   Var{e(ij)} = Sigma(i)^2

      Model A3:         Yij = Mu(i) + e(ij)
                   Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

      Model  R:         Yij = Mu + e(i)
                   Var{e(ij)} = Sigma^2



                          Likelihoods of Interest

                  Model      Log(likelihood)      DF        AIC
                  -------    -----------------    ----    ------------
                    A1         -54.38526            5       118.7705
                    A2         -51.88568            8       119.7714
                    A3         -54.38526            5       118.7705
                     R         -57.45429            2       118.9086
                     2         -55.57522            3       117.1504



   Additive constant for all log-likelihoods =      -22.05.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                          Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)
   Test 4:  Does Model 2 fit the data? (A3 vs. 2)



                            Tests of Interest

     Test         -2*log(Likelihood Ratio)         D. F.          p-value
     --------     ------------------------         ------      --------------
     Test 1                 11.14                     6            0.08423
     Test 2                 4.999                     3            0.1719
     Test 3                 4.999                     3            0.1719
     Test 4                  2.38                     2            0.3042
```

The p-value for Test 1 is greater than .05. There may not be a
diffence between responses and/or variances among the dose levels
Modelling the data with a dose/response curve may not be appropriate.

The p-value for Test 2 is greater than .1. A homogeneous
variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled
variance appears to be appropriate here.

The p-value for Test 4 is greater than .1. Model 2 seems
to adequately describe the data.

Benchmark Dose Computations:

   Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

   Confidence Level = 0.950000

                BMD =   8.56961

               BMDL =   2.88708

G.2.29.3. *Figure for Selected Model: Exponential (M2)*

Exponential Model 2 with 0.95 Confidence Level

10:55 02/08 2010

1 **G.2.30. Markowski et al. ([2001](#)): FR2 Revolutions**

2 **G.2.30.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.236	217.219	8.486E+00	3.232E+00	
Exponential (M3)	2	0.236	217.219	8.486E+00	3.232E+00	power hit bound (*d* = 1)
Exponential (M4)	1	0.263	217.583	3.413E+00	1.766E−02	
Exponential (M5)	0	N/A	218.532	2.415E+00	9.313E−01	
Hill[b]	**1**	**0.654**	**216.532**	**1.840E+00**	**5.992E−01**	***n* upper bound hit (*n* = 18)**
Linear	2	0.180	217.764	1.058E+01	5.602E+00	
Polynomial, 3-degree	2	0.180	217.764	1.058E+01	5.602E+00	
Power	2	0.180	217.764	1.058E+01	5.602E+00	power bound hit (power = 1)
Power, unrestricted[c]	1	0.161	218.294	5.739E+00	1.032E−14	unrestricted (power = 0.318)

[a] Constant variance model selected (*p* = 0.1092).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

3
4
5 **G.2.30.2.** *Output for Selected Model: Hill*

6 Markowski et al. ([2001](#)): FR2 Revolutions
7
8
```
9    =========================================================================
10          Hill Model. (Version: 2.14;  Date: 06/26/2008)
11          Input Data File: C:\1\Blood\34_Mark_2001_FR2rev_HillCV_1.(d)
12          Gnuplot Plotting File:  C:\1\Blood\34_Mark_2001_FR2rev_HillCV_1.plt
13                                          Mon Feb 08 10:55:47 2010
14    =========================================================================
15
16    Table 3
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the response function is:
20
21     Y[dose] = intercept + v*dose^n/(k^n + dose^n)
22
23
24     Dependent variable = Mean
25     Independent variable = Dose
26     rho is set to 0
27     Power parameter restricted to be greater than 1
28     A constant variance model is fit
29
30     Total number of dose groups = 4
31     Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                          alpha =      2598.74
                            rho =            0    Specified
                      intercept =       119.29
                              v =       -62.79
                              n =      2.13752
                              k =      2.53662



           Asymptotic Correlation Matrix of Parameter Estimates


         ( *** The model parameter(s)   -rho     -n
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                     alpha    intercept           v            k

       alpha             1    1.2e-008      1e-009     3.5e-008

    intercept     1.2e-008           1       -0.81        -0.52

         v        1e-009       -0.81           1         0.37

         k      3.5e-008       -0.52        0.37            1




                             Parameter Estimates


                                                     95.0% Wald
Confidence Interval
      Variable          Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
        alpha           2183.85          630.425           948.245
3419.46
      intercept          119.29          17.6629           84.6713
153.909
           v           -56.5223          21.9082          -99.4615
-13.5831
           n                 18               NA
           k            1.68653         0.295154           1.10804
2.26502


NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.




     Table of Data and Estimated Values of Interest
```

```
 Dose        N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------       ---  --------     --------   -----------  -----------   ---------
-


    0         7      119          119         69.9          46.7      -2.41e-007
1.557         4      109          108           61          46.7       2.29e-007
 4.03         6     56.5         62.8         31.2          46.7        -0.329
10.32         7     68.1         62.8         33.2          46.7         0.304




Model Descriptions for likelihoods calculated


Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                    Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
            A1         -104.165520            5      218.331040
            A2         -101.140174            8      218.280349
            A3         -104.165520            5      218.331040
         fitted        -104.266162            4      216.532324
            R          -107.599268            2      219.198536



                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

  Test     -2*log(Likelihood Ratio)   Test df        p-value

  Test 1              12.9182            6            0.04435
  Test 2               6.05069           3            0.1092
  Test 3               6.05069           3            0.1092
```

```
   Test 4                0.201284        1              0.6537

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


          Benchmark Dose Computation

Specified effect =             1

Risk Type         =     Estimated standard deviations from the control mean

Confidence level =          0.95

          BMD =        1.83952

          BMDL =       0.599228
```

1   **G.2.30.3.** *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

10:55 02/08 2010

2
3
4   **G.2.30.4.** *Output for Additional Model Presented: Power, Unrestricted*

5   Markowski et al. (2001): FR2 Revolutions
6
7
8   ```
    ===
9   Power Model. (Version: 2.15; Date: 04/07/2008)
10   Input Data File: C:\1\Blood\34_Mark_2001_FR2rev_PowerCV_U_1.(d)
11   Gnuplot Plotting File:
12   C:\1\Blood\34_Mark_2001_FR2rev_PowerCV_U_1.plt
13   Mon Feb 08 10:55:49 2010
14   ===
15
16   Table 3
17   ~~~~~~
18
19   The form of the response function is:
20
21   Y[dose] = control + slope * dose^power
22
23
24   Dependent variable = Mean
    ```

```
Independent variable = Dose
rho is set to 0
The power is not restricted
A constant variance model is fit

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          alpha =        2598.74
                            rho =              0    Specified
                        control =         119.29
                          slope =       -10.3599
                          power =       0.824761


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -rho
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                    alpha        control         slope         power

     alpha             1        -3e-010       6.9e-010      9.9e-010

   control       -3e-010              1         -0.63         -0.28

     slope      6.9e-010          -0.63             1          0.87

     power      9.9e-010          -0.28          0.87             1




                              Parameter Estimates


                                                        95.0% Wald
Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
        alpha          2350.22          678.449              1020.48
3679.95
        control        120.082          18.0782              84.6491
155.514
        slope         -27.8164          24.2447             -75.3352
19.7023
        power         0.317923         0.350841            -0.369713
1.00556
```

```
      Table of Data and Estimated Values of Interest

 Dose        N    Obs Mean     Est Mean    Obs Std Dev   Est Std Dev   Scaled
Res.
 ------      ---  --------     --------    -----------   -----------   ---------
-


    0        7      119          120          69.9          48.5        -0.0432
1.557        4      109         88.1           61           48.5         0.843
 4.03        6     56.5         76.8          31.2          48.5         -1.02
10.32        7     68.1         61.7          33.2          48.5         0.353




 Model Descriptions for likelihoods calculated


 Model A1:          Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:          Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:          Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:          Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                    Likelihoods of Interest

            Model      Log(likelihood)    # Param's       AIC
             A1         -104.165520          5         218.331040
             A2         -101.140174          8         218.280349
             A3         -104.165520          5         218.331040
           fitted       -105.147159          4         218.294317
             R          -107.599268          2         219.198536


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test     -2*log(Likelihood Ratio)   Test df        p-value

   Test 1              12.9182            6            0.04435
   Test 2              6.05069            3            0.1092
```

```
   Test 3              6.05069          3           0.1092
   Test 4              1.96328          1           0.1612


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data


The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here



The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here


The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data



                 Benchmark Dose Computation

Specified effect =            1

Risk Type        =    Estimated standard deviations from the control mean

Confidence level =         0.95

            BMD = 5.73906


            BMDL = 1.03181e-014
```

1   **G.2.30.5.** *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

10:55 02/08 2010

2
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4

1 **G.2.31. Markowski et al. ([2001](#)): FR5 Run Opportunities**

2 **G.2.31.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	2	0.205	133.193	5.078E+00	2.439E+00	
Exponential (M3)	2	0.205	133.193	5.078E+00	2.439E+00	power hit bound (*d* = 1)
Exponential (M4)	1	0.254	133.328	2.160E+00	6.854E−01	
Exponential (M5)	0	N/A	134.032	2.124E+00	9.667E−01	
Hill[b]	**1**	**0.939**	**132.032**	**1.723E+00**	**9.085E−01**	***n* upper bound hit (*n* = 18)**
Linear	2	0.122	134.229	7.234E+00	4.430E+00	
Polynomial, 3-degree	2	0.122	134.229	7.234E+00	4.430E+00	
Power	2	0.122	134.229	7.234E+00	4.430E+00	power bound hit (power = 1)
Power, unrestricted[c]	1	0.134	134.268	2.666E+00	1.032E−14	unrestricted (power = 0.392)

[a] Constant variance model selected (*p* = 0.2262).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

3
4
5 **G.2.31.2.** *Output for Selected Model: Hill*

6 Markowski et al. ([2001](#)): FR5 Run Opportunities
7
8
9 ```
    ==
10   Hill Model. (Version: 2.14; Date: 06/26/2008)
11   Input Data File: C:\1\Blood\35_Mark_2001_FR5opp_HillCV_1.(d)
12   Gnuplot Plotting File: C:\1\Blood\35_Mark_2001_FR5opp_HillCV_1.plt
13   Mon Feb 08 10:56:24 2010
14   ==
15
16   Table 3
17 ~~~~~~
18
19   The form of the response function is:
20
21   Y[dose] = intercept + v*dose^n/(k^n + dose^n)
22
23
24   Dependent variable = Mean
25   Independent variable = Dose
26   rho is set to 0
27   Power parameter restricted to be greater than 1
28   A constant variance model is fit
29
30   Total number of dose groups = 4
31   Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                           alpha =       77.4849
                             rho =             0    Specified
                       intercept =         26.14
                               v =        -13.34
                               n =       2.77257
                               k =       2.48811



          Asymptotic Correlation Matrix of Parameter Estimates


          ( *** The model parameter(s)  -rho     -n
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )


                    alpha    intercept            v            k

      alpha             1    -3.2e-009     1.9e-008     6.2e-008

  intercept     -3.2e-009            1        -0.81        -0.51

          v      1.9e-008        -0.81            1         0.36

          k      6.2e-008        -0.51         0.36            1




                            Parameter Estimates


                                              95.0% Wald
Confidence Interval
        Variable         Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
          alpha         64.5863          18.6445              28.0438
101.129
        intercept         26.14          3.03753              20.1865
32.0935
              v        -13.1569           3.7676             -20.5413
-5.77257
              n              18               NA
              k         1.68073         0.208677              1.27173
2.08973


NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.




     Table of Data and Estimated Values of Interest
```

```
 Dose        N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------      ---   --------     --------   -----------  -----------   ---------
-

    0        7      26.1         26.1        12.3         8.04       -1.9e-008
1.557        4      23.5         23.5        7.04         8.04       -1.94e-007
 4.03        6      12.8           13        6.17         8.04        -0.0558
10.32        7      13.1           13        7.14         8.04         0.0517



 Model Descriptions for likelihoods calculated


 Model A1:          Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:          Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:          Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:          Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                    Likelihoods of Interest


            Model      Log(likelihood)   # Param's      AIC
             A1          -62.013133          5        134.026266
             A2          -59.839035          8        135.678070
             A3          -62.013133          5        134.026266
          fitted         -62.016025          4        132.032049
              R          -67.530040          2        139.060081


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test     -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              15.382             6          0.01748
   Test 2              4.3482             3          0.2262
   Test 3              4.3482             3          0.2262
```

```
   Test 4          0.00578335         1         0.9394
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

         Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

          BMD =   1.72335

         BMDL =   0.908491

1   **G.2.31.3.** *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

10:56 02/08 2010

2
3
4   **G.2.31.4.** *Output for Additional Model Presented: Power, Unrestricted*

5   Markowski et al. (2001): FR5 Run Opportunities
6
7
8   ```
     ==
9   Power Model. (Version: 2.15; Date: 04/07/2008)
10   Input Data File: C:\1\Blood\35_Mark_2001_FR5opp_PwrCV_U_1.(d)
11   Gnuplot Plotting File: C:\1\Blood\35_Mark_2001_FR5opp_PwrCV_U_1.plt
12   Mon Feb 08 10:56:24 2010
13   ==
14
15   Table 3
16   ~~~~~~
17
18   The form of the response function is:
19
20   Y[dose] = control + slope * dose^power
21
22
23   Dependent variable = Mean
     ```

```
Independent variable = Dose
rho is set to 0
The power is not restricted
A constant variance model is fit

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                  Default Initial Parameter Values
                        alpha =      77.4849
                          rho =            0   Specified
                      control =        26.14
                        slope =      -2.3827
                        power =     0.844532


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha        control        slope        power

    alpha             1      -9.3e-009      1.4e-008     9.3e-009

  control     -9.3e-009              1         -0.64        -0.34

    slope      1.4e-008          -0.64             1          0.9

    power      9.3e-009          -0.34           0.9            1




                           Parameter Estimates


                                                        95.0% Wald
Confidence Interval
       Variable        Estimate       Std. Err.     Lower Conf. Limit
Upper Conf. Limit
        alpha          70.8926         20.4649             30.7821
111.003
        control        26.3582         3.12902             20.2254
32.4909
        slope         -5.73309         4.02937            -13.6305
2.16433
        power         0.391903        0.281862           -0.160536
0.944342
```

```
       Table of Data and Estimated Values of Interest

 Dose       N     Obs Mean     Est Mean    Obs Std Dev   Est Std Dev    Scaled
 Res.
 ------     ---   --------     --------    -----------   -----------   ---------
 -

     0       7      26.1         26.4         12.3          8.42         -0.0686
 1.557       4      23.5         19.5         7.04          8.42          0.941
  4.03       6      12.8         16.5         6.17          8.42         -1.06
 10.32       7      13.1           12         7.14          8.42          0.343



 Model Descriptions for likelihoods calculated


 Model A1:          Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:          Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:          Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:          Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                    Likelihoods of Interest

            Model     Log(likelihood)   # Param's      AIC
            A1         -62.013133           5        134.026266
            A2         -59.839035           8        135.678070
            A3         -62.013133           5        134.026266
          fitted       -63.134001           4        134.268002
            R          -67.530040           2        139.060081


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)   Test df        p-value

   Test 1              15.382            6           0.01748
   Test 2              4.3482            3            0.2262
```

```
   Test 3                4.3482          3           0.2262
   Test 4                2.24174         1           0.1343
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

                 Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

             BMD = 2.66625

            BMDL = 1.03181e-014

1   **G.2.31.5.** *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

10:56 02/08 2010

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G.2.32. Miettinen et al. ([2006](#)): Cariogenic Lesions, Pups

G.2.32.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	3	0.410	162.280	3.401E+00	1.889E+00	power bound hit (power = 1)
Logistic	3	0.371	162.518	4.108E+00	2.450E+00	
Log-logistic[a]	**3**	**0.602**	**161.292**	**1.428E+00**	**5.175E−01**	**slope bound hit (slope = 1)**
Log-probit	3	0.300	163.040	6.321E+00	3.127E+00	slope bound hit (slope = 1)
Multistage, 4-degree	3	0.410	162.280	3.401E+00	1.889E+00	final ß = 0
Probit	3	0.350	162.656	4.548E+00	2.889E+00	
Weibull	3	0.410	162.280	3.401E+00	1.889E+00	power bound hit (power = 1)
Gamma, unrestricted	2	0.798	161.801	3.374E−03	8.884E−242	unrestricted (power = 0.215)
Log-logistic, unrestricted[b]	2	0.728	161.983	4.942E−02	error	unrestricted (slope = 0.465)
Log-probit, unrestricted	2	0.732	161.972	6.495E−02	error	unrestricted (slope = 0.289)
Weibull, unrestricted	2	0.766	161.884	1.792E−02	error	unrestricted (power = 0.324)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.2.32.2. *Output for Selected Model: Log-Logistic*

Miettinen et al. ([2006](#)): Cariogenic Lesions, Pups

```
    =====================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\36_Miet_2006_Cariogenic_LogLogistic_1.(d)
         Gnuplot Plotting File:
C:\1\Blood\36_Miet_2006_Cariogenic_LogLogistic_1.plt
                                          Mon Feb 08 10:56:59 2010
    =====================================================================

 Table 2 converting the percentage into the number of animals, and control is
Control II from the study. Dose is in ng per kg and is from Table 1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
```

```
   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =     0.595238
                       intercept =       -2.494
                           slope =           1



          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -slope
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

              background    intercept

background             1        -0.66

 intercept         -0.66            1




                            Parameter Estimates

                                                95.0% Wald
Confidence Interval
      Variable         Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
     background       0.644165             *                  *
*
       intercept      -2.55354             *                  *
*
          slope             1              *                  *
*


* - Indicates that this value is not calculated.




                         Analysis of Deviance Table

      Model        Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model       -77.6769          5
   Fitted model       -78.646           2        1.93832      3
0.5853
```

```
Reduced model          -83.2067          1          11.0597          4
0.0259

          AIC:          161.292


                         Goodness  of  Fit
                                                              Scaled
     Dose      Est._Prob.    Expected     Observed     Size    Residual
    -------------------------------------------------------------------
    0.0000      0.6442        27.055       25.000        42      -0.662
    2.2195      0.6966        20.200       23.000        29       1.131
    6.2259      0.7603        19.007       19.000        25      -0.003
   16.0142      0.8416        20.198       20.000        24      -0.111
   46.6355      0.9231        29.540       29.000        32      -0.358

 Chi^2 = 1.86     d.f. = 3       P-value = 0.6024


   Benchmark Dose Computation

Specified effect =          0.1

Risk Type         =      Extra risk

Confidence level =          0.95

          BMD =       1.42805

          BMDL =      0.517495
```

1   **G.2.32.3.** *Figure for Selected Model: Log-Logistic*

Log-Logistic Model with 0.95 Confidence Level

10:56 02/08 2010

2
3
4   **G.2.32.4.** *Output for Additional Model Presented: Log-Logistic, Unrestricted*

5   Miettinen et al. (2006): Cariogenic Lesions, Pups

6
7
8   ```
     ==
9   Logistic Model. (Version: 2.12; Date: 05/16/2008)
10   Input Data File:
11   C:\1\Blood\36_Miet_2006_Cariogenic_LogLogistic_U_1.(d)
12   Gnuplot Plotting File:
13   C:\1\Blood\36_Miet_2006_Cariogenic_LogLogistic_U_1.plt
14   Mon Feb 08 10:56:59 2010
15   ==
16
17   Table 2 converting the percentage into the number of animals, and control is
18   Control II from the study. Dose is in ng per kg and is from Table 1
19   ~~~~~~
20
21   The form of the probability function is:
22
23   P[response] = background+(1-background)/[1+EXP(-intercept-
24   slope*Log(dose))]
     ```
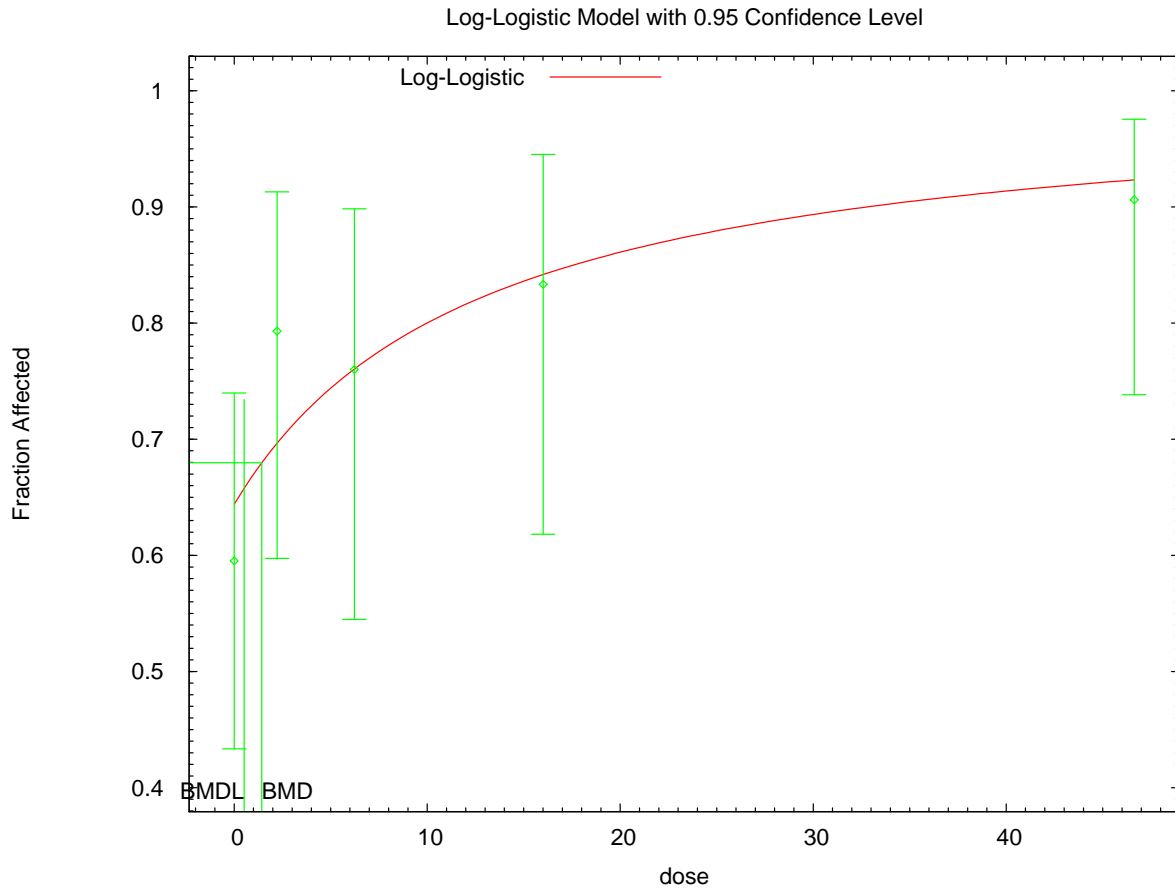
```
Dependent variable = DichEff
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =     0.595238
                      intercept =    -0.739403
                          slope =     0.442847


         Asymptotic Correlation Matrix of Parameter Estimates

               background      intercept         slope

background             1          -0.51           0.24

 intercept         -0.51              1          -0.89

    slope           0.24          -0.89              1




                            Parameter Estimates

                                                  95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
     background        0.597745              *                  *
*
      intercept       -0.798024              *                  *
*
         slope        0.465259              *                  *
*


* - Indicates that this value is not calculated.




                         Analysis of Deviance Table

     Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model       -77.6769          5
```

```
   Fitted model          -77.9915           3        0.629204         2
0.7301
   Reduced model         -83.2067           1        11.0597          4
0.0259


          AIC:              161.983


                              Goodness  of  Fit
                                                              Scaled
     Dose      Est._Prob.    Expected      Observed      Size    Residual
   -------------------------------------------------------------------------
    0.0000      0.5977       25.105        25.000         42      -0.033
    2.2195      0.7566       21.940        23.000         29       0.458
    6.2259      0.8042       20.105        19.000         25      -0.557
   16.0142      0.8474       20.338        20.000         24      -0.192
   46.6355      0.8910       28.512        29.000         32       0.277


 Chi^2 = 0.63      d.f. = 2       P-value = 0.7281


   Benchmark Dose Computation

Specified effect =              0.1

Risk Type        =       Extra risk

Confidence level =              0.95

          BMD =          0.049422

          Benchmark dose computation failed.  Lower limit includes zero.
```

1 **G.2.32.5.** *Figure for Additional Model Presented: Log-Logistic, Unrestricted*

Log-Logistic Model

10:57 02/08 2010

2
3
4
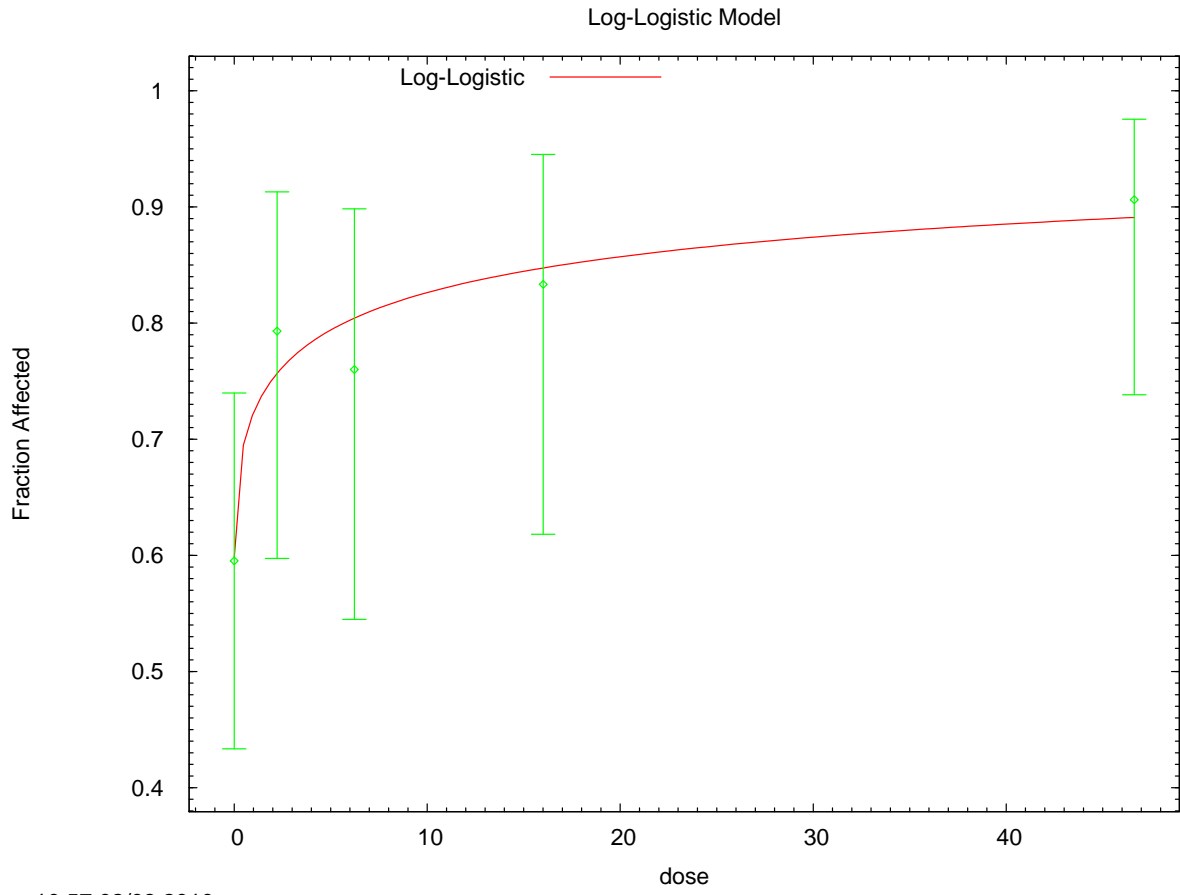
G.2.33. Murray et al. ([1979](#)): Fertility in F2 Generation

2 **G.2.33.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 p-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	0	N/A	61.729	4.481E+00	1.590E+00	
Logistic	1	0.051	61.318	2.420E+00	1.722E+00	
Log-logistic	0	N/A	61.729	4.971E+00	1.565E+00	
Multistage, 1-degree	1	0.031	63.154	1.598E+00	8.747E−01	
Multistage, 2-degree[a]	**1**	**0.079**	**60.464**	**2.733E+00**	**1.366E+00**	
Probit	1	0.048	61.544	2.250E+00	1.590E+00	
Weibull	0	N/A	61.729	5.042E+00	1.604E+00	
Log-probit, unrestricted	0	N/A	61.729	4.244E+00	1.506E+00	unrestricted (slope = 3.182)

[a] Best-fitting model, BMDS output presented in this appendix.

3
4

5 **G.2.33.2.** *Output for Selected Model: Multistage, 2-Degree*

6 Murray et al. ([1979](#)): Fertility in F2 Generation
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34

```
 ====================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\Murray_1979_fert_index_f2_Multi2_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\Murray_1979_fert_index_f2_Multi2_1.plt
                                        Wed Feb 10 16:06:28 2010
 ====================================================================

 Table 1 but expressed as number of dams who do not produce offspring
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
```

```
Degree of polynomial = 2


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                        Background =    0.0567204
                           Beta(1) =            0
                           Beta(2) =    0.0155037



           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)
                   have been estimated at a boundary point, or have been
specified by the user,
                   and do not appear in the correlation matrix )

                 Background       Beta(2)

Background               1          -0.45

   Beta(2)          -0.45              1




                                Parameter Estimates

                                                    95.0% Wald
Confidence Interval
        Variable          Estimate          Std. Err.        Lower Conf. Limit
Upper Conf. Limit
      Background         0.0780188               *                    *
*
         Beta(1)                0               *                    *
*
         Beta(2)         0.0141051               *                    *
*

* - Indicates that this value is not calculated.




                        Analysis of Deviance Table

        Model        Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model         -25.8194          3
     Fitted model        -28.2318          2        4.82474        1
0.02805
     Reduced model       -34.0009          1        16.363         2
0.0002798

          AIC:          60.4636
```

```
                           Goodness  of  Fit
                                                           Scaled
        Dose     Est._Prob.    Expected    Observed    Size    Residual
     ------------------------------------------------------------------------
       0.0000     0.0780        2.497       4.000        32      0.991
       1.1242     0.0943        1.886       0.000        20     -1.443
       5.8831     0.4341        8.683       9.000        20      0.143


   Chi^2 = 3.08      d.f. = 1        P-value = 0.0790



      Benchmark Dose Computation

   Specified effect =           0.1

   Risk Type        =      Extra risk

   Confidence level =           0.95

              BMD =        2.73307

             BMDL =        1.36619

             BMDU =        4.10938

   Taken together, (1.36619, 4.10938) is a 90     % two-sided confidence
   interval for the BMD
```

1   **G.2.33.3.** *Figure for Selected Model: Multistage, 2-Degree*

Multistage Model with 0.95 Confidence Level

16:06 02/10 2010
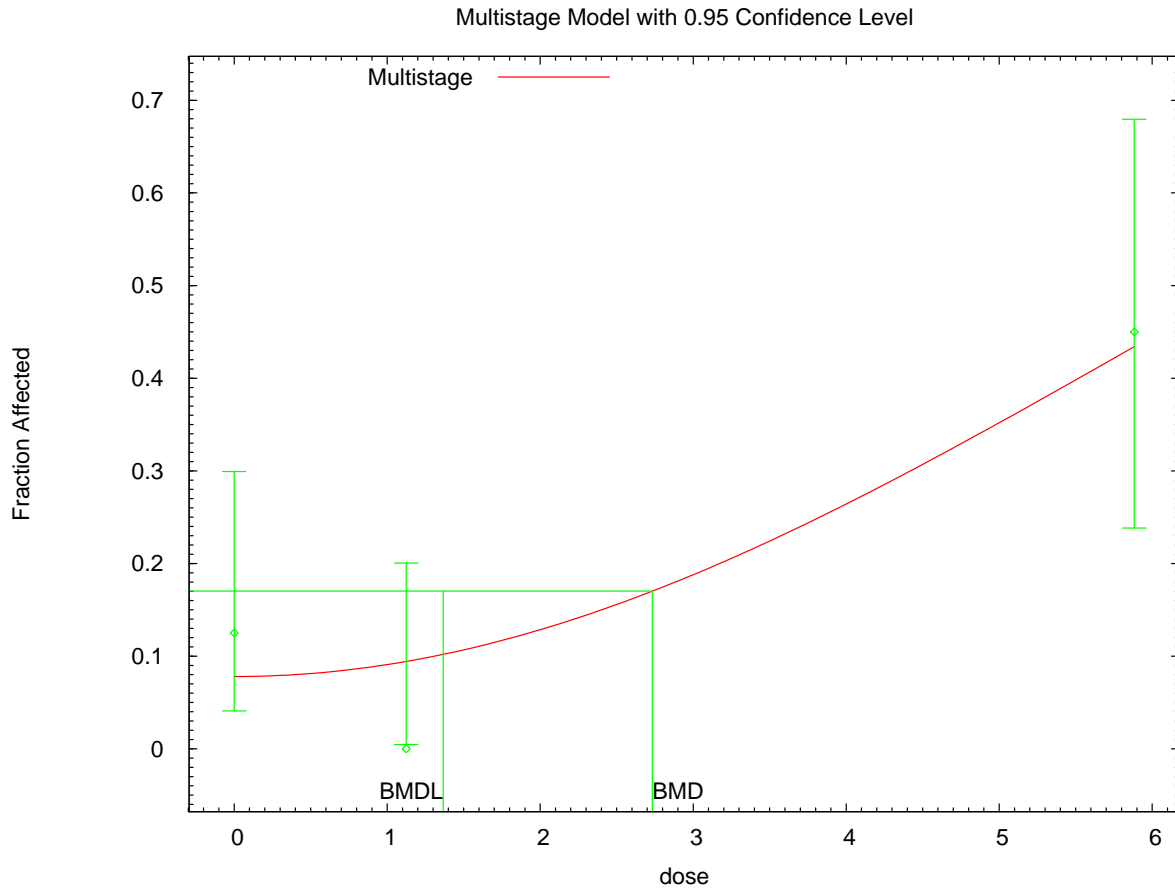
2
3
4   **G.2.34. National Toxicology Program (1982): Toxic Hepatitis, Male Mice**

5   **G.2.34.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	1	0.027	113.103	3.823E+00	2.005E+00	
Logistic	2	0.092	110.352	3.108E+00	2.465E+00	
Log-logistic	1	0.026	113.089	3.797E+00	2.141E+00	
Log-probit	1	0.027	113.111	3.565E+00	2.294E+00	
Multistage, 3-degree[a]	**1**	**0.036**	**112.045**	**2.782E+00**	**1.343E+00**	
Probit	2	0.082	110.512	2.763E+00	2.241E+00	
Weibull	1	0.025	113.044	3.967E+00	1.704E+00	

[a] Best-fitting model, BMDS output presented in this appendix.

G.2.34.2. *Output for Selected Model: Multistage, 3-Degree*

National Toxicology Program ([1982](#)): Toxic Hepatitis, Male Mice

```
    ====================================================================
           Multistage Model. (Version: 3.0;  Date: 05/16/2008)
           Input Data File: C:\1\Blood\37_NTP_1982_ToxHep_Multi3_1.(d)
           Gnuplot Plotting File:  C:\1\Blood\37_NTP_1982_ToxHep_Multi3_1.plt
                                          Mon Feb 08 10:57:32 2010
    ====================================================================

  0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008




                 Default Initial Parameter Values
                     Background =   0.0471757
                        Beta(1) =   0.00749116
                        Beta(2) =          0
                        Beta(3) =   0.00139828



         Asymptotic Correlation Matrix of Parameter Estimates

         ( *** The model parameter(s)  -Beta(2)
               have been estimated at a boundary point, or have been
specified by the user,
               and do not appear in the correlation matrix )

              Background      Beta(1)      Beta(3)

Background             1        -0.77         0.69
```

```
   Beta(1)          -0.77             1           -0.95

   Beta(3)           0.69           -0.95             1



                              Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable          Estimate         Std. Err.      Lower Conf. Limit
Upper Conf. Limit
       Background        0.0267933             *                 *
*
         Beta(1)         0.0283198             *                 *
*
         Beta(2)                0              *                 *
*
         Beta(3)         0.0012342             *                 *
*

* - Indicates that this value is not calculated.



                          Analysis of Deviance Table

        Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -51.0633          4
    Fitted model        -53.0224          3        3.91812        1
0.04777
    Reduced model       -121.743          1        141.358        3        <.0001

          AIC:          112.045



                              Goodness  of  Fit
                                                              Scaled
     Dose      Est._Prob.   Expected    Observed     Size    Residual
    -------------------------------------------------------------------
    0.0000     0.0268        1.956       1.000        73      -0.693
    0.7665     0.0482        2.363       5.000        49       1.759
    2.2711     0.1005        4.925       3.000        49      -0.915
   11.2437     0.8775       43.877      44.000        50       0.053

 Chi^2 = 4.41     d.f. = 1       P-value = 0.0357


   Benchmark Dose Computation

Specified effect =          0.1

Risk Type       =      Extra risk

Confidence level =          0.95

          BMD =        2.78201
```

```
1
2          BMDL =          1.34308
3
4          BMDU =           4.5214
5
6  Taken together, (1.34308, 4.5214 ) is a 90     % two-sided confidence
7  interval for the BMD
8
9
```

10 **G.2.34.3.** *Figure for Selected Model: Multistage, 3-Degree*

Multistage Model with 0.95 Confidence Level

10:57 02/08 2010
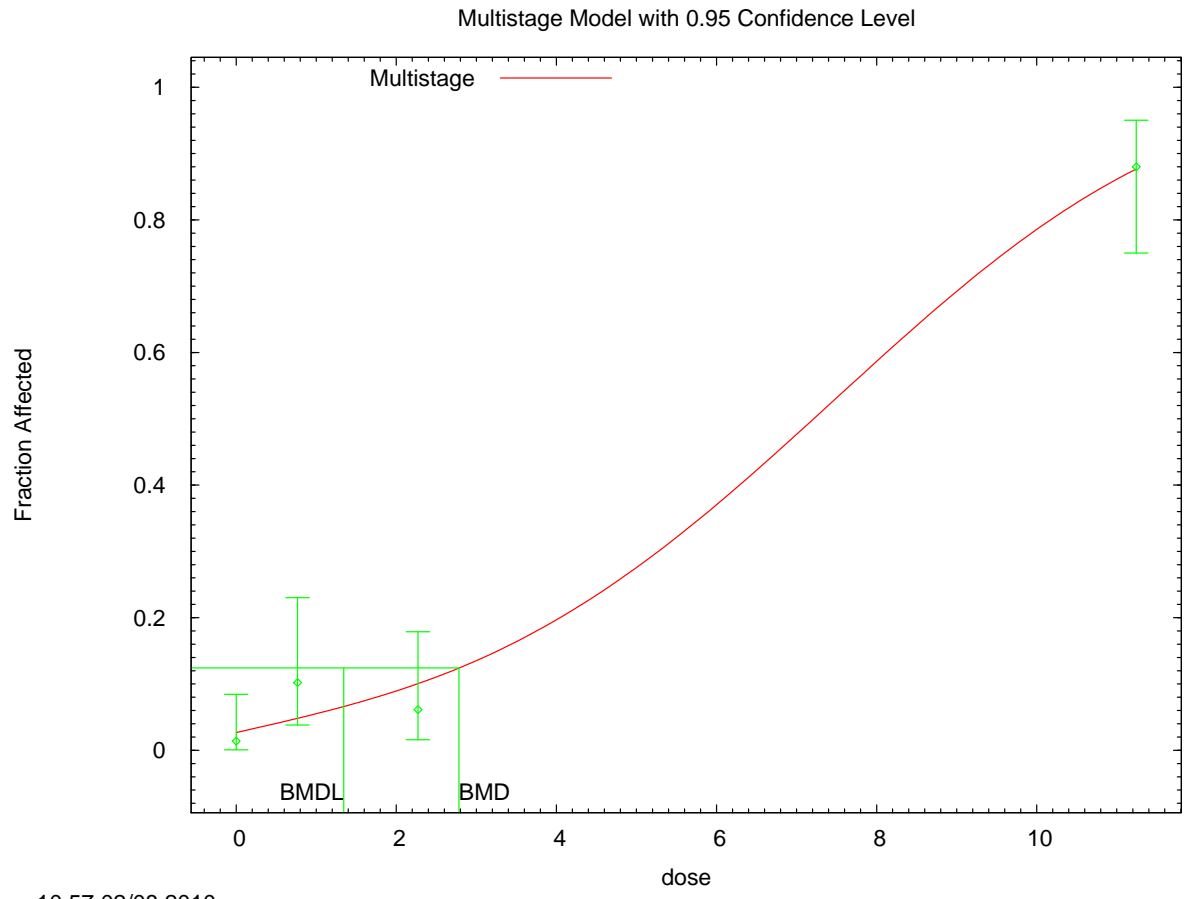
11
12
13

1 **G.2.35. National Toxicology Program ([2006](#)): Alveolar Metaplasia**

2 **G.2.35.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	4	0.010	320.093	9.886E−01	8.393E−01	power bound hit (power = 1)
Logistic	4	<0.001	343.283	2.389E+00	2.052E+00	
Log-logistic[a]	**3**	**0.723**	**312.558**	**6.497E−01**	**3.751E−01**	
Log-probit	4	0.024	318.680	1.566E+00	1.318E+00	slope bound hit (slope = 1)
Multistage, 5-degree	4	0.010	320.093	9.886E−01	8.393E−01	final ß = 0
Probit	4	<0.001	347.071	2.542E+00	2.219E+00	
Weibull	4	0.010	320.093	9.886E−01	8.393E−01	power bound hit (power = 1)
Gamma, unrestricted	3	0.426	314.011	1.642E−01	1.874E−02	unrestricted (power = 0.503)
Log-probit, unrestricted	3	0.696	312.677	6.818E−01	2.740E−01	unrestricted (slope = 0.677)
Weibull, unrestricted	3	0.522	313.492	2.644E−01	6.947E−02	unrestricted (power = 0.661)

[a] Best-fitting model, BMDS output presented in this appendix.

3
4

5 **G.2.35.2.** *Output for Selected Model: Log-Logistic*

6 National Toxicology Program ([2006](#)): Alveolar Metaplasia
7

```
9    ========================================================================
10         Logistic Model. (Version: 2.12; Date: 05/16/2008)
11         Input Data File: C:\1\Blood\40_NTP_2006_AlvMeta_LogLogistic_1.(d)
12         Gnuplot Plotting File:
13   C:\1\Blood\40_NTP_2006_AlvMeta_LogLogistic_1.plt
14                                       Mon Feb 08 10:58:58 2010
15    ========================================================================

17   0
18   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

20     The form of the probability function is:

22     P[response] = background+(1-background)/[1+EXP(-intercept-
23   slope*Log(dose))]


26     Dependent variable = DichEff
27     Independent variable = Dose
28     Slope parameter is restricted as slope >= 1

30     Total number of observations = 6
31     Total number of records with missing values = 0
32     Maximum number of iterations = 250
```

```
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


                 Default Initial Parameter Values
                       background =    0.0377358
                        intercept =    -1.69494
                            slope =    1.12282



        Asymptotic Correlation Matrix of Parameter Estimates

               background      intercept        slope

background             1          -0.21           0.1


 intercept         -0.21              1          -0.93


    slope           0.1          -0.93              1




                            Parameter Estimates


                                                   95.0% Wald
Confidence Interval
      Variable         Estimate       Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background       0.0373462            *                 *
*
      intercept        -1.70923            *                 *
*
        slope          1.13164            *                 *
*

* - Indicates that this value is not calculated.




                        Analysis of Deviance Table

     Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
    Full model       -152.615         6
   Fitted model      -153.279         3       1.32728       3
0.7227
  Reduced model      -216.802         1       128.374       5       <.0001

        AIC:         312.558




                        Goodness  of  Fit
                                                          Scaled
    Dose    Est._Prob.   Expected   Observed     Size    Residual
```

G-220   DRAFT – DO NOT CITE OR QUOTE

```
     ----------------------------------------------------------------------
      0.0000        0.0373         1.979      2.000           53       0.015
      2.5565        0.3682        19.881     19.000           54      -0.249
      5.6937        0.5807        30.776     33.000           53       0.619
      9.7882        0.7162        37.243     35.000           52      -0.690
     16.5688        0.8197        43.446     45.000           53       0.555
     29.6953        0.8976        46.674     46.000           52      -0.308

  Chi^2 = 1.33       d.f. = 3        P-value = 0.7232


     Benchmark Dose Computation

 Specified effect =             0.1

 Risk Type         =        Extra risk

 Confidence level =            0.95

           BMD =        0.64971

           BMDL =       0.375051
```

G.2.35.3. *Figure for Selected Model: Log-Logistic*

Log-Logistic Model with 0.95 Confidence Level

10:58 02/08 2010

1 **G.2.36. National Toxicology Program (2006): Eosinophilic Focus, Liver**

2 **G.2.36.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	3	0.293	331.902	3.573E+00	2.225E+00	
Logistic	4	0.405	330.400	5.949E+00	5.137E+00	
Log-logistic	3	0.152	333.515	4.139E+00	2.077E+00	
Log-probit	4	0.192	332.312	4.889E+00	3.980E+00	slope bound hit (slope = 1)
Multistage, 5-degree	3	0.752	329.328	3.393E+00	2.466E+00	
Probit[a]	**4**	**0.459**	**329.945**	**5.583E+00**	**4.864E+00**	
Weibull	3	0.324	331.628	3.770E+00	2.249E+00	
Log-probit, unrestricted	3	0.116	334.150	4.146E+00	2.152E+00	unrestricted (slope = 0.895)

[a] Best-fitting model, BMDS output presented in this appendix.

3
4

5 **G.2.36.2.** *Output for Selected Model: Probit*

6 National Toxicology Program (2006): Eosinophilic Focus, Liver
7
8
9
```
   ==========================================================================
10        Probit Model. (Version: 3.1;  Date: 05/16/2008)
11        Input Data File: C:\1\Blood\45_NTP_2006_LivEosFoc_Probit_1.(d)
12        Gnuplot Plotting File:  C:\1\Blood\45_NTP_2006_LivEosFoc_Probit_1.plt
13                                    Mon Feb 08 11:00:54 2010
14   ==========================================================================
15
16   0
17 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19    The form of the probability function is:
20
21    P[response] = CumNorm(Intercept+Slope*Dose),
22
23    where CumNorm(.) is the cumulative normal distribution function
24
25
26    Dependent variable = DichEff
27    Independent variable = Dose
28    Slope parameter is not restricted
29
30    Total number of observations = 6
31    Total number of records with missing values = 0
32    Maximum number of iterations = 250
33    Relative Function Convergence has been set to: 1e-008
34    Parameter Convergence has been set to: 1e-008
35
```

```
                   Default Initial (and Specified) Parameter Values
                      background =           0   Specified
                       intercept =     -1.28017
                           slope =    0.0712441


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -background
                    have been estimated at a boundary point, or have been
   specified by the user,
                    and do not appear in the correlation matrix )

                    intercept        slope

    intercept              1         -0.77

        slope          -0.77            1




                              Parameter Estimates

                                                      95.0% Wald
   Confidence Interval
         Variable         Estimate        Std. Err.      Lower Conf. Limit
   Upper Conf. Limit
         intercept        -1.23453         0.125132            -1.47979
   -0.989279
            slope        0.0688678        0.00823346            0.0527305
   0.085005




                              Analysis of Deviance Table

         Model        Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
         Full model        -161.07          6
       Fitted model      -162.972          2       3.80461        4
   0.4331
      Reduced model      -202.816          1      83.4925        5        <.0001

           AIC:          329.945




                              Goodness  of  Fit
                                                                  Scaled
        Dose      Est._Prob.    Expected    Observed     Size     Residual
     -------------------------------------------------------------------------
        0.0000       0.1085       5.751       3.000       53      -1.215
        2.5565       0.1449       7.826       8.000       54       0.067
        5.6937       0.1998      10.588      14.000       53       1.172
        9.7882       0.2876      15.242      17.000       53       0.533
       16.5688       0.4628      24.526      22.000       53      -0.696
       29.6953       0.7912      41.932      42.000       53       0.023
```

G-223   DRAFT – DO NOT CITE OR QUOTE

```
1
2   Chi^2 = 3.62        d.f. = 4        P-value = 0.4593
3
4
5      Benchmark Dose Computation
6
7   Specified effect =              0.1
8
9   Risk Type        =       Extra risk
10
11  Confidence level =              0.95
12
13           BMD =           5.58309
14
15          BMDL =           4.86394
16
17
```

18 **G.2.36.3.** *Figure for Selected Model: Probit*

Probit Model with 0.95 Confidence Level

11:00 02/08 2010
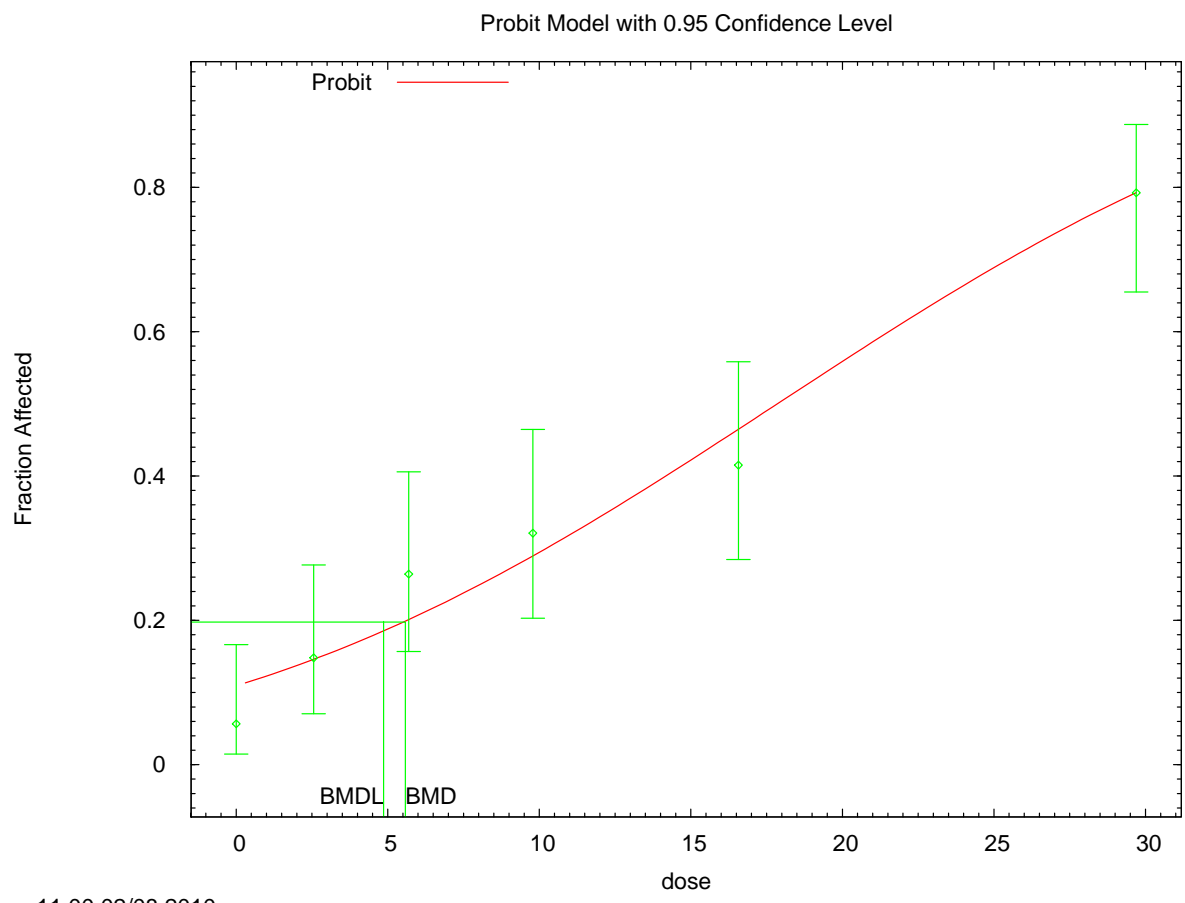
19
20
21

1   **G.2.37. National Toxicology Program (2006): Fatty Change Diffuse, Liver**

2   **G.2.37.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	4	0.659	252.348	4.028E+00	2.923E+00	
Logistic	4	0.056	262.132	5.890E+00	5.042E+00	
Log-logistic	4	0.359	254.413	4.254E+00	3.228E+00	
Log-probit	4	0.367	254.428	4.204E+00	3.277E+00	
Multistage, 5-degree	3	0.581	254.045	3.524E+00	2.234E+00	
Probit	4	0.075	260.915	5.567E+00	4.784E+00	
Weibull[a]	**4**	**0.724**	**251.989**	**3.917E+00**	**2.856E+00**	

[a] Best-fitting model, BMDS output presented in this appendix.

3

4

5   **G.2.37.2.** *Output for Selected Model: Weibull*

6   National Toxicology Program (2006): Fatty Change Diffuse, Liver

7

8

9   ```
    ==
10   Weibull Model using Weibull Model (Version: 2.12; Date: 05/16/2008)
11   Input Data File: C:\1\Blood\47_NTP_2006_LivFatDiff_Weibull_1.(d)
12   Gnuplot Plotting File:
13   C:\1\Blood\47_NTP_2006_LivFatDiff_Weibull_1.plt
14   Mon Feb 08 11:01:56 2010
15   ==

16
17   NTP_liver_fatty_change_diffuse
18   ~~~~~~
19
20   The form of the probability function is:
21
22   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]
23
24
25   Dependent variable = DichEff
26   Independent variable = Dose
27   Power parameter is restricted as power >=1
28
29   Total number of observations = 6
30   Total number of records with missing values = 0
31   Maximum number of iterations = 250
32   Relative Function Convergence has been set to: 1e-008
33   Parameter Convergence has been set to: 1e-008
34
35
36
    ```

```
                    Default Initial (and Specified) Parameter Values
                        Background =   0.00925926
                             Slope =   0.00721355
                             Power =      1.69678



              Asymptotic Correlation Matrix of Parameter Estimates


           ( *** The model parameter(s)  -Background
                   have been estimated at a boundary point, or have been
    specified by the user,
                   and do not appear in the correlation matrix )


                         Slope          Power


       Slope              1            -0.98


       Power           -0.98              1




                                Parameter Estimates


                                                      95.0% Wald
    Confidence Interval
         Variable          Estimate        Std. Err.      Lower Conf. Limit
    Upper Conf. Limit
         Background              0              NA
              Slope        0.0135075      0.00640459          0.00095478
    0.0260603
              Power        1.50444         0.168981            1.17324
    1.83564


    NA - Indicates that this parameter has hit a bound
         implied by some inequality constraint and thus
         has no standard error.




                            Analysis of Deviance Table


         Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
         Full model       -122.992          6
       Fitted model       -123.995          2       2.00444        4
    0.7349
      Reduced model       -204.846          1       163.708        5        <.0001


            AIC:         251.989




                             Goodness  of  Fit

                                                                  Scaled
        Dose      Est._Prob.    Expected    Observed     Size     Residual
      ------------------------------------------------------------------------
        0.0000      0.0000       0.000       0.000        53        0.000
        2.5565      0.0539       2.912       2.000        54       -0.550
        5.6937      0.1688       8.949      12.000        53        1.119
```

```
  9.7882      0.3415        18.102     17.000        53        -0.319
 16.5688      0.6024        31.929     30.000        53        -0.542
 29.6953      0.8913        47.238     48.000        53         0.336

 Chi^2 = 2.06      d.f. = 4        P-value = 0.7243


    Benchmark Dose Computation

Specified effect =            0.1

Risk Type       =      Extra risk

Confidence level =           0.95

           BMD =        3.91723

          BMDL =        2.85566
```

G.2.37.3. *Figure for Selected Model: Weibull*

Weibull Model with 0.95 Confidence Level

11:01 02/08 2010

G.2.38. National Toxicology Program ([2006](#)): Gingival Hyperplasia, Squamous, 2 Years

2 **G.2.38.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	4	0.036	314.985	7.743E+00	5.166E+00	power bound hit (power = 1)
Logistic	4	0.016	318.602	1.392E+01	1.056E+01	
Log-logistic[a]	**4**	**0.055**	**313.351**	**5.850E+00**	**3.730E+00**	**slope bound hit (slope = 1)**
Log-probit	4	0.005	321.426	1.535E+01	1.038E+01	slope bound hit (slope = 1)
Multistage, 5-degree	4	0.036	314.985	7.743E+00	5.166E+00	final ß = 0
Probit	4	0.018	318.240	1.318E+01	9.924E+00	
Weibull	4	0.036	314.985	7.743E+00	5.166E+00	power bound hit (power = 1)
Gamma, unrestricted	3	0.633	307.618	5.309E−01	9.859E−07	unrestricted (power = 0.282)
Log-logistic, unrestricted[b]	3	0.655	307.507	7.049E−01	1.260E−05	unrestricted (slope = 0.374)
Log-probit, unrestricted	3	0.668	307.444	8.357E−01	4.796E−05	unrestricted (slope = 0.22)
Weibull, unrestricted	3	0.644	307.562	6.143E−01	3.872E−06	unrestricted (power = 0.325)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

3
4
5 **G.2.38.2.** *Output for Selected Model: Log-Logistic*

6 National Toxicology Program ([2006](#)): Gingival Hyperplasia, Squamous, 2 Years
7
8
```
9    =====================================================================
10        Logistic Model. (Version: 2.12; Date: 05/16/2008)
11        Input Data File: C:\1\Blood\42_NTP_2006_GingHypSq_LogLogistic_1.(d)
12        Gnuplot Plotting File:
13   C:\1\Blood\42_NTP_2006_GingHypSq_LogLogistic_1.plt
14                                    Mon Feb 08 10:59:57 2010
15    =====================================================================
16
17    [insert study notes]
18   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
19
20      The form of the probability function is:
21
22      P[response] = background+(1-background)/[1+EXP(-intercept-
23   slope*Log(dose))]
24
25
26      Dependent variable = DichEff
27      Independent variable = Dose
28      Slope parameter is restricted as slope >= 1
29
```

```
Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


                   Default Initial Parameter Values
                       background =    0.0188679
                        intercept =     -3.75308
                            slope =           1



          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                background    intercept

background             1        -0.79

 intercept          -0.79            1




                             Parameter Estimates

                                                 95.0% Wald
Confidence Interval
      Variable        Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
      background       0.0671812           *                   *
*
       intercept       -3.96371           *                   *
*
          slope              1            *                   *
*

* - Indicates that this value is not calculated.




                        Analysis of Deviance Table

       Model        Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -149.95          6
     Fitted model      -154.675          2       9.45085       4
0.05077
     Reduced model     -162.631          1       25.3627       5
0.0001186
```

```
          AIC:          313.351


                     Goodness  of  Fit
                                                   Scaled
     Dose      Est._Prob.    Expected    Observed      Size    Residual
   ------------------------------------------------------------------------
    0.0000     0.0672       3.561       1.000         53      -1.405
    2.5565     0.1104       5.960       7.000         54       0.452
    5.6937     0.1582       8.385      14.000         53       2.113
    9.7882     0.2134      11.311      13.000         53       0.566
   16.5688     0.2905      15.394      15.000         53      -0.119
   29.6953     0.4036      21.389      16.000         53      -1.509

 Chi^2 = 9.26     d.f. = 4      P-value = 0.0550


   Benchmark Dose Computation

Specified effect =          0.1

Risk Type         =      Extra risk

Confidence level =          0.95

           BMD =       5.85026

           BMDL =       3.7296
```

1 **G.2.38.3.** *Figure for Selected Model: Log-Logistic*

Log-Logistic Model with 0.95 Confidence Level

10:59 02/08 2010

2
3
4 **G.2.38.4.** *Output for Additional Model Presented: Log-Logistic, Unrestricted*

5 National Toxicology Program ([2006](#)): Gingival Hyperplasia, Squamous, 2 Years

6
7
```
8  ====================================================================
9         Logistic Model. (Version: 2.12; Date: 05/16/2008)
10        Input Data File: C:\1\Blood\42_NTP_2006_GingHypSq_LogLogistic_U_1.(d)
11        Gnuplot Plotting File:
12 C:\1\Blood\42_NTP_2006_GingHypSq_LogLogistic_U_1.plt
13                                        Mon Feb 08 10:59:57 2010
14 ====================================================================
15
16 [insert study notes]
17 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19   The form of the probability function is:
20
21   P[response] = background+(1-background)/[1+EXP(-intercept-
22 slope*Log(dose))]
23
24
```

```
Dependent variable = DichEff
Independent variable = Dose
Slope parameter is not restricted
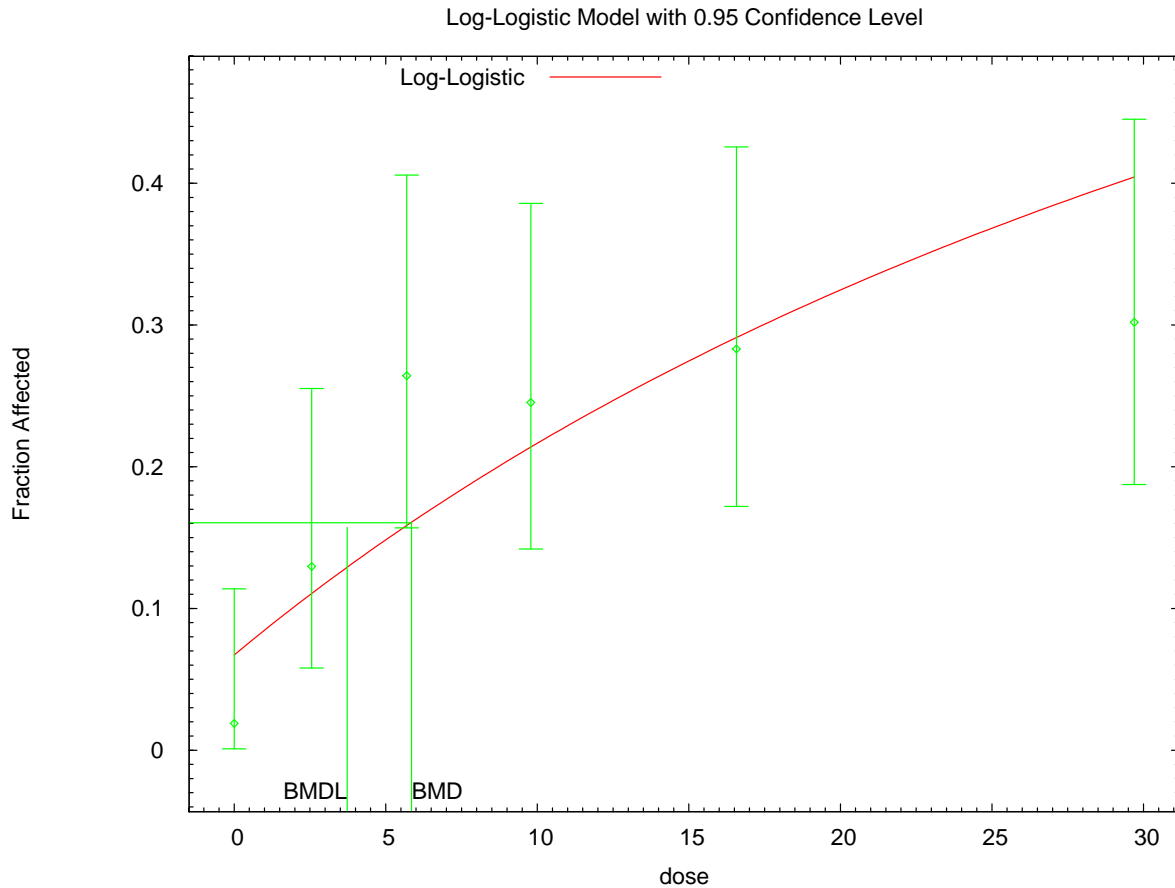
Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =    0.0188679
                      intercept =         -2.2
                          slope =     0.424326


          Asymptotic Correlation Matrix of Parameter Estimates

                 background      intercept          slope

background              1          -0.27           0.11

 intercept          -0.27              1          -0.93

    slope            0.11          -0.93              1




                            Parameter Estimates

                                                   95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
     background        0.0185138              *                  *
*
       intercept        -2.06653              *                  *
*
          slope        0.373721              *                  *
*

* - Indicates that this value is not calculated.




                         Analysis of Deviance Table

     Model        Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
    Full model         -149.95           6
   Fitted model        -150.753          3       1.60697      3
0.6578
```

```
Reduced model        -162.631           1        25.3627        5
0.0001186

          AIC:           307.507


                         Goodness   of   Fit
                                                          Scaled
     Dose      Est._Prob.    Expected    Observed    Size    Residual
     -----------------------------------------------------------------
     0.0000     0.0185        0.981       1.000        53      0.019
     2.5565     0.1681        9.078       7.000        54     -0.756
     5.6937     0.2101       11.136      14.000        53      0.966
     9.7882     0.2433       12.893      13.000        53      0.034
    16.5688     0.2792       14.795      15.000        53      0.063
    29.6953     0.3230       17.117      16.000        53     -0.328

 Chi^2 = 1.62     d.f. = 3       P-value = 0.6554


    Benchmark Dose Computation

Specified effect =          0.1

Risk Type       =      Extra risk

Confidence level =          0.95

          BMD =      0.704898
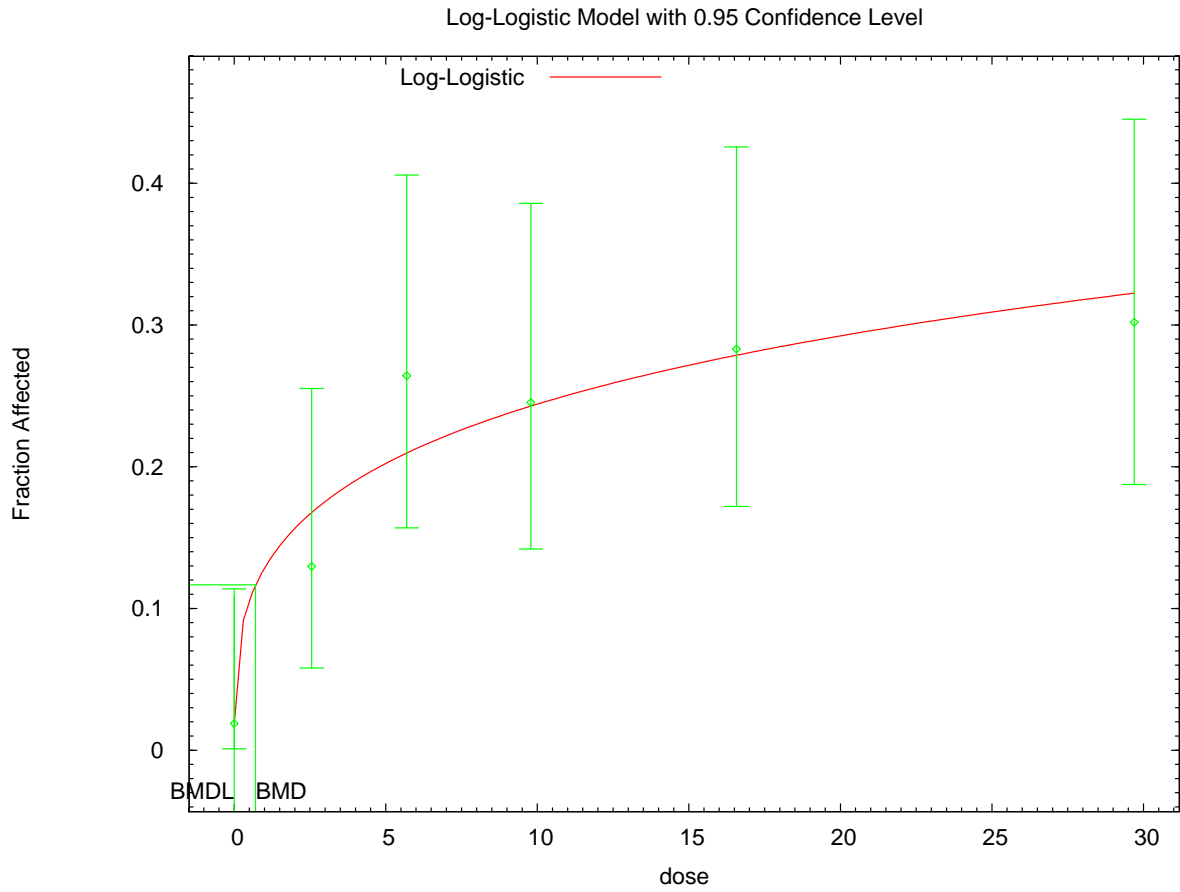
          BMDL =   1.26034e-005
```

1   **G.2.38.5.** *Figure for Additional Model Presented: Log-Logistic, Unrestricted*

Log-Logistic Model with 0.95 Confidence Level

10:59 02/08 2010

2
3
4

G.2.39. National Toxicology Program ([2006](#)): Hepatocyte Hypertrophy, 2 Years

G.2.39.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	5	0.034	273.875	9.091E−01	7.868E−01	power bound hit (power = 1)
Logistic	4	<0.001	297.895	2.475E+00	2.122E+00	
Log-logistic	4	0.006	279.210	1.137E+00	6.491E−01	
Log-probit	5	0.006	277.800	1.530E+00	1.321E+00	
Multistage, 5-degree[a]	**4**	**0.018**	**275.693**	**9.272E−01**	**7.906E−01**	
Probit	4	<0.001	299.731	2.453E+00	2.137E+00	
Weibull	5	0.034	273.875	9.091E−01	7.868E−01	power bound hit (power = 1)
Gamma, unrestricted	4	0.027	275.270	error	error	unrestricted (power = 0.844)
Log-probit, unrestricted	4	0.008	278.360	1.191E+00	7.038E−01	unrestricted (slope = 0.864)
Weibull, unrestricted	4	0.024	275.439	7.345E−01	3.588E−01	unrestricted (power = 0.92)

[a] Best-fitting model, BMDS output presented in this appendix.

G.2.39.2. *Output for Selected Model: Multistage, 5-Degree*

National Toxicology Program ([2006](#)): Hepatocyte Hypertrophy, 2 Years

```
=====================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\43_NTP_2006_HepHyper_Multi5_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\43_NTP_2006_HepHyper_Multi5_1.plt
                                    Mon Feb 08 11:00:25 2010
=====================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
              -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-
beta5*dose^5)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
```

```
Total number of parameters in model = 6
Total number of specified parameters = 0
Degree of polynomial = 5


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                       Background =     0.112745
                          Beta(1) =    0.0950808
                          Beta(2) =            0
                          Beta(3) =            0
                          Beta(4) =            0
                          Beta(5) = 4.39515e-008


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)    -Beta(3)
    -Beta(4)
                    have been estimated at a boundary point, or have been
    specified by the user,
                    and do not appear in the correlation matrix )

                   Beta(1)        Beta(5)

      Beta(1)            1            -0.5

      Beta(5)         -0.5               1




                                Parameter Estimates

                                                      95.0% Wald
    Confidence Interval
          Variable        Estimate        Std. Err.    Lower Conf. Limit
    Upper Conf. Limit
         Background               0            *                   *
    *
           Beta(1)        0.113632            *                   *
    *
           Beta(2)               0            *                   *
    *
           Beta(3)               0            *                   *
    *
           Beta(4)               0            *                   *
    *
           Beta(5)    1.71322e-008            *                   *
    *

    * - Indicates that this value is not calculated.
```

```
                       Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.  P-value
        Full model      -129.986         6
      Fitted model      -135.847         2       11.7216       4
0.01955
     Reduced model      -219.97          1       179.968       5        <.0001

            AIC:         275.693


                             Goodness  of  Fit
                                                              Scaled
        Dose      Est._Prob.    Expected    Observed    Size   Residual
      ----------------------------------------------------------------------
        0.0000      0.0000        0.000       0.000       53     0.000
        2.5565      0.2521       13.614      19.000       54     1.688
        5.6937      0.4764       25.251      19.000       53    -1.719
        9.7882      0.6717       35.599      42.000       53     1.872
       16.5688      0.8510       45.106      41.000       53    -1.584
       29.6953      0.9769       51.778      52.000       53     0.203

 Chi^2 = 11.86     d.f. = 4       P-value = 0.0184


     Benchmark Dose Computation

Specified effect =          0.1

Risk Type        =     Extra risk

Confidence level =          0.95

           BMD =        0.92721

          BMDL =        0.790637

          BMDU =        1.14523

Taken together, (0.790637, 1.14523) is a 90     % two-sided confidence
interval for the BMD
```

1 **G.2.39.3.** *Figure for Selected Model: Multistage, 5-Degree*

Multistage Model with 0.95 Confidence Level

11:00 02/08 2010

2
3

1

1   **G.2.40. National Toxicology Program (2006): Necrosis, Liver**

2   **G.2.40.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	4	0.939	234.400	8.655E+00	6.340E+00	power bound hit (power = 1)
Logistic	4	0.601	236.742	1.484E+01	1.240E+01	
Log-logistic	4	0.943	234.382	7.928E+00	5.605E+00	slope bound hit (slope = 1)
Log-probit	4	0.572	236.863	1.333E+01	1.024E+01	slope bound hit (slope = 1)
Multistage, 5-degree	4	0.939	234.400	8.655E+00	6.340E+00	final ß = 0
Probit	4	0.666	236.293	1.393E+01	1.154E+01	
Weibull	4	0.939	234.400	8.655E+00	6.340E+00	power bound hit (power = 1)
Gamma, unrestricted	3	0.883	236.290	7.726E+00	3.453E+00	unrestricted (power = 0.87)
Log-logistic, unrestricted	3	0.860	236.377	7.733E+00	3.536E+00	unrestricted (slope = 0.974)
Log-probit, unrestricted[a]	**3**	**0.805**	**236.598**	**7.501E+00**	**3.504E+00**	**unrestricted (slope = 0.517)**
Weibull, unrestricted	3	0.879	236.302	7.763E+00	3.508E+00	unrestricted (power = 0.895)

[a] Best-fitting model, BMDS output presented in this appendix.

3
4

5   **G.2.40.2.** *Output for Selected Model: Log-Probit, Unrestricted*

6   National Toxicology Program (2006): Necrosis, Liver
7

```
8      ========================================================================
9             Probit Model. (Version: 3.1;  Date: 05/16/2008)
10            Input Data File: C:\1\Blood\50_NTP_2006_LivNec_LogProbit_U_1.(d)
11            Gnuplot Plotting File:
12     C:\1\Blood\50_NTP_2006_LivNec_LogProbit_U_1.plt
13                                         Mon Feb 08 11:29:30 2010
14     ========================================================================
15
16      NTP_liver_necrosis
17     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19        The form of the probability function is:
20
21        P[response] = Background
22                    + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
23
24        where CumNorm(.) is the cumulative normal distribution function
25
26
27        Dependent variable = DichEff
28        Independent variable = Dose
29        Slope parameter is not restricted
30
```

```
Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


                 Default Initial (and Specified) Parameter Values
                       background =    0.0188679
                        intercept =     -2.16223
                            slope =     0.457376



           Asymptotic Correlation Matrix of Parameter Estimates

                    background     intercept        slope

background                  1         -0.65         0.55


 intercept             -0.65             1         -0.97


    slope               0.55         -0.97             1




                                   Parameter Estimates


                                                            95.0% Wald
Confidence Interval
      Variable         Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
    background        0.0221151        0.0221351         -0.0212689
0.065499
      intercept        -2.32352         0.556343           -3.41393
-1.23311
        slope         0.517104         0.185064           0.154385
0.879823




                        Analysis of Deviance Table

     Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
   Full model       -114.813          6
  Fitted model      -115.299          3      0.972184       3
0.808
 Reduced model      -127.98           1       26.3331        5        <.0001

        AIC:         236.598



                        Goodness   of   Fit
                                                        Scaled
```

```
     Dose       Est._Prob.      Expected      Observed      Size        Residual
   ------------------------------------------------------------------------------
     0.0000       0.0221          1.172         1.000          53         -0.161
     2.5565       0.0544          2.938         4.000          54          0.637
     5.6937       0.0976          5.174         4.000          53         -0.543
     9.7882       0.1457          7.720         8.000          53          0.109
    16.5688       0.2096         11.106        10.000          53         -0.373
    29.6953       0.3002         15.908        17.000          53          0.327


 Chi^2 = 0.99       d.f. = 3          P-value = 0.8048



   Benchmark Dose Computation

 Specified effect =          0.1

 Risk Type       =      Extra risk

 Confidence level =          0.95

          BMD =        7.50077

          BMDL =        3.5039
```

G.2.40.3. *Figure for Selected Model: Log-Probit, Unrestricted*

LogProbit Model with 0.95 Confidence Level

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G.2.41. National Toxicology Program ([2006](#)): Oval Cell Hyperplasia

2 **G.2.41.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	3	0.074	199.468	6.739E+00	5.074E+00	
Logistic	4	0.171	196.803	6.064E+00	5.145E+00	
Log-logistic	3	0.042	201.659	6.936E+00	5.604E+00	
Log-probit	3	0.072	200.121	7.090E+00	5.931E+00	
Multistage, 5-degree	3	0.207	195.962	4.785E+00	3.105E+00	
Probit[a]	**4**	**0.227**	**195.448**	**5.673E+00**	**4.793E+00**	
Weibull[b]	3	0.077	198.375	5.718E+00	4.088E+00	

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

3
4

5 **G.2.41.2.** *Output for Selected Model: Probit*

6 National Toxicology Program ([2006](#)): Oval Cell Hyperplasia
7

```
8
9    ========================================================================
10         Probit Model. (Version: 3.1;  Date: 05/16/2008)
11         Input Data File: C:\1\Blood\53_NTP_2006_OvalHyper_Probit_1.(d)
12         Gnuplot Plotting File:  C:\1\Blood\53_NTP_2006_OvalHyper_Probit_1.plt
13                                        Mon Feb 08 13:25:23 2010
14    ========================================================================
15
16    0
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the probability function is:
20
21     P[response] = CumNorm(Intercept+Slope*Dose),
22
23     where CumNorm(.) is the cumulative normal distribution function
24
25
26     Dependent variable = DichEff
27     Independent variable = Dose
28     Slope parameter is not restricted
29
30     Total number of observations = 6
31     Total number of records with missing values = 0
32     Maximum number of iterations = 250
33     Relative Function Convergence has been set to: 1e-008
34     Parameter Convergence has been set to: 1e-008
35
```

```
                  Default Initial (and Specified) Parameter Values
                        background =            0   Specified
                         intercept =     -2.29925
                             slope =      0.169545


              Asymptotic Correlation Matrix of Parameter Estimates

              ( *** The model parameter(s)  -background
                      have been estimated at a boundary point, or have been
      specified by the user,
                      and do not appear in the correlation matrix )


                    intercept          slope

       intercept            1          -0.87

          slope         -0.87              1




                                  Parameter Estimates


                                                        95.0% Wald
      Confidence Interval
           Variable         Estimate        Std. Err.     Lower Conf. Limit
      Upper Conf. Limit
           intercept        -2.18988        0.208021            -2.5976
      -1.78217
              slope          0.172453        0.0182446           0.136694
      0.208211




                              Analysis of Deviance Table

           Model        Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
          Full model        -92.4898          6
        Fitted model        -95.7242          2        6.46873        4
      0.1668
        Reduced model       -210.191          1        235.402        5       <.0001

             AIC:           195.448



                                  Goodness  of  Fit
                                                                      Scaled
          Dose      Est._Prob.    Expected     Observed      Size     Residual
        ------------------------------------------------------------------------
          0.0000      0.0143        0.756       0.000         53       -0.876
          2.5565      0.0401        2.168       4.000         54        1.270
          5.6937      0.1135        6.017       3.000         53       -1.306
          9.7882      0.3079       16.317      20.000         53        1.096
         16.5688      0.7478       39.631      38.000         53       -0.516
         29.6953      0.9983       52.911      53.000         53        0.299
```

```
1
2    Chi^2 = 5.64       d.f. = 4        P-value = 0.2274
3
4
5       Benchmark Dose Computation
6
7    Specified effect =            0.1
8
9    Risk Type        =       Extra risk
10
11   Confidence level =            0.95
12
13             BMD =        5.67298
14
15            BMDL =        4.79341
16
17
```

18 **G.2.41.3.** *Figure for Selected Model: Probit*

Probit Model with 0.95 Confidence Level

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19
20

G.2.41.4. *Output for Additional Model Presented: Weibull*

National Toxicology Program (2006): Oval Cell Hyperplasia

```
 ====================================================================
        Weibull Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\53_NTP_2006_OvalHyper_Weibull_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\53_NTP_2006_OvalHyper_Weibull_1.plt
                                        Mon Feb 08 13:25:23 2010
 ====================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]


   Dependent variable = DichEff
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




                  Default Initial (and Specified) Parameter Values
                     Background =   0.00925926
                          Slope =   0.00296825
                          Power =      2.17092


         Asymptotic Correlation Matrix of Parameter Estimates

               Background        Slope         Power

Background             1        -0.72           0.7

    Slope         -0.72            1          -0.99

    Power           0.7        -0.99             1




                            Parameter Estimates

                                           95.0% Wald
Confidence Interval
      Variable         Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
```

```
        Background        0.0164137         0.0221488           -0.0269971
0.0598245
           Slope         0.00162074        0.00202897         -0.00235596
0.00559745
           Power          2.39427           0.455116            1.50226
3.28628



                      Analysis of Deviance Table

       Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -92.4898          6
    Fitted model       -96.1875          3        7.3953       3
0.06031
   Reduced model       -210.191          1        235.402      5         <.0001

          AIC:          198.375


                          Goodness  of  Fit
                                                              Scaled
     Dose     Est._Prob.     Expected     Observed     Size    Residual
    ------------------------------------------------------------------------
    0.0000      0.0164         0.870        0.000        53      -0.940
    2.5565      0.0314         1.695        4.000        54       1.799
    5.6937      0.1138         6.034        3.000        53      -1.312
    9.7882      0.3285        17.411       20.000        53       0.757
   16.5688      0.7440        39.431       38.000        53      -0.450
   29.6953      0.9957        52.774       53.000        53       0.476

 Chi^2 = 6.85      d.f. = 3        P-value = 0.0770


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =       Extra risk

Confidence level =           0.95

           BMD =        5.71754

           BMDL =       4.08823
```

1   **G.2.41.5.** *Figure for Additional Model Presented: Weibull*

Weibull Model with 0.95 Confidence Level

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2
3
4   **G.2.42. National Toxicology Program (2006): Pigmentation, Liver**

5   **G.2.42.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	3	0.552	196.971	2.172E+00	1.493E+00	
Logistic	4	0.247	197.066	1.853E+00	1.521E+00	
Log-logistic	3	0.984	195.530	2.566E+00	1.937E+00	
Log-probit[a]	**3**	**0.962**	**195.526**	**2.463E+00**	**1.890E+00**	
Multistage, 5-degree	3	0.058	199.955	1.822E+00	9.916E−01	final ß = 0
Probit	4	0.004	200.504	1.710E+00	1.430E+00	
Weibull	3	0.219	199.007	1.756E+00	1.190E+00	

[a] Best-fitting model, BMDS output presented in this appendix.

G.2.42.2. *Output for Selected Model: Log-Probit*

National Toxicology Program (2006): Pigmentation, Liver

```
   ====================================================================
          Probit Model. (Version: 3.1;  Date: 05/16/2008)
          Input Data File: C:\1\Blood\54_NTP_2006_Pigment_LogProbit_1.(d)
          Gnuplot Plotting File:
   C:\1\Blood\54_NTP_2006_Pigment_LogProbit_1.plt
                                         Mon Feb 08 13:25:55 2010
   ====================================================================
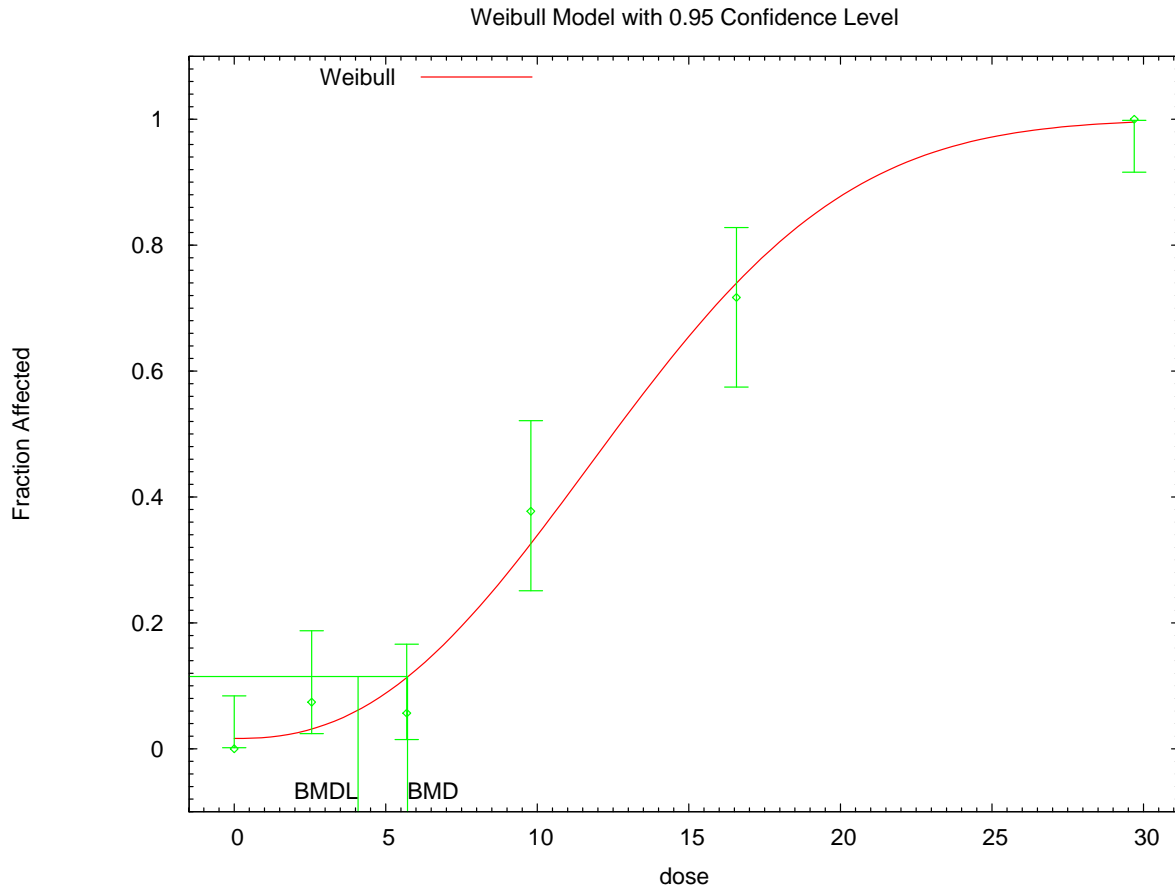
 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = Background
                 + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                   Default Initial (and Specified) Parameter Values
                       background =    0.0754717
                        intercept =     -2.48683
                            slope =      1.53221


           Asymptotic Correlation Matrix of Parameter Estimates

               background      intercept         slope

background             1          -0.42           0.33

 intercept         -0.42              1          -0.96

    slope          0.33          -0.96              1
```

```
                        Parameter Estimates

                                                   95.0% Wald
Confidence Interval
      Variable        Estimate       Std. Err.      Lower Conf. Limit
Upper Conf. Limit
      background      0.0725473       0.0338856          0.00613263
0.138962
      intercept       -2.93268        0.487158            -3.8875
-1.97787
         slope         1.83184        0.246868             1.34798
2.31569




                     Analysis of Deviance Table

      Model      Log(likelihood)  # Param's  Deviance  Test d.f.  P-value
    Full model      -94.6177           6
   Fitted model     -94.7632           3       0.291072       3
0.9617
   Reduced model    -210.717           1       232.198        5        <.0001

         AIC:         195.526



                        Goodness  of  Fit
                                                          Scaled
     Dose      Est._Prob.    Expected    Observed    Size    Residual
   ------------------------------------------------------------------
     0.0000      0.0725       3.845       4.000       53      0.082
     2.5565      0.1769       9.553       9.000       54     -0.197
     5.6937      0.6291      33.342      34.000       53      0.187
     9.7882      0.9013      47.771      48.000       53      0.105
    16.5688      0.9874      52.334      52.000       53     -0.412
    29.6953      0.9995      52.974      53.000       53      0.160

 Chi^2 = 0.29      d.f. = 3      P-value = 0.9624


   Benchmark Dose Computation

Specified effect =          0.1

Risk Type        =      Extra risk

Confidence level =          0.95

         BMD =        2.46293

         BMDL =       1.88981
```

1   **G.2.42.3.** *Figure for Selected Model: Log-Probit*

LogProbit Model with 0.95 Confidence Level

13:25 02/08 2010

2
3
4   **G.2.43. National Toxicology Program ([2006](#)): Toxic Hepatopathy**

5   **G.2.43.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	4	0.754	185.763	4.302E+00	3.463E+00	
Logistic	4	0.159	191.136	4.833E+00	4.068E+00	
Log-logistic	3	0.391	189.577	4.697E+00	3.818E+00	
Log-probit	3	0.394	189.580	4.972E+00	3.780E+00	
Multistage, 5-degree[a]	**4**	**0.693**	**185.924**	**3.980E+00**	**3.059E+00**	**final ß = 0**
Probit	4	0.231	189.820	4.621E+00	3.860E+00	
Weibull	4	0.716	185.785	4.089E+00	3.215E+00	

[a] Best-fitting model, BMDS output presented in this appendix.

G.2.43.2. *Output for Selected Model: Multistage, 5-Degree*

National Toxicology Program (2006): Toxic Hepatopathy

```
====================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\1\Blood\55_NTP_2006_ToxHepa_Multi5_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\55_NTP_2006_ToxHepa_Multi5_1.plt
                                        Mon Feb 08 13:26:28 2010
====================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-
beta5*dose^5)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 6
 Total number of specified parameters = 0
 Degree of polynomial = 5


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008




                  Default Initial Parameter Values
                      Background =            0
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) =            0
                        Beta(4) =            0
                        Beta(5) = 4.36963e+012



           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(4)
-Beta(5)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )
```

```
                    Beta(2)        Beta(3)


     Beta(2)              1          -0.95


     Beta(3)          -0.95              1




                              Parameter Estimates


                                              95.0% Wald
Confidence Interval
         Variable          Estimate         Std. Err.      Lower Conf. Limit
Upper Conf. Limit
     Background                  0              *                 *
*
         Beta(1)                 0              *                 *
*
         Beta(2)        0.00639021             *                 *
*
         Beta(3)        6.5404e-005            *                 *
*
         Beta(4)                 0              *                 *
*
         Beta(5)                 0              *                 *
*


* - Indicates that this value is not calculated.




                         Analysis of Deviance Table


        Model       Log(likelihood)  # Param's  Deviance  Test d.f.  P-value
      Full model        -89.8076         6
     Fitted model       -90.9619         2       2.30853      4
0.6792
    Reduced model       -218.207         1       256.799      5        <.0001


          AIC:           185.924




                              Goodness  of  Fit
                                                                Scaled
      Dose      Est._Prob.     Expected     Observed     Size     Residual
     ------------------------------------------------------------------------
      0.0000     0.0000         0.000        0.000        53       0.000
      2.5565     0.0420         2.265        2.000        54      -0.180
      5.6937     0.1969        10.434        8.000        53      -0.841
      9.7882     0.4901        25.976       30.000        53       1.106
     16.5688     0.8715        46.189       45.000        53      -0.488
     29.6953     0.9994        52.966       53.000        53       0.185


  Chi^2 = 2.23     d.f. = 4       P-value = 0.6928



   Benchmark Dose Computation
```

```
Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

          BMD =        3.98025

          BMDL =       3.05855

          BMDU =       4.89735

Taken together, (3.05855, 4.89735) is a 90    % two-sided confidence
interval for the BMD
```

G.2.43.3. *Figure for Selected Model: Multistage, 5-Degree*

Multistage Model with 0.95 Confidence Level

13:26 02/08 2010

G.2.44. Ohsako et al. (2001): Ano-Genital Length, PND 120

G.2.44.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	3	0.027	171.073	2.592E+01	1.750E+01	
Exponential (M3)	3	0.027	171.073	2.592E+01	1.750E+01	power hit bound (*d* = 1)
Exponential (M4)	2	0.106	168.392	2.248E+00	8.445E−01	
Exponential (M5)	1	0.049	169.789	2.193E+00	9.382E−01	
Hill[b]	**2**	**0.154**	**167.647**	**2.879E+00**	**8.028E−01**	***n* lower bound hit (*n* = 1)**
Linear	3	0.025	171.258	2.700E+01	1.881E+01	
Polynomial, 4-degree	3	0.025	171.258	2.700E+01	1.881E+01	
Power	3	0.025	171.258	2.700E+01	1.881E+01	power bound hit (power = 1)
Hill, unrestricted[c]	1	0.056	169.555	3.494E+00	3.046E−01	unrestricted (*n* = 0.591)
Power, unrestricted	2	0.153	167.654	4.151E+00	2.395E−01	unrestricted (power = 0.291)

[a] Constant variance model selected (*p* = 0.165).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.44.2. *Output for Selected Model: Hill*

Ohsako et al. (2001): Ano-Genital Length, PND 120


```
   ====================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\Blood\56_Ohsako_2001_Anogen_HillCV_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\56_Ohsako_2001_Anogen_HillCV_1.plt
                                 Mon Feb 08 13:27:02 2010
   ====================================================================

 Figure 7
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 5
```

```
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                        Default Initial Parameter Values
                             alpha =      7.27386
                               rho =            0   Specified
                         intercept =       28.905
                                 v =      -5.1065
                                 n =      1.57046
                                 k =       2.4317



           Asymptotic Correlation Matrix of Parameter Estimates


            ( *** The model parameter(s)  -rho    -n
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                      alpha     intercept             v             k

      alpha             1     4.4e-008     -9.8e-008      7.2e-008

  intercept      4.4e-008            1         -0.57         -0.52

          v     -9.8e-008        -0.57             1         -0.23

          k      7.2e-008        -0.52         -0.23             1




                            Parameter Estimates


                                                      95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          7.07394          1.36138               4.40568
9.7422
       intercept         28.9732          0.74996               27.5034
30.4431
              v         -5.02686          1.05086              -7.08651
-2.9672
              n                1               NA
              k          2.56203          2.11462              -1.58255
6.70661


NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

```
     Table of Data and Estimated Values of Interest

 Dose      N     Obs Mean     Est Mean    Obs Std Dev   Est Std Dev   Scaled
Res.
------    ---   --------     --------    -----------   -----------   ---------
-

    0     12      28.9          29         3.13          2.66        -0.0889
 1.04     10      27.9         27.5         2.5          2.66         0.495
 3.471    10      25.2         26.1        3.21          2.66        -1.09
11.36     10       26          24.9        2.85          2.66         1.35
38.42     12      23.8         24.3        1.56          2.66        -0.602




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                  Likelihoods of Interest

          Model      Log(likelihood)   # Param's      AIC
           A1         -77.952340           6        167.904680
           A2         -74.703868          10        169.407736
           A3         -77.952340           6        167.904680
         fitted       -79.823277           4        167.646555
           R          -89.824703           2        183.649405


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                  Tests of Interest

   Test    -2*log(Likelihood Ratio)   Test df       p-value

   Test 1            30.2417             8         0.0001916
```

```
Test 2                6.49694        4            0.165
Test 3                6.49694        4            0.165
Test 4                3.74187        2            0.154


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =            1

Risk Type        =      Estimated standard deviations from the control mean

Confidence level =        0.95

         BMD =       2.87863

         BMDL =      0.802782
```

1   **G.2.44.3.** *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

13:27 02/08 2010

2
3
4   **G.2.44.4.** *Output for Additional Model Presented: Hill, Unrestricted*

5   Ohsako et al. (2001): Ano-Genital Length, PND 120

6
7
8   ```
     ==
9   Hill Model. (Version: 2.14; Date: 06/26/2008)
10   Input Data File: C:\1\Blood\56_Ohsako_2001_Anogen_HillCV_U_1.(d)
11   Gnuplot Plotting File:
12   C:\1\Blood\56_Ohsako_2001_Anogen_HillCV_U_1.plt
13   Mon Feb 08 13:27:04 2010
14   ==
15
16   Figure 7
17   ~~~~~~
18
19   The form of the response function is:
20
21   Y[dose] = intercept + v*dose^n/(k^n + dose^n)
22
23   ```

```
Dependent variable = Mean
Independent variable = Dose
rho is set to 0
Power parameter is not restricted
A constant variance model is fit

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                     Default Initial Parameter Values
                            alpha =       7.27386
                              rho =             0   Specified
                        intercept =        28.905
                                v =       -5.1065
                                n =       1.57046
                                k =        2.4317



          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha    intercept          v            n            k

     alpha            1    -3.1e-008    7.5e-009    1.7e-008    -8.8e-009

 intercept    -3.1e-008            1        0.001       0.0016        -0.13

         v     7.5e-009        0.001            1         0.98        -0.99

         n     1.7e-008       0.0016         0.98            1        -0.97

         k    -8.8e-009        -0.13        -0.99        -0.97            1




                             Parameter Estimates


                                                     95.0% Wald
Confidence Interval
     Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
        alpha          7.06192         1.35907              4.3982
9.72564
    intercept          28.9618        0.754441             27.4831
30.4404
            v         -6.82284         11.1104             -28.5989
14.9532
```

```
        n        0.591421         1.04        -1.44695
2.62979
        k        7.47064         48.002       -86.6115
101.553



    Table of Data and Estimated Values of Interest

 Dose      N    Obs Mean    Est Mean   Obs Std Dev  Est Std Dev  Scaled
Res.
 ------    ---  --------    --------   -----------  -----------  ---------
-

    0     12     28.9        29          3.13         2.66        -0.074
 1.04    10     27.9        27.3         2.5          2.66         0.71
3.471    10     25.2        26.3         3.21         2.66        -1.36
11.36    10      26         25.1         2.85         2.66         1.04
38.42    12     23.8        24           1.56         2.66        -0.284




 Model Descriptions for likelihoods calculated


 Model A1:      Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2

 Model A2:      Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma(i)^2

 Model A3:      Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:      Yi = Mu + e(i)
         Var{e(i)} = Sigma^2


                  Likelihoods of Interest

          Model      Log(likelihood)   # Param's      AIC
           A1         -77.952340           6       167.904680
           A2         -74.703868          10       169.407736
           A3         -77.952340           6       167.904680
         fitted       -79.777354           5       169.554709
           R          -89.824703           2       183.649405


                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
```

```
    (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                      Tests of Interest

    Test    -2*log(Likelihood Ratio)  Test df        p-value

    Test 1              30.2417            8         0.0001916
    Test 2              6.49694            4             0.165
    Test 3              6.49694            4             0.165
    Test 4              3.65003            1           0.05607

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model



         Benchmark Dose Computation

Specified effect =              1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

           BMD =       3.49389

          BMDL =      0.304602
```

1 **G.2.44.5.** *Figure for Additional Model Presented: Hill, Unrestricted*

Hill Model with 0.95 Confidence Level

13:27 02/08 2010

2
3
4

G.2.45. Sewall et al. (1995): T4 In Serum

G.2.45.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	3	0.722	204.495	1.869E+01	1.243E+01	
Exponential (M3)	3	0.722	204.495	1.869E+01	1.243E+01	power hit bound (*d* = 1)
Exponential (M4)	2	0.854	205.483	1.106E+01	4.650E+00	
Exponential (M5)	2	0.854	205.483	1.106E+01	4.650E+00	power hit bound (*d* = 1)
Hill[b]	**2**	**0.898**	**205.382**	**1.031E+01**	**3.603E+00**	***n* lower bound hit (*n* = 1)**
Linear	3	0.576	205.150	2.238E+01	1.619E+01	
Polynomial, 4-degree	3	0.576	205.150	2.238E+01	1.619E+01	
Power	3	0.576	205.150	2.238E+01	1.619E+01	power bound hit (power = 1)
Hill, unrestricted[c]	1	0.864	207.196	9.706E+00	1.973E+00	unrestricted (*n* = 0.569)
Power, unrestricted	2	0.985	205.197	9.726E+00	1.914E+00	unrestricted (power = 0.538)

[a] Constant variance model selected (*p* = 0.4078).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.45.2. *Output for Selected Model: Hill*

Sewall et al. (1995): T4 In Serum

```
  =====================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\58_Sewall_1995_T4_HillCV_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\58_Sewall_1995_T4_HillCV_1.plt
                                    Mon Feb 08 13:28:15 2010
  =====================================================================

 Figure 1, Saline noninitiated
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 5
   Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                             alpha =       33.0913
                               rho =             0    Specified
                         intercept =       30.6979
                                 v =      -12.2937
                                 n =      0.950815
                                 k =       12.5808



           Asymptotic Correlation Matrix of Parameter Estimates


           ( *** The model parameter(s)  -rho     -n
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                     alpha    intercept            v            k

       alpha            1   -1.2e-009    -1.8e-008     1.5e-008

   intercept    -1.2e-009           1          0.3        -0.65

         v      -1.8e-008         0.3            1        -0.89

         k       1.5e-008       -0.65        -0.89            1




                            Parameter Estimates


                                                     95.0% Wald
Confidence Interval
       Variable      Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
         alpha        29.5556         6.23087              17.3433
41.7679
       intercept      30.3957         1.68747              27.0883
33.7031
           v         -18.2488         7.72836             -33.3961
-3.10154
           n                1              NA
           k          24.2883         26.743              -28.127
76.7035


NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.




     Table of Data and Estimated Values of Interest
```

```
 Dose       N    Obs Mean    Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------    --------   -----------  -----------   ---------
-

    0       9      30.7        30.4        4.66         5.44         0.167
3.291       9      27.9        28.2        7.17         5.44        -0.188
7.107       9      25.9        26.3        6.81         5.44        -0.204
16.63       9      23.6          23        5.38         5.44         0.319
44.66       9      18.4        18.6        4.12         5.44        -0.0942



 Model Descriptions for likelihoods calculated


 Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:          Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

             Model      Log(likelihood)   # Param's      AIC
              A1          -98.583448          6        209.166896
              A2          -96.590204         10        213.180407
              A3          -98.583448          6        209.166896
           fitted         -98.691143          4        205.382286
              R          -109.013252          2        222.026503


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test     -2*log(Likelihood Ratio)   Test df        p-value

   Test 1            24.8461              8           0.001651
   Test 2            3.98649              4           0.4078
```

```
   Test 3                3.98649          4              0.4078
   Test 4                0.21539          2              0.8979


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data


The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here



The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data



         Benchmark Dose Computation

Specified effect =              1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

          BMD =          10.306

          BMDL =        3.60269
```

1 **G.2.45.3.** *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

13:28 02/08 2010

2
3
4 **G.2.45.4.** *Output for Additional Model Presented: Hill, Unrestricted*

5 Sewall et al. (1995): T4 In Serum

```
======================================================================
       Hill Model. (Version: 2.14;  Date: 06/26/2008)
       Input Data File: C:\1\Blood\58_Sewall_1995_T4_HillCV_U_1.(d)
       Gnuplot Plotting File:  C:\1\Blood\58_Sewall_1995_T4_HillCV_U_1.plt
                                    Mon Feb 08 13:28:15 2010
======================================================================

 Figure 1, Saline noninitiated
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter is not restricted
   A constant variance model is fit

   Total number of dose groups = 5
```

```
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          alpha =       33.0913
                            rho =             0   Specified
                      intercept =       30.6979
                              v =      -12.2937
                              n =      0.950815
                              k =       12.5808



           Asymptotic Correlation Matrix of Parameter Estimates


            ( *** The model parameter(s)  -rho
                  have been estimated at a boundary point, or have been
    specified by the user,
                  and do not appear in the correlation matrix )

                    alpha    intercept            v            n            k

      alpha             1   -3.9e-005      0.00022      0.00021     -0.00022

   intercept    -3.9e-005            1        -0.17        -0.31         0.18

         v        0.00022        -0.17            1         0.97           -1

         n        0.00021        -0.31         0.97            1        -0.98

         k       -0.00022         0.18           -1        -0.98            1




                              Parameter Estimates


                                                          95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
          alpha         29.4337          6.20518             17.2718
41.5957
       intercept        30.7096          1.79801             27.1855
34.2336
             v         -143.244          3972.28            -7928.78
7642.29
             n         0.569063         0.947248            -1.28751
2.42564
             k          2856.29           171186             -332662
338374



     Table of Data and Estimated Values of Interest
```

```
 Dose        N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------      ---   --------     --------   -----------  -----------   ---------
-

    0        9      30.7         30.7        4.66         5.43      -0.00646
3.291        9      27.9         27.7        7.17         5.43       0.0842
7.107        9      25.9         26.1        6.81         5.43      -0.134
16.63        9      23.6         23.4        5.38         5.43       0.0657
44.66        9      18.4         18.4        4.12         5.43      -0.00948
```

Model Descriptions for likelihoods calculated

Model A1:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model R: Yi = Mu + e(i)
          Var{e(i)} = Sigma^2

                    Likelihoods of Interest

```
            Model      Log(likelihood)   # Param's      AIC
            A1          -98.583448          6        209.166896
            A2          -96.590204         10        213.180407
            A3          -98.583448          6        209.166896
         fitted         -98.598183          5        207.196367
            R          -109.013252          2        222.026503
```


                    Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

```
  Test    -2*log(Likelihood Ratio)   Test df        p-value

  Test 1            24.8461             8           0.001651
  Test 2             3.98649            4           0.4078
```

```
   Test 3                 3.98649           4           0.4078
   Test 4                 0.0294713         1           0.8637
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

           Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

          BMD =   9.70574

          BMDL =   1.97319

1   **G.2.45.5.** *Figure for Additional Model Presented: Hill, Unrestricted*

Hill Model with 0.95 Confidence Level

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1 **G.2.46. Shi et al. ([2007](#)): Estradiol 17B, PE9**

2 **G.2.46.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	3	0.010	391.638	6.976E+00	3.761E+00	
Exponential (M3)	3	0.010	391.638	6.976E+00	3.761E+00	power hit bound ($d = 1$)
Exponential (M4)[b]	**2**	**0.690**	**382.969**	**8.068E−01**	**3.544E−01**	
Exponential (M5)	2	0.690	382.969	8.068E−01	3.544E−01	power hit bound ($d = 1$)
Hill	2	0.975	382.278	7.239E−01	error	*n* lower bound hit ($n = 1$)
Linear	3	0.003	394.308	9.841E+00	6.687E+00	
Polynomial, 4-degree	3	0.003	394.308	9.841E+00	6.687E+00	
Power	3	0.003	394.308	9.841E+00	6.687E+00	power bound hit (power = 1)
Hill, unrestricted	1	0.897	384.243	7.086E−01	error	unrestricted ($n = 0.875$)
Power, unrestricted	2	0.506	383.590	6.280E−01	3.304E−02	unrestricted (power = 0.222)

[a] Nonconstant variance model selected ($p = 0.0521$).
[b] Best-fitting model, BMDS output presented in this appendix.

3
4

5 **G.2.46.2.** *Output for Selected Model: Exponential (M4)*

6 Shi et al. ([2007](#)): Estradiol 17B, PE9

7
```
8  ======================================================================
9         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
10        Input Data File: C:\1\Blood\59_Shi_2007_Estradiol_Exp_1.(d)
11        Gnuplot Plotting File:
12                                     Mon Feb 08 13:28:52 2010
13 ======================================================================
14
15 Figure 4 PE9 only
16 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18   The form of the response function by Model:
19      Model 2:     Y[dose] = a * exp{sign * b * dose}
20      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
21      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
22      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
23
24    Note: Y[dose] is the median response for exposure = dose;
25          sign = +1 for increasing trend in data;
26          sign = -1 for decreasing trend.
27
28      Model 2 is nested within Models 3 and 4.
29      Model 3 is nested within Model 5.
30      Model 4 is nested within Model 5.
31
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


MLE solution provided: Exact



                  Initial Parameter Values

                  Variable          Model 4
                  --------          --------
                    lnalpha           2.65881
                      rho           0.913414
                        a               108
                        b           0.277637
                        c           0.340136
                        d                 1




                  Parameter Estimates

                  Variable          Model 4
                  --------          -------
                    lnalpha           1.66773
                      rho           1.15314
                        a           103.146
                        b           1.00685
                        c           0.418742
                        d                 1



          Table of Stats From Input Data

    Dose      N        Obs Mean      Obs Std Dev
    -----     ---      ----------    -------------
        0     10        102.9          41.41
   0.3418     10         86.19         19.58
    1.075     10         63.33         29.36
     5.23     10         48.1          18.82
    13.91     10         38.57         22.59



             Estimated Values of Interest

     Dose      Est Mean      Est Std     Scaled Residual
    ------    ----------    ---------    ----------------
        0        103.1         33.35        -0.02738
```

```
   0.3418           85.69           29.96            0.05296
   1.075            63.51           25.21           -0.02238
   5.23             43.5            20.27            0.7167
  13.91             43.19           20.19           -0.7237




   Other models for which likelihoods are calculated:

      Model A1:         Yij = Mu(i) + e(ij)
                  Var{e(ij)} = Sigma^2

      Model A2:         Yij = Mu(i) + e(ij)
                  Var{e(ij)} = Sigma(i)^2

      Model A3:         Yij = Mu(i) + e(ij)
                  Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

      Model  R:         Yij = Mu + e(i)
                  Var{e(ij)} = Sigma^2


                          Likelihoods of Interest

                  Model      Log(likelihood)      DF         AIC
                  -------    ----------------    ----    ------------
                    A1         -188.3615           6       388.7231
                    A2         -183.667           10       387.3339
                    A3         -186.1132           7       386.2263
                     R         -203.3606           2       410.7211
                     4         -186.4844           5       382.9687



   Additive constant for all log-likelihoods =    -45.95.  This constant
 added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                          Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
 R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 6a: Does Model 4 fit the data? (A3 vs 4)



                          Tests of Interest

    Test         -2*log(Likelihood Ratio)         D. F.         p-value
    --------     ------------------------         ------    --------------
    Test 1                39.39                      8         < 0.0001
    Test 2                9.389                      4          0.05208
    Test 3                4.892                      3          0.1798
    Test 6a               0.7424                     2          0.6899
```

```
 1
 2
 3      The p-value for Test 1 is less than .05.  There appears to be a
 4      difference between response and/or variances among the dose
 5      levels, it seems appropriate to model the data.
 6
 7      The p-value for Test 2 is less than .1.  A non-homogeneous
 8      variance model appears to be appropriate.
 9
10      The p-value for Test 3 is greater than .1.  The modeled
11      variance appears to be appropriate here.
12
13      The p-value for Test 6a is greater than .1.  Model 4 seems
14      to adequately describe the data.
15
16
17   Benchmark Dose Computations:
18
19      Specified Effect = 1.000000
20
21            Risk Type = Estimated standard deviations from control
22
23      Confidence Level = 0.950000
24
25                  BMD =     0.806817
26
27                 BMDL =     0.354366
28
29
```

1 **G.2.46.3.** *Figure for Selected Model: Exponential (M4)*

Exponential Model 4 with 0.95 Confidence Level

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G.2.47. Smialowicz et al. ([2008](#)): PFC per 10^6 Cells

G.2.47.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	3	0.101	901.897	8.343E+00	5.064E+00	
Exponential (M3)	3	0.101	901.897	8.343E+00	5.064E+00	power hit bound ($d = 1$)
Exponential (M4)	2	0.044	903.897	8.325E+00	1.465E+00	
Exponential (M5)	2	0.044	903.897	8.325E+00	1.465E+00	power hit bound ($d = 1$)
Hill	2	0.063	903.192	3.669E+00	6.970E−01	*n* lower bound hit ($n = 1$)
Linear	3	0.048	903.585	1.373E+01	1.053E+01	
Polynomial, 4-degree	3	0.048	903.585	1.374E+01	1.053E+01	
Power	3	0.048	903.585	1.373E+01	1.053E+01	power bound hit (power = 1)
Hill, unrestricted	1	0.213	901.219	1.928E+00	2.208E−01	unrestricted ($n = 0.35$)
Power, unrestricted[b]	**2**	**0.481**	**899.130**	**1.902E+00**	**2.158E−01**	**unrestricted (power = 0.333)**

[a] Constant variance model selected ($p = <0.0001$).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.47.2. *Output for Selected Model: Power, Unrestricted*

Smialowicz et al. ([2008](#)): PFC per 10^6 Cells

```
   ========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\Blood\60_Smial_2008_PFCcells_PwrCV_U_1.(d)
         Gnuplot Plotting File:
C:\1\Blood\60_Smial_2008_PFCcells_PwrCV_U_1.plt
                                         Mon Feb 08 13:29:38 2010
   ========================================================================

 Anti Response to SRBCs, PFC per 10to6 cells, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function is:

    Y[dose] = control + slope * dose^power


    Dependent variable = Mean
    Independent variable = Dose
    rho is set to 0
    The power is not restricted
    A constant variance model is fit

    Total number of dose groups = 5
```

```
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                           alpha =      232385
                             rho =           0   Specified
                         control =        1491
                           slope =    -491.716
                           power =    0.288021



           Asymptotic Correlation Matrix of Parameter Estimates


           ( *** The model parameter(s)  -rho
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                   alpha       control        slope        power

      alpha            1     -3.4e-009     1.8e-009     -1.2e-010

    control    -3.4e-009            1         -0.82        -0.65

      slope     1.8e-009         -0.82            1         0.94

      power    -1.2e-010         -0.65         0.94            1




                             Parameter Estimates


                                                  95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         alpha          219793           37974.5              145365
294222
        control         1470.48           123.73             1227.98
1712.99
         slope         -378.406          157.002            -686.125
-70.6872
         power         0.333124         0.113501            0.110666
0.555581




   Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean      Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
 ------     ---  --------      --------   -----------  -----------   ---------
 -
```

```
    0    15  1.49e+003   1.47e+003          716          469       0.169
0.438    14  1.13e+003   1.18e+003          171          469      -0.431
2.464    15        945         959          516          469       -0.12
 13.4    15        677         572          465          469       0.867
31.65     8        161         274          117          469      -0.684




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
            A1          -444.832859           6      901.665718
            A2          -425.402825          10      870.805651
            A3          -444.832859           6      901.665718
          fitted        -445.564823           4      899.129647
            R           -463.753685           2      931.507371



                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)


                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df       p-value

   Test 1            76.7017            8          <.0001
   Test 2            38.8601            4          <.0001
   Test 3            38.8601            4          <.0001
   Test 4            1.46393            2           0.481

 The p-value for Test 1 is less than .05.  There appears to be a
 difference between response and/or variances among the dose levels
```

It seems appropriate to model the data

The p-value for Test 2 is less than .1. Consider running a
non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a
different variance model

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

                    Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

               BMD = 1.90249

               BMDL = 0.215843

1 **G.2.47.3.** *Figure for Selected Model: Power, Unrestricted*

Power Model with 0.95 Confidence Level

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G.2.48. Smialowicz et al. ([2008](#)): PFC per Spleen

G.2.48.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	3	0.124	377.565	1.334E+01	8.593E+00	
Exponential (M3)	2	0.069	379.138	1.536E+01	8.895E+00	
Exponential (M4)	3	0.124	377.565	1.334E+01	8.593E+00	
Exponential (M5)	1	0.021	381.138	1.536E+01	8.895E+00	
Hill	2	0.116	378.108	1.568E+01	error	*n* lower bound hit (*n* = 1)
Linear	3	0.126	377.522	2.055E+01	1.624E+01	
Polynomial, 4-degree	3	0.126	377.522	2.055E+01	1.624E+01	
Power	3	0.126	377.522	2.055E+01	1.624E+01	power bound hit (power = 1)
Hill, unrestricted	1	0.103	378.463	1.202E+01	error	unrestricted (*n* = 0.544)
Power, unrestricted[b]	**2**	**0.270**	**376.420**	**1.187E+01**	**3.762E+00**	**unrestricted (power = 0.531)**

[a] Nonconstant variance model selected (*p* = 0.0011).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.48.2. *Output for Selected Model: Power, Unrestricted*

Smialowicz et al. ([2008](#)): PFC per Spleen

```
   =========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\Blood\61_Smial_2008_PFCspleen_Pwr_U_1.(d)
         Gnuplot Plotting File:
C:\1\Blood\61_Smial_2008_PFCspleen_Pwr_U_1.plt
                                        Mon Feb 08 13:30:16 2010
   =========================================================================

 Anti Response to SRBCs - PFC x 10 to the 4 per spleen, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 5
   Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                    Default Initial Parameter Values
                          lalpha =       4.76607
                             rho =             0
                         control =          27.8
                           slope =      -9.21898
                           power =       0.286443


          Asymptotic Correlation Matrix of Parameter Estimates

                    lalpha         rho       control        slope        power

     lalpha              1       -0.98          0.25        -0.28        -0.22

        rho          -0.98           1          -0.3         0.28         0.22

    control           0.25        -0.3             1        -0.83        -0.74

      slope          -0.28        0.28         -0.83            1         0.99

      power          -0.22        0.22         -0.74         0.99            1




                              Parameter Estimates


                                                         95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
           lalpha       0.746922         1.02058            -1.25337
2.74721
              rho       1.36826          0.355827            0.67085
2.06567
          control       25.3816          2.96691             19.5666
31.1967
            slope       -3.5662          2.52558            -8.51626
1.38385
            power       0.531216         0.175728            0.186796
0.875637




     Table of Data and Estimated Values of Interest

 Dose        N    Obs Mean     Est Mean    Obs Std Dev   Est Std Dev    Scaled
Res.
 ------      ---   --------     --------    ----------    ----------    ---------
 -

     0     15       27.8         25.4          13.4          13.3          0.706
```

```
1   0.438    14        21        23.1       13.6      12.4       -0.626
2   2.464    15        17.6      19.6       9.4       11.1       -0.704
3   13.4     15        12.6      11.2       8.7       7.6        0.702
4   31.65    8         3         3.03       3.1       3.1        -0.0313
5
6
7
8    Model Descriptions for likelihoods calculated
9
10
11   Model A1:          Yij = Mu(i) + e(ij)
12            Var{e(ij)} = Sigma^2
13
14   Model A2:          Yij = Mu(i) + e(ij)
15            Var{e(ij)} = Sigma(i)^2
16
17   Model A3:          Yij = Mu(i) + e(ij)
18            Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
19      Model A3 uses any fixed variance parameters that
20      were specified by the user
21
22   Model  R:          Yi = Mu + e(i)
23            Var{e(i)} = Sigma^2
24
25
26                    Likelihoods of Interest
27
28            Model      Log(likelihood)   # Param's      AIC
29             A1          -190.565019          6      393.130038
30             A2          -181.476284         10      382.952569
31             A3          -181.900030          7      377.800059
32          fitted         -183.210137          5      376.420274
33             R           -204.636496          2      413.272993
34
35
36                    Explanation of Tests
37
38   Test 1:  Do responses and/or variances differ among Dose levels?
39           (A2 vs. R)
40   Test 2:  Are Variances Homogeneous? (A1 vs A2)
41   Test 3:  Are variances adequately modeled? (A2 vs. A3)
42   Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
43   (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
44
45                    Tests of Interest
46
47    Test    -2*log(Likelihood Ratio)  Test df       p-value
48
49   Test 1            46.3204            8           <.0001
50   Test 2            18.1775            4           0.001139
51   Test 3            0.84749            3           0.8381
52   Test 4            2.62021            2           0.2698
53
54   The p-value for Test 1 is less than .05.  There appears to be a
55   difference between response and/or variances among the dose levels
56   It seems appropriate to model the data
57
```

```
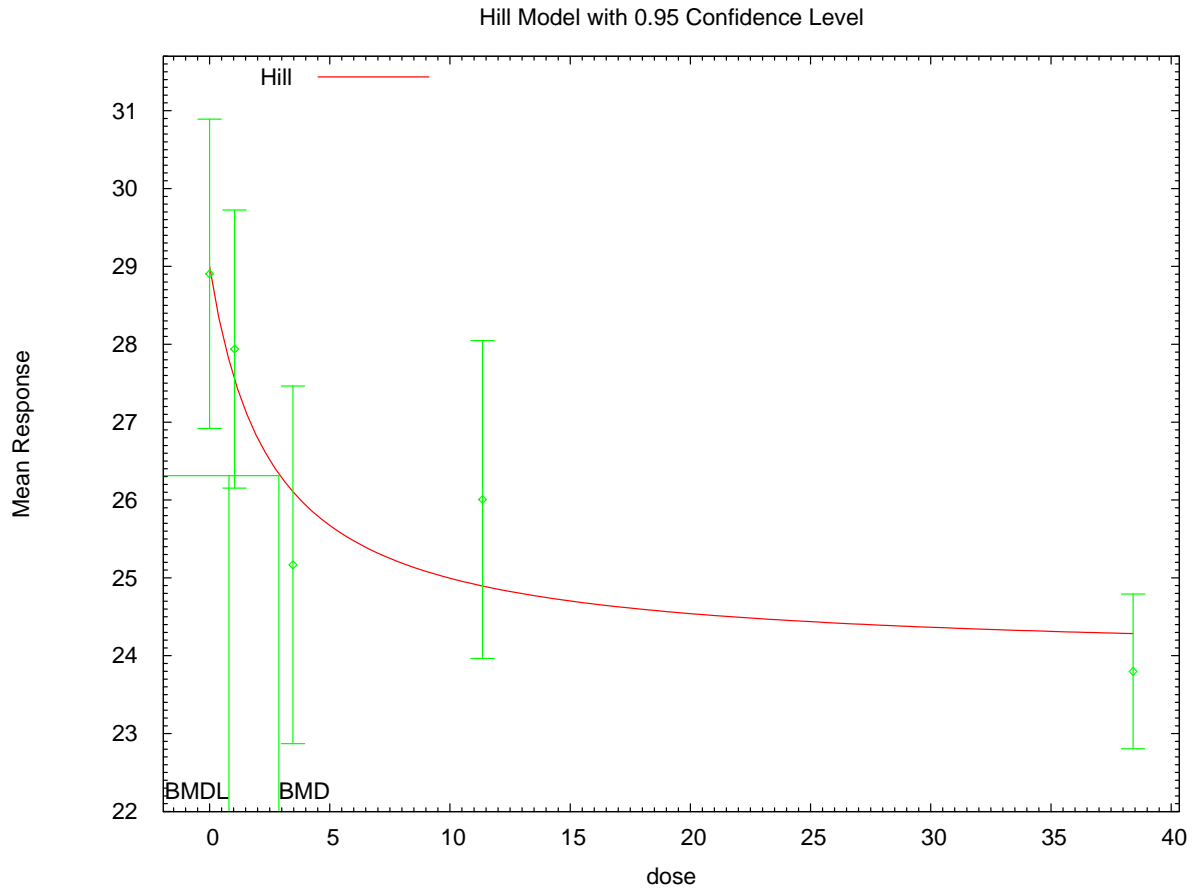The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


                   Benchmark Dose Computation

Specified effect =              1

Risk Type        =       Estimated standard deviations from the control mean

Confidence level =         0.95

            BMD = 11.8748


            BMDL = 3.76161
```

G.2.48.3. *Figure for Selected Model: Power, Unrestricted*

Power Model with 0.95 Confidence Level

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G.2.49. Smith et al. ([1976](#)): Cleft Palate in Pups

2 **G.2.49.1.** *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	3	0.4216	69.75	3.242E+01	1.123E+01	
Logistic	4	0.5620	68.48	4.592E+01	3.437E+01	
Log-logistic [a]	**3**	**0.4218**	**69.79**	**3.525E+01**	**1.064E+01**	
Log-probit	3	0.4667	69.96	3.854E+01	1.903E+01	
Multistage, 5th degree	3	0.4490	69.41	2.504E+01	1.165E+01	
Probit	4	0.6133	67.98	4.096E+01	3.113E+01	
Weibull	3	0.4340	69.64	3.104E+01	1.136E+01	
Gamma, unrestricted	3	0.4216	69.75	3.242E+01	8.310E+00	
Log-logistic, unrestricted	3	0.4218	69.79	3.525E+01	1.064E+01	
Log-probit, unrestricted	3	0.4134	69.89	3.806E+01	1.086E+01	
Weibull, unrestricted	3	0.4339	69.64	3.104E+01	9.231E+00	

[a] Best-fitting model, BMDS output presented in this appendix.

3
4
5 **G.2.49.2.** *Output for Selected Model: Log-Logistic*

```
6  ======================================================================
7          Logistic Model. (Version: 2.12; Date: 05/16/2008)
8          Input Data File:
9  C:\USEPA\BMDS21\1a\76_Smith_1976_cleft_palate_b_LogLogistic_1.(d)
10         Gnuplot Plotting File:
11 C:\USEPA\BMDS21\1a\76_Smith_1976_cleft_palate_b_LogLogistic_1.plt
12                                     Fri Sep 02 08:12:55 2011
13  ======================================================================
14
15  Table 3 cleft palate
16 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18    The form of the probability function is:
19
20    P[response] = background+(1-background)/[1+EXP(-intercept-
21 slope*Log(dose))]
22
23
24    Dependent variable = DichEff
25    Independent variable = Dose
26    Slope parameter is restricted as slope >= 1
27
28    Total number of observations = 6
29    Total number of records with missing values = 0
30    Maximum number of iterations = 250
31    Relative Function Convergence has been set to: 1e-008
```

```
Parameter Convergence has been set to: 1e-008


User has chosen the log transformed model


                  Default Initial Parameter Values
                      background =          0
                       intercept =    -4.88569
                           slope =          1


        Asymptotic Correlation Matrix of Parameter Estimates

              background    intercept        slope

background            1        -0.22         0.21

 intercept        -0.22            1        -0.99

    slope         0.21        -0.99            1



                          Parameter Estimates

                                                    95.0% Wald
Confidence Interval
      Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background      0.0259253            *                  *
*
      intercept       -10.1275            *                  *
*
         slope        2.22613            *                  *
*


* - Indicates that this value is not calculated.



                       Analysis of Deviance Table

     Model      Log(likelihood)   # Param's   Deviance   Test d.f.   P-value
     Full model     -29.9486          6
   Fitted model     -31.8949          3       3.89258        3
0.2733
  Reduced model     -52.2767          1       44.6562        5       <.0001


        AIC:        69.7899



                          Goodness  of  Fit
                                                           Scaled
     Dose     Est._Prob.   Expected   Observed    Size     Residual
   -----------------------------------------------------------------------
```

```
 1      0.0000      0.0259        0.881      0.000         34        -0.951
 2      0.1242      0.0259        1.063      2.000         41         0.921
 3      1.0125      0.0260        0.493      0.000         19        -0.712
 4      7.1100      0.0290        0.493      1.000         17         0.733
 5     50.5906      0.2197        4.175      4.000         19        -0.097
 6    138.0663      0.7067        9.894     10.000         14         0.062
 7
 8   Chi^2 = 2.81       d.f. = 3          P-value = 0.4218
 9
10
11      Benchmark Dose Computation
12
13   Specified effect =            0.1
14
15   Risk Type        =      Extra risk
16
17   Confidence level =           0.95
18
19             BMD =        35.2466
20
21            BMDL =        10.6443
22
23
```

24   **G.2.49.3.** *Figure for Selected Model: Log-Logistic*

Log-Logistic Model with 0.95 Confidence Level

25   08:12 09/02 2011
26

G.2.50. Sparschu et al. (1976): Fetal Body Weight, Male

G.2.50.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	3	0.0002	-247.04	6.844E+01	4.399E+01	
Exponential (M3)	3	0.0002	-247.04	6.844E+01	4.399E+01	
Exponential (M4)	2	0.0001	-246.68	6.436E+01	3.808E+01	
Exponential (M5) [b]	**1**	**<0.0001**	**-246.18**	**5.736E+01**	**1.685E+01**	
Hill	1	<.0001	-246.76	5.421E+01	error	
Linear	3	0.0001	-246.33	7.217E+01	4.697E+01	
Polynomial, 3-degree	0	NA	-151.65	6.931E+01	2.162E+01	
Power	3	0.0001	-246.33	7.217E+01	4.697E+01	
Hill, unrestricted	1	<.0001	-246.76	5.421E+01	error	
Power, unrestricted	2	<.0001	-244.93	7.132E+01	4.420E+01	

[a] Modeled variance model presented (*p* < 0.0001); variance not appropriately captured (*p*-test 3 = 0.008).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.50.2. *Output for Selected Model: exponential (M5)*

```
=====================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File:
C:\USEPA\BMDS21\1a\74_Sparschu_1971_pup_bw_male_b_Exp_1.(d)
         Gnuplot Plotting File:
                                        Thu Sep 01 14:59:46 2011
 =====================================================================

 Table 4 males
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


    Dependent variable = Mean
```

```
1     Independent variable = Dose
2     Data are assumed to be distributed: normally
3     Variance Model: exp(lnalpha +rho *ln(Y[dose]))
4     The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
5
6     Total number of dose groups = 5
7     Total number of records with missing values = 0
8     Maximum number of iterations = 250
9     Relative Function Convergence has been set to: 1e-008
10    Parameter Convergence has been set to: 1e-008
11
12    MLE solution provided: Exact
13
14
15                    Initial Parameter Values
16
17                Variable           Model 5
18                --------           --------
19                 lnalpha            -4.28192
20                    rho             1.66816
21                      a             4.347
22                      b             0.0041752
23                      c             0.312859
24                      d                    1
25
26
27
28                  Parameter Estimates
29
30                Variable           Model 5
31                --------           -------
32                 lnalpha            16.8213
33                    rho            -13.5946
34                      a             4.04383
35                      b             0.0163183
36                      c             0.86046
37                      d             1.40496
38
39
40          Table of Stats From Input Data
41
42     Dose      N        Obs Mean      Obs Std Dev
43     -----    ---      ----------    -------------
44        0     117        4.03           0.37
45     5.09      55        4.14           0.26
46    16.28      66        3.85           0.35
47    52.87      39        3.86           0.61
48    188.3       3        2.72           0.25
49
50
51          Estimated Values of Interest
52
53     Dose      Est Mean     Est Std      Scaled Residual
54     ------    ----------   ---------    ----------------
55        0        4.044       0.3374         -0.4433
56     5.09        4.027       0.3471          2.415
57    16.28        3.963       0.3873         -2.363
```

```
     52.87           3.73        0.5844              1.39
    188.3            3.484       0.929              -1.424



   Other models for which likelihoods are calculated:

      Model A1:        Yij = Mu(i) + e(ij)
                Var{e(ij)} = Sigma^2

      Model A2:        Yij = Mu(i) + e(ij)
                Var{e(ij)} = Sigma(i)^2

      Model A3:        Yij = Mu(i) + e(ij)
                Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

      Model  R:        Yij = Mu + e(i)
                Var{e(ij)} = Sigma^2


                         Likelihoods of Interest

                  Model      Log(likelihood)      DF        AIC
                  -------    ----------------     ----    -----------
                    A1          126.4055           6       -240.8109
                    A2          145.7666          10       -271.5331
                    A3          137.4206           7       -260.8413
                     R          101.5293           2       -199.0587
                     5          129.0908           6       -246.1816


   Additive constant for all log-likelihoods =     -257.3.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                         Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 7a: Does Model 5 fit the data? (A3 vs 5)



                         Tests of Interest

     Test          -2*log(Likelihood Ratio)         D. F.        p-value
    --------       ------------------------         ------     --------------
     Test 1                    88.47                   8         < 0.0001
     Test 2                    38.72                   4         < 0.0001
     Test 3                    16.69                   3         0.0008177
    Test 7a                    16.66                   1         < 0.0001
```

```
The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose
levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1.  A non-homogeneous
variance model appears to be appropriate.

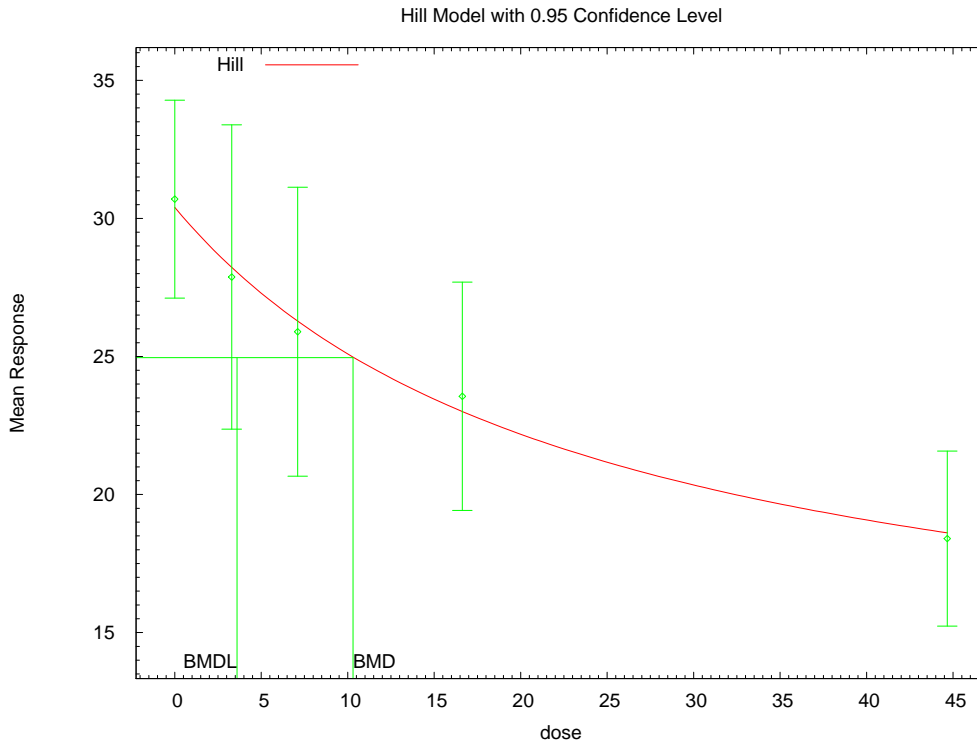The p-value for Test 3 is less than .1.  You may want to
consider a different variance model.

The p-value for Test 7a is less than .1.  Model 5 may not adequately
describe the data; you may want to consider another model.


Benchmark Dose Computations:

  Specified Effect = 1.000000

        Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

              BMD =      57.3555

             BMDL =      16.8535
```

1   **G.2.50.3.** *Figure for Selected Model: Exponential (M5)*

Exponential_beta Model 5 with 0.95 Confidence Level

2   14:59 09/01 2011
3
4

G.2.51. Sparschu et al. ([1971](#)): Fetal Body Weight, Female

G.2.51.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2) [b]	**3**	**0.0340**	**-229.963**	**1.027E+02**	**6.523E+01**	
Exponential (M3)	2	0.0025	-224.657	1.713E+02	5.467E+01	
Exponential (M4)	2	0.0146	-228.182	1.044E+02	6.131E+01	
Exponential (M5)	1	0.0037	-226.196	1.037E+02	6.028E+01	
Hill	1	0.0037	-226.226	1.044E+02	6.055E+01	
Linear	3	0.0315	-229.794	1.035E+02	6.725E+01	
Polynomial, 3-degree	3	0.0315	-229.794	1.035E+02	6.725E+01	
Power	2	0.0025	-224.657	1.746E+02	5.742E+01	
Hill, unrestricted	1	0.0037	-226.226	1.044E+02	6.055E+01	
Power, unrestricted	2	0.0136	-228.035	1.054E+02	6.491E+01	

[a] Modeled variance model presented ($p = 0.001$)); variance not appropriately captured (*p*-test 3 = 0.005).
[b] Best-fitting model, BMDS output presented in this appendix.

G.2.51.2. *Output for Selected Model: Exponential (M2)*

```
=========================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File:
C:\USEPA\BMDS21\1a\75_Sparschu_1971_pup_bw_fm_b_Exp_1.(d)
         Gnuplot Plotting File:
                                    Thu Sep 01 15:03:28 2011
  =========================================================================

 Table 4 females
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
```

```
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                    Initial Parameter Values

                  Variable          Model 2
                  --------          --------
                   lnalpha          -7.22746
                       rho           4.02075
                         a           3.74918
                         b        0.00140938
                         c                 0
                         d                 1



                    Parameter Estimates

                  Variable          Model 2
                  --------          -------
                   lnalpha           11.1109
                       rho          -9.58142
                         a           3.90142
                         b       0.000999148
                         c                 0
                         d                 1


            Table of Stats From Input Data

     Dose      N        Obs Mean     Obs Std Dev
     -----     ---      ----------   -------------
         0     129        3.89          0.39
      5.09      60        3.98          0.35
     16.28      58        3.71          0.37
     52.87      54        3.78          0.54
     188.3       4        2.69          0.19



                 Estimated Values of Interest

      Dose     Est Mean     Est Std     Scaled Residual
      ------   ----------   ---------   ----------------
         0       3.901       0.3805         -0.3408
      5.09       3.882       0.3899          1.955
     16.28       3.838       0.4113         -2.379
```

```
       52.87          3.701          0.49              1.189
       188.3          3.232         0.9369            -1.158



   Other models for which likelihoods are calculated:

     Model A1:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma^2

     Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

     Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

     Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                          Likelihoods of Interest

                   Model      Log(likelihood)      DF         AIC
                   -------    ----------------     ----    -----------
                     A1          123.0729           6       -234.1458
                     A2          132.131           10        -244.262
                     A3          123.3163           7       -232.6326
                      R          100.5646           2       -197.1292
                      2          118.9813           4       -229.9626


   Additive constant for all log-likelihoods =     -280.3.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                          Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)
   Test 4:  Does Model 2 fit the data? (A3 vs. 2)



                          Tests of Interest

     Test        -2*log(Likelihood Ratio)         D. F.        p-value
    --------     ------------------------        ------      --------------
     Test 1                   63.13                8           < 0.0001
     Test 2                   18.12                4            0.001171
     Test 3                   17.63                3           0.0005244
     Test 4                    8.67                3            0.03402



   The p-value for Test 1 is less than .05.  There appears to be a
```

```
 1     difference between response and/or variances among the dose
 2     levels, it seems appropriate to model the data.
 3
 4     The p-value for Test 2 is less than .1.  A non-homogeneous
 5     variance model appears to be appropriate.
 6
 7     The p-value for Test 3 is less than .1.  You may want to
 8     consider a different variance model.
 9
10     The p-value for Test 4 is less than .1.  Model 2 may not adequately
11     describe the data; you may want to consider another model.
12
13
14  Benchmark Dose Computations:
15
16     Specified Effect = 1.000000
17
18           Risk Type = Estimated standard deviations from control
19
20     Confidence Level = 0.950000
21
22                 BMD =      102.699
23
24                BMDL =      65.2254
25
26
```

1 **G.2.51.3.** *Figure for Selected Model: Exponential (M2)*

Exponential_beta Model 2 with 0.95 Confidence Level

2   15:03 09/01 2011
3
4

1   **G.2.52. Toth et al. ([1979](#)): Amyloidosis**

2   **G.2.52.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	2	0.040	149.120	1.965E+01	1.283E+01	power bound hit (power = 1)
Logistic	2	0.019	151.340	3.701E+01	2.858E+01	
Log-logistic[a]	**2**	**0.053**	**148.269**	**1.503E+01**	**8.747E+00**	**slope bound hit (slope = 1)**
Log-probit	2	0.009	152.855	3.782E+01	2.502E+01	slope bound hit (slope = 1)
Multistage, 3-degree	2	0.040	149.120	1.965E+01	1.283E+01	final ß = 0
Probit	2	0.021	151.115	3.467E+01	2.657E+01	
Weibull	2	0.040	149.120	1.965E+01	1.283E+01	power bound hit (power = 1)
Gamma, unrestricted	2	0.959	140.119	4.349E−01	2.891E−03	unrestricted (power = 0.254)
Log-logistic, unrestricted[b]	2	0.903	140.240	4.843E−01	5.312E−03	unrestricted (slope = 0.326)
Log-probit, unrestricted	2	0.870	140.315	4.960E−01	7.292E−03	unrestricted (slope = 0.186)
Weibull, unrestricted	2	0.933	140.174	4.641E−01	4.069E−03	unrestricted (power = 0.289)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

3
4
5   **G.2.52.2.** *Output for Selected Model: Log-Logistic*

6   Toth et al. ([1979](#)): Amyloidosis
7
8
9   ```
     ===
10   Logistic Model. (Version: 2.12; Date: 05/16/2008)
11   Input Data File: C:\1\Blood\62_Toth_1979_Amy1yr_LogLogistic_1.(d)
12   Gnuplot Plotting File:
13   C:\1\Blood\62_Toth_1979_Amy1yr_LogLogistic_1.plt
14   Mon Feb 08 13:30:54 2010
15   ===
16
17   Table 2
18   ~~~~~~
19
20   The form of the probability function is:
21
22   P[response] = background+(1-background)/[1+EXP(-intercept-
23   slope*Log(dose))]
24   ```

```
Dependent variable = DichEff
Independent variable = Dose
Slope parameter is restricted as slope >= 1

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


                 Default Initial Parameter Values
                     background =            0
                      intercept =     -4.54593
                          slope =            1


        Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -slope
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

              background    intercept

background            1        -0.49

 intercept        -0.49            1




                         Parameter Estimates

                                                95.0% Wald
Confidence Interval
       Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
      background      0.0699918             *                 *
*
       intercept      -4.90704              *                 *
*
          slope             1              *                 *
*


* - Indicates that this value is not calculated.




                         Analysis of Deviance Table

        Model     Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
```

```
   Full model           -68.017              4
  Fitted model          -72.1346             2        8.23525        2
0.01628
  Reduced model         -82.0119             1        27.99          3          <.0001

         AIC:            148.269


                                   Goodness  of  Fit
                                                               Scaled
    Dose       Est._Prob.     Expected     Observed     Size   Residual
   ----------------------------------------------------------------------
    0.0000       0.0700         2.660        0.000        38    -1.691
    0.5732       0.0739         3.252        5.000        44     1.007
   14.2123       0.1584         6.971       10.000        44     1.251
   91.2070       0.4446        19.117       17.000        43    -0.650

 Chi^2 = 5.86      d.f. = 2        P-value = 0.0534


   Benchmark Dose Computation

Specified effect =              0.1

Risk Type         =       Extra risk

Confidence level =              0.95

          BMD =         15.0264

          BMDL =        8.74665
```

1

G.2.52.3. *Figure for Selected Model: Log-Logistic*

Log-Logistic Model with 0.95 Confidence Level

13:30 02/08 2010

G.2.52.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Toth et al. (1979): Amyloidosis

```
==========================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\62_Toth_1979_Amy1yr_LogLogistic_U_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\62_Toth_1979_Amy1yr_LogLogistic_U_1.plt
                                        Mon Feb 08 13:30:54 2010
==========================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]
```

```
Dependent variable = DichEff
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


                  Default Initial Parameter Values
                      background =            0
                       intercept =     -1.92722
                           slope =      0.314472



          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -background
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

              intercept         slope

 intercept              1         -0.84

     slope         -0.84             1




                            Parameter Estimates

                                                    95.0% Wald
Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     background               0              *                    *
*
      intercept        -1.96073              *                    *
*
         slope         0.326156              *                    *
*


* - Indicates that this value is not calculated.




                        Analysis of Deviance Table


      Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
```

```
  Full model          -68.017          4
 Fitted model         -68.1201         2        0.206341        2
0.902
 Reduced model        -82.0119         1          27.99         3          <.0001

          AIC:          140.24


                        Goodness  of  Fit
                                                      Scaled
    Dose      Est._Prob.     Expected     Observed     Size     Residual
    -------------------------------------------------------------------
   0.0000      0.0000          0.000       0.000        38        0.000
   0.5732      0.1051          4.623       5.000        44        0.186
  14.2123      0.2507         11.029      10.000        44       -0.358
  91.2070      0.3802         16.348      17.000        43        0.205

 Chi^2 = 0.20      d.f. = 2       P-value = 0.9028


    Benchmark Dose Computation

Specified effect =           0.1

Risk Type         =      Extra risk

Confidence level =           0.95

           BMD =        0.484272
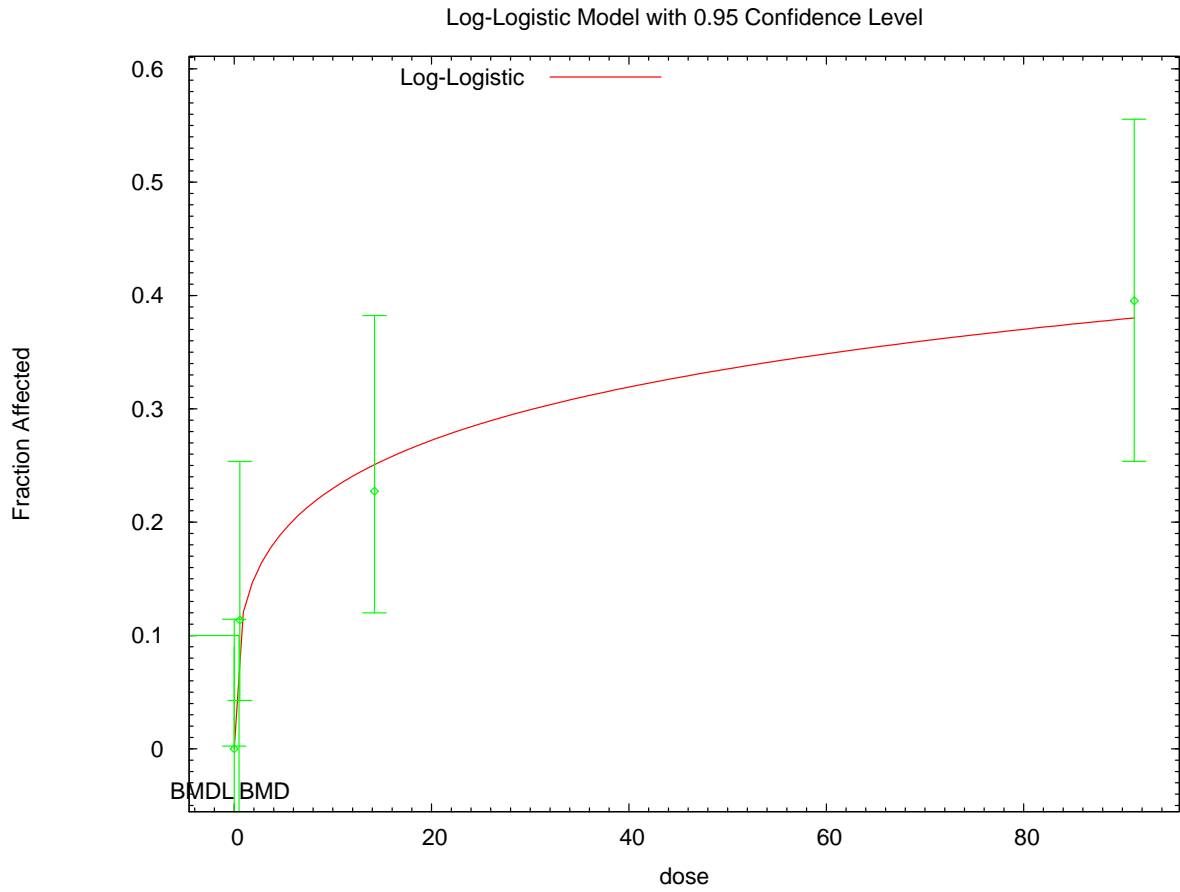
          BMDL =      0.00531211
```

1 **G.2.52.5.** *Figure for Additional Model Presented: Log-Logistic, Unrestricted*

Log-Logistic Model with 0.95 Confidence Level

13:30 02/08 2010

2
3
4

G.2.53. Toth et al. ([1979](#)): Skin Lesions

G.2.53.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Gamma	2	0.032	156.346	1.037E+01	7.470E+00	power bound hit (power = 1)
Logistic	2	0.005	161.421	2.487E+01	1.982E+01	
Log-logistic[a]	**2**	**0.078**	**153.963**	**6.413E+00**	**4.025E+00**	**slope bound hit (slope = 1)**
Log-probit	2	0.003	161.788	1.887E+01	1.280E+01	slope bound hit (slope = 1)
Multistage, 3-degree	2	0.032	156.346	1.037E+01	7.470E+00	final ß = 0
Probit	2	0.006	160.991	2.309E+01	1.858E+01	
Weibull	2	0.032	156.346	1.037E+01	7.470E+00	power bound hit (power = 1)
Gamma, unrestricted	2	0.945	147.148	error	error	unrestricted (power = 0.341)
Log-logistic, unrestricted[b]	2	0.744	147.631	5.969E−01	6.773E−02	unrestricted (slope = 0.48)
Log-probit, unrestricted	2	0.670	147.844	5.939E−01	8.147E−02	unrestricted (slope = 0.279)
Weibull, unrestricted	2	0.866	147.324	5.539E−01	5.181E−02	unrestricted (power = 0.405)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.2.53.2. *Output for Selected Model: Log-Logistic*

Toth et al. ([1979](#)): Skin Lesions

```
=====================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\Blood\63_Toth_1979_SkinLes_LogLogistic_1.(d)
        Gnuplot Plotting File:
C:\1\Blood\63_Toth_1979_SkinLes_LogLogistic_1.plt
                                        Wed Feb 10 14:47:53 2010
=====================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
```

```
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


                    Default Initial Parameter Values
                       background =           0
                        intercept =    -3.94312
                            slope =           1



        Asymptotic Correlation Matrix of Parameter Estimates


        ( *** The model parameter(s)  -slope
               have been estimated at a boundary point, or have been
specified by the user,
               and do not appear in the correlation matrix )


             background    intercept


background            1        -0.43


 intercept        -0.43             1




                            Parameter Estimates


                                                95.0% Wald
Confidence Interval
      Variable         Estimate       Std. Err.      Lower Conf. Limit
Upper Conf. Limit
     background       0.0564562             *                *
*
      intercept        -4.05558             *                *
*
         slope               1             *                *
*


* - Indicates that this value is not calculated.




                         Analysis of Deviance Table


      Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model       -71.5177          4
    Fitted model      -74.9813          2       6.92722       2
0.03132
    Reduced model     -95.8498          1      48.6642        3        <.0001


         AIC:          153.963
```

```
                         Goodness  of  Fit
                                                        Scaled
        Dose      Est._Prob.    Expected    Observed    Size    Residual
     --------------------------------------------------------------------
      0.0000       0.0565         2.145       0.000       38     -1.508
      0.5732       0.0657         2.892       5.000       44      1.282
     14.2123       0.2429        10.687      13.000       44      0.813
     91.2070       0.6343        27.275      25.000       43     -0.720


  Chi^2 = 5.10       d.f. = 2         P-value = 0.0782



    Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =       Extra risk

Confidence level =            0.95

            BMD =        6.4132

           BMDL =        4.0249
```

Log-Logistic Model with 0.95 Confidence Level

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2
3
4 **G.2.53.4.** *Output for Additional Model Presented: Log-Logistic, Unrestricted*

5 Toth et al. (1979): Skin Lesions

6
7
```
8   ========================================================================
9           Logistic Model. (Version: 2.12; Date: 05/16/2008)
10          Input Data File: C:\1\Blood\63_Toth_1979_SkinLes_LogLogistic_U_1.(d)
11          Gnuplot Plotting File:
12  C:\1\Blood\63_Toth_1979_SkinLes_LogLogistic_U_1.plt
13                                          Wed Feb 10 14:47:54 2010
14  ========================================================================
15
16  Table 2
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the probability function is:
20
21     P[response] = background+(1-background)/[1+EXP(-intercept-
22  slope*Log(dose))]
23
24
25     Dependent variable = DichEff
26     Independent variable = Dose
27     Slope parameter is not restricted
```

```
   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =            0
                      intercept =     -1.87608
                          slope =     0.458888



          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -background
                   have been estimated at a boundary point, or have been
   specified by the user,
                   and do not appear in the correlation matrix )

                  intercept          slope

    intercept             1          -0.86

       slope         -0.86              1




                            Parameter Estimates

                                                     95.0% Wald
   Confidence Interval
        Variable          Estimate        Std. Err.      Lower Conf. Limit
   Upper Conf. Limit
       background                0             *                *
   *
         intercept         -1.94946             *                *
   *
            slope          0.4802              *                *
   *


   * - Indicates that this value is not calculated.




                          Analysis of Deviance Table

        Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
        Full model       -71.5177         4
      Fitted model       -71.8153         2      0.59526       2
   0.7426
     Reduced model       -95.8498         1      48.6642       3        <.0001
```

```
          AIC:           147.631


                     Goodness  of  Fit
                                                     Scaled
     Dose     Est._Prob.    Expected    Observed    Size    Residual
    ----------------------------------------------------------------------
    0.0000    0.0000        0.000       0.000        38      0.000
    0.5732    0.0983        4.323       5.000        44      0.343
   14.2123    0.3374       14.845      13.000        44     -0.588
   91.2070    0.5542       23.832      25.000        43      0.358


 Chi^2 = 0.59      d.f. = 2       P-value = 0.7438


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =           0.95

          BMD =        0.596932

          BMDL =       0.06773
```

1   **G.2.53.5.** *Figure for Additional Model Presented: Log-Logistic, Unrestricted*

Log-Logistic Model with 0.95 Confidence Level

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2
3
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G.2.54. van Birgelen et al. (1995): Hepatic Retinol

2 ***G.2.54.1. Summary Table of BMDS Modeling Results***

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	4	<0.0001	159.735	7.790E+00	4.150E+00	
Exponential (M3)	4	<0.0001	3,222.700	5.542E+01	error	power hit bound ($d = 1$)
Exponential (M4)[b]	**3**	**<0.001**	**141.454**	**2.488E+01**	**3.363E+00**	
Exponential (M5)	3	<0.001	141.454	2.488E+01	3.363E+00	power hit bound ($d = 1$)
Hill	3	0.239	124.865	5.316E+00	error	*n* lower bound hit ($n = 1$)
Linear	4	<0.0001	176.828	1.877E+02	1.437E+02	
Polynomial, 5-degree	4	<0.0001	176.828	1.877E+02	1.437E+02	
Power	4	<0.0001	176.828	1.877E+02	1.437E+02	power bound hit (power = 1)
Hill, unrestricted	2	0.241	125.495	3.595E+00	error	unrestricted ($n = 0.763$)
Power, unrestricted[c]	3	0.011	131.771	3.802E−01	1.393E−02	unrestricted (power = 0.14)

[a] Nonconstant variance model selected ($p = $ <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

3
4
5 ***G.2.54.2. Output for Selected Model: Exponential (M4)***

6 van Birgelen et al. (1995): Hepatic Retinol
7
8
9
```
     ====================================================================
10         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
11         Input Data File: C:\1\Blood\65_VanB_1995a_HepRet_Exp_1.(d)
12         Gnuplot Plotting File:
13                                        Mon Feb 08 13:32:00 2010
14     ====================================================================
15
16   Tbl3, hepatic retinol
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the response function by Model:
20        Model 2:    Y[dose] = a * exp{sign * b * dose}
21        Model 3:    Y[dose] = a * exp{sign * (b * dose)^d}
22        Model 4:    Y[dose] = a * [c-(c-1) * exp{-b * dose}]
23        Model 5:    Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
24
25      Note: Y[dose] is the median response for exposure = dose;
26           sign = +1 for increasing trend in data;
27           sign = -1 for decreasing trend.
28
29        Model 2 is nested within Models 3 and 4.
30        Model 3 is nested within Model 5.
```

```
       Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                   Initial Parameter Values

                   Variable          Model 4
                   --------          --------
                    lnalpha          -1.16065
                       rho           1.53688
                         a            15.645
                         b          0.0254351
                         c          0.0365247
                         d                  1



                   Parameter Estimates

                   Variable          Model 4
                   --------          -------
                    lnalpha          -0.92683
                       rho           1.77262
                         a           11.5049
                         b          0.0286598
                         c          0.0653043
                         d                  1


           Table of Stats From Input Data

    Dose      N        Obs Mean      Obs Std Dev
    -----    ---      ----------     ------------
        0     8          14.9          8.768
    7.204     8           8.4          3.394
    11.76     8           8.2          2.263
    18.09     8           5.1          0.8485
    86.41     8           2.2          0.8485
    250.2     8           0.6          0.5657



               Estimated Values of Interest
```

```
       Dose      Est Mean      Est Std    Scaled Residual
     ------    ----------    ---------    ----------------
         0          11.5        5.483              1.751
     7.204         9.499        4.627            -0.6719
     11.76         8.428        4.161            -0.1552
     18.09         7.154        3.599             -1.615
     86.41         1.655       0.9832              1.568
     250.2        0.7596       0.4931            -0.9155




   Other models for which likelihoods are calculated:

      Model A1:         Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma^2

      Model A2:         Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma(i)^2

      Model A3:         Yij = Mu(i) + e(ij)
                 Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

      Model  R:         Yij = Mu + e(i)
                 Var{e(ij)} = Sigma^2



                          Likelihoods of Interest

                    Model      Log(likelihood)      DF         AIC
                   -------    -----------------    ----    ------------
                     A1          -87.1567            7       188.3134
                     A2         -47.28742           12       118.5748
                     A3         -55.32422            8       126.6484
                      R          -109.967            2        223.934
                      4         -65.72714            5       141.4543



   Additive constant for all log-likelihoods =     -44.11.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                           Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 6a: Does Model 4 fit the data? (A3 vs 4)



                             Tests of Interest

     Test        -2*log(Likelihood Ratio)         D. F.        p-value
   --------      ----------------------         ------      --------------
```

```
Test 1                              125.4        10        < 0.0001
Test 2                              79.74         5        < 0.0001
Test 3                              16.07         4        0.002922
Test 6a                            20.81         3        0.0001155
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose
levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous
variance model appears to be appropriate.

The p-value for Test 3 is less than .1. You may want to
consider a different variance model.

The p-value for Test 6a is less than .1. Model 4 may not adequately
describe the data; you may want to consider another model.

Benchmark Dose Computations:

   Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

   Confidence Level = 0.950000

                 BMD =   24.8811

                 BMDL =   3.36281

```

1    **G.2.54.3.** *Figure for Selected Model: Exponential (M4)*



Exponential Model 4 with 0.95 Confidence Level

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2
3
4    **G.2.54.4.** *Output for Additional Model Presented: Power, Unrestricted*

5    van Birgelen et al. (1995): Hepatic Retinol

6
7       ========================================================================
8              Power Model. (Version: 2.15;  Date: 04/07/2008)
9              Input Data File: C:\1\Blood\65_VanB_1995a_HepRet_Pwr_U_1.(d)
10             Gnuplot Plotting File:  C:\1\Blood\65_VanB_1995a_HepRet_Pwr_U_1.plt
11                                       Mon Feb 08 13:32:03 2010
12      ========================================================================
13
14   Tbl3, hepatic retinol
15   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
16
17      The form of the response function is:
18
19      Y[dose] = control + slope * dose^power
20
21
22      Dependent variable = Mean
23      Independent variable = Dose
24      The power is not restricted

The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


                    Default Initial Parameter Values
                          lalpha =        2.76506
                             rho =              0
                         control =           14.9
                           slope =       -3.98831
                           power =       0.231232


          Asymptotic Correlation Matrix of Parameter Estimates

                   lalpha          rho       control        slope        power

     lalpha             1         -0.8       -0.042        0.038        0.063

        rho          -0.8            1       -0.089       0.0044         -0.1

    control        -0.042       -0.089            1        -0.95        -0.81

      slope         0.038       0.0044        -0.95            1         0.95

      power         0.063         -0.1        -0.81         0.95            1



                              Parameter Estimates

                                                         95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          lalpha       -0.986251         0.394722          -1.75989
-0.212609
             rho         1.67858         0.202896           1.28091
2.07625
         control         16.9266          2.23237           12.5513
21.302
           slope        -7.51118          2.04379          -11.5169
-3.50543
           power        0.139871        0.0269576         0.0870351
0.192707



     Table of Data and Estimated Values of Interest

 Dose        N    Obs Mean      Est Mean    Obs Std Dev   Est Std Dev    Scaled
Res.

```
 ------   ---   --------   --------   -----------   -----------   ---------
 -

     0   8   14.9   16.9   8.77   6.56   -0.874
 7.204   8   8.4   7.03   3.39   3.14   1.24
 11.76   8   8.2   6.32   2.26   2.87   1.85
 18.09   8   5.1   5.67   0.849   2.62   -0.611
 86.41   8   2.2   2.91   0.849   1.5   -1.34
 250.2   8   0.6   0.666   0.566   0.434   -0.427

  Model Descriptions for likelihoods calculated

  Model A1:   Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

  Model A2:   Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

  Model A3:   Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

  Model R: Yi = Mu + e(i)
           Var{e(i)} = Sigma^2

                    Likelihoods of Interest

            Model   Log(likelihood)   # Param's   AIC
            A1   -87.156698   7   188.313395
            A2   -47.287416   12   118.574833
            A3   -55.324218   8   126.648436
         fitted   -60.885746   5   131.771493
            R   -109.967018   2   223.934036

                    Explanation of Tests

  Test 1: Do responses and/or variances differ among Dose levels?
           (A2 vs. R)
  Test 2: Are Variances Homogeneous? (A1 vs A2)
  Test 3: Are variances adequately modeled? (A2 vs. A3)
  Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
  (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test   -2*log(Likelihood Ratio) Test df   p-value

   Test 1   125.359   10   <.0001
   Test 2   79.7386   5   <.0001
   Test 3   16.0736   4   0.002922
   Test 4   11.1231   3   0.01108
```

```
1
2    The p-value for Test 1 is less than .05.  There appears to be a
3    difference between response and/or variances among the dose levels
4    It seems appropriate to model the data
5
6    The p-value for Test 2 is less than .1.  A non-homogeneous variance
7    model appears to be appropriate
8
9    The p-value for Test 3 is less than .1.  You may want to consider a
10   different variance model
11
12   The p-value for Test 4 is less than .1.  You may want to try a different
13   model
14
15
16                    Benchmark Dose Computation
17
18   Specified effect =              1
19
20   Risk Type        =     Estimated standard deviations from the control mean
21
22   Confidence level =          0.95
23
24             BMD = 0.380208
25
26
27           BMDL = 0.013927
28
29
```

1   **G.2.54.5.** *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

13:32 02/08 2010

2
3
4

1   **G.2.55. van Birgelen et al. ([1995](#)): Hepatic Retinol Palmitate**

2   **G.2.55.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 p-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	4	<0.0001	460.282	error	error	
Exponential (M3)	4	<0.0001	460.282	error	error	power hit bound ($d = 1$)
Exponential (M4)[b]	**3**	**<0.0001**	**446.995**	**1.415E+02**	**3.647E+01**	
Exponential (M5)	3	<0.0001	446.995	1.415E+02	3.647E+01	power hit bound ($d = 1$)
Hill	3	0.009	416.233	3.657E+00	error	*n* lower bound hit ($n = 1$)
Linear	4	<0.0001	486.375	3.487E+02	2.412E+02	
Polynomial, 5-degree	0	N/A	584.170	error	5.617E+02	
Power	4	<0.0001	486.375	3.487E+02	2.412E+02	power bound hit (power = 1)
Hill, unrestricted	3	<0.0001	527.310	6.875E−14	6.875E−14	unrestricted ($n = 0.613$)
Power, unrestricted[c]	3	0.239	408.982	5.262E−02	5.889E−05	unrestricted (power = 0.064)

[a] Nonconstant variance model selected ($p = $ <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

3
4
5   **G.2.55.2.** *Output for Selected Model: Exponential (M4)*

6   van Birgelen et al. ([1995](#)): Hepatic Retinol Palmitate
7
8
9
```
10        =====================================================================
11             Exponential Model. (Version: 1.61;  Date: 7/24/2009)
12             Input Data File: C:\1\Blood\66_VanB_1995a_HepRetPalm_Exp_1.(d)
13             Gnuplot Plotting File:
                                            Mon Feb 08 13:32:41 2010
14        =====================================================================
15
16     Tbl3, hepatic retinol palmitate
17   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19      The form of the response function by Model:
20         Model 2:     Y[dose] = a * exp{sign * b * dose}
21         Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
22         Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
23         Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
24
25       Note: Y[dose] is the median response for exposure = dose;
26             sign = +1 for increasing trend in data;
27             sign = -1 for decreasing trend.
28
29         Model 2 is nested within Models 3 and 4.
30         Model 3 is nested within Model 5.
```

```
        Model 4 is nested within Model 5.


    Dependent variable = Mean
    Independent variable = Dose
    Data are assumed to be distributed: normally
    Variance Model: exp(lnalpha +rho *ln(Y[dose]))
    The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

    Total number of dose groups = 6
    Total number of records with missing values = 0
    Maximum number of iterations = 250
    Relative Function Convergence has been set to: 1e-008
    Parameter Convergence has been set to: 1e-008


    MLE solution provided: Exact


                        Initial Parameter Values

                        Variable          Model 4
                        --------          --------
                          lnalpha          0.284674
                             rho           1.77158
                               a             495.6
                               b         0.0337826
                               c        0.00576502
                               d                 1




                         Parameter Estimates

                        Variable          Model 4
                        --------          -------
                          lnalpha         -0.241601
                             rho           2.03456
                               a           223.848
                               b         0.0300737
                               c         0.0129253
                               d                 1


      NC = No Convergence


          Table of Stats From Input Data

      Dose      N        Obs Mean      Obs Std Dev
      -----     ---      ----------     -------------
          0      8          472           271.5
      7.204      8           94           67.88
      11.76      8          107           76.37
      18.09      8           74            39.6
      86.41      8           22           22.63
      250.2      8            3           2.828
```

```
                    Estimated Values of Interest

       Dose      Est Mean      Est Std      Scaled Residual
      ------    ----------    ---------     ----------------
          0         223.8        217.8                3.222
      7.204         180.8        175.3               -1.401
      11.76           158        152.9              -0.9443
      18.09         131.1        126.4               -1.278
      86.41         19.33        18.03               0.4197
      250.2         3.013        2.721             -0.01317




   Other models for which likelihoods are calculated:

      Model A1:        Yij = Mu(i) + e(ij)
                Var{e(ij)} = Sigma^2

      Model A2:        Yij = Mu(i) + e(ij)
                Var{e(ij)} = Sigma(i)^2

      Model A3:        Yij = Mu(i) + e(ij)
                Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

      Model  R:        Yij = Mu + e(i)
                Var{e(ij)} = Sigma^2



                       Likelihoods of Interest

                Model    Log(likelihood)     DF        AIC
                -------   ----------------    ----    ------------
                  A1        -250.5548          7        515.1096
                  A2        -196.7557         12        417.5115
                  A3        -197.3832          8        410.7663
                   R        -276.7896          2        557.5793
                   4        -218.4977          5        446.9954



   Additive constant for all log-likelihoods =      -44.11.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                          Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 6a: Does Model 4 fit the data? (A3 vs 4)



                          Tests of Interest
```

```
      Test              -2*log(Likelihood Ratio)         D. F.          p-value
    --------            ------------------------          ------      --------------
    Test 1                           160.1                 10          < 0.0001
    Test 2                           107.6                  5          < 0.0001
    Test 3                           1.255                  4             0.869
   Test 6a                           42.23                  3          < 0.0001
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose
levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous
variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled
variance appears to be appropriate here.

The p-value for Test 6a is less than .1. Model 4 may not adequately
describe the data; you may want to consider another model.

Benchmark Dose Computations:

  Specified Effect = 1.000000

        Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

              BMD =   141.528

              BMDL =   36.4721

1 **G.2.55.3.** *Figure for Selected Model: Exponential (M4)*

Exponential Model 4 with 0.95 Confidence Level

13:32 02/08 2010

2
3
4 **G.2.55.4.** *Output for Additional Model Presented: Power, Unrestricted*

5 van Birgelen et al. (1995): Hepatic Retinol Palmitate

6
7
```
8  ====================================================================
9       Power Model. (Version: 2.15;  Date: 04/07/2008)
10      Input Data File: C:\1\Blood\66_VanB_1995a_HepRetPalm_Pwr_U_1.(d)
11      Gnuplot Plotting File:
12 C:\1\Blood\66_VanB_1995a_HepRetPalm_Pwr_U_1.plt
13                                    Mon Feb 08 13:32:47 2010
14  ====================================================================
15
16  Tbl3, hepatic retinol palmitate
17 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19    The form of the response function is:
20
21    Y[dose] = control + slope * dose^power
22
23
```

```
 1    Dependent variable = Mean
 2    Independent variable = Dose
 3    The power is not restricted
 4    The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
 5
 6    Total number of dose groups = 6
 7    Total number of records with missing values = 0
 8    Maximum number of iterations = 250
 9    Relative Function Convergence has been set to: 1e-008
10    Parameter Convergence has been set to: 1e-008
11
12
13
14                    Default Initial Parameter Values
15                          lalpha =       9.57332
16                             rho =             0
17                         control =           472
18                           slope =      -320.514
19                           power =     0.0711173
20
21
22        Asymptotic Correlation Matrix of Parameter Estimates
23
24              lalpha          rho       control         slope          power
25
26    lalpha          1        -0.95           0.3         -0.31          -0.3
27
28       rho      -0.95            1         -0.41          0.39          0.29
29
30   control        0.3        -0.41             1         -0.98         -0.82
31
32     slope      -0.31         0.39         -0.98             1           0.9
33
34     power       -0.3         0.29         -0.82           0.9             1
35
36
37
38                            Parameter Estimates
39
40                                                      95.0% Wald
41   Confidence Interval
42        Variable        Estimate       Std. Err.    Lower Conf. Limit
43   Upper Conf. Limit
44        lalpha        0.0640168        0.859472            -1.62052
45   1.74855
46           rho         1.81132         0.197468             1.42429
47   2.19835
48       control          464.29         87.5705             292.655
49   635.925
50         slope        -324.216         83.3327            -487.545
51   -160.887
52         power       0.0639088       0.0139778           0.0365129
53   0.0913048
54
55
56
57      Table of Data and Estimated Values of Interest
```

```
 Dose        N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------      ---   --------     --------   -----------  -----------   ---------
-


    0        8       472          464          272          269        0.0812
7.204        8        94         96.5         67.9         64.7        -0.108
11.76        8       107         84.8         76.4         57.6         1.09
18.09        8        74         74.2         39.6           51        -0.00941
86.41        8        22         33.2         22.6         24.6         -1.28
250.2        8         3         2.86         2.83         2.68        0.145




 Model Descriptions for likelihoods calculated


 Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                    Likelihoods of Interest

            Model     Log(likelihood)   # Param's       AIC
            A1          -250.554817          7       515.109634
            A2          -196.755746         12       417.511491
            A3          -197.383174          8       410.766347
         fitted         -199.490808          5       408.981615
            R           -276.789644          2       557.579287



                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)   Test df        p-value

   Test 1            160.068              10           <.0001
```

```
Test 2                 107.598          5              <.0001
Test 3                 1.25486          4               0.869
Test 4                 4.21527          3              0.2391


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


                  Benchmark Dose Computation

Specified effect =               1

Risk Type        =       Estimated standard deviations from the control mean

Confidence level =            0.95

           BMD = 0.0526247



          BMDL = 5.88883e-005
```

1   **G.2.55.5. *Figure for Additional Model Presented: Power, Unrestricted***

Power Model with 0.95 Confidence Level

13:32 02/08 2010

2
3
4

G.2.56. White et al. ([1986](#)): CH50

G.2.56.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg)	BMDL (ng/kg)	Notes
Exponential (M2)	5	0.002	389.664	1.957E+01	1.261E+01	
Exponential (M3)	5	0.002	389.664	1.957E+01	1.261E+01	power hit bound (*d* = 1)
Exponential (M4)	4	0.001	390.632	1.411E+01	5.177E+00	
Exponential (M5)	4	0.001	390.632	1.411E+01	5.177E+00	power hit bound (*d* = 1)
Hill[b]	**4**	**0.002**	**389.601**	**8.632E+00**	**1.498E+00**	***n* lower bound hit (*n* = 1)**
Linear	5	<0.001	394.446	3.497E+01	2.568E+01	
Polynomial, 6-degree	5	<0.001	394.446	3.497E+01	2.568E+01	
Power	5	<0.001	394.446	3.497E+01	2.568E+01	power bound hit (power = 1)
Hill, unrestricted[c]	3	0.071	381.520	1.481E−01	4.351E−03	unrestricted (*n* = 0.246)
Power, unrestricted	4	0.148	379.265	1.211E−01	1.225E−03	unrestricted (power = 0.227)

[a] Nonconstant variance model selected (*p* = 0.0871).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.2.56.2. *Output for Selected Model: Hill*

White et al. ([1986](#)): CH50

```
 =====================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\Blood\71_White_1986_CH50_Hill_1.(d)
        Gnuplot Plotting File:  C:\1\Blood\71_White_1986_CH50_Hill_1.plt
                                    Mon Feb 08 13:35:56 2010
 =====================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   Power parameter restricted to be greater than 1
   The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

   Total number of dose groups = 7
   Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          lalpha =      5.60999
                             rho =            0
                       intercept =           91
                               v =          -74
                               n =     0.118036
                               k =        1.094



            Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -n
                   have been estimated at a boundary point, or have been
specified by the user,
                   and do not appear in the correlation matrix )

                lalpha          rho     intercept             v             k

    lalpha           1        -0.99          0.27          0.23         -0.32

       rho       -0.99            1         -0.28         -0.24          0.33

 intercept        0.27        -0.28             1          0.39         -0.78

         v        0.23        -0.24          0.39             1         -0.85

         k       -0.32         0.33         -0.78         -0.85             1




                              Parameter Estimates

                                                      95.0% Wald
Confidence Interval
        Variable       Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
         lalpha          4.581          1.66273              1.32211
7.83989
            rho        0.31293         0.431616            -0.533022
1.15888
      intercept        74.6365          6.33673              62.2167
87.0562
              v       -66.2096          14.7876             -95.1928
-37.2264
              n              1               NA
              k        20.8286          21.3237              -20.965
62.6223


NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

```
      Table of Data and Estimated Values of Interest

  Dose        N     Obs Mean     Est Mean    Obs Std Dev   Est Std Dev   Scaled
Res.
 ------       ---   --------     --------    -----------   -----------   ---------
 -

     0        8        91        74.6           14.1          19.4          2.39
 1.094        8        54        71.3           8.49          19.3         -2.54
 4.085        8        63        63.8           11.3          18.9         -0.117
  7.14        8        56        57.7           25.5          18.6         -0.263
 26.81        8        41        37.4           17            17.4          0.589
 48.72        8        32        28.3           17            16.7          0.636
 90.56        8        17        20.8           17            15.9         -0.678



Model Descriptions for likelihoods calculated


 Model A1:         Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:         Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:         Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:          Yi = Mu + e(i)
           Var{e(i)} = Sigma^2



                      Likelihoods of Interest

             Model       Log(likelihood)    # Param's      AIC
             A1          -181.340979            8        378.681959
             A2          -175.820265           14        379.640529
             A3          -181.238690            9        380.477380
          fitted         -189.800288            5        389.600575
             R           -212.367055            2        428.734109



                      Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

```
                        Tests of Interest

     Test     -2*log(Likelihood Ratio)   Test df        p-value

     Test 1              73.0936              12           <.0001
     Test 2              11.0414               6           0.0871
     Test 3              10.8369               5           0.05471
     Test 4              17.1232               4           0.001829

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model



          Benchmark Dose Computation

Specified effect =              1

Risk Type        =      Estimated standard deviations from the control mean

Confidence level =            0.95

           BMD =         8.63239

          BMDL =        1.49823
```

1   **G.2.56.3.** *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

13:35 02/08 2010

2
3
4   **G.2.56.4.** *Output for Additional Model Presented: Hill, Unrestricted*

5   White et al. (1986): CH50

6
7
8   ```
9   Hill Model. (Version: 2.14; Date: 06/26/2008)
10   Input Data File: C:\1\Blood\71_White_1986_CH50_Hill_U_1.(d)
11   Gnuplot Plotting File: C:\1\Blood\71_White_1986_CH50_Hill_U_1.plt
12   Mon Feb 08 13:35:57 2010
13   ===
14
15   [insert study notes]
16   ~~~~~~
17
18   The form of the response function is:
19
20   Y[dose] = intercept + v*dose^n/(k^n + dose^n)
21
22
23   Dependent variable = Mean
24   Independent variable = Dose
```
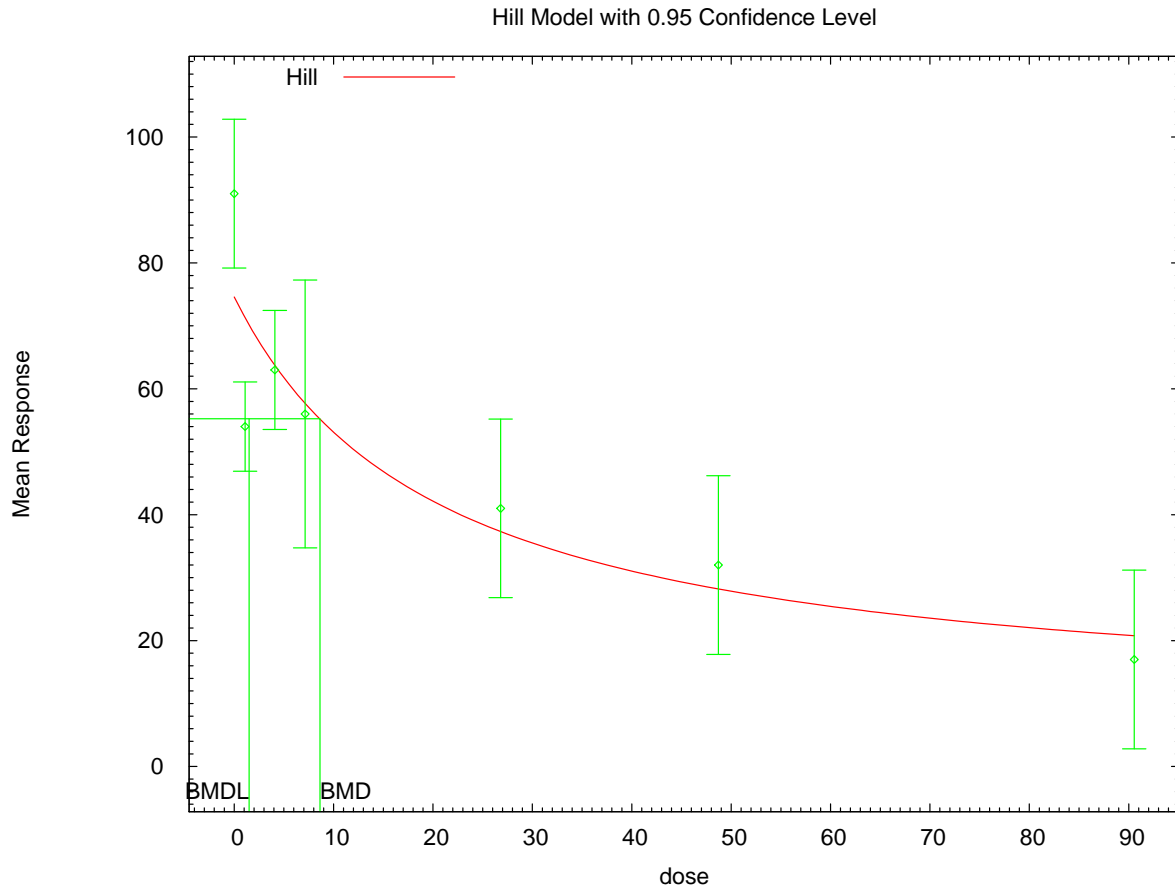
```
    Power parameter is not restricted
    The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

    Total number of dose groups = 7
    Total number of records with missing values = 0
    Maximum number of iterations = 250
    Relative Function Convergence has been set to: 1e-008
    Parameter Convergence has been set to: 1e-008




                     Default Initial Parameter Values
                          lalpha =        5.60999
                             rho =              0
                       intercept =             91
                               v =            -74
                               n =       0.118036
                               k =          1.094


           Asymptotic Correlation Matrix of Parameter Estimates

                     lalpha          rho     intercept             v             n
  k

      lalpha              1           -1          0.16          0.19          -0.4
  -0.014

         rho             -1            1         -0.16         -0.19           0.4
  0.011

   intercept           0.16        -0.16             1          0.15         -0.58
  0.015

           v           0.19        -0.19          0.15             1         -0.02
  -0.93

           n           -0.4          0.4         -0.58         -0.02             1
  -0.35

           k         -0.014        0.011         0.015         -0.93         -0.35
  1




                              Parameter Estimates


                                                        95.0% Wald
Confidence Interval
        Variable         Estimate         Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha          6.54093           2.08879               2.44698
10.6349
            rho        -0.245847          0.541645              -1.30745
0.815757
      intercept          89.6302           5.59428               78.6656
100.595
```

```
            v         -628.486           727.973           -2055.29
798.315
            n          0.246409          0.058636           0.131484
0.361333
            k            493877        2.74838e+006        -4.89284e+006
5.88059e+006




    Table of Data and Estimated Values of Interest

 Dose        N     Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
 ------      ---   --------     --------   -----------  -----------   ---------
 -

     0       8          91         89.6         14.1         15.1        0.256
1.094        8          54         65.2         8.49         15.8        -2.01
4.085        8          63         56.3         11.3           16         1.17
 7.14        8          56         51.7         25.5         16.2        0.746
26.81        8          41         38.3           17         16.8        0.453
48.72        8          32         30.9           17         17.3        0.175
90.56        8          17         22.3           17           18       -0.831




 Model Descriptions for likelihoods calculated


 Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

          Model     Log(likelihood)   # Param's       AIC
           A1        -181.340979           8       378.681959
           A2        -175.820265          14       379.640529
           A3        -181.238690           9       380.477380
         fitted      -184.759769           6       381.519538
            R        -212.367055           2       428.734109



                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
```

```
          (A2 vs. R)
  Test 2:  Are Variances Homogeneous? (A1 vs A2)
  Test 3:  Are variances adequately modeled? (A2 vs. A3)
  Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
  (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)


                    Tests of Interest


    Test    -2*log(Likelihood Ratio)  Test df       p-value


    Test 1            73.0936          12           <.0001
    Test 2            11.0414           6            0.0871
    Test 3            10.8369           5            0.05471
    Test 4            7.04216           3            0.07057
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1. You may want to consider a
different variance model

The p-value for Test 4 is less than .1. You may want to try a different
model


```
          Benchmark Dose Computation

Specified effect =               1

Risk Type        =      Estimated standard deviations from the control mean

Confidence level =            0.95

          BMD =       0.148074

          BMDL =    0.00435112
```

1 **G.2.56.5.** *Figure for Additional Model Presented: Hill, Unrestricted*

Hill Model with 0.95 Confidence Level

13:35 02/08 2010

2
3
4 **G.3. ADMINISTERED DOSE: BMDS RESULTS**

5 **G.3.1. Amin et al. (2000): 0.25% Saccharin Consumed, Female**

6 **G.3.1.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear[b]	**1**	**0.358**	**179.702**	**8.816E+01**	**5.890E+01**	
Polynomial, 2-degree	1	0.358	179.702	8.816E+01	5.890E+01	
Power	1	0.358	179.702	8.816E+01	5.890E+01	power bound hit (power = 1)
Power, unrestricted[c]	0	N/A	180.858	7.530E+01	2.537E+01	unrestricted (power = 0.605)

[a] Nonconstant variance model selected (*p* = 0.0005).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

7

G.3.1.2. *Output for Selected Model: Linear*

Amin et al. (2000): 0.25% Saccharin Consumed, Female

```
====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\1_Amin_2000_25_SC_Linear_1.(d)
        Gnuplot Plotting File:  C:\1\1_Amin_2000_25_SC_Linear_1.plt
                                        Tue Feb 16 17:22:16 2010
====================================================================

 -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                          lalpha =      5.29482
                             rho =            0
                          beta_0 =      30.8266
                          beta_1 =    -0.204134



        Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha           rho        beta_0        beta_1

     lalpha            1         -0.99        -0.016          0.03

        rho        -0.99             1         0.013        -0.026

     beta_0       -0.016         0.013             1         -0.94

     beta_1         0.03        -0.026         -0.94             1




                         Parameter Estimates
```

```
                                                          95.0% Wald
Confidence Interval
        Variable          Estimate          Std. Err.      Lower Conf. Limit
Upper Conf. Limit
          lalpha         -2.55843           1.66185              -5.8156
0.698746
            rho           2.42056          0.545617              1.35117
3.48995
         beta_0          30.3968           4.03582              22.4868
38.3069
         beta_1         -0.196699         0.0443352            -0.283594
-0.109803




     Table of Data and Estimated Values of Interest

 Dose       N     Obs Mean       Est Mean    Obs Std Dev   Est Std Dev    Scaled
Res.
 ------     ---   --------       --------    -----------   -----------   ---------
-

    0       10      31.7           30.4         20.6          17.3          0.233
   25       10      24.6           25.5          12            14          -0.2
  100       10      10.7           10.7         5.33          4.92         -0.0204




 Model Descriptions for likelihoods calculated


 Model A1:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:          Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                   Likelihoods of Interest

          Model     Log(likelihood)    # Param's        AIC
          A1         -92.841935             4        193.683870
          A2         -85.255316             6        182.510632
          A3         -85.429148             5        180.858295
        fitted       -85.851107             4        179.702213
          R          -98.136607             2        200.273213



                   Explanation of Tests
```

```
Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)


                      Tests of Interest


  Test     -2*log(Likelihood Ratio)  Test df        p-value

  Test 1               25.7626           4            <.0001
  Test 2               15.1732           2          0.0005072
  Test 3              0.347663           1            0.5554
  Test 4              0.843918           1            0.3583


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data



                  Benchmark Dose Computation

Specified effect =              1

Risk Type       =      Estimated standard deviations from the control mean

Confidence level =         0.95

           BMD =        88.1623


           BMDL =       58.9029
```

1 **G.3.1.3.** *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

17:22 02/16 2010

2
3
4 **G.3.1.4.** *Output for Additional Model Presented: Power, Unrestricted*

5 Amin et al. (2000): 0.25% Saccharin Consumed, Female
6
7
```
8    =====================================================================
9          Power Model. (Version: 2.15;   Date: 04/07/2008)
10         Input Data File: C:\1\1_Amin_2000_25_SC_Pwr_U_1.(d)
11         Gnuplot Plotting File:  C:\1\1_Amin_2000_25_SC_Pwr_U_1.plt
12                                      Tue Feb 16 17:22:17 2010
13   =====================================================================
14
15   -
16 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18    The form of the response function is:
19
20    Y[dose] = control + slope * dose^power
21
22
23    Dependent variable = Mean
24    Independent variable = Dose
```

```
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          lalpha =        5.29482
                             rho =              0
                         control =        31.6727
                           slope =      -0.567889
                           power =       0.783745


          Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho        control         slope          power

      lalpha          1        -0.99           0.34         -0.14         -0.061

         rho      -0.99            1          -0.42          0.15          0.068

     control       0.34        -0.42              1         -0.67          -0.56

       slope      -0.14         0.15          -0.67             1           0.99

       power     -0.061        0.068          -0.56          0.99              1




                              Parameter Estimates


                                                      95.0% Wald
Confidence Interval
       Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
         lalpha        -2.48291          2.08669           -6.57274
1.60693
            rho         2.38455         0.692047            1.02817
3.74094
        control           32.99          5.40754            22.3914
43.5886
          slope        -1.36469          2.01258           -5.30927
2.5799
          power        0.605364         0.288476          0.0399625
1.17077




     Table of Data and Estimated Values of Interest
```

```
Dose       N    Obs Mean     Est Mean  Obs Std Dev  Est Std Dev   Scaled
Res.
------    ---   --------     --------  -----------  -----------   ---------
-

    0     10      31.7          33         20.6         18.7        -0.223
   25     10      24.6        23.4          12         12.4         0.302
  100     10      10.7        10.8        5.33         4.94         -0.08
```

Warning: Likelihood for fitted model larger than the Likelihood for model
A3.

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2
```

Likelihoods of Interest

```
          Model    Log(likelihood)   # Param's      AIC
           A1        -92.841935           4      193.683870
           A2        -85.255316           6      182.510632
           A3        -85.429148           5      180.858295
        fitted       -85.429148           5      180.858295
           R         -98.136607           2      200.273213
```

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

```
  Test     -2*log(Likelihood Ratio)   Test df        p-value

  Test 1            25.7626               4          <.0001
  Test 2            15.1732               2         0.0005072
```

```
   Test 3            0.347663           1             0.5554
   Test 4           -8.2423e-013        0             NA
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-
Square
     test for fit is not valid

                 Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

              BMD = 75.2994

              BMDL = 25.3717

1 **G.3.1.5.** *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

17:22 02/16 2010

2
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4 **G.3.2.** **Amin et al. (2000): 0.25% Saccharin Preference Ratio, Female**

5 **G.3.2.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear[b]	**1**	**0.002**	**228.094**	**1.264E+02**	**6.128E+01**	
Polynomial, 2-degree	1	0.002	228.094	1.264E+02	6.128E+01	
Power	1	0.002	228.094	1.264E+02	6.128E+01	power bound hit (power = 1)

[a] Nonconstant variance model selected (*p* = 0.0135).
[b] Best-fitting model, BMDS output presented in this appendix.

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G.3.2.2. *Output for Selected Model: Linear*

Amin et al. (2000): 0.25% Saccharin Preference Ratio, Female

```
  ====================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\1\2_Amin_2000_25_SP_Linear_1.(d)
         Gnuplot Plotting File:  C:\1\2_Amin_2000_25_SP_Linear_1.plt
                                        Tue Feb 16 17:22:44 2010
  ====================================================================

 -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                          lalpha =      6.34368
                             rho =            0
                          beta_0 =       74.2008
                          beta_1 =     -0.219781



        Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho        beta_0        beta_1

     lalpha            1           -1           0.2         -0.28

        rho           -1            1         -0.19          0.28

     beta_0          0.2        -0.19             1         -0.76

     beta_1        -0.28         0.28         -0.76             1




                        Parameter Estimates
```

```
                                                   95.0% Wald
Confidence Interval
        Variable         Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
         lalpha          0.338774         9.23768          -17.7667
18.4443
            rho          1.43998          2.21674          -2.90476
5.78472
         beta_0          73.6633          6.6623            60.6054
86.7211
         beta_1         -0.207175         0.101074         -0.405276
-0.00907442




     Table of Data and Estimated Values of Interest

 Dose       N     Obs Mean      Est Mean    Obs Std Dev   Est Std Dev   Scaled
Res.
 ------     ---   --------      --------    -----------   -----------   ---------
-

    0       10     82.1          73.7          13.3          26.2          1.02
   25       10     58.1          68.5          33.9          24.8         -1.32
  100       10     54.9          52.9          19.5          20.6          0.295




 Model Descriptions for likelihoods calculated


 Model A1:         Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:         Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:         Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                    Likelihoods of Interest

          Model     Log(likelihood)    # Param's      AIC
          A1         -108.574798            4       225.149597
          A2         -104.269377            6       220.538754
          A3         -105.147952            5       220.295903
        fitted       -110.046917            4       228.093834
          R          -112.382522            2       228.765045


                  Explanation of Tests
```

```
Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test     -2*log(Likelihood Ratio)  Test df       p-value

   Test 1                16.2263          4          0.00273
   Test 2                8.61084          2          0.0135
   Test 3                1.75715          1           0.185
   Test 4                9.79793          1          0.001747

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


                  Benchmark Dose Computation

Specified effect =              1

Risk Type        =      Estimated standard deviations from the control mean

Confidence level =          0.95

          BMD =         126.365


          BMDL =        61.2812
```

1   **G.3.2.3.**   *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

17:22 02/16 2010

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4   **G.3.3.   Amin et al. ([2000](#)): 0.50% Saccharin Consumed, Female**

5   **G.3.3.1.**   *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear[b]	**1**	**0.031**	**159.737**	**9.874E+01**	**6.417E+01**	
Polynomial, 2-degree	1	0.031	159.737	9.874E+01	6.417E+01	
Power	1	0.031	159.737	9.874E+01	6.417E+01	power bound hit (power = 1)
Power, unrestricted[c]	0	N/A	157.060	5.610E+01	6.781E+00	unrestricted (power = 0.325)

[a] Nonconstant variance model selected (p = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

6
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8

G.3.3.2.   *Output for Selected Model: Linear*

Amin et al. (2000): 0.50% Saccharin Consumed, Female

```
====================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\1\3_Amin_2000_50_SC_Linear_1.(d)
        Gnuplot Plotting File:  C:\1\3_Amin_2000_50_SC_Linear_1.plt
                                        Tue Feb 16 17:23:14 2010
====================================================================

 -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




                 Default Initial Parameter Values
                        lalpha =      4.68512
                           rho =            0
                        beta_0 =      19.3484
                        beta_1 =    -0.158141



        Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho         beta_0         beta_1

    lalpha             1        -0.97          0.018        -0.0021

       rho         -0.97            1         -0.027          0.014

    beta_0         0.018       -0.027              1          -0.95

    beta_1       -0.0021        0.014          -0.95              1




                        Parameter Estimates
```

```
                                                    95.0% Wald
Confidence Interval
       Variable          Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
         lalpha         -0.997428         0.992786            -2.94325
0.948397
            rho          2.13634          0.404989             1.34257
2.9301
         beta_0          18.1144          3.10302             12.0326
24.1962
         beta_1         -0.135736         0.0331501           -0.200709
-0.0707631




    Table of Data and Estimated Values of Interest

 Dose       N     Obs Mean      Est Mean    Obs Std Dev   Est Std Dev    Scaled
Res.
 ------     ---   --------      --------    -----------   -----------   ---------
-

     0      10      22.4          18.1           16           13.4             1
    25      10      11.4          14.7          7.66          10.7         -0.983
   100      10      4.54          4.54          3.33          3.06       -0.00393




 Model Descriptions for likelihoods calculated


 Model A1:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:          Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                     Likelihoods of Interest

          Model      Log(likelihood)    # Param's        AIC
           A1         -83.696404             4        175.392808
           A2         -73.511830             6        159.023660
           A3         -73.530233             5        157.060467
         fitted       -75.868688             4        159.737377
           R          -90.294746             2        184.589492



                    Explanation of Tests
```

```
Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                   Tests of Interest

  Test     -2*log(Likelihood Ratio)  Test df       p-value

  Test 1              33.5658          4           <.0001
  Test 2              20.3691          2           <.0001
  Test 3              0.0368066        1           0.8479
  Test 4              4.67691          1           0.03057
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different
model


```
                 Benchmark Dose Computation

Specified effect =              1

Risk Type         =      Estimated standard deviations from the control mean

Confidence level =          0.95

           BMD =         98.7409


           BMDL =         64.169
```

G.3.3.3. *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

17:23 02/16 2010

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4 **G.3.3.4.** *Output for Additional Model Presented: Power, Unrestricted*

5 Amin et al. (2000): 0.50% Saccharin Consumed, Female

6
7
```
8  =====================================================================
9          Power Model. (Version: 2.15;  Date: 04/07/2008)
10         Input Data File: C:\1\3_Amin_2000_50_SC_Pwr_U_1.(d)
11         Gnuplot Plotting File:  C:\1\3_Amin_2000_50_SC_Pwr_U_1.plt
12                                     Tue Feb 16 17:23:15 2010
13  =====================================================================
14
15  -
16 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18    The form of the response function is:
19
20    Y[dose] = control + slope * dose^power
21
22
23    Dependent variable = Mean
24    Independent variable = Dose
```

```
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                      Default Initial Parameter Values
                             lalpha =       4.68512
                                rho =             0
                            control =       22.3564
                              slope =      -3.55874
                              power =      0.349799


            Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho        control         slope         power

     lalpha            1        -0.96           0.34         -0.26         -0.15

        rho        -0.96            1          -0.47           0.3          0.15

    control         0.34        -0.47              1         -0.73         -0.52

      slope        -0.26          0.3          -0.73             1          0.96

      power        -0.15         0.15          -0.52          0.96             1




                               Parameter Estimates


                                                           95.0% Wald
Confidence Interval
        Variable        Estimate         Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha        -0.708629            1.298            -3.25267
1.83541
            rho         1.96142         0.529653            0.923323
2.99953
        control         22.6293          4.48416             13.8405
31.4181
          slope        -4.03215          3.21302            -10.3296
2.26526
          power        0.325414         0.138761            0.053447
0.597381




     Table of Data and Estimated Values of Interest
```

```
 Dose       N    Obs Mean    Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------    ---   --------    --------   -----------  -----------   ---------
-

    0    10      22.4        22.6          16          15        -0.0577
   25    10      11.4        11.1         7.66        7.46         0.105
  100    10      4.54        4.58         3.33        3.12        -0.0475

 Warning: Likelihood for fitted model larger than the Likelihood for model
A3.




 Model Descriptions for likelihoods calculated


 Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

            Model     Log(likelihood)   # Param's      AIC
             A1        -83.696404           4       175.392808
             A2        -73.511830           6       159.023660
             A3        -73.530233           5       157.060467
          fitted       -73.530233           5       157.060467
             R         -90.294746           2       184.589492


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df       p-value

   Test 1              33.5658          4          <.0001
   Test 2              20.3691          2          <.0001
```

```
Test 3              0.0368066        1            0.8479
Test 4             -2.84217e-014     0              NA
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-
Square
     test for fit is not valid

                 Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

          BMD = 56.0967

          BMDL = 6.78112

```

1 **G.3.3.5.** *Figure for Additional Model Presented: Power, Unrestricted*



Power Model with 0.95 Confidence Level

17:23 02/16 2010

2
3
4 **G.3.4.** **Amin et al. (2000): 0.50% Saccharin Preference Ratio, Female**

5 **G.3.4.1.** *Summary Table of BMDS Modeling Results*

| Model[a] | Degrees of freedom | $\chi^2$ p-value | AIC | BMD (ng/kg-day) | BMDL (ng/kg-day) | Notes |
|---|---|---|---|---|---|---|
| **Linear[b]** | **1** | **0.088** | **234.936** | **8.278E+01** | **5.100E+01** | |
| Polynomial, 2-degree | 1 | 0.088 | 234.936 | 8.278E+01 | 5.100E+01 | |
| Power | 1 | 0.088 | 234.936 | 8.278E+01 | 5.100E+01 | power bound hit (power = 1) |
| Power, unrestricted[c] | 0 | N/A | 234.020 | 1.817E+01 | 1.000E−13 | unrestricted (power = 0.232) |

[a] Constant variance model selected ($p$ = 0.5593).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

6
7
8

## G.3.4.2. *Output for Selected Model: Linear*

Amin et al. ([2000](#)): 0.50% Saccharin Preference Ratio, Female

```
==
       Polynomial Model. (Version: 2.13; Date: 04/08/2008)
       Input Data File: C:\1\4_Amin_2000_50_SP_LinearCV_1.(d)
       Gnuplot Plotting File: C:\1\4_Amin_2000_50_SP_LinearCV_1.plt
                                        Tue Feb 16 17:23:43 2010
==

 -
~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

                  Default Initial Parameter Values
                        alpha =   764.602
                          rho =   0   Specified
                       beta_0 =   64.1858
                       beta_1 =   -0.332668

          Asymptotic Correlation Matrix of Parameter Estimates

          (*** The model parameter(s) -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix)

                  alpha   beta_0   beta_1

     alpha   1   2e-008   1.4e-009

    beta_0   2e-008   1   -0.7

    beta_1   1.4e-009   -0.7   1

```

```
                              Parameter Estimates

                                                     95.0% Wald
Confidence Interval
       Variable   Estimate   Std. Err.   Lower Conf. Limit
Upper Conf. Limit
         alpha   758.396   195.817   374.602
1142.19
       beta_0   64.1858   7.04184   50.3841
77.9876
       beta_1   -0.332668   0.118327   -0.564584
-0.100752

    Table of Data and Estimated Values of Interest

 Dose   N   Obs Mean   Est Mean   Obs Std Dev Est Std Dev   Scaled
 Res.
 ------   ---   --------   --------   ----------- -----------   ---------
 -

    0   10   72.7   64.2   24.6   27.5   0.981
   25   10   44.5   55.9   32.9   27.5   -1.31
  100   10   33.8   30.9   24.6   27.5   0.327

 Model Descriptions for likelihoods calculated

 Model A1:   Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2

 Model A2:   Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma(i)^2

 Model A3:   Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model R: Yi = Mu + e(i)
         Var{e(i)} = Sigma^2

                      Likelihoods of Interest

          Model   Log(likelihood)   # Param's   AIC
          A1   -113.009921   4   234.019841
          A2   -112.428886   6   236.857773
          A3   -113.009921   4   234.019841
        fitted   -114.468091   3   234.936183
           R   -117.976057   2   239.952114
```

```
                      Explanation of Tests

  Test 1:  Do responses and/or variances differ among Dose levels?
           (A2 vs. R)
  Test 2:  Are Variances Homogeneous? (A1 vs A2)
  Test 3:  Are variances adequately modeled? (A2 vs. A3)
  Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
  (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                       Tests of Interest

     Test    -2*log(Likelihood Ratio)  Test df        p-value

     Test 1              11.0943           4           0.02552
     Test 2              1.16207           2            0.5593
     Test 3              1.16207           2            0.5593
     Test 4              2.91634           1            0.08769

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model



                 Benchmark Dose Computation

Specified effect =              1

Risk Type        =      Estimated standard deviations from the control mean

Confidence level =         0.95

           BMD =        82.7823


           BMDL =        50.9971
```

G.3.4.3.   *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

G.3.4.4.   *Output for Additional Model Presented: Power, Unrestricted*

Amin et al. (2000): 0.50% Saccharin Preference Ratio, Female

```
      ======================================================================
          Power Model. (Version: 2.15;  Date: 04/07/2008)
          Input Data File: C:\1\4_Amin_2000_50_SP_PwrCV_U_1.(d)
          Gnuplot Plotting File:  C:\1\4_Amin_2000_50_SP_PwrCV_U_1.plt
                                        Tue Feb 16 17:23:44 2010
      ======================================================================

   -
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
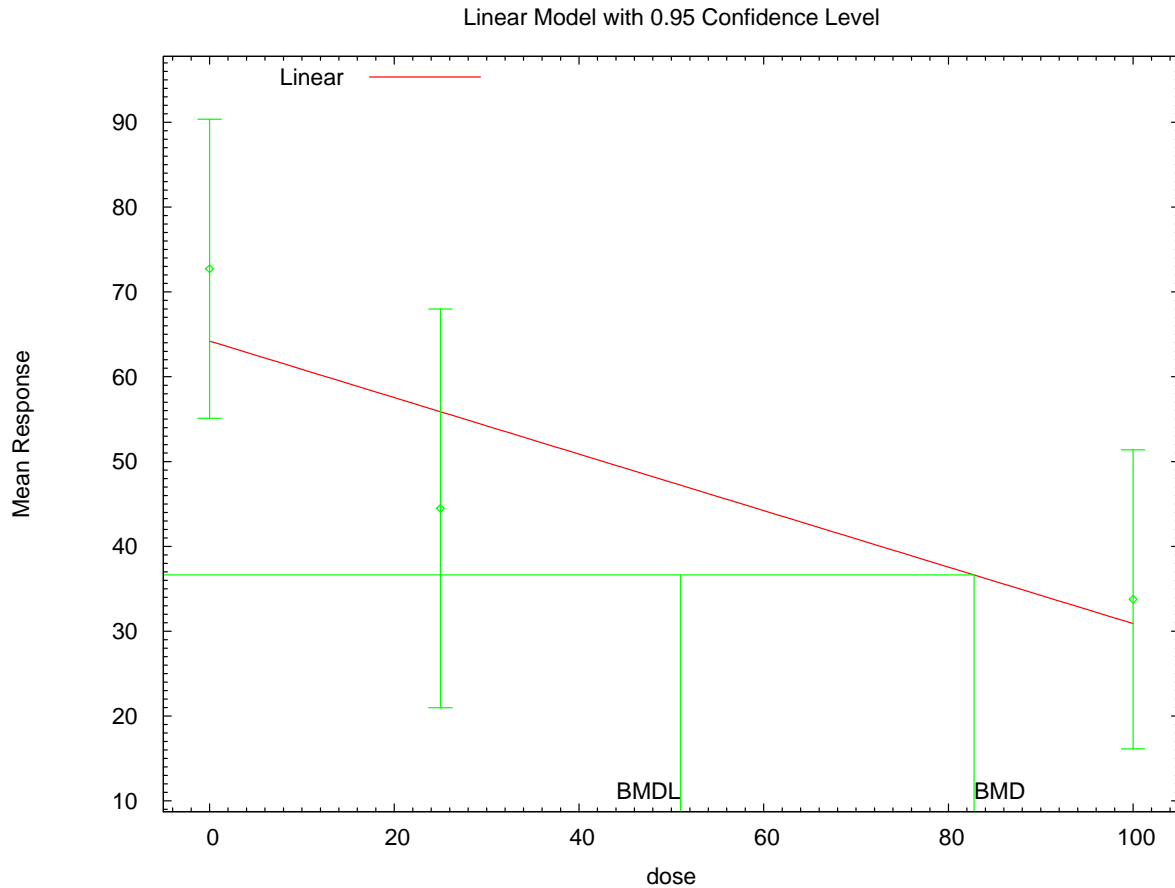
   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
```

```
rho is set to 0
The power is not restricted
A constant variance model is fit


Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          alpha =      764.602
                            rho =            0    Specified
                        control =      72.7273
                          slope =      -13.387
                          power =     0.231973



           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                    alpha        control        slope         power

      alpha            1        -1.3e-008      5.9e-009      2.5e-009

    control      -1.3e-008           1           -0.4          -0.22

      slope       5.9e-009         -0.4            1            0.97

      power       2.5e-009        -0.22          0.97            1




                              Parameter Estimates

                                                         95.0% Wald
Confidence Interval
         Variable        Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
          alpha          688.142          177.677               339.9
1036.38
          control        72.7273          8.29543              56.4686
88.986
          slope          -13.387          15.9957              -44.738
17.9639
          power          0.231973         0.268067            -0.293429
0.757376




     Table of Data and Estimated Values of Interest
```

```
 Dose        N    Obs Mean      Est Mean    Obs Std Dev   Est Std Dev    Scaled
Res.
------      ---   --------      --------    -----------   -----------    ---------
-


    0       10     72.7          72.7          24.6          26.2        5.16e-008
   25       10     44.5          44.5          32.9          26.2       -1.27e-008
  100       10     33.8          33.8          24.6          26.2         -2e-008


Degrees of freedom for Test A3 vs fitted <= 0




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

           Model      Log(likelihood)    # Param's      AIC
            A1         -113.009921            4       234.019841
            A2         -112.428886            6       236.857773
            A3         -113.009921            4       234.019841
         fitted        -113.009921            4       234.019841
            R          -117.976057            2       239.952114


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test     -2*log(Likelihood Ratio)   Test df        p-value

   Test 1            11.0943               4           0.02552
   Test 2            1.16207               2           0.5593
```

```
Test 3                1.16207        2            0.5593
Test 4                     0         0               NA
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0. The Chi-
Square
     test for fit is not valid

                 Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

              BMD = 18.1732

              BMDL = 1e-013

1 **G.3.4.5.** *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

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G.3.5. Bell et al. (2007): Balano-Preputial Separation, PND 49

G.3.5.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	2	0.369	113.514	7.332E+00	4.687E+00	power bound hit (power = 1)
Logistic	2	0.237	114.853	1.501E+01	1.137E+01	
Log-logistic[a]	**2**	**0.456**	**112.952**	**5.209E+00**	**2.870E+00**	**slope bound hit (slope = 1)**
Log-probit	2	0.178	115.488	1.428E+01	9.138E+00	slope bound hit (slope = 1)
Multistage, 3-degree	2	0.369	113.514	7.332E+00	4.687E+00	final ß = 0
Probit	2	0.248	114.723	1.399E+01	1.061E+01	
Weibull	2	0.369	113.514	7.332E+00	4.687E+00	power bound hit (power = 1)
Gamma, unrestricted	1	0.566	113.746	1.894E+00	7.609E−02	unrestricted (power = 0.506)
Log-logistic, unrestricted[b]	1	0.484	113.908	2.127E+00	1.363E−01	unrestricted (slope = 0.67)
Log-probit, unrestricted	1	0.439	114.021	2.179E+00	1.671E−01	unrestricted (slope = 0.389)
Weibull, unrestricted	1	0.534	113.802	2.007E+00	1.075E−01	unrestricted (power = 0.574)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.3.5.2. *Output for Selected Model: Log-Logistic*

Bell et al. (2007): Balano-Preputial Separation, PND 49

```
==========================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\5_Bell_2007_BPS_LogLogistic_1.(d)
        Gnuplot Plotting File:  C:\1\5_Bell_2007_BPS_LogLogistic_1.plt
                                        Tue Feb 16 17:24:10 2010
==========================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
   Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


                    Default Initial Parameter Values
                        background =    0.0333333
                         intercept =     -3.75371
                             slope =            1


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -slope
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

              background     intercept

background              1        -0.58

 intercept          -0.58             1




                                Parameter Estimates

                                                  95.0% Wald
Confidence Interval
      Variable          Estimate          Std. Err.      Lower Conf. Limit
Upper Conf. Limit
      background       0.0635251               *                  *
*
        intercept       -3.84765               *                  *
*
           slope              1                *                  *
*

* - Indicates that this value is not calculated.




                        Analysis of Deviance Table

      Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model       -53.7077          4
     Fitted model      -54.476           2       1.53661       2
0.4638
     Reduced model     -63.9797          1       20.544        3
0.0001309

          AIC:          112.952
```

```
                           Goodness  of  Fit
                                                             Scaled
        Dose      Est._Prob.    Expected    Observed    Size    Residual
     -------------------------------------------------------------------
       0.0000      0.0635        1.906       1.000        30    -0.678
       2.4000      0.1091        3.274       5.000        30     1.011
       8.0000      0.2000        6.001       6.000        30    -0.000
      46.0000      0.5273       15.819      15.000        30    -0.300


  Chi^2 = 1.57      d.f. = 2         P-value = 0.4559



     Benchmark Dose Computation

  Specified effect =            0.1

  Risk Type         =      Extra risk

  Confidence level =            0.95

              BMD =        5.20918

              BMDL =       2.86991
```

1 ### G.3.5.3. *Figure for Selected Model: Log-Logistic*

Log-Logistic Model with 0.95 Confidence Level

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4 ### G.3.5.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

5 Bell et al. (2007): Balano-Preputial Separation, PND 49

6
7
8
```
    ==================================================================
9         Logistic Model. (Version: 2.12; Date: 05/16/2008)
10        Input Data File: C:\1\5_Bell_2007_BPS_LogLogistic_U_1.(d)
11        Gnuplot Plotting File:  C:\1\5_Bell_2007_BPS_LogLogistic_U_1.plt
12                                    Tue Feb 16 17:24:10 2010
13    ==================================================================
14
15   0
16 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18    The form of the probability function is:
19
20    P[response] = background+(1-background)/[1+EXP(-intercept-
21 slope*Log(dose))]
22
23
24    Dependent variable = DichEff
25    Independent variable = Dose
26    Slope parameter is not restricted
27
28    Total number of observations = 4
```

```
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


                   Default Initial Parameter Values
                        background =    0.0333333
                         intercept =     -2.54947
                             slope =     0.615936



        Asymptotic Correlation Matrix of Parameter Estimates

                background     intercept        slope

background              1         -0.49         0.35


 intercept          -0.49             1        -0.93


    slope            0.35         -0.93            1




                            Parameter Estimates

                                                95.0% Wald
Confidence Interval
       Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
      background      0.0354714              *               *
*
       intercept      -2.70296               *               *
*
          slope       0.670238              *               *
*

* - Indicates that this value is not calculated.




                        Analysis of Deviance Table

     Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model      -53.7077         4
    Fitted model     -53.9541         3      0.492844       1
0.4827
   Reduced model     -63.9797         1      20.544         3
0.0001309

        AIC:          113.908


```

```
                              Goodness  of  Fit
                                                      Scaled
      Dose     Est._Prob.    Expected    Observed    Size    Residual
    -------------------------------------------------------------------
     0.0000     0.0355        1.064       1.000       30      -0.063
     2.4000     0.1392        4.176       5.000       30       0.435
     8.0000     0.2405        7.216       6.000       30      -0.520
    46.0000     0.4848       14.544      15.000       30       0.167


  Chi^2 = 0.49      d.f. = 1        P-value = 0.4836



    Benchmark Dose Computation

Specified effect =          0.1

Risk Type       =      Extra risk

Confidence level =         0.95

           BMD =      2.12667

           BMDL =     0.13633
```

1   **G.3.5.5.** *Figure for Additional Model Presented: Log-Logistic, Unrestricted*

Log-Logistic Model with 0.95 Confidence Level

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2
3

G.3.6. Cantoni et al. ([1981](#)): Urinary Coproporhyrins, 3 Months

G.3.6.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 p-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.002	33.792	1.101E+02	5.318E+01	
Exponential (M3)	2	0.002	33.792	1.101E+02	5.318E+01	power hit bound ($d = 1$)
Exponential (M4)[b]	**1**	**0.341**	**23.881**	**3.741E−01**	**1.253E−01**	
Exponential (M5)	1	0.341	23.881	3.741E−01	1.253E−01	power hit bound ($d = 1$)
Hill	1	0.535	23.359	3.273E−01	error	*n* lower bound hit ($n = 1$)
Linear	2	0.002	33.301	7.734E+01	1.975E+01	
Polynomial, 3-degree	2	0.002	33.301	7.734E+01	1.975E+01	
Power	2	0.002	33.301	7.734E+01	1.975E+01	power bound hit (power = 1)
Power, unrestricted[c]	1	0.665	23.162	4.637E−03	8.796E−08	unrestricted (power = 0.22)
Hill, unrestricted	0	N/A	24.974	7.264E−02	1.656E−04	unrestricted ($n = 0.48$)

[a] Nonconstant variance model selected ($p = 0.0039$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.6.2. *Output for Selected Model: Exponential (M4)*

Cantoni et al. ([1981](#)): Urinary Coproporhyrins, 3 Months

```
   =====================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\6_Cantoni_1981_UriCopro_Exp_1.(d)
        Gnuplot Plotting File:
                                    Tue Feb 16 17:24:39 2010
   =====================================================================

 Figure1-UrinaryCoproporphyrin_3months
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
```

```
        Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

   MLE solution provided: Exact


                   Initial Parameter Values

                   Variable          Model 4
                   --------          --------
                     lnalpha          -1.50063
                        rho           2.60979
                          a           0.704303
                          b           0.0205927
                          c           4.47268
                          d                  1



                   Parameter Estimates

                   Variable          Model 4
                   --------          -------
                     lnalpha          -1.74154
                        rho           2.66803
                          a           0.755982
                          b            0.3715
                          c           3.93845
                          d                  1


         Table of Stats From Input Data

     Dose      N        Obs Mean     Obs Std Dev
     -----    ---      ----------    -------------
        0      4        0.7414        0.3475
     1.43      4         1.807        0.8341
     14.3      4         2.734         1.506
      143      4             3           2.6



              Estimated Values of Interest

     Dose      Est Mean       Est Std     Scaled Residual
     ------    ----------     ---------    ----------------
```

```
        0           0.756         0.2882        -0.1014
      1.43          1.671         0.8307         0.3265
     14.3           2.966         1.786         -0.2607
    143             2.977         1.794          0.02532




   Other models for which likelihoods are calculated:

     Model A1:        Yij = Mu(i) + e(ij)
               Var{e(ij)} = Sigma^2

     Model A2:        Yij = Mu(i) + e(ij)
               Var{e(ij)} = Sigma(i)^2

     Model A3:        Yij = Mu(i) + e(ij)
               Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

     Model  R:        Yij = Mu + e(i)
               Var{e(ij)} = Sigma^2


                         Likelihoods of Interest

                  Model      Log(likelihood)     DF         AIC
                  -------    ----------------    ----    ------------
                    A1         -12.90166           5       35.80333
                    A2          -6.203643          8       28.40729
                    A3          -6.487204          6       24.97441
                     R         -15.73713           2       35.47427
                     4          -6.940389          5       23.88078



    Additive constant for all log-likelihoods =      -14.7.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                          Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 6a: Does Model 4 fit the data? (A3 vs 4)



                          Tests of Interest

     Test          -2*log(Likelihood Ratio)         D. F.          p-value
     --------      ------------------------         ------      --------------
     Test 1                  19.07                     6            0.004052
     Test 2                  13.4                      3            0.003854
     Test 3                   0.5671                   2            0.7531
     Test 6a                  0.9064                   1            0.3411
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose
levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous
variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled
variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems
to adequately describe the data.

Benchmark Dose Computations:

   Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

   Confidence Level = 0.950000

                BMD =   0.374114

               BMDL =   0.125287

G.3.6.3. *Figure for Selected Model: Exponential (M4)*

Exponential_beta Model 4 with 0.95 Confidence Level

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G.3.6.4. *Output for Additional Model Presented: Power, Unrestricted*

5 Cantoni et al. ([1981](#)): Urinary Coproporhyrins, 3 Months

```
8    ========================================================================
9           Power Model. (Version: 2.15;  Date: 04/07/2008)
10          Input Data File: C:\1\6_Cantoni_1981_UriCopro_Pwr_U_1.(d)
11          Gnuplot Plotting File:  C:\1\6_Cantoni_1981_UriCopro_Pwr_U_1.plt
12                                      Tue Feb 16 17:24:41 2010
13   ========================================================================
14
15    Figure1-UrinaryCoproporphyrin_3months
16   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18      The form of the response function is:
19
20      Y[dose] = control + slope * dose^power
21
22
23      Dependent variable = Mean
24      Independent variable = Dose
25      The power is not restricted
26      The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
27
28      Total number of dose groups = 4
```

```
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                      Default Initial Parameter Values
                              lalpha =      0.90039
                                 rho =            0
                             control =     0.741372
                               slope =      1.00533
                               power =     0.163111



           Asymptotic Correlation Matrix of Parameter Estimates

                      lalpha          rho      control        slope        power

       lalpha             1        -0.62        -0.53       -0.038        0.027

          rho         -0.62            1         0.43        -0.24        -0.16

      control         -0.53         0.43            1         -0.3         0.09

        slope        -0.038        -0.24         -0.3            1        -0.72

        power         0.027        -0.16         0.09        -0.72            1




                              Parameter Estimates

                                                            95.0% Wald
Confidence Interval
         Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
           lalpha        -1.78404         0.61698             -2.9933
-0.57478
              rho          2.6428         0.74449             1.18363
4.10197
          control        0.757242        0.139966            0.482915
1.03157
            slope        0.927009        0.325923            0.288212
1.56581
            power        0.220276       0.0964599            0.031218
0.409334




     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
 ------     ---  --------     --------   -----------  -----------   ---------
 -
```

```
   0      4      0.741        0.757        0.348        0.284       -0.112
1.43      4      1.81         1.76         0.834        0.865        0.108
14.3      4      2.73         2.42         1.51         1.32         0.471
 143      4         3         3.52          2.6         2.16        -0.483
```

Model Descriptions for likelihoods calculated

Model A1:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model R: Yi = Mu + e(i)
          Var{e(i)} = Sigma^2

                    Likelihoods of Interest

            Model   Log(likelihood)   # Param's   AIC
             A1   -12.901663   5   35.803325
             A2   -6.203643   8   28.407287
             A3   -6.487204   6   24.974409
          fitted   -6.580755   5   23.161510
             R   -15.737135   2   35.474269

                    Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

  Test   -2*log(Likelihood Ratio) Test df   p-value

  Test 1   19.067   6   0.004052
  Test 2   13.396   3   0.003854
  Test 3   0.567122   2   0.7531
  Test 4   0.187101   1   0.6653

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

```
The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


                  Benchmark Dose Computation

Specified effect =                1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =        0.95

            BMD = 0.00463746


            BMDL = 8.79634e-008
```

1   **G.3.6.5.** *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

17:24 02/16 2010

2
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4

G.3.7. Cantoni et al. ([1981](#)): Urinary Porphyrins

G.3.7.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)[b]	**2**	**<0.0001**	**58.753**	**1.223E+01**	**9.037E+00**	
Exponential (M3)	2	<0.0001	58.753	1.223E+01	9.037E+00	power hit bound (*d* = 1)
Exponential (M4)	1	<0.0001	63.138	2.227E−01	1.137E−01	
Exponential (M5)	1	<0.0001	63.138	2.227E−01	1.137E−01	power hit bound (*d* = 1)
Hill	0	N/A	62.356	9.363E+00	4.664E+00	
Linear	2	<0.0001	62.487	7.732E−01	2.816E−01	
Polynomial, 3-degree	1	<0.0001	10.000	error	error	
Power	2	<0.0001	62.487	7.732E−01	2.816E−01	power bound hit (power = 1)
Power, unrestricted	1	<0.0001	59.914	1.025E−01	2.389E−02	unrestricted (power = 0.746)

[a] Nonconstant variance model selected (*p* = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.7.2. *Output for Selected Model: Exponential (M2)*

Cantoni et al. ([1981](#)): Urinary Porphyrins

```
=======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\7_Cantoni_1981_UriPor_Exp_1.(d)
        Gnuplot Plotting File:
                                        Tue Feb 16 17:25:14 2010
=======================================================================

 Table 1, dose converted to ng per kg per day
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
     Model 2:     Y[dose] = a * exp{sign * b * dose}
     Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
     Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

   Note: Y[dose] is the median response for exposure = dose;
         sign = +1 for increasing trend in data;
         sign = -1 for decreasing trend.

     Model 2 is nested within Models 3 and 4.
     Model 3 is nested within Model 5.
     Model 4 is nested within Model 5.
```

```
1    Dependent variable = Mean
2    Independent variable = Dose
3    Data are assumed to be distributed: normally
4    Variance Model: exp(lnalpha +rho *ln(Y[dose]))
5    The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
6
7    Total number of dose groups = 4
8    Total number of records with missing values = 0
9    Maximum number of iterations = 250
10   Relative Function Convergence has been set to: 1e-008
11   Parameter Convergence has been set to: 1e-008
12
13   MLE solution provided: Exact
14
15
16                 Initial Parameter Values
17
18                 Variable          Model 2
19                 --------          --------
20                  lnalpha          -3.57509
21                     rho           2.23456
22                      a            3.83141
23                      b            0.0277822
24                      c                   0
25                      d                   1
26
27
28
29                 Parameter Estimates
30
31                 Variable          Model 2
32                 --------          -------
33                  lnalpha          -1.55886
34                     rho           1.77962
35                      a            4.17268
36                      b            0.0270415
37                      c                   0
38                      d                   1
39
40
41          Table of Stats From Input Data
42
43    Dose       N       Obs Mean      Obs Std Dev
44    -----     ---      ----------    -------------
45       0       4         2.27           0.49
46    1.43       4         5.55           0.85
47    14.3       3         7.62           1.79
48     143       3        196.9          63.14
49
50
51          Estimated Values of Interest
52
53    Dose      Est Mean      Est Std      Scaled Residual
54    ------    ----------    ---------    ----------------
55       0        4.173         1.635          -2.327
56    1.43        4.337         1.692           1.433
57    14.3        6.143         2.307           1.109
```

```
      143          199.4          51.04          -0.08645



    Other models for which likelihoods are calculated:

      Model A1:        Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma^2

      Model A2:        Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma(i)^2

      Model A3:        Yij = Mu(i) + e(ij)
                 Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

      Model  R:        Yij = Mu + e(i)
                 Var{e(ij)} = Sigma^2


                             Likelihoods of Interest

                      Model       Log(likelihood)     DF         AIC
                      -------     ----------------    ----    ------------
                        A1          -51.42175           5       112.8435
                        A2          -15.31211           8        46.62422
                        A3          -15.66963           6        43.33925
                         R          -68.75058           2       141.5012
                         2          -25.37651           4        58.75302


    Additive constant for all log-likelihoods =     -12.87.  This constant
added to the
    above values gives the log-likelihood including the term that does not
    depend on the model parameters.



                             Explanation of Tests

    Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
    Test 2:  Are Variances Homogeneous? (A2 vs. A1)
    Test 3:  Are variances adequately modeled? (A2 vs. A3)
    Test 4:  Does Model 2 fit the data? (A3 vs. 2)



                             Tests of Interest

      Test          -2*log(Likelihood Ratio)        D. F.        p-value
    --------        ------------------------        ------      --------------
    Test 1                    106.9                   6           < 0.0001
    Test 2                    72.22                   3           < 0.0001
    Test 3                    0.715                   2             0.6994
    Test 4                    19.41                   2           < 0.0001



    The p-value for Test 1 is less than .05.  There appears to be a
    difference between response and/or variances among the dose
```
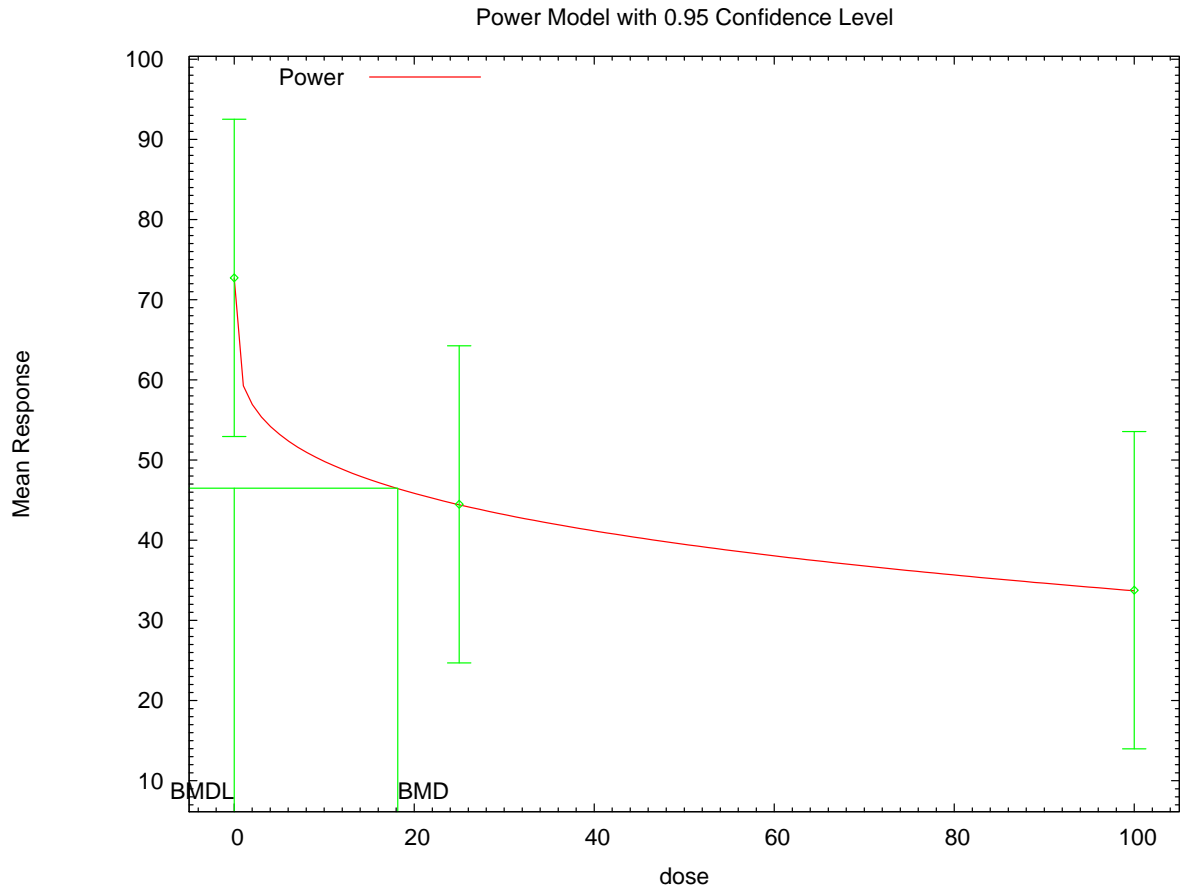
levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous
variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled
variance appears to be appropriate here.

The p-value for Test 4 is less than .1. Model 2 may not adequately
describe the data; you may want to consider another model.

Benchmark Dose Computations:

   Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

   Confidence Level = 0.950000

                BMD =   12.2272

                BMDL =   9.03732

G.3.7.3. *Figure for Selected Model: Exponential (M2)*

Exponential_beta Model 2 with 0.95 Confidence Level

17:25 02/16 2010

G.3.8. Crofton et al. ([2005](#)): Serum, T4

G.3.8.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 p-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	8	<0.0001	518.241	2.136E+03	1.157E+03	
Exponential (M3)	8	<0.0001	518.241	2.136E+03	1.157E+03	power hit bound ($d = 1$)
Exponential (M4)[b]	**7**	**0.957**	**476.204**	**5.633E+01**	**3.006E+01**	
Exponential (M5)	7	0.957	476.204	5.633E+01	3.006E+01	power hit bound ($d = 1$)
Hill	6	0.973	477.434	5.564E+01	2.590E+01	
Linear	8	<0.0001	523.518	4.246E+03	3.086E+03	
Polynomial, 8-degree	8	<0.0001	523.518	4.246E+03	3.086E+03	
Power	8	<0.0001	523.518	4.246E+03	3.086E+03	power bound hit (power = 1)
Power, unrestricted	7	0.030	489.670	2.179E+01	2.271E+00	unrestricted (power = 0.217)

[a] Constant variance model selected ($p = 0.7647$).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.8.2. *Output for Selected Model: Exponential (M4)*

Crofton et al. ([2005](#)): Serum, T4

```
   ======================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\8_Crofton_2005_T4_ExpCV_1.(d)
        Gnuplot Plotting File:
                                   Tue Feb 16 17:26:01 2010
   ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 10
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                    Initial Parameter Values

                  Variable          Model 4
                  --------          --------
                   lnalpha           5.47437
                      rho(S)               0
                        a           104.999
                        b        0.000371694
                        c           0.445764
                        d                 1

    (S) = Specified




                    Parameter Estimates

                  Variable          Model 4
                  --------          -------
                   lnalpha           5.50283
                      rho                 0
                        a            99.776
                        b        0.00728387
                        c          0.533516
                        d                 1



          Table of Stats From Input Data

    Dose      N        Obs Mean     Obs Std Dev
    -----    ---      ----------    -------------
        0     14           100      15.44
      0.1      6         96.27      14.98
        3     12         98.57      18.11
       10      6         99.76      19.04
       30      6         93.32      12.11
      100      6         70.94      12.74
      300      6         62.52      14.75
     1000      6         52.68      22.73
     3000      6         54.66      19.71
```

```
       1e+004          4          49.15          11.15


                   Estimated Values of Interest

        Dose       Est Mean       Est Std      Scaled Residual
       ------     ----------     ---------     ----------------
           0          99.78         15.66           0.05325
         0.1          99.74         15.66          -0.5434
           3          98.77         15.66          -0.04357
          10          96.51         15.66           0.5085
          30          90.64         15.66           0.4195
         100           75.7         15.66          -0.744
         300          58.47         15.66           0.6334
        1000          53.26         15.66          -0.09133
        3000          53.23         15.66           0.2237
       1e+004         53.23         15.66          -0.5218




   Other models for which likelihoods are calculated:

     Model A1:         Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma^2

     Model A2:         Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma(i)^2

     Model A3:         Yij = Mu(i) + e(ij)
                 Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

     Model  R:         Yij = Mu + e(i)
                 Var{e(ij)} = Sigma^2



                       Likelihoods of Interest

                 Model      Log(likelihood)     DF        AIC
                 -------    ----------------    ----   ------------
                   A1         -233.0774          11      488.1549
                   A2         -230.2028          20      500.4056
                   A3         -233.0774          11      488.1549
                    R         -268.4038           2      540.8076
                    4         -234.1019           4      476.2038



   Additive constant for all log-likelihoods =     -66.16.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                        Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
```

```
Test 3:  Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)


                        Tests of Interest

   Test          -2*log(Likelihood Ratio)      D. F.        p-value
  --------       ------------------------      ------      --------------
   Test 1                          76.4          18         < 0.0001
   Test 2                         5.749           9           0.7647
   Test 3                         5.749           9           0.7647
  Test 6a                         2.049           7           0.9571


   The p-value for Test 1 is less than .05.  There appears to be a
   difference between response and/or variances among the dose
   levels, it seems appropriate to model the data.

   The p-value for Test 2 is greater than .1.  A homogeneous
   variance model appears to be appropriate here.

   The p-value for Test 3 is greater than .1.  The modeled
   variance appears to be appropriate here.

   The p-value for Test 6a is greater than .1.  Model 4 seems
   to adequately describe the data.


Benchmark Dose Computations:

   Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

   Confidence Level = 0.950000

               BMD =      56.3321

               BMDL =      30.0635
```

1　**G.3.8.3.** *Figure for Selected Model: Exponential (M4)*

Exponential_beta Model 4 with 0.95 Confidence Level

17:26 02/16 2010

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G.3.9. Franc et al. (2001): S-D Rats, Relative Liver Weight

G.3.9.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Hill	1	0.797	236.371	1.826E+01	5.463E+00	*n* lower bound hit (*n* = 1)
Exponential (M2)	2	0.935	234.440	2.262E+01	1.757E+01	
Exponential (M3)	2	0.935	234.440	2.262E+01	1.757E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.797	236.371	1.827E+01	6.112E+00	
Exponential (M5)	1	0.797	236.371	1.827E+01	6.112E+00	power hit bound (*d* = 1)
Linear	2	0.967	234.372	1.861E+01	1.339E+01	
Polynomial, 3-degree	2	0.967	234.372	1.861E+01	1.339E+01	
Power[b]	**2**	**0.967**	**234.372**	**1.861E+01**	**1.339E+01**	**power bound hit (power = 1)**
Hill, unrestricted	0	N/A	238.366	1.726E+01	2.022E+00	unrestricted (*n* = 0.965)
Power, unrestricted[c]	1	0.805	236.365	1.725E+01	2.003E+00	unrestricted (power = 0.962)

[a] Constant variance model selected (*p* = 0.107).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.9.2. *Output for Selected Model: Power*

Franc et al. (2001): S-D Rats, Relative Liver Weight

```
   =====================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\88_Franc_2001_SD_RelLivWt_PowerCV_1.(d)
         Gnuplot Plotting File:  C:\1\88_Franc_2001_SD_RelLivWt_PowerCV_1.plt
                                         Fri Apr 16 16:28:45 2010
   =====================================================================

 Figure 5, SD rats, relative liver weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The power is restricted to be greater than or equal to 1
   A constant variance model is fit

   Total number of dose groups = 4
```

```
    Total number of records with missing values = 0
    Maximum number of iterations = 250
    Relative Function Convergence has been set to: 1e-008
    Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          alpha =      527.447
                            rho =            0   Specified
                        control =          100
                          slope =      1.15946
                          power =     0.839423



            Asymptotic Correlation Matrix of Parameter Estimates


            ( *** The model parameter(s)  -rho    -power
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                     alpha       control        slope

      alpha              1     1.3e-012     -6.2e-013

    control      1.3e-012            1         -0.67

      slope     -6.2e-013        -0.67             1




                             Parameter Estimates


                                                     95.0% Wald
Confidence Interval
       Variable          Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         alpha          462.485          115.621             235.872
689.099
       control          101.047          5.10511             91.0415
111.053
         slope         0.542984        0.0973507            0.352181
0.733788
         power                1               NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.




     Table of Data and Estimated Values of Interest

 Dose      N    Obs Mean     Est Mean    Obs Std Dev   Est Std Dev    Scaled
Res.
```

```
------      ---    --------      --------    -----------   -----------   ---------
-

     0      8       100           101             14          21.5        -0.138
    10      8       108           106           16.9          21.5         0.208
    30      8       117           117           25.9          21.5        -0.0702
   100      8       155           155           30.9          21.5        0.000298
```

Model Descriptions for likelihoods calculated

Model A1:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model R: Yi = Mu + e(i)
          Var{e(i)} = Sigma^2

                    Likelihoods of Interest

            Model   Log(likelihood)   # Param's   AIC
             A1   -114.152281   5   238.304562
             A2   -111.103649   8   238.207299
             A3   -114.152281   5   238.304562
          fitted   -114.185827   3   234.371654
             R   -125.052064   2   254.104127

                    Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

  Test   -2*log(Likelihood Ratio) Test df   p-value

  Test 1   27.8968   6   <.0001
  Test 2   6.09726   3   0.107
  Test 3   6.09726   3   0.107
  Test 4   0.0670927   2   0.967

The p-value for Test 1 is less than .05. There appears to be a
```

difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


                    Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =     Relative risk

Confidence level =           0.95

             BMD = 18.6096


            BMDL = 13.3879

1 **G.3.9.3.** *Figure for Selected Model: Power*



Power Model with 0.95 Confidence Level

16:28 04/16 2010

2
3
4 **G.3.9.4.** *Output for Additional Model Presented: Power, Unrestricted*

5 Franc et al. (2001): S-D Rats, Relative Liver Weight
6
7
```
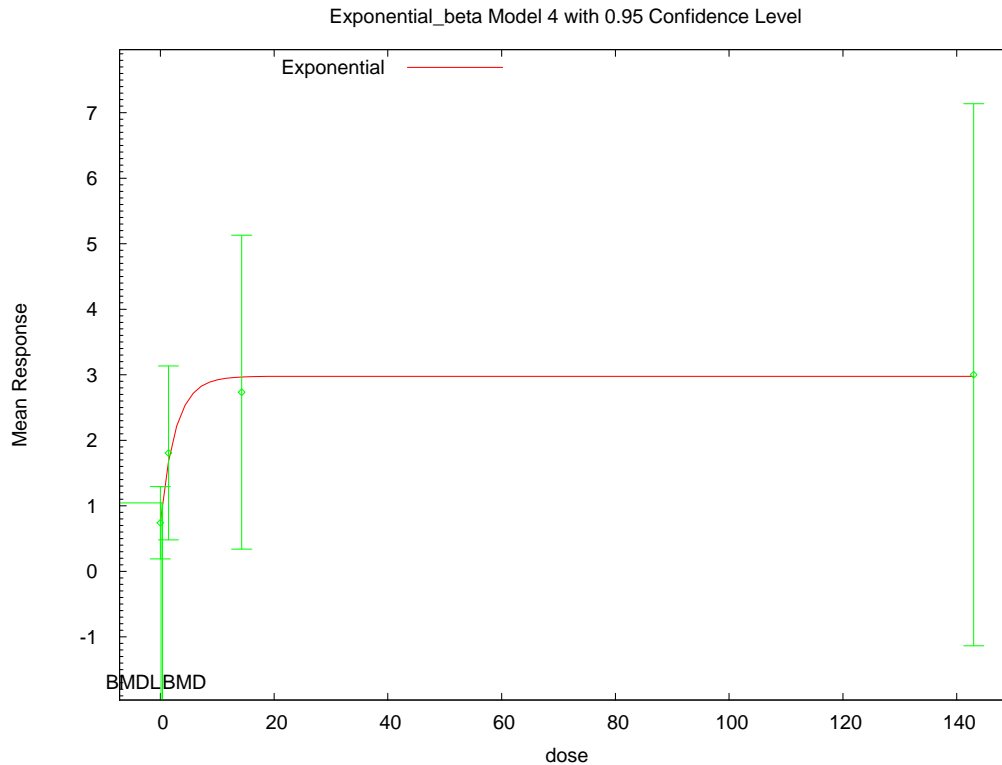8   ==
9   Power Model. (Version: 2.15; Date: 04/07/2008)
10   Input Data File: C:\1\88_Franc_2001_SD_RelLivWt_PowerCV_U_1.(d)
11   Gnuplot Plotting File:
12   C:\1\88_Franc_2001_SD_RelLivWt_PowerCV_U_1.plt
13   Fri Apr 16 16:28:46 2010
14   ==
15
16   Figure 5, SD rats, relative liver weight
17   ~~~~~~
18
19   The form of the response function is:
20
21   Y[dose] = control + slope * dose^power
22
23
24   Dependent variable = Mean
25   Independent variable = Dose
26   rho is set to 0
27   The power is not restricted
```

```
A constant variance model is fit


Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                         alpha =       527.447
                           rho =             0    Specified
                       control =           100
                         slope =       1.15946
                         power =      0.839423



             Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -rho
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                     alpha         control          slope          power

     alpha               1          1e-009       -6.2e-010       4.7e-010

   control          1e-009               1           -0.74           0.71

     slope       -6.2e-010           -0.74               1             -1

     power        4.7e-010            0.71              -1              1




                              Parameter Estimates

                                                          95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
          alpha         462.394          115.598              235.825
688.963
        control         100.636          7.29156              86.3448
114.927
          slope        0.650456          1.43713             -2.16627
3.46718
          power        0.961853         0.465182            0.0501134
1.87359




    Table of Data and Estimated Values of Interest
```

```
   Dose       N    Obs Mean     Est Mean    Obs Std Dev  Est Std Dev   Scaled
Res.
   ------     ---  --------     --------    -----------  -----------   ---------
-

      0        8      100          101           14          21.5        -0.0836
     10        8      108          107         16.9          21.5         0.192
     30        8      117          118         25.9          21.5        -0.128
    100        8      155          155         30.9          21.5         0.0192
```

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2
```

                    Likelihoods of Interest

```
            Model      Log(likelihood)   # Param's      AIC
            A1         -114.152281            5      238.304562
            A2         -111.103649            8      238.207299
            A3         -114.152281            5      238.304562
         fitted        -114.182670            4      236.365340
            R          -125.052064            2      254.104127
```

                    Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

```
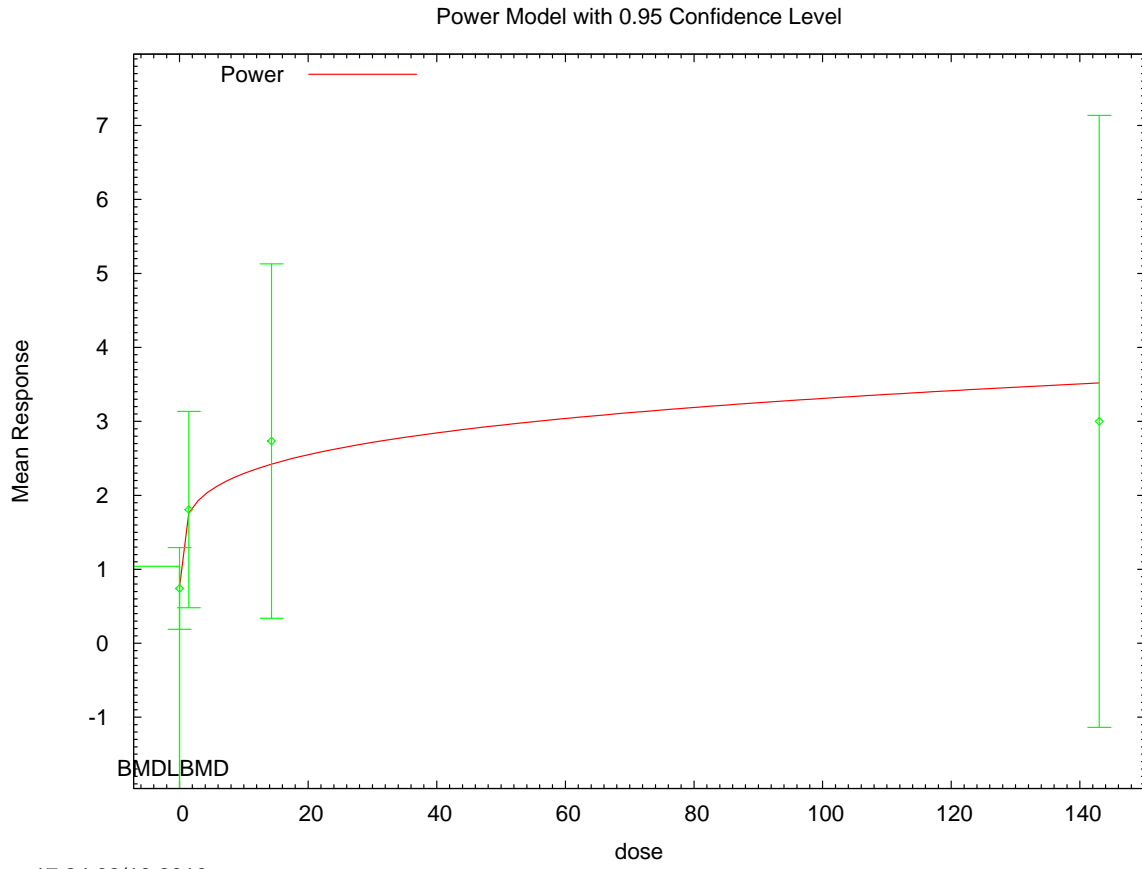   Test    -2*log(Likelihood Ratio)   Test df        p-value

   Test 1            27.8968            6           <.0001
   Test 2            6.09726            3            0.107
   Test 3            6.09726            3            0.107
   Test 4            0.0607785          1            0.8053
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

                    Benchmark Dose Computation

Specified effect =   0.1

Risk Type   =   Relative risk

Confidence level =   0.95

             BMD = 17.2469

            BMDL = 2.00336

1   **G.3.9.5.** *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

16:28 04/16 2010

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G.3.10. Franc et al. ([2001](#)): Long-Evans (L-E) Rats, Relative Liver Weight

G.3.10.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.245	210.148	5.143E+01	3.188E+01	
Exponential (M3)	2	0.245	210.148	5.143E+01	3.188E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.607	209.599	1.476E+01	3.702E+00	
Exponential (M5)	1	0.607	209.599	1.476E+01	3.702E+00	power hit bound (*d* = 1)
Hill[b]	**1**	**0.703**	**209.480**	**1.321E+01**	**1.591E+00**	***n* lower bound hit (*n* = 1)**
Linear	2	0.273	209.933	4.753E+01	2.788E+01	
Polynomial, 3-degree	1	<0.0001	10.000	1.505E+01	error	
Power	2	0.273	209.933	4.753E+01	2.788E+01	power bound hit (power = 1)
Hill, unrestricted[c]	0	N/A	211.341	1.163E+01	9.756E−01	unrestricted (*n* = 0.418)
Power, unrestricted	1	0.940	209.340	1.155E+01	1.513E−02	unrestricted (power = 0.394)

[a] Nonconstant variance model selected (*p* = 0.0632).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.10.2. *Output for Selected Model: Hill*

Franc et al. ([2001](#)): L-E Rats, Relative Liver Weight

```
    =======================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\89_Franc_2001_LE_RelLivWt_Hill_1.(d)
         Gnuplot Plotting File:  C:\1\89_Franc_2001_LE_RelLivWt_Hill_1.plt
                                       Fri Apr 16 16:29:20 2010
    =======================================================================

 Figure 5, L-E rats, relative liver weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function is:

    Y[dose] = intercept + v*dose^n/(k^n + dose^n)


    Dependent variable = Mean
    Independent variable = Dose
    Power parameter restricted to be greater than 1
    The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

    Total number of dose groups = 4
    Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                         lalpha =       5.41581
                            rho =             0
                      intercept =           100
                              v =        22.225
                              n =      0.329526
                              k =       40.8403



            Asymptotic Correlation Matrix of Parameter Estimates

             ( *** The model parameter(s)  -n
                      have been estimated at a boundary point, or have been
specified by the user,
                      and do not appear in the correlation matrix )

                      lalpha          rho    intercept             v             k

      lalpha               1           -1        -0.18          0.38           0.2

         rho              -1            1         0.17         -0.38          -0.2

   intercept           -0.18         0.17            1         -0.13          0.39

           v            0.38        -0.38        -0.13             1          0.77

           k             0.2         -0.2         0.39          0.77             1




                               Parameter Estimates


                                                     95.0% Wald
Confidence Interval
         Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
         lalpha         -15.3958          17.0376             -48.7889
17.9973
            rho          4.38043          3.61867             -2.71204
11.4729
      intercept          99.5667           3.7178                92.28
106.853
              v          28.8965          12.6477              4.10739
53.6856
              n                1               NA
              k          25.1273           30.138             -33.9421
84.1966


NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

```
      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
 ------     ---  --------     --------   -----------  -----------   ---------
-

    0       8      100         99.6          10          10.8        0.114
   10       8      106          108        17.9          12.8       -0.329
   30       8      117          115        8.97          14.9        0.288
  100       8      122          123        19.9            17       -0.0723


Model Descriptions for likelihoods calculated


Model A1:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:          Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

          Model      Log(likelihood)    # Param's       AIC
           A1        -100.516456             5        211.032912
           A2         -96.870820             8        209.741641
           A3         -99.666984             6        211.333969
         fitted       -99.739888             5        209.479776
            R        -105.717087             2        215.434174


                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value
```

```
     Test 1              17.6925          6          0.007048
     Test 2               7.29127         3          0.06317
     Test 3               5.59233         2          0.06104
     Test 4               0.145807        1          0.7026
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1. You may want to consider a
different variance model

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data


```
        Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Relative risk

Confidence level =           0.95

          BMD =        13.2094

          BMDL =       1.59127
```

1 **G.3.10.3.** *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

16:29 04/16 2010

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4 **G.3.10.4.** *Output for Additional Model Presented: Hill, Unrestricted*

5 Franc et al. (2001): L-E Rats, Relative Liver Weight
6
7
```
8  ==================================================================
9        Hill Model. (Version: 2.14;   Date: 06/26/2008)
10       Input Data File: C:\1\89_Franc_2001_LE_RelLivWt_Hill_U_1.(d)
11       Gnuplot Plotting File:  C:\1\89_Franc_2001_LE_RelLivWt_Hill_U_1.plt
12                                   Fri Apr 16 16:29:27 2010
13 ==================================================================
14
15 Figure 5, L-E rats, relative liver weight
16 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18    The form of the response function is:
19
20    Y[dose] = intercept + v*dose^n/(k^n + dose^n)
21
22
23    Dependent variable = Mean
24    Independent variable = Dose
```

```
Power parameter is not restricted
The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                      Default Initial Parameter Values
                            lalpha =        5.41581
                               rho =              0
                         intercept =            100
                                 v =         22.225
                                 n =       0.329526
                                 k =        40.8403


         Asymptotic Correlation Matrix of Parameter Estimates

                   lalpha          rho      intercept            v            n
k

     lalpha             1           -1        -0.21       -0.099         0.23
-0.13

        rho            -1            1         0.21        0.099        -0.23
0.13

  intercept         -0.21         0.21            1        0.023         0.14
0.011

          v        -0.099        0.099        0.023            1        -0.84
1

          n          0.23        -0.23         0.14        -0.84            1
-0.88

          k         -0.13         0.13        0.011            1        -0.88
1




                            Parameter Estimates


                                                      95.0% Wald
Confidence Interval
        Variable        Estimate       Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha        -18.8355         18.0637            -54.2397
16.5688
            rho          5.1098         3.83743            -2.41144
12.631
      intercept          99.526         3.53402             92.5994
106.453
```

```
                     v          286.422            4487.2             -8508.33
9081.17
                     n          0.418159          0.457476           -0.478477
1.31479
                     k          32981.9          1.52481e+006        -2.95559e+006
3.02155e+006



      Table of Data and Estimated Values of Interest

  Dose        N    Obs Mean     Est Mean    Obs Std Dev  Est Std Dev   Scaled
Res.
 ------      ---   --------     --------    -----------  -----------   ---------
 -

    0         8      100         99.5          10          10.3          0.13
   10         8      106         109           17.9        13           -0.563
   30         8      117         114           8.97        14.6          0.529
  100         8      122         123           19.9        17.7         -0.0942

Degrees of freedom for Test A3 vs fitted <= 0




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                    Likelihoods of Interest

            Model     Log(likelihood)   # Param's      AIC
             A1        -100.516456          5       211.032912
             A2         -96.870820          8       209.741641
             A3         -99.666984          6       211.333969
           fitted       -99.670736          6       211.341472
             R         -105.717087          2       215.434174



                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
```

```
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                      Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df       p-value

   Test 1            17.6925            6          0.007048
   Test 2            7.29127            3          0.06317
   Test 3            5.59233            2          0.06104
   Test 4            0.00750301         0             NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


          Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =     Relative risk

Confidence level =           0.95

           BMD =        11.6342

          BMDL =       0.975601
```

1   **G.3.10.5.** *Figure for Additional Model Presented: Hill, Unrestricted*

Hill Model with 0.95 Confidence Level

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G.3.11. Franc et al. (2001): S-D Rats, Relative Thymus Weight

G.3.11.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.551	285.890	6.730E+00	3.627E+00	
Exponential (M3)	1	<0.0001	303.995	3.858E+02	6.615E−01	
Exponential (M4)[b]	**1**	**0.972**	**286.698**	**3.559E+00**	**1.714E+00**	
Exponential (M5)	0	N/A	288.696	3.796E+00	1.714E+00	
Hill	0	N/A	288.696	4.299E+00	9.311E−01	
Linear	2	0.252	287.456	1.330E+01	1.062E+01	
Polynomial, 3-degree[c]	2	0.252	287.456	1.330E+01	1.062E+01	
Power	2	0.252	287.456	1.330E+01	1.062E+01	power bound hit (power = 1)
Power, unrestricted	1	0.510	287.131	5.049E−01	4.411E−04	unrestricted (power = 0.388)

[a] Nonconstant variance model selected (*p* = 0.0320).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.11.2. *Output for Selected Model: Exponential (M4)*

Franc et al. (2001): S-D Rats, Relative Thymus Weight

```
    ======================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\91_Franc_2001_SD_RelThyWt_Exp_1.(d)
         Gnuplot Plotting File:
                                    Fri Apr 16 16:30:07 2010
    ======================================================================

 Figure 5, SD rats, relative thymus weight
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:    Y[dose] = a * exp{sign * b * dose}
      Model 3:    Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:    Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:    Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
         sign = +1 for increasing trend in data;
         sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


MLE solution provided: Exact


                   Initial Parameter Values

                Variable            Model 4
                --------            --------
                 lnalpha             3.35464
                    rho             1.08199
                      a                 105
                      b           0.0424361
                      c            0.206726
                      d                   1




                   Parameter Estimates

                Variable            Model 4
                --------            -------
                 lnalpha             2.54324
                    rho             1.25901
                      a             108.904
                      b           0.0379343
                      c            0.208146
                      d                   1


          Table of Stats From Input Data

      Dose      N       Obs Mean     Obs Std Dev
      -----    ---     ----------    -------------
         0      8            100          83.2
        10      8          91.17         47.97
        30      8          51.41         43.48
       100      8          22.79         29.98



             Estimated Values of Interest

      Dose     Est Mean      Est Std      Scaled Residual
      ------   ----------    ---------    ----------------
         0        108.9         68.33          -0.3686
        10        81.68         57.01           0.4706
```

```
          30             50.3            42.02              0.0748
         100            24.61            26.79             -0.192



    Other models for which likelihoods are calculated:

      Model A1:        Yij = Mu(i) + e(ij)
               Var{e(ij)} = Sigma^2

      Model A2:        Yij = Mu(i) + e(ij)
               Var{e(ij)} = Sigma(i)^2

      Model A3:        Yij = Mu(i) + e(ij)
               Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

      Model  R:        Yij = Mu + e(i)
               Var{e(ij)} = Sigma^2


                          Likelihoods of Interest

                    Model     Log(likelihood)     DF        AIC
                    -------   ----------------    ----    ------------
                      A1        -141.9834           5       293.9669
                      A2        -137.5818           8       291.1637
                      A3        -138.3482           6       288.6964
                       R        -146.9973           2       297.9946
                       4        -138.3488           5       286.6976


    Additive constant for all log-likelihoods =    -29.41.  This constant
added to the
    above values gives the log-likelihood including the term that does not
    depend on the model parameters.



                          Explanation of Tests

    Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
    Test 2:  Are Variances Homogeneous? (A2 vs. A1)
    Test 3:  Are variances adequately modeled? (A2 vs. A3)

    Test 6a: Does Model 4 fit the data? (A3 vs 4)



                          Tests of Interest

     Test          -2*log(Likelihood Ratio)      D. F.        p-value
     --------      ------------------------      ------     --------------
     Test 1                       18.83             6         0.004459
     Test 2                       8.803             3         0.03203
     Test 3                       1.533             2         0.4647
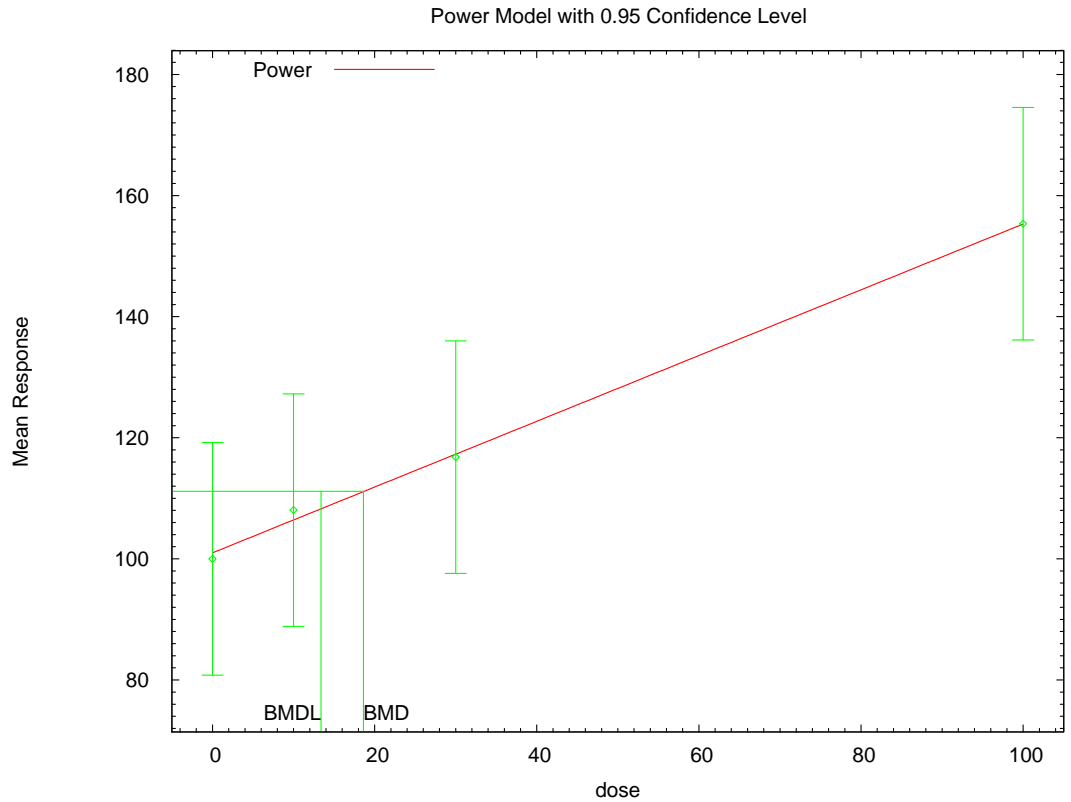    Test 6a                    0.001216             1         0.9722
```

```
The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose
levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1.  A non-homogeneous
variance model appears to be appropriate.

The p-value for Test 3 is greater than .1.  The modeled
variance appears to be appropriate here.

The p-value for Test 6a is greater than .1.  Model 4 seems
to adequately describe the data.


Benchmark Dose Computations:

   Specified Effect = 0.100000

          Risk Type = Relative deviation

   Confidence Level = 0.950000

                BMD =     3.55883

               BMDL =     1.71399
```

1 **G.3.12. Figure for Selected Model: Exponential (M4)**

Exponential_beta Model 4 with 0.95 Confidence Level

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2
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4 **G.3.13. Output for Additional Model Presented: Polynomial, 3-Degree**

5 Franc et al. (2001): S-D Rats, Relative Thymus Weight

6
7
8   ==
9   Polynomial Model. (Version: 2.13;   Date: 04/08/2008)
10   Input Data File: C:\1\91_Franc_2001_SD_RelThyWt_Poly_1.(d)
11   Gnuplot Plotting File: C:\1\91_Franc_2001_SD_RelThyWt_Poly_1.plt
12   Fri Apr 16 16:30:11 2010
13   ==
14
15 Figure 5, SD rats, relative thymus weight
16 ~~~~~~
17
18   The form of the response function is:
19
20   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
21
22
23   Dependent variable = Mean
24   Independent variable = Dose
25   The polynomial coefficients are restricted to be negative

```
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                        lalpha =        8.0075
                           rho =             0
                        beta_0 =           100
                        beta_1 =     -0.352259
                        beta_2 =    -0.0585481
                        beta_3 =             0



            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -beta_2    -beta_3
                   have been estimated at a boundary point, or have been
specified by the user,
                   and do not appear in the correlation matrix )

                    lalpha          rho        beta_0       beta_1

      lalpha             1        -0.99         0.031       -0.016

         rho         -0.99            1        -0.034        0.022

      beta_0         0.031       -0.034             1        -0.84

      beta_1        -0.016        0.022         -0.84            1




                              Parameter Estimates


                                                    95.0% Wald
Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
        lalpha          2.92328           1.7394          -0.485884
6.33243
           rho          1.18295         0.423359           0.353177
2.01271
        beta_0           89.841          13.7418            62.9076
116.774
        beta_1        -0.675682         0.175538           -1.01973
-0.331634
        beta_2                0               NA
        beta_3                0               NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
```

```
   has no standard error.


   Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev   Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------   -----------   ---------
-

    0       8        100        89.8          83.2          61.7       0.466
   10       8       91.2        83.1            48          58.9       0.388
   30       8       51.4        69.6          43.5            53      -0.968
  100       8       22.8        22.3            30            27       0.0543



Model Descriptions for likelihoods calculated


Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:          Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1          -141.983433           5     293.966865
            A2          -137.581833           8     291.163667
            A3          -138.348184           6     288.696368
         fitted         -139.728204           4     287.456407
            R           -146.997301           2     297.994602



                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest
```

```
    Test    -2*log(Likelihood Ratio)  Test df        p-value

    Test 1              18.8309          6           0.004459
    Test 2               8.8032          3           0.03203
    Test 3               1.5327          2           0.4647
    Test 4               2.76004         2           0.2516
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

                Benchmark Dose Computation

Specified effect =   0.1

Risk Type   =   Relative risk

Confidence level =   0.95

            BMD =   13.2963

            BMDL =   10.6163
```

1   **G.3.13.1.** *Figure for Additional Model Presented: Polynomial, 3-Degree*

Polynomial Model with 0.95 Confidence Level

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G.3.14. Franc et al. (2001): Long-Evans (L-E) Rats, Relative Thymus Weight

G.3.14.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.394	301.666	6.406E+00	2.122E+00	
Exponential (M3)	2	0.394	301.666	6.406E+00	2.122E+00	power hit bound (*d* = 1)
Exponential (M4)[b]	**1**	**0.317**	**302.808**	**3.520E+00**	**1.067E+00**	
Exponential (M5)	0	N/A	303.805	1.280E+01	1.450E+00	
Hill	0	N/A	303.805	1.195E+01	9.965E−01	
Linear	2	0.236	302.690	1.429E+01	9.087E+00	
Polynomial, 3-degree	2	0.236	302.690	1.429E+01	9.087E+00	
Power	2	0.236	302.690	1.429E+01	9.087E+00	power bound hit (power = 1)
Power, unrestricted	1	0.175	303.643	1.297E+00	2.703E−08	unrestricted (power = 0.454)

[a] Constant variance model selected (*p* = 0.5063).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.14.2. *Output for Selected Model: Exponential (M4)*

Franc et al. (2001): L-E Rats, Relative Thymus Weight

```
=====================================================================
       Exponential Model. (Version: 1.61;  Date: 7/24/2009)
       Input Data File: C:\1\92_Franc_2001_LE_RelThyWt_ExpCV_1.(d)
       Gnuplot Plotting File:
                                   Fri Apr 16 16:30:58 2010
=====================================================================

Figure 5, L-E rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the response function by Model:
     Model 2:     Y[dose] = a * exp{sign * b * dose}
     Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
     Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

   Note: Y[dose] is the median response for exposure = dose;
         sign = +1 for increasing trend in data;
         sign = -1 for decreasing trend.

     Model 2 is nested within Models 3 and 4.
     Model 3 is nested within Model 5.
     Model 4 is nested within Model 5.
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.


Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


MLE solution provided: Exact


                      Initial Parameter Values

                      Variable          Model 4
                      --------          --------
                        lnalpha            8.1814
                          rho(S)                0
                            a                 105
                            b           0.0413945
                            c              0.3173
                            d                   1


    (S) = Specified




                       Parameter Estimates

                      Variable          Model 4
                      --------          -------
                        lnalpha           8.21275
                          rho                   0
                            a              106.57
                            b           0.0425967
                            c             0.28189
                            d                   1




          Table of Stats From Input Data

     Dose      N          Obs Mean     Obs Std Dev
     -----     ---        ----------   -------------
         0     8                100    54.72
        10     8              95.41    70.46
        30     8              38.69    47.97
       100     8              34.98    77.96




                    Estimated Values of Interest

      Dose      Est Mean      Est Std     Scaled Residual
```

```
     ------      ----------      ---------      ----------------
        0          106.6           60.73           -0.306
       10           80.03          60.73            0.7164
       30           51.36          60.73           -0.5902
      100           31.12          60.73            0.1798




   Other models for which likelihoods are calculated:

     Model A1:         Yij = Mu(i) + e(ij)
                Var{e(ij)} = Sigma^2

     Model A2:         Yij = Mu(i) + e(ij)
                Var{e(ij)} = Sigma(i)^2

     Model A3:         Yij = Mu(i) + e(ij)
                Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

     Model  R:         Yij = Mu + e(i)
                Var{e(ij)} = Sigma^2



                           Likelihoods of Interest

                  Model      Log(likelihood)      DF         AIC
                  -------    ----------------     ----    ------------
                    A1         -146.9024            5        303.8049
                    A2         -145.7361            8        307.4723
                    A3         -146.9024            5        303.8049
                     R         -150.6049            2        305.2098
                     4         -147.404             4        302.8079



   Additive constant for all log-likelihoods =     -29.41.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                           Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 6a: Does Model 4 fit the data? (A3 vs 4)



                           Tests of Interest

     Test          -2*log(Likelihood Ratio)          D. F.          p-value
     --------      ------------------------          ------      --------------
     Test 1                   9.738                      6            0.1362
     Test 2                   2.333                      3            0.5063
     Test 3                   2.333                      3            0.5063
```

```
   Test 6a                          1.003          1            0.3166


      The p-value for Test 1 is greater than .05.  There may not be a
      diffence between responses and/or variances among the dose levels
      Modelling the data with a dose/response curve may not be appropriate.

      The p-value for Test 2 is greater than .1.  A homogeneous
      variance model appears to be appropriate here.

      The p-value for Test 3 is greater than .1.  The modeled
      variance appears to be appropriate here.

      The p-value for Test 6a is greater than .1.  Model 4 seems
      to adequately describe the data.


   Benchmark Dose Computations:

      Specified Effect = 0.100000

              Risk Type = Relative deviation

      Confidence Level = 0.950000

                    BMD =      3.52038

                   BMDL =      1.06729
```

1   **G.3.14.3.** *Figure for Selected Model: Exponential (M4)*

Exponential_beta Model 4 with 0.95 Confidence Level

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G.3.15. Franc et al. (2001): Han/Wistar (H/W) Rats, Relative Thymus Weight

2 **G.3.15.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)[b]	2	0.682	261.694	1.366E+01	8.014E+00	
Exponential (M3)	2	0.682	261.694	1.366E+01	8.014E+00	power hit bound (*d* = 1)
Exponential (M4)[c]	**1**	**0.512**	**263.358**	**8.820E+00**	**3.219E+00**	
Exponential (M5)	0	N/A	264.927	1.776E+01	3.500E+00	
Hill	0	N/A	264.927	1.701E+01	2.729E+00	
Linear	2	0.543	262.148	1.919E+01	1.373E+01	
Polynomial, 3-degree	2	0.543	262.148	1.919E+01	1.373E+01	
Power	2	0.543	262.148	1.919E+01	1.373E+01	power bound hit (power = 1)
Power, unrestricted	1	0.381	263.694	8.127E+00	1.406E−01	unrestricted (power = 0.665)

[a] Constant variance model selected (*p* = 0.4331).
[b] Alternate model, BMDS output also presented in this appendix.
[c] Best-fitting model, BMDS output presented in this appendix.

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4
5 **G.3.15.2.** *Output for Selected Model: Exponential (M2)*

6 Franc et al. (2001): H/W Rats, Relative Thymus Weight
7
8
9
```
     ==================================================================
10         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
11         Input Data File: C:\1\93_Franc_2001_HW_RelThyWt_ExpCV_1.(d)
12         Gnuplot Plotting File:
13                                     Fri Apr 16 16:31:40 2010
14     ==================================================================
15
16   Figure 5, H/W rats, relative thymus weight
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the response function by Model:
20        Model 2:     Y[dose] = a * exp{sign * b * dose}
21        Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
22        Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
23        Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
24
25     Note: Y[dose] is the median response for exposure = dose;
26           sign = +1 for increasing trend in data;
27           sign = -1 for decreasing trend.
28
29        Model 2 is nested within Models 3 and 4.
30        Model 3 is nested within Model 5.
31        Model 4 is nested within Model 5.
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.


Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


MLE solution provided: Exact


                    Initial Parameter Values

                    Variable          Model 2
                    --------          --------
                      lnalpha           6.96647
                         rho(S)               0
                           a          59.5084
                           b          0.00715458
                           c                  0
                           d                  1


   (S) = Specified




                    Parameter Estimates

                    Variable          Model 2
                    --------          -------
                      lnalpha           6.99043
                         rho                  0
                           a          99.7761
                           b          0.00771341
                           c                  0
                           d                  1



        Table of Stats From Input Data

   Dose      N        Obs Mean     Obs Std Dev
   -----    ---       ----------   -------------
      0      8          100         35.98
     10      8         97.53        32.98
     30      8         71.02        23.99
    100      8         49.29        43.48



             Estimated Values of Interest
```

```
        Dose       Est Mean      Est Std    Scaled Residual
       ------     ----------    ---------   ----------------
          0         99.78         32.96         0.01921
         10         92.37         32.96         0.4426
         30         79.16         32.96        -0.6986
        100         46.14         32.96         0.271
```

Other models for which likelihoods are calculated:

```
   Model A1:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma^2

   Model A2:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma(i)^2

   Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

   Model  R:        Yij = Mu + e(i)
            Var{e(ij)} = Sigma^2
```

                         Likelihoods of Interest

```
                Model     Log(likelihood)      DF        AIC
                -------   ----------------     ----   ------------
                  A1         -127.4636          5      264.9271
                  A2         -126.0925          8       268.185
                  A3         -127.4636          5      264.9271
                   R         -132.935           2       269.87
                   2         -127.8469          3      261.6939
```

   Additive constant for all log-likelihoods =   -29.41. This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.

                         Explanation of Tests

   Test 1: Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2: Are Variances Homogeneous? (A2 vs. A1)
   Test 3: Are variances adequately modeled? (A2 vs. A3)
   Test 4: Does Model 2 fit the data? (A3 vs. 2)

                         Tests of Interest

```
    Test          -2*log(Likelihood Ratio)         D. F.          p-value
   --------       ------------------------        ------        --------------
    Test 1                 13.69                     6             0.03336
    Test 2                 2.742                     3             0.4331
    Test 3                 2.742                     3             0.4331
```

```
Test 4                          0.7668           2              0.6815


    The p-value for Test 1 is less than .05.  There appears to be a
    difference between response and/or variances among the dose
    levels, it seems appropriate to model the data.

    The p-value for Test 2 is greater than .1.  A homogeneous
    variance model appears to be appropriate here.

    The p-value for Test 3 is greater than .1.  The modeled
    variance appears to be appropriate here.

    The p-value for Test 4 is greater than .1.  Model 2 seems
    to adequately describe the data.


Benchmark Dose Computations:

    Specified Effect = 0.100000

           Risk Type = Relative deviation

    Confidence Level = 0.950000

                 BMD =      13.6594

                BMDL =      8.01373
```

G.3.15.3. *Figure for Selected Model: Exponential (M2)*

Exponential_beta Model 2 with 0.95 Confidence Level

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G.3.15.4. *Output for Additional Model Presented: Exponential (M4)*

Franc et al. ([2001](#)): H/W Rats, Relative Thymus Weight

```
==================================================================
       Exponential Model. (Version: 1.61;  Date: 7/24/2009)
       Input Data File: C:\1\93_Franc_2001_HW_RelThyWt_ExpCV_1.(d)
       Gnuplot Plotting File:
                                   Fri Apr 16 16:31:40 2010
==================================================================

 Figure 5, H/W rats, relative thymus weight
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
```

```
            sign = +1 for increasing trend in data;
            sign = -1 for decreasing trend.


    Model 2 is nested within Models 3 and 4.
    Model 3 is nested within Model 5.
    Model 4 is nested within Model 5.



Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.


Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


MLE solution provided: Exact


                Initial Parameter Values

                Variable          Model 4
                --------          --------
                  lnalpha              6.96647
                     rho(S)                  0
                       a                    105
                       b               0.03169
                       c              0.447105
                       d                     1


   (S) = Specified




                Parameter Estimates

                Variable          Model 4
                --------          -------
                  lnalpha              6.97993
                     rho                    0
                       a               103.091
                       b               0.02048
                       c              0.394904
                       d                     1



            Table of Stats From Input Data

     Dose      N        Obs Mean      Obs Std Dev
     -----     ---      ----------    -------------
         0       8            100           35.98
        10       8          97.53           32.98
```

```
          30         8         71.02          23.99
         100         8         49.29          43.48


                    Estimated Values of Interest

         Dose      Est Mean      Est Std     Scaled Residual
         ------    ----------    ---------   ----------------
            0         103.1        32.78         -0.2667
           10        91.54        32.78          0.5166
           30        74.46        32.78         -0.2961
          100        48.76        32.78          0.04621




   Other models for which likelihoods are calculated:

      Model A1:          Yij = Mu(i) + e(ij)
                  Var{e(ij)} = Sigma^2

      Model A2:          Yij = Mu(i) + e(ij)
                  Var{e(ij)} = Sigma(i)^2

      Model A3:          Yij = Mu(i) + e(ij)
                  Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

      Model  R:          Yij = Mu + e(i)
                  Var{e(ij)} = Sigma^2



                         Likelihoods of Interest

                    Model      Log(likelihood)      DF        AIC
                    -------    -----------------    ----    ------------
                      A1          -127.4636          5        264.9271
                      A2          -126.0925          8        268.185
                      A3          -127.4636          5        264.9271
                       R          -132.935           2        269.87
                       4          -127.6789          4        263.3577


   Additive constant for all log-likelihoods =     -29.41.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.


                         Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 6a: Does Model 4 fit the data? (A3 vs 4)
```

```
                       Tests of Interest

    Test              -2*log(Likelihood Ratio)         D. F.          p-value
    --------          ------------------------         ------         --------------
    Test 1                      13.69                    6              0.03336
    Test 2                      2.742                    3              0.4331
    Test 3                      2.742                    3              0.4331
   Test 6a                      0.4306                   1              0.5117


    The p-value for Test 1 is less than .05.  There appears to be a
    difference between response and/or variances among the dose
    levels, it seems appropriate to model the data.

    The p-value for Test 2 is greater than .1.  A homogeneous
    variance model appears to be appropriate here.

    The p-value for Test 3 is greater than .1.  The modeled
    variance appears to be appropriate here.

    The p-value for Test 6a is greater than .1.  Model 4 seems
    to adequately describe the data.


 Benchmark Dose Computations:

    Specified Effect = 0.100000

           Risk Type = Relative deviation

    Confidence Level = 0.950000

               BMD =      8.82023

               BMDL =      3.21928
```

1 **G.3.15.5.** *Figure for Additional Model Presented: Exponential (M4)*

Exponential_beta Model 4 with 0.95 Confidence Level

16:31 04/16 2010

2
3

1 **G.3.16. Hojo et al. ([2002](#)): DRL Reinforce per Minute**

2 **G.3.16.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
hill	0	N/A	6.465	2.060E+01	1.713E−05	
linear[b]	**2**	**0.008**	**9.552**	**2.677E+02**	**1.100E+02**	
polynomial, 3-degree	2	0.008	9.552	2.677E+02	1.100E+02	
power	2	0.008	9.552	2.677E+02	1.100E+02	power bound hit (power = 1)
power, unrestricted	1	0.025	6.780	2.187E+00	4.612E−08	unrestricted (power = 0.089)
exponential (M2)	2	0.006	9.894	3.043E+02	1.505E+02	
exponential (M3)	2	0.006	9.894	3.043E+02	1.505E+02	power hit bound (*d* = 1)
exponential (M4)[c]	1	0.062	5.241	1.734E+01	3.827E−02	
exponential (M5)	0	N/A	6.465	2.140E+01	1.240E−05	

[a] Constant variance model selected (*p* = 0.4321).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

3
4
5 **G.3.16.2.** *Output for Selected Model: Linear*

6 Hojo et al. ([2002](#)): DRL Reinforce Per Minute
7
8
9
```
     =======================================================================
10           Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
11           Input Data File: C:\1\20_Hojo_2002_DRLrein_LinearCV_1.(d)
12           Gnuplot Plotting File:  C:\1\20_Hojo_2002_DRLrein_LinearCV_1.plt
13                                     Tue Feb 16 17:29:42 2010
14     =======================================================================
15
16   Table 5
17 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19    The form of the response function is:
20
21    Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
22
23
24    Dependent variable = Mean
25    Independent variable = Dose
26    rho is set to 0
27    Signs of the polynomial coefficients are not restricted
28    A constant variance model is fit
29
30    Total number of dose groups = 4
31    Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          alpha =      0.337763
                            rho =            0    Specified
                         beta_0 =        -0.404
                         beta_1 =    0.00249615



          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                   alpha        beta_0        beta_1

     alpha             1      -1.4e-008      2.2e-008

    beta_0     -1.4e-008             1         -0.69

    beta_1      2.2e-008         -0.69             1




                             Parameter Estimates


                                              95.0% Wald
Confidence Interval
       Variable        Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
          alpha        0.435671        0.134451             0.172152
0.69919
         beta_0       -0.372098        0.198702            -0.761547
0.017352
         beta_1      0.00246548      0.00211361          -0.00167711
0.00660807




    Table of Data and Estimated Values of Interest

 Dose      N    Obs Mean      Est Mean    Obs Std Dev  Est Std Dev   Scaled
Res.
 ------    ---   --------     --------    -----------  -----------   --------
-

    0      5     -0.814       -0.372         0.448         0.66         -1.5
   20      5     -0.364       -0.323         0.821         0.66        -0.14
   60      6      0.374       -0.224          0.54         0.66         2.22
  180      5     -0.163       0.0717         0.443         0.66       -0.795
```

```
Model Descriptions for likelihoods calculated


Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                   Likelihoods of Interest

          Model     Log(likelihood)   # Param's      AIC
           A1          3.115550            5        3.768900
           A2          4.489557            8        7.020886
           A3          3.115550            5        3.768900
         fitted       -1.775882            3        9.551763
           R          -2.435087            2        8.870174


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                   Tests of Interest

  Test     -2*log(Likelihood Ratio)  Test df        p-value

  Test 1            13.8493            6            0.03137
  Test 2            2.74801            3            0.4321
  Test 3            2.74801            3            0.4321
  Test 4            9.78286            2            0.007511

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
```

1   to be appropriate here
2
3   The p-value for Test 4 is less than .1. You may want to try a different
4   model
5
6
7   Benchmark Dose Computation
8
9   Specified effect =   1
10
11 Risk Type   =   Estimated standard deviations from the control mean
12
13 Confidence level =   0.95
14
15   BMD =   267.718
16
17
18   BMDL =   110.032
19
20
21 **G.3.16.3.** *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

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22
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G.3.16.4. *Output for Additional Model Presented: Exponential (M4)*

Hojo et al. ([2002](#)): DRL Reinforce Per Minute

```
=====================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\21_Hojo_2002_DRLrein_ExpCV_1.(d)
        Gnuplot Plotting File:
                                      Tue Feb 16 17:30:21 2010
=====================================================================

 Table 5, values adjusted by a constant to allow exponential model
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:      Y[dose] = a * exp{sign * b * dose}
      Model 3:      Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:      Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:      Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   rho is set to 0.
   A constant variance model is fit.


   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


   MLE solution provided: Exact



                  Initial Parameter Values

                  Variable          Model 4
                  --------          --------
                    lnalpha          -1.29672
                      rho(S)                0
                        a            0.0817
                        b          0.00880867
                        c            16.3733
                        d                 1
```

```
(S) = Specified



                     Parameter Estimates

                  Variable        Model 4
                  --------        -------
                  lnalpha        -1.13136
                     rho                0
                       a        0.0542868
                       b        0.0525016
                       c         18.5072
                       d               1



                Table of Stats From Input Data

     Dose       N      Obs Mean     Obs Std Dev
     -----     ---    ----------    -------------
        0       5       0.086          0.448
       20       5       0.536          0.821
       60       6       1.274          0.54
      180       5       0.737          0.443



                Estimated Values of Interest

     Dose      Est Mean      Est Std      Scaled Residual
     ------    ----------    ---------    ----------------
        0       0.05429        0.568           0.1249
       20       0.6721         0.568          -0.5359
       60       0.964          0.568           1.337
      180       1.005          0.568          -1.054




Other models for which likelihoods are calculated:

   Model A1:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma^2

   Model A2:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma(i)^2

   Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

   Model  R:        Yij = Mu + e(i)
            Var{e(ij)} = Sigma^2



                        Likelihoods of Interest

                  Model    Log(likelihood)    DF        AIC
                  -------  ----------------   ----   ------------
                    A1        3.11555           5       3.7689
```

```
                                A2         4.489557          8        7.020886
                                A3          3.11555          5          3.7689
                                 R        -2.435087          2        8.870174
                                 4         1.379312          4        5.241376



    Additive constant for all log-likelihoods =      -19.3.  This constant
added to the
    above values gives the log-likelihood including the term that does not
    depend on the model parameters.



                            Explanation of Tests

    Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
    Test 2:  Are Variances Homogeneous? (A2 vs. A1)
    Test 3:  Are variances adequately modeled? (A2 vs. A3)

    Test 6a: Does Model 4 fit the data? (A3 vs 4)



                            Tests of Interest

       Test            -2*log(Likelihood Ratio)        D. F.         p-value
    --------           ------------------------       ------       --------------
     Test 1                         13.85               6            0.03137
     Test 2                         2.748               3             0.4321
     Test 3                         2.748               3             0.4321
    Test 6a                         3.472               1             0.0624



    The p-value for Test 1 is less than .05.  There appears to be a
    difference between response and/or variances among the dose
    levels, it seems appropriate to model the data.

    The p-value for Test 2 is greater than .1.  A homogeneous
    variance model appears to be appropriate here.

    The p-value for Test 3 is greater than .1.  The modeled
    variance appears to be appropriate here.

    The p-value for Test 6a is less than .1.  Model 4 may not adequately
    describe the data; you may want to consider another model.



    Benchmark Dose Computations:

    Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

    Confidence Level = 0.950000

               BMD =      17.3391

              BMDL =    0.0382689
```

1 **G.3.16.5.** *Figure for Additional Model Presented: Exponential (M4)*

Exponential_beta Model 4 with 0.95 Confidence Level

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G.3.17. Hojo et al. (2002): DRL Response per Minute

G.3.17.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Hill	0	N/A	126.353	1.646E+01	1.800E−13	
Linear	2	0.004	132.825	2.067E+02	9.757E+01	
Polynomial, 3-degree	2	0.004	132.825	2.067E+02	9.757E+01	
Power	2	0.004	132.825	2.067E+02	9.757E+01	power bound hit (power = 1)
Power, unrestricted	2	0.741	122.455	1.800E+04	error	unrestricted (power = 0)
Exponential (M2)	2	0.568	122.985	6.184E+00	error	
Exponential (M3)	2	0.568	122.985	6.184E+00	error	power hit bound (*d* = 1)
Exponential (M4)[b]	**1**	**0.479**	**124.356**	**4.775E+00**	**2.704E−01**	
Exponential (M5)	0	N/A	126.353	1.118E+01	2.127E−01	

[a] Constant variance model selected ($p = 0.3004$).
[b] Best-fitting model, BMDS output presented in this appendix.

3
4
G.3.17.2. *Output for Selected Model: Exponential (M4)*

6 Hojo et al. (2002): DRL Response Per Minute
7
8
```
9    ======================================================================
10          Exponential Model. (Version: 1.61;  Date: 7/24/2009)
11          Input Data File: C:\1\23_Hojo_2002_DRLresp_ExpCV_1.(d)
12          Gnuplot Plotting File:
13                                        Tue Feb 16 17:31:24 2010
14    ======================================================================
15
16   Table 5, values adjusted by a constant to allow exponential model
17   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19      The form of the response function by Model:
20         Model 2:     Y[dose] = a * exp{sign * b * dose}
21         Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
22         Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
23         Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
24
25       Note: Y[dose] is the median response for exposure = dose;
26            sign = +1 for increasing trend in data;
27            sign = -1 for decreasing trend.
28
29         Model 2 is nested within Models 3 and 4.
30         Model 3 is nested within Model 5.
31         Model 4 is nested within Model 5.
32
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.


Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


MLE solution provided: Exact


                    Initial Parameter Values

                    Variable          Model 4
                    --------          --------
                      lnalpha          4.51689
                         rho(S)              0
                           a          24.6362
                           b        0.0212679
                           c        0.0184785
                           d                1


   (S) = Specified




                      Parameter Estimates

                    Variable          Model 4
                    --------          -------
                      lnalpha          4.54075
                         rho                0
                           a           23.465
                           b          0.12859
                           c         0.100615
                           d                1




        Table of Stats From Input Data

    Dose      N         Obs Mean     Obs Std Dev
    -----    ---       ----------    -------------
        0      5         23.46        7.986
       20      5         4.013        10.96
       60      6         0.478        7.194
      180      5         4.594        15.23




                   Estimated Values of Interest

     Dose      Est Mean        Est Std     Scaled Residual
```

```
------      ----------      ---------      ----------------
     0        23.47          9.683          -0.0004677
    20         3.973         9.683           0.009182
    60         2.37          9.683          -0.4787
   180         2.361         9.683           0.5157
```

Other models for which likelihoods are calculated:

```
Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-57.92733	5	125.8547
A2	-56.09669	8	128.1934
A3	-57.92733	5	125.8547
R	-64.49611	2	132.9922
4	-58.17787	4	124.3557

Additive constant for all log-likelihoods =   -19.3. This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)

Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	16.8	6	0.01005
Test 2	3.661	3	0.3004
Test 3	3.661	3	0.3004

```
Test 6a                        0.5011          1              0.479
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose
levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous
variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled
variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems
to adequately describe the data.

Benchmark Dose Computations:

   Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

   Confidence Level = 0.950000

                BMD =   4.77493

               BMDL =   0.270447

1   **G.3.17.3.** *Figure for Selected Model: Exponential (M4)*

Exponential_beta Model 4 with 0.95 Confidence Level

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G.3.18. Kattainen et al. ([2001](#)): 3rd Molar Eruption, Female

G.3.18.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Logistic	3	0.292	89.060	1.941E+02	1.390E+02	negative intercept (intercept = −1.508)
Log-logistic[a]	**3**	**0.923**	**85.535**	**4.763E+01**	**2.481E+01**	**slope bound hit (slope = 1)**
Log-probit	3	0.390	88.231	1.574E+02	9.512E+01	slope bound hit (slope = 1)
Probit	3	0.306	88.919	1.858E+02	1.370E+02	negative intercept (intercept = −0.927)
Multistage, 4-degree	3	0.641	86.798	8.677E+01	5.520E+01	final ß = 0
Log-logistic, unrestricted[b]	2	0.952	87.157	2.599E+01	1.730E+00	unrestricted (slope = 0.794)
Log-probit, unrestricted	2	0.941	87.179	2.813E+01	2.334E+00	unrestricted (slope = 0.478)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.3.18.2. *Output for Selected Model: Log-Logistic*

Kattainen et al. ([2001](#)): 3rd Molar Eruption, Female

```
    =====================================================================
          Logistic Model. (Version: 2.12; Date: 05/16/2008)
          Input Data File: C:\1\24_Katt_2001_Erup_LogLogistic_BMR1.(d)
          Gnuplot Plotting File:  C:\1\24_Katt_2001_Erup_LogLogistic_BMR1.plt
                                  Tue Feb 16 17:31:52 2010
    =====================================================================

  Figure 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the probability function is:

    P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


    Dependent variable = DichEff
    Independent variable = Dose
    Slope parameter is restricted as slope >= 1

    Total number of observations = 5
    Total number of records with missing values = 0
    Maximum number of iterations = 250
    Relative Function Convergence has been set to: 1e-008
    Parameter Convergence has been set to: 1e-008
```

```
User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =       0.0625
                      intercept =       -6.063
                          slope =            1



          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -slope
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

              background    intercept

background             1        -0.56

 intercept         -0.56             1




                              Parameter Estimates

                                                    95.0% Wald
Confidence Interval
        Variable         Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
      background      0.0846785               *                 *
*
        intercept      -6.06063               *                 *
*
           slope             1               *                 *
*

* - Indicates that this value is not calculated.




                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model       -40.5286         5
    Fitted model      -40.7674         2       0.477533       3
0.9238
    Reduced model     -50.7341         1        20.411        4
0.0004142


        AIC:          85.5347



                            Goodness   of   Fit
```

```
                                                         Scaled
        Dose      Est._Prob.     Expected    Observed    Size      Residual
      ------------------------------------------------------------------------
        0.0000      0.0847         1.355       1.000       16       -0.319
       30.0000      0.1445         2.457       3.000       17        0.374
      100.0000      0.2578         3.867       4.000       15        0.078
      300.0000      0.4615         5.538       6.000       12        0.267
     1000.0000      0.7254        13.782      13.000       19       -0.402

  Chi^2 = 0.48      d.f. = 3         P-value = 0.9231


     Benchmark Dose Computation

  Specified effect =          0.1

  Risk Type       =      Extra risk

  Confidence level =          0.95

            BMD =      47.6274
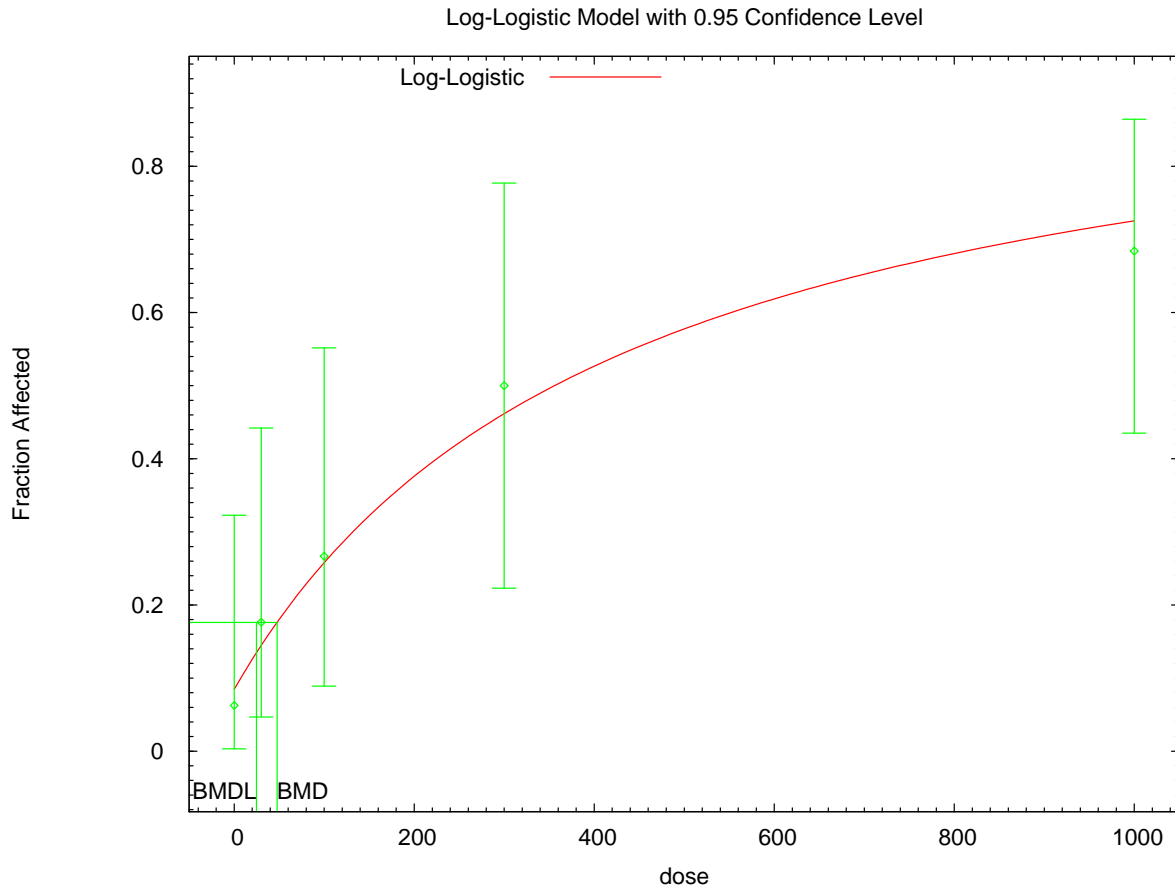
            BMDL =     24.8121
```

1   **G.3.18.3.** *Figure for Selected Model: Log-Logistic*

Log-Logistic Model with 0.95 Confidence Level

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4   **G.3.18.4.** *Output for Additional Model Presented: Log-Logistic, Unrestricted*

5   Kattainen et al. (2001): 3rd Molar Eruption, Female

6
7
```
8    ====================================================================
9          Logistic Model. (Version: 2.12; Date: 05/16/2008)
10         Input Data File: C:\1\24_Katt_2001_Erup_LogLogistic_U_BMR1.(d)
11         Gnuplot Plotting File:  C:\1\24_Katt_2001_Erup_LogLogistic_U_BMR1.plt
12                                      Tue Feb 16 17:31:53 2010
13    ====================================================================
14
15    Figure 2
16    ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18       The form of the probability function is:
19
20       P[response] = background+(1-background)/[1+EXP(-intercept-
21    slope*Log(dose))]
22
23
24       Dependent variable = DichEff
```

```
     Independent variable = Dose
     Slope parameter is not restricted

     Total number of observations = 5
     Total number of records with missing values = 0
     Maximum number of iterations = 250
     Relative Function Convergence has been set to: 1e-008
     Parameter Convergence has been set to: 1e-008




     User has chosen the log transformed model


                    Default Initial Parameter Values
                        background =      0.0625
                         intercept =     -4.71231
                             slope =     0.782659


          Asymptotic Correlation Matrix of Parameter Estimates

                  background      intercept          slope

background              1          -0.48           0.39

 intercept          -0.48              1          -0.98

    slope            0.39          -0.98              1




                             Parameter Estimates

                                                      95.0% Wald
Confidence Interval
        Variable          Estimate         Std. Err.      Lower Conf. Limit
Upper Conf. Limit
     background          0.0633217              *                  *
*
       intercept         -4.78282               *                  *
*
          slope          0.793723               *                  *
*

* - Indicates that this value is not calculated.




                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model       -40.5286         5
    Fitted model       -40.5783         3     0.0994416      2
0.9515
    Reduced model      -50.7341         1       20.411       4
0.0004142
```

```
          AIC:              87.1566


                          Goodness  of  Fit
                                                            Scaled
       Dose     Est._Prob.    Expected    Observed    Size    Residual
     ------------------------------------------------------------------
       0.0000    0.0633        1.013       1.000       16     -0.013
      30.0000    0.1670        2.840       3.000       17      0.104
     100.0000    0.2924        4.387       4.000       15     -0.219
     300.0000    0.4721        5.666       6.000       12      0.193
    1000.0000    0.6892       13.095      13.000       19     -0.047

   Chi^2 = 0.10     d.f. = 2       P-value = 0.9518


      Benchmark Dose Computation

   Specified effect =          0.1

   Risk Type        =      Extra risk

   Confidence level =          0.95

              BMD =          25.986

             BMDL =          1.73001
```

1   **G.3.18.5.** *Figure for Additional Model Presented: Log-Logistic, Unrestricted*

Log-Logistic Model with 0.95 Confidence Level

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G.3.19. Kattainen et al. ([2001](#)): 3rd Molar Length, Female

2 **G.3.19.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	3	<0.0001	−122.954	4.027E+02	2.366E+02	
Exponential (M3)	3	<0.0001	−122.954	4.027E+02	2.366E+02	power hit bound (*d* = 1)
Exponential (M4)	2	<0.0001	−80.747	error	error	
Exponential (M5)	1	<0.0001	−78.747	error	error	
Hill[b]	**2**	**0.013**	**−151.152**	**4.052E+00**	**2.144E+00**	***n* lower bound hit (*n* = 1)**
Linear	3	<0.0001	−122.325	4.659E+02	2.963E+02	
Polynomial, 4-degree	3	<0.0001	−122.325	4.659E+02	2.963E+02	
Power	3	<0.0001	−122.325	4.659E+02	2.963E+02	power bound hit (power = 1)
Hill, unrestricted[c]	1	0.087	−154.939	1.913E−02	1.928E−04	unrestricted (*n* = 0.197)
Power, unrestricted	2	0.250	−157.093	9.098E−03	9.097E−03	unrestricted (power = 0.169)

[a] Nonconstant variance model selected (*p* = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

3
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5 **G.3.19.2.** *Output for Selected Model: Hill*

6 Kattainen et al. ([2001](#)): 3rd Molar Length, Female
7

8
9
```
       =====================================================================
10        Hill Model. (Version: 2.14;  Date: 06/26/2008)
11        Input Data File: C:\1\25_Katt_2001_Length_Hill_1.(d)
12        Gnuplot Plotting File:  C:\1\25_Katt_2001_Length_Hill_1.plt
13                                      Tue Feb 16 17:32:21 2010
14        =====================================================================
15
16   Figure 3 female only
17 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19      The form of the response function is:
20
21      Y[dose] = intercept + v*dose^n/(k^n + dose^n)
22
23
24      Dependent variable = Mean
25      Independent variable = Dose
26      Power parameter restricted to be greater than 1
27      The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))
28
29      Total number of dose groups = 5
30      Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                         lalpha =    -2.37155
                            rho =           0
                      intercept =     1.85591
                              v =   -0.507874
                              n =    0.826204
                              k =     27.3305


              Asymptotic Correlation Matrix of Parameter Estimates

              ( *** The model parameter(s)  -n
                    have been estimated at a boundary point, or have been
specified by the user,
                    and do not appear in the correlation matrix )

                   lalpha         rho    intercept           v           k

     lalpha             1       -0.98       -0.16        0.84       -0.37

        rho         -0.98           1         0.2       -0.79        0.39

  intercept         -0.16         0.2           1       -0.31       -0.11

          v          0.84       -0.79       -0.31           1       -0.48

          k         -0.37        0.39       -0.11       -0.48           1




                              Parameter Estimates


                                                        95.0% Wald
Confidence Interval
      Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
        lalpha         3.34561          1.40443             0.592981
6.09824
           rho        -14.3325          2.62129             -19.4701
-9.19484
     intercept          1.8548        0.0159017              1.82364
1.88597
             v        -0.441166        0.058852             -0.556513
-0.325818
             n               1               NA
             k         24.0343          7.84495              8.65852
39.4101

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

```
      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
 ------     ---  --------     --------   -----------  -----------   ---------
-

    0       16     1.86         1.85       0.0661       0.0637        0.0692
   30       17     1.58         1.61       0.185        0.176        -0.768
  100       15     1.6          1.5        0.265        0.293         1.28
  300       12     1.5          1.45       0.221        0.378         0.527
 1000       19     1.35         1.42       0.515        0.423        -0.783
```

Model Descriptions for likelihoods calculated


```
Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2
```

                     Likelihoods of Interest

```
          Model      Log(likelihood)   # Param's       AIC
           A1          56.758717           6       -101.517434
           A2          85.856450          10       -151.712901
           A3          84.934314           7       -155.868628
         fitted        80.575940           5       -151.151880
            R          45.373551           2        -86.747101
```

                     Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

                      Tests of Interest

```
     Test    -2*log(Likelihood Ratio)  Test df        p-value

     Test 1                80.9658         8          <.0001
     Test 2                58.1955         4          <.0001
     Test 3                1.84427         3          0.6053
     Test 4                8.71675         2          0.0128
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different
model

          Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

          BMD =   4.05231

          BMDL =   2.14357

1   **G.3.19.3.** *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

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2
3
4   **G.3.19.4.** *Output for Additional Model Presented: Hill, Unrestricted*

5   Kattainen et al. (2001): 3rd Molar Length, Female
6
7
8   ```
     ===
9   Hill Model. (Version: 2.14; Date: 06/26/2008)
10   Input Data File: C:\1\25_Katt_2001_Length_Hill_U_1.(d)
11   Gnuplot Plotting File: C:\1\25_Katt_2001_Length_Hill_U_1.plt
12   Tue Feb 16 17:32:21 2010
13   ===
14
15   Figure 3 female only
16   ~~~~~~
17
18   The form of the response function is:
19
20   Y[dose] = intercept + v*dose^n/(k^n + dose^n)
21
22
23   Dependent variable = Mean
24   Independent variable = Dose
     ```

```
Power parameter is not restricted
The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          lalpha =      -2.37155
                             rho =             0
                       intercept =       1.85591
                               v =     -0.507874
                               n =      0.826204
                               k =       27.3305


          Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho    intercept            v            n
 k

     lalpha            1        -0.98        -0.18         0.18        -0.28
 -0.011

        rho        -0.98            1         0.22        -0.18         0.29
 0.011

  intercept        -0.18         0.22            1       -0.025       -0.059
 0.0019

          v         0.18        -0.18       -0.025            1         0.51
 -0.96

          n        -0.28         0.29       -0.059         0.51            1
 -0.71

          k       -0.011        0.011       0.0019        -0.96        -0.71
 1




                              Parameter Estimates


                                                       95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
          lalpha         3.21882           1.4221             0.431563
6.00607
             rho        -14.0862          2.68292              -19.3446
-8.82777
       intercept         1.85564        0.0160224              1.82424
1.88704
```

```
              v          -2.48572           2.89658              -8.16291
3.19148
              n          0.196925          0.0499318             0.0990606
0.29479
              k        1.92967e+006      1.60869e+007           -2.96e+007
3.34593e+007




     Table of Data and Estimated Values of Interest

 Dose         N    Obs Mean      Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
 ------       ---   --------      --------   -----------  -----------   ---------
-

     0        16      1.86          1.86       0.0661       0.0643       0.0164
    30        17      1.58          1.6        0.185        0.18        -0.598
   100        15      1.6           1.54       0.265        0.234        0.857
   300        12      1.5           1.48       0.221        0.316        0.259
  1000        19      1.35          1.4        0.515        0.471       -0.466




  Model Descriptions for likelihoods calculated


  Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

  Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                    Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1           56.758717          6       -101.517434
             A2           85.856450         10       -151.712901
             A3           84.934314          7       -155.868628
           fitted        83.469680          6       -154.939361
             R           45.373551          2        -86.747101



                    Explanation of Tests

  Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
  Test 2:  Are Variances Homogeneous? (A1 vs A2)
```

```
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                      Tests of Interest

  Test     -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              80.9658            8            <.0001
  Test 2              58.1955            4            <.0001
  Test 3              1.84427            3            0.6053
  Test 4              2.92927            1            0.08699
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different
model

```
          Benchmark Dose Computation

Specified effect =              1

Risk Type        =      Estimated standard deviations from the control mean

Confidence level =           0.95

            BMD =      0.0191282

           BMDL =     0.0001928
```

G.3.19.5. *Figure for Additional Model Presented: Hill, Unrestricted*

Hill Model with 0.95 Confidence Level

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G.3.20. Keller et al. ([2007](#)): Missing Mandibular Molars, CBA J

G.3.20.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	1	0.105	52.490	7.293E+01	2.027E+01	
Logistic	2	0.320	50.095	7.168E+01	5.142E+01	
Log-logistic	1	0.105	52.524	9.278E+01	5.273E+01	
Log-probit	1	0.105	52.524	8.849E+01	5.297E+01	
Multistage, 1-degree[a]	**3**	**0.276**	**49.409**	**2.778E+01**	**1.884E+01**	
Multistage, 2-degree	1	0.126	51.515	4.619E+01	2.214E+01	
Multistage, 3-degree	1	0.141	51.222	4.253E+01	2.212E+01	
Probit	2	0.325	50.032	6.848E+01	4.775E+01	
Weibull	1	0.108	52.216	6.079E+01	2.078E+01	

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.20.2. *Output for Selected Model: Multistage, 1-Degree*

Keller et al. ([2007](#)): Missing Mandibular Molars, CBA J


```
    =====================================================================
          Multistage Model. (Version: 3.0;  Date: 05/16/2008)
          Input Data File: C:\1\26_Keller_2007_Molars_Multi1_1.(d)
          Gnuplot Plotting File:  C:\1\26_Keller_2007_Molars_Multi1_1.plt
                                          Tue Feb 16 17:32:56 2010
    =====================================================================

 Table 1 using mandibular molars only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
```

```
Degree of polynomial = 1


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                        Background =          0
                          Beta(1) = 1.02909e+017



            Asymptotic Correlation Matrix of Parameter Estimates

              ( *** The model parameter(s)  -Background
                    have been estimated at a boundary point, or have been
specified by the user,
                    and do not appear in the correlation matrix )

                  Beta(1)


     Beta(1)              1




                              Parameter Estimates


                                                        95.0% Wald
Confidence Interval
        Variable          Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
       Background               0              *                   *
*
          Beta(1)      0.00379264             *                   *
*


* - Indicates that this value is not calculated.




                         Analysis of Deviance Table

       Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
       Full model       -21.5798          4
     Fitted model       -23.7044          1      4.24924       3
0.2358
    Reduced model       -71.326           1      99.4926       3       <.0001

          AIC:         49.4088



                              Goodness  of  Fit
                                                              Scaled
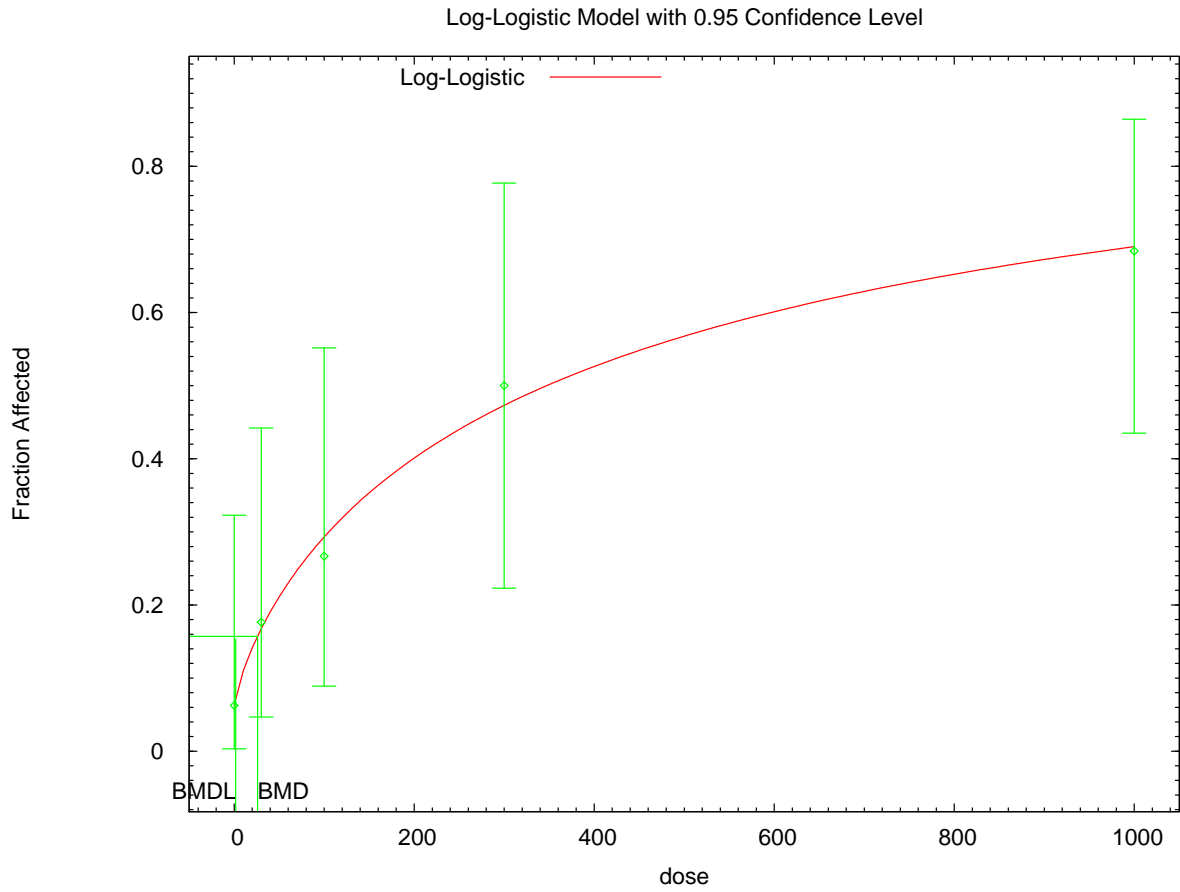       Dose      Est._Prob.   Expected   Observed    Size       Residual
     ------------------------------------------------------------------------
```

```
    0.0000      0.0000        0.000    0.000        29      0.000
   10.0000      0.0372        0.856    2.000        23      1.260
  100.0000      0.3156        9.153    6.000        29     -1.260
 1000.0000      0.9775       29.324   30.000        30      0.832


 Chi^2 = 3.87      d.f. = 3        P-value = 0.2762


    Benchmark Dose Computation

Specified effect =              0.1

Risk Type        =      Extra risk

Confidence level =              0.95

           BMD =        27.7803

          BMDL =        18.8447

          BMDU =        41.7256

Taken together, (18.8447, 41.7256) is a 90      % two-sided confidence
interval for the BMD
```

1   **G.3.20.3.** *Figure for Selected Model: Multistage, 1-Degree*

Multistage Model with 0.95 Confidence Level

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2
3
4
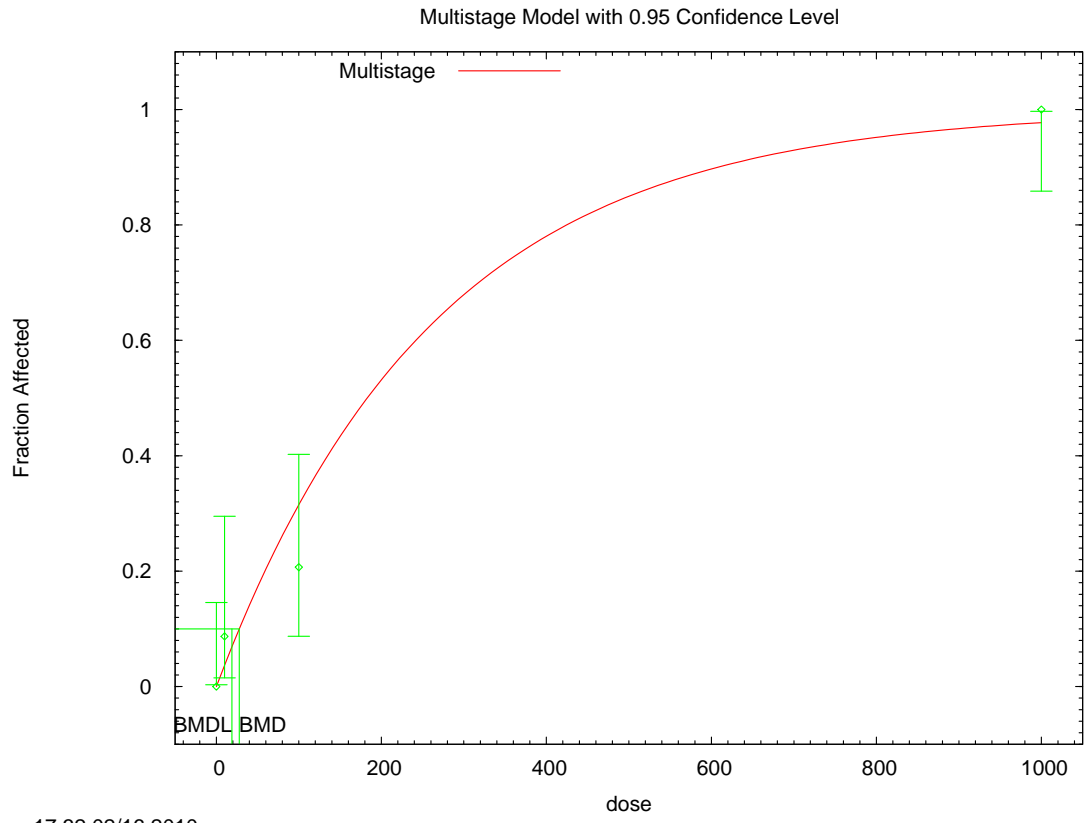
G.3.21. Kociba et al. ([1978](#)): Urinary Coproporphyrin, Females

G.3.21.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	<0.0001	84.006	7.054E+01	4.341E+01	
Exponential (M3)	2	<0.0001	84.006	7.054E+01	4.341E+01	power hit bound (d = 1)
Exponential (M4)[b]	**1**	**0.040**	**70.556**	**1.625E+00**	**7.300E−01**	
Exponential (M5)	0	N/A	69.092	3.128E+00	1.024E+00	
Hill	0	N/A	69.047	6.677E+00	error	
Linear	2	<0.0001	83.713	6.195E+01	3.112E+01	
Polynomial, 3-degree	2	<0.0001	83.713	6.195E+01	3.112E+01	
Power	2	<0.0001	83.713	6.195E+01	3.112E+01	power bound hit (power = 1)
Power, unrestricted	1	0.001	78.260	7.808E−01	1.693E−08	unrestricted (power = 0.306)

[a] Nonconstant variance model selected (p = 0.0298).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.21.2. *Output for Selected Model: Exponential (M4)*

Kociba et al. ([1978](#)): Urinary Coproporphyrin, Females

```
   ======================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\29_Kociba_1978_Copro_Exp_1.(d)
         Gnuplot Plotting File:
                                       Tue Feb 16 17:34:45 2010
   ======================================================================

 Table2-UrinaryCoproporphyrin
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


MLE solution provided: Exact


                   Initial Parameter Values

                   Variable          Model 4
                   --------          --------
                    lnalpha              -5.58269
                       rho               2.98472
                         a                  8.17
                         b             0.0259469
                         c               2.23623
                         d                     1




                   Parameter Estimates

                   Variable          Model 4
                   --------          -------
                    lnalpha              -4.94473
                       rho               2.76088
                         a               8.93039
                         b              0.136554
                         c                1.9753
                         d                     1



          Table of Stats From Input Data

     Dose      N        Obs Mean     Obs Std Dev
     -----     ---      ----------    -------------
         0     5           9.8          1.3
         1     5           8.6          2
        10     5          16.4          4.7
       100     5          17.4          4



              Estimated Values of Interest

     Dose      Est Mean      Est Std     Scaled Residual
     ------    ----------    ---------    ----------------
         0        8.93         1.733          1.122
         1       10.04         2.038         -1.582
```

```
        10           15.42         3.683              0.5967
        100          17.64         4.436             -0.1211



   Other models for which likelihoods are calculated:

     Model A1:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma^2

     Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

     Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

     Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                           Likelihoods of Interest

                  Model      Log(likelihood)     DF        AIC
                  -------    ----------------    ----    ------------
                    A1         -31.69739           5       73.39478
                    A2         -27.21541           8       70.43081
                    A3         -28.16434           6       68.32868
                     R         -41.73188           2       87.46376
                     4         -30.27804           5       70.55608


   Additive constant for all log-likelihoods =    -18.38.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                           Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 6a: Does Model 4 fit the data? (A3 vs 4)



                           Tests of Interest

     Test          -2*log(Likelihood Ratio)        D. F.        p-value
     --------      ------------------------        ------      --------------
     Test 1                       29.03               6         < 0.0001
     Test 2                       8.964               3          0.02977
     Test 3                       1.898               2          0.3872
    Test 6a                       4.227               1          0.03978
```

```
The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose
levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1.  A non-homogeneous
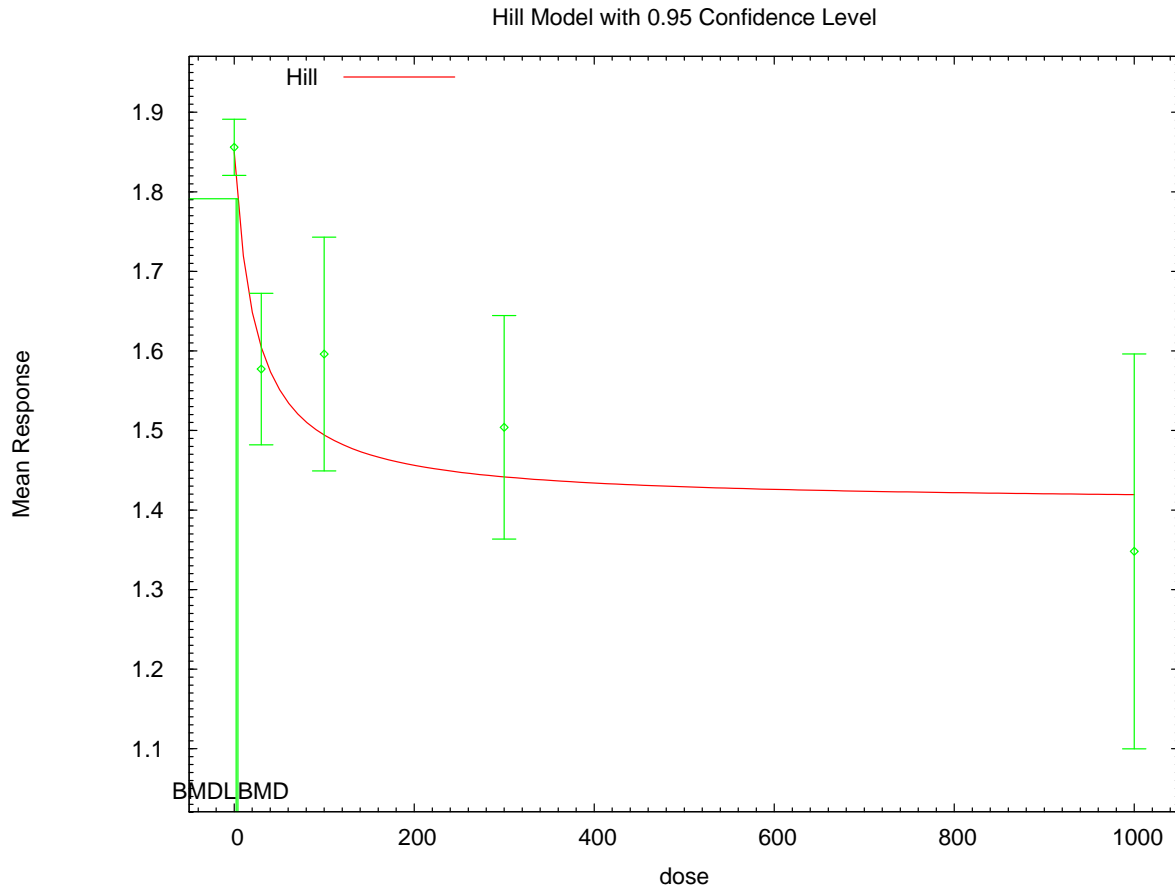variance model appears to be appropriate.

The p-value for Test 3 is greater than .1.  The modeled
variance appears to be appropriate here.

The p-value for Test 6a is less than .1.  Model 4 may not adequately
describe the data; you may want to consider another model.


Benchmark Dose Computations:

   Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

   Confidence Level = 0.950000

                BMD =     1.62505

               BMDL =     0.729987
```

1   **G.3.21.3.** *Figure for Selected Model: Exponential (M4)*

Exponential_beta Model 4 with 0.95 Confidence Level

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2
3
4

G.3.22. Kociba et al. (1978): Uroporphyrin per Creatinine, Female

2   **G.3.22.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.661	−93.561	4.357E+01	3.328E+01	
Exponential (M3)	2	0.661	−93.561	4.357E+01	3.328E+01	power hit bound ($d = 1$)
Exponential (M4)	1	0.576	−92.078	1.719E+01	5.516E+00	
Exponential (M5)	0	N/A	−90.190	1.080E+01	5.613E+00	
Hill	0	N/A	−90.190	1.099E+01	5.088E+00	
Linear[b]	**2**	**0.720**	**−93.735**	**3.522E+01**	**2.500E+01**	
Polynomial, 3-degree	2	0.720	−93.735	3.522E+01	2.500E+01	
Power	2	0.720	−93.735	3.522E+01	2.500E+01	power bound hit (power = 1)
Power, unrestricted	1	0.515	−91.967	2.274E+01	3.334E+00	unrestricted (power = 0.731)

[a] Constant variance model selected ($p = 0.4919$).
[b] Best-fitting model, BMDS output presented in this appendix.

3
4
5   **G.3.22.2.** *Output for Selected Model: Linear*

6   Kociba et al. (1978): Uroporphyrin per Creatinine, Female
7
8
```
9    =======================================================================
10          Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
11          Input Data File: C:\1\28_Kociba_1978_Uropor_LinearCV_1.(d)
12          Gnuplot Plotting File:  C:\1\28_Kociba_1978_Uropor_LinearCV_1.plt
13                                      Tue Feb 16 17:34:12 2010
14    =======================================================================
15
16    Table 2
17    ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19       The form of the response function is:
20
21       Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
22
23
24       Dependent variable = Mean
25       Independent variable = Dose
26       rho is set to 0
27       Signs of the polynomial coefficients are not restricted
28       A constant variance model is fit
29
30       Total number of dose groups = 4
31       Total number of records with missing values = 0
32       Maximum number of iterations = 250
```

```
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                          alpha =    0.0030385
                            rho =          0   Specified
                        beta_0 =     0.154759
                        beta_1 =    0.0014231



          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                    alpha       beta_0       beta_1

     alpha             1    -2.2e-009     3.5e-009

    beta_0     -2.2e-009            1        -0.55

    beta_1      3.5e-009        -0.55            1




                            Parameter Estimates

                                                        95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
          alpha       0.00251184      0.000794315        0.000955015
0.00406867
         beta_0         0.154759        0.0134422           0.128413
0.181105
         beta_1        0.0014231      0.000267497        0.000898818
0.00194739



    Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean    Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
 ------     ---  --------    --------   -----------  -----------   ---------
-

    0       5     0.157       0.155        0.05        0.0501         0.1
    1       5     0.143       0.156        0.037       0.0501        -0.588
   10       5     0.181       0.169        0.053       0.0501         0.536
  100       5     0.296       0.297        0.074       0.0501        -0.0477
```

```
Model Descriptions for likelihoods calculated


Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

          Model      Log(likelihood)    # Param's      AIC
           A1          50.195349            5        -90.390697
           A2          51.400051            8        -86.800103
           A3          50.195349            5        -90.390697
         fitted        49.867385            3        -93.734769
           R           41.049755            2        -78.099510


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test     -2*log(Likelihood Ratio)   Test df        p-value

   Test 1            20.7006              6           0.002076
   Test 2            2.40941              3            0.4919
   Test 3            2.40941              3            0.4919
   Test 4            0.655928             2            0.7204

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here
```

```
 1
 2    The p-value for Test 4 is greater than .1.   The model chosen seems
 3    to adequately describe the data
 4
 5
 6                  Benchmark Dose Computation
 7
 8    Specified effect =                1
 9
10    Risk Type        =       Estimated standard deviations from the control mean
11
12    Confidence level =          0.95
13
14              BMD =           35.2176
15
16
17              BMDL =          25.0024
18
19
20  G.3.22.3.  *Figure for Selected Model: Linear*
```


Linear Model with 0.95 Confidence Level

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```
21
22
23
```

G.3.23. Kuchiiwa et al. ([2002](#)): Immunoreactive Neurons in Dorsalis, Males

2 **G.3.23.1.** *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	0	N/A [c]	93.91	1.646E−01	1.163E−01	

[a] Constant variance model selected ($p = 0.530$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] *p*-value could not be calculated because there were no available degrees of freedom.

3
4
5 **G.3.23.2.** *Output for Selected Model: Linear*

```
6   ======================================================================
7           Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
8           Input Data File:
9   C:\USEPA\BMDS21\1\75_Kuchiiwa_2002_dors_admin_dd_LinearCV_1.(d)
10          Gnuplot Plotting File:
11  C:\USEPA\BMDS21\1\75_Kuchiiwa_2002_dors_admin_dd_LinearCV_1.plt
12                                          Tue Aug 16 13:41:50 2011
13   ======================================================================
14
15   number_labeled_cells_dorsalis
16  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18     The form of the response function is:
19
20     Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
21
22
23     Dependent variable = Mean
24     Independent variable = Dose
25     rho is set to 0
26     Signs of the polynomial coefficients are not restricted
27     A constant variance model is fit
28
29     Total number of dose groups = 2
30     Total number of records with missing values = 0
31     Maximum number of iterations = 250
32     Relative Function Convergence has been set to: 1e-008
33     Parameter Convergence has been set to: 1e-008
34
35
36
37                   Default Initial Parameter Values
38                         alpha =        670.324
39                           rho =              0   Specified
40                        beta_0 =        237.097
41                        beta_1 =       -143.626
42
43
44           Asymptotic Correlation Matrix of Parameter Estimates
```

```
              ( *** The model parameter(s)  -rho
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                      alpha        beta_0        beta_1

      alpha              1       3.8e-008      -1.9e-008

    beta_0      3.8e-008            1            -0.71

    beta_1     -1.9e-008         -0.71              1




                              Parameter Estimates

                                                        95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha         558.603          228.049            111.636
1005.57
          beta_0        237.097          9.64886            218.186
256.008
          beta_1       -143.626          19.4936           -181.833
-105.419




     Table of Data and Estimated Values of Interest

 Dose       N     Obs Mean      Est Mean    Obs Std Dev  Est Std Dev   Scaled
Res.
 ------     ---   --------      --------    -----------  -----------   ---------
-

    0        6       237           237          29          23.6      -9.42e-008
   0.7       6       137           137         22.4         23.6      -2.9e-008

Degrees of freedom for Test A3 vs fitted <= 0




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
```

```
       were specified by the user

  Model  R:          Yi = Mu + e(i)
              Var{e(i)} = Sigma^2



                       Likelihoods of Interest

              Model      Log(likelihood)   # Param's      AIC
               A1          -43.952634           3       93.905267
               A2          -43.755407           4       95.510815
               A3          -43.952634           3       93.905267
            fitted         -43.952634           3       93.905267
               R           -54.206960           2      112.413921



                       Explanation of Tests

  Test 1:  Do responses and/or variances differ among Dose levels?
           (A2 vs. R)
  Test 2:  Are Variances Homogeneous? (A1 vs A2)
  Test 3:  Are variances adequately modeled? (A2 vs. A3)
  Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
  (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                       Tests of Interest

    Test     -2*log(Likelihood Ratio)  Test df         p-value

    Test 1              20.9031           2           <.0001
    Test 2             0.394453           1            0.53
    Test 3             0.394453           1            0.53
    Test 4         8.95284e-013           0             NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid



                       Benchmark Dose Computation

Specified effect =            1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =         0.95
```

1
2   BMD =   0.164558
3
4   BMDL =   0.116266
5
6
7 **G.3.23.3.** *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

13:41 08/16 2011

8

G.3.24. Kuchiiwa et al. (2002): Immunoreactive Neurons in Medianus, Males

2 **G.3.24.1.** *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	0	N/A[c]	65.97	1.342E−01	8.786E−02	

[a] Modeled variance model selected ($p = 0.025$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] *p*-value could not be calculated because there were no available degrees of freedom.

3
4
5 **G.3.24.2.** *Output for Selected Model: Linear*

```
6  =====================================================================
7          Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
8          Input Data File:
9  C:\USEPA\BMDS21\1\76_Kuchiiwa_2002_med_admin_dd_Linear_1.(d)
10         Gnuplot Plotting File:
11 C:\USEPA\BMDS21\1\76_Kuchiiwa_2002_med_admin_dd_Linear_1.plt
12                                     Tue Aug 16 13:44:08 2011
13  =====================================================================
14
15  number_labeled_cells_medianus
16  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18     The form of the response function is:
19
20     Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
21
22
23     Dependent variable = Mean
24     Independent variable = Dose
25     Signs of the polynomial coefficients are not restricted
26     The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
27
28     Total number of dose groups = 2
29     Total number of records with missing values = 0
30     Maximum number of iterations = 250
31     Relative Function Convergence has been set to: 1e-008
32     Parameter Convergence has been set to: 1e-008
33
34
35
36                 Default Initial Parameter Values
37                      lalpha =      4.43247
38                         rho =            0
39                      beta_0 =      91.1157
40                      beta_1 =     -82.6446
41
42
```

```
          Asymptotic Correlation Matrix of Parameter Estimates

                    lalpha          rho        beta_0        beta_1

     lalpha              1        -0.99       2.7e-009      -1.9e-009

        rho          -0.99            1        -3e-009       2.2e-009

     beta_0       2.7e-009      -3e-009            1          -0.94

     beta_1      -1.9e-009     2.2e-009        -0.94              1



                          Parameter Estimates

                                                 95.0% Wald
Confidence Interval
      Variable        Estimate       Std. Err.    Lower Conf. Limit
Upper Conf. Limit
        lalpha        -3.97249         3.27352          -10.3885
2.44349
           rho          1.9468        0.810306          0.358628
3.53497
        beta_0         91.1157         4.52665           82.2436
99.9878
        beta_1        -82.6446         6.90638          -96.1808
-69.1083



    Table of Data and Estimated Values of Interest

 Dose        N     Obs Mean     Est Mean    Obs Std Dev   Est Std Dev   Scaled
Res.
------      ---    --------     --------    -----------   -----------   ---------
-

    0        6        91.1         91.1          12.1          11.1      4.41e-009
  0.7        6        33.3         33.3          4.55          4.16     -4.19e-009

Degrees of freedom for Test A2 vs A3 <= 0

 Warning: Likelihood for fitted model larger than the Likelihood for model
A3.



 Model Descriptions for likelihoods calculated


 Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2
```

```
Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
       Model A3 uses any fixed variance parameters that
       were specified by the user

  Model  R:        Yi = Mu + e(i)
             Var{e(i)} = Sigma^2


                     Likelihoods of Interest

             Model     Log(likelihood)    # Param's       AIC
              A1         -31.500916             3        69.001832
              A2         -28.985335             4        65.970670
              A3         -28.985335             4        65.970670
           fitted        -28.985335             4        65.970670
              R          -46.859574             2        97.719148


                     Explanation of Tests

  Test 1:  Do responses and/or variances differ among Dose levels?
           (A2 vs. R)
  Test 2:  Are Variances Homogeneous? (A1 vs A2)
  Test 3:  Are variances adequately modeled? (A2 vs. A3)
  Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
  (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test     -2*log(Likelihood Ratio)   Test df         p-value

   Test 1              35.7485             2            <.0001
   Test 2               5.03116            1            0.0249
   Test 3         2.47269e-012             0               NA
   Test 4        -2.47269e-012             0               NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

NA - Degrees of freedom for Test 3 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


                     Benchmark Dose Computation

Specified effect =              1
```

```
Risk Type          =        Estimated standard deviations from the control mean

Confidence level =           0.95

          BMD =           0.134165


          BMDL =       0.0878581
```

G.3.24.3. *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

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G.3.25. Kuchiiwa et al. (2002): Immunoreactive Neurons in B9, Males

G.3.25.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	0	N/A[c]	86.12	1.136E−01	8.208E−02	

[a] Constant variance model selected ($p = 0.504$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] *p*-value could not be calculated because there were no available degrees of freedom.

G.3.25.2. *Output for Selected Model: Linear*

```
=======================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File:
C:\USEPA\BMDS21\1\77_Kuchiiwa_2002_b9_admin_dd_LinearCV_1.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\1\77_Kuchiiwa_2002_b9_admin_dd_LinearCV_1.plt
                                        Tue Aug 16 13:48:05 2011
 =======================================================================

 number_labeled_cells_b9
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 2
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




                 Default Initial Parameter Values
                       alpha =      350.225
                         rho =            0   Specified
                      beta_0 =      152.086
                      beta_1 =     -150.415

```

```
          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                    alpha        beta_0        beta_1

    alpha                 1      1e-031      -2.9e-016

    beta_0      9.2e-032          1            -0.71

    beta_1    -2.9e-016         -0.71             1




                          Parameter Estimates


                                                  95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
          alpha          291.854          119.149             58.3265
525.381
          beta_0         152.086          6.9744              138.416
165.756
          beta_1        -150.415          14.0904            -178.031
-122.798




     Table of Data and Estimated Values of Interest

  Dose        N     Obs Mean      Est Mean    Obs Std Dev  Est Std Dev    Scaled
Res.
 ------       ---   --------      --------    -----------  -----------   ---------
-

    0         6        152          152           16          17.1             0
   0.7        6       46.8         46.8          21.1         17.1      1.02e-015

Degrees of freedom for Test A3 vs fitted <= 0




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
```

```
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:          Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                   Likelihoods of Interest

          Model      Log(likelihood)   # Param's      AIC
           A1          -40.057520          3        86.115041
           A2          -39.834453          4        87.668907
           A3          -40.057520          3        86.115041
        fitted         -40.057520          3        86.115041
           R           -54.163617          2       112.327234


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                   Tests of Interest

   Test     -2*log(Likelihood Ratio)  Test df       p-value

   Test 1             28.6583            2           <.0001
   Test 2             0.446134           1           0.5042
   Test 3             0.446134           1           0.5042
   Test 4         1.37845e-012           0             NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
    test for fit is not valid



                   Benchmark Dose Computation

Specified effect =              1

Risk Type       =      Estimated standard deviations from the control mean
```

```
1    Confidence level =          0.95
2
3             BMD =          0.113578
4
5            BMDL =         0.0820848
6
7
```

8 **G.3.25.3.** *Figure for Selected Model: Linear*

9

Linear Model with 0.95 Confidence Level

13:48 08/16 2011

10
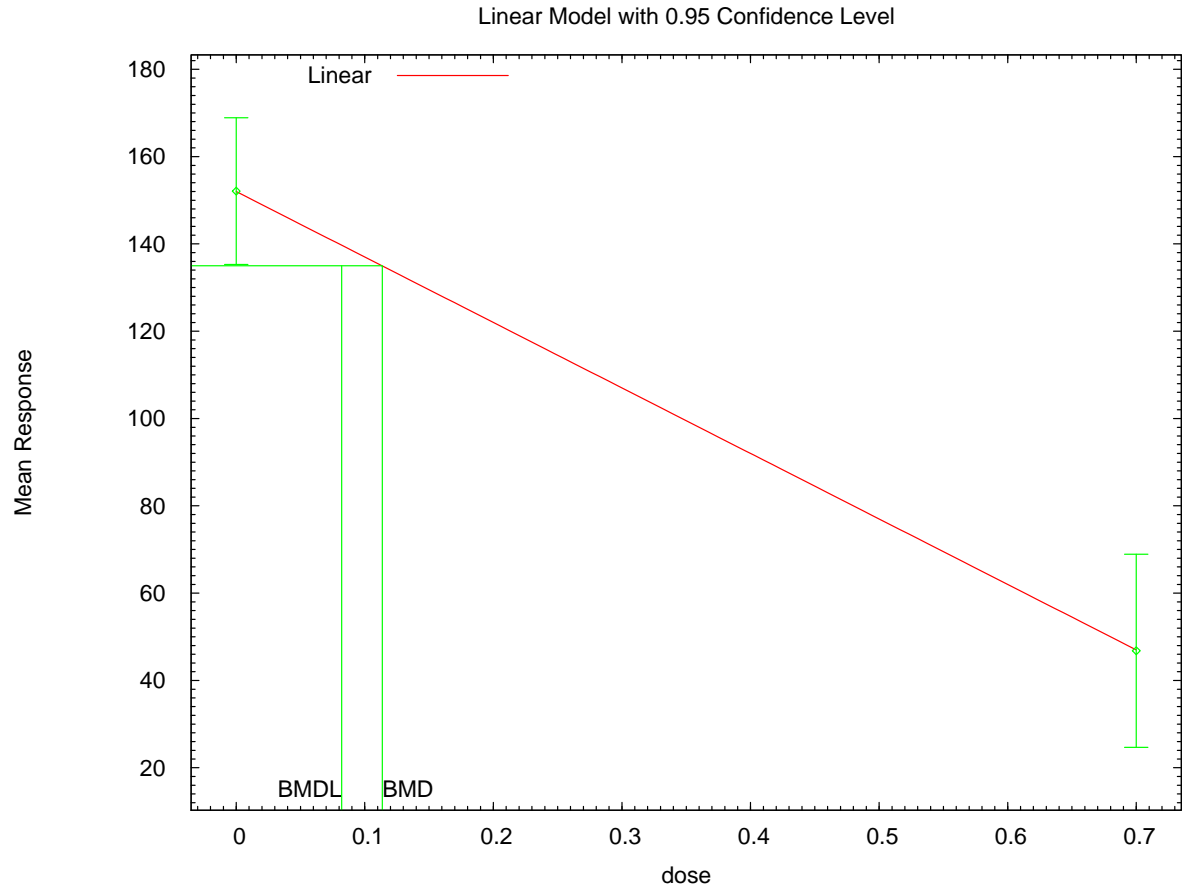
G.3.26. Kuchiiwa et al. ([2002](#)): Immunoreactive Neurons in Magnus, Males

G.3.26.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of freedom	χ^2 *p-value*	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Linear [b]	0	N/A [c]	60.36	9.131E−02	5.577E−02	

[a] Modeled variance model selected ($p = 0.013$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] *p*-value could not be calculated because there were no available degrees of freedom.

G.3.26.2. *Output for Selected Model: Linear*

```
====================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File:
C:\USEPA\BMDS21\1\78_Kuchiiwa_2002_mag_admin_dd_Linear_1.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\1\78_Kuchiiwa_2002_mag_admin_dd_Linear_1.plt
                                        Tue Aug 16 13:46:34 2011
 ====================================================================

 number_labeled_cells_magnus
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 2
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




                 Default Initial Parameter Values
                       lalpha =      4.05645
                          rho =            0
                       beta_0 =      43.6123
                       beta_1 =     -33.9836



         Asymptotic Correlation Matrix of Parameter Estimates
```

```
              lalpha          rho        beta_0        beta_1

   lalpha             1        -0.99      4.1e-009      -5.6e-008

      rho         -0.99            1     -4.6e-009       5.3e-008

   beta_0     4.1e-009    -4.6e-009             1         -0.32

   beta_1    -5.6e-008     5.3e-008         -0.32             1
```

                            Parameter Estimates

                                                      95.0% Wald
Confidence Interval
      Variable   Estimate   Std. Err.   Lower Conf. Limit
Upper Conf. Limit
         lalpha   12.7854   3.52508   5.87638
19.6944
            rho   -2.78668   1.03556   -4.81635
-0.757015
         beta_0   43.6123   1.26679   41.1294
46.0952
         beta_1   -33.9836   5.72265   -45.1998
-22.7674

   Table of Data and Estimated Values of Interest

 Dose   N   Obs Mean   Est Mean   Obs Std Dev   Est Std Dev   Scaled
Res.
 ------   ---   --------   --------   -----------   -----------   ---------
-

    0   6   43.6   43.6   3.4   3.1   1.13e-008
  0.7   6   19.8   19.8   10.2   9.31   1.88e-008

Degrees of freedom for Test A2 vs A3 <= 0

Degrees of freedom for Test A3 vs fitted <= 0

 Model Descriptions for likelihoods calculated

 Model A1:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that

```
     were specified by the user

 Model  R:          Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                    Likelihoods of Interest

           Model     Log(likelihood)   # Param's      AIC
            A1         -29.244768         3         64.489536
            A2         -26.179929         4         60.359859
            A3         -26.179929         4         60.359859
          fitted       -26.179929         4         60.359859
            R          -37.469939         2         78.939878



                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test     -2*log(Likelihood Ratio)  Test df        p-value

   Test 1                22.58           2            <.0001
   Test 2              6.12968           1           0.01329
   Test 3         7.10543e-015           0              NA
   Test 4                   0            0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

NA - Degrees of freedom for Test 3 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid



                    Benchmark Dose Computation

Specified effect =              1

Risk Type        =      Estimated standard deviations from the control mean

Confidence level =         0.95
```

1
2   BMD =   0.0913086
3
4   BMDL =   0.0557686
5
6
7 **G.3.26.3.** *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

8 13:46 08/16 2011
9

1   **G.3.27. Latchoumycandane and Mathur ([2002](#)): Sperm Production**

2   **G.3.27.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	<0.0001	95.106	7.640E+01	3.992E+01	
Exponential (M3)	2	<0.0001	95.106	7.640E+01	3.992E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.699	75.263	2.435E−01	1.016E−01	
Exponential (M5)	0	N/A	77.263	3.697E−01	1.016E−01	
Hill[b]	1	0.859	75.144	1.450E−01	1.559E−02	*n* lower bound hit (*n* = 1)
Linear	2	<0.0001	95.308	8.275E+01	4.852E+01	
Polynomial, 3-degree	2	<0.0001	95.308	8.275E+01	4.852E+01	
Power	2	<0.0001	95.308	8.275E+01	4.852E+01	power bound hit (power = 1)
Hill, unrestricted[c]	0	N/A	77.113	6.943E−02	2.060E−06	unrestricted (*n* = 0.709)
Power, unrestricted	1	0.499	75.570	2.706E−07	2.706E−07	unrestricted (power = 0.067)

[a] Constant variance model selected (*p* = 0.8506).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

3
4

5   **G.3.27.2.** *Output for Selected Model: Hill*

6   Latchoumycandane and Mathur ([2002](#)): Sperm Production
7
8
9   ```
     ===
10   Hill Model. (Version: 2.14; Date: 06/26/2008)
11   Input Data File: C:\1\30_Latch_2002_Sperm_HillCV_1.(d)
12   Gnuplot Plotting File: C:\1\30_Latch_2002_Sperm_HillCV_1.plt
13   Tue Feb 16 18:13:20 2010
14   ===
15
16   (x10^6) Table 1 without Vitamin E
17 ~~~~~~
18
19   The form of the response function is:
20
21   Y[dose] = intercept + v*dose^n/(k^n + dose^n)
22
23
24   Dependent variable = Mean
25   Independent variable = Dose
26   rho is set to 0
27   Power parameter restricted to be greater than 1
28   A constant variance model is fit
29
30   Total number of dose groups = 4
     ```

```
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          alpha =      7.23328
                            rho =            0    Specified
                      intercept =        22.19
                              v =        -9.09
                              n =      1.80484
                              k =     0.697086



           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho     -n
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                      alpha    intercept           v           k

      alpha              1    6.3e-010       3e-008    8.3e-009

   intercept     6.3e-010           1       -0.78       -0.23

           v        3e-008       -0.78           1       -0.17

           k     8.3e-009       -0.23       -0.17           1




                            Parameter Estimates


                                                        95.0% Wald
Confidence Interval
      Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
         alpha         6.03567         1.74235              2.62073
9.45061
      intercept        22.1885         1.00316              20.2223
24.1547
             v        -9.00869         1.26801             -11.4939
-6.52343
             n               1              NA
             k        0.386669        0.265663            -0.134021
0.907359

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

```
      Table of Data and Estimated Values of Interest

 Dose        N     Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
 Res.
 ------      ---   --------     --------   -----------  -----------   ---------
 -

     0       6      22.2         22.2         2.67         2.46        0.00151
     1       6      15.7         15.7         2.65         2.46       -0.0218
    10       6      13.7         13.5         2.19         2.46        0.134
   100       6      13.1         13.2         3.16         2.46       -0.114




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                   Likelihoods of Interest

           Model      Log(likelihood)   # Param's      AIC
            A1          -33.556444          5        77.112888
            A2          -33.158811          8        82.317623
            A3          -33.556444          5        77.112888
          fitted        -33.572245          4        75.144490
            R           -47.392394          2        98.784788


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                   Tests of Interest

   Test     -2*log(Likelihood Ratio)   Test df        p-value

   Test 1            28.4672              6            <.0001
   Test 2            0.795266             3            0.8506
```

```
Test 3              0.795266        3           0.8506
Test 4              0.031602        1           0.8589
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

          Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

          BMD =   0.144988

          BMDL =   0.0155926

1 **G.3.27.3.** *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

18:13 02/16 2010

2
3
4 **G.3.27.4.** *Output for Additional Model Presented: Hill, Unrestricted*

5 Latchoumycandane and Mathur (2002): Sperm Production
6
7
8 ```
   ===
9   Hill Model. (Version: 2.14;   Date: 06/26/2008)
10   Input Data File: C:\1\30_Latch_2002_Sperm_HillCV_U_1.(d)
11   Gnuplot Plotting File: C:\1\30_Latch_2002_Sperm_HillCV_U_1.plt
12   Tue Feb 16 18:13:21 2010
13 ===
14
15 (x10^6) Table 1 without Vitamin E
16 ~~~~~~
17
18   The form of the response function is:
19
20   Y[dose] = intercept + v*dose^n/(k^n + dose^n)
21
22
23   Dependent variable = Mean
   ```

```
Independent variable = Dose
rho is set to 0
Power parameter is not restricted
A constant variance model is fit

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                  Default Initial Parameter Values
                        alpha =      7.23328
                          rho =            0    Specified
                    intercept =        22.19
                            v =        -9.09
                            n =      1.80484
                            k =     0.697086


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha    intercept          v            n            k

     alpha           1    -7.6e-009      8e-008       5e-008     1.9e-008

 intercept   -7.6e-009            1        -0.5       -0.015        -0.13

         v      8e-008         -0.5           1         0.75         0.55

         n      5e-008       -0.015        0.75            1         0.86

         k    1.9e-008        -0.13        0.55         0.86            1




                              Parameter Estimates

                                                    95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
        alpha        6.02773          1.74006              2.61728
9.43818
        intercept      22.19          1.00231              20.2255
24.1545
            v        -9.23433         2.02073             -13.1949
-5.27378
            n        0.709305         1.28329              -1.8059
3.22451
```

```
               k          0.290697        0.548737          -0.784807
1.3662




     Table of Data and Estimated Values of Interest

 Dose      N     Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
 ------    ---   --------     --------   -----------  -----------   ---------
-

    0      6      22.2         22.2         2.67         2.46       2.62e-008
    1      6      15.7         15.7         2.65         2.46       -1.5e-008
   10      6      13.7         13.7         2.19         2.46       -4.56e-008
  100      6      13.1         13.1         3.16         2.46       -3.52e-007

Degrees of freedom for Test A3 vs fitted <= 0




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:        Yi = Mu + e(i)
         Var{e(i)} = Sigma^2



                  Likelihoods of Interest

          Model      Log(likelihood)   # Param's      AIC
          A1          -33.556444            5       77.112888
          A2          -33.158811            8       82.317623
          A3          -33.556444            5       77.112888
       fitted         -33.556444            5       77.112888
          R           -47.392394            2       98.784788



                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

```
                          Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df         p-value

   Test 1              28.4672            6            <.0001
   Test 2             0.795266            3            0.8506
   Test 3             0.795266            3            0.8506
   Test 4          2.84217e-014           0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


          Benchmark Dose Computation

Specified effect =              1

Risk Type        =      Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =     0.0694325

            BMDL =  2.06007e-006
```

1   **G.3.27.5.** *Figure for Additional Model Presented: Hill, Unrestricted*

Hill Model with 0.95 Confidence Level

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2
3
4
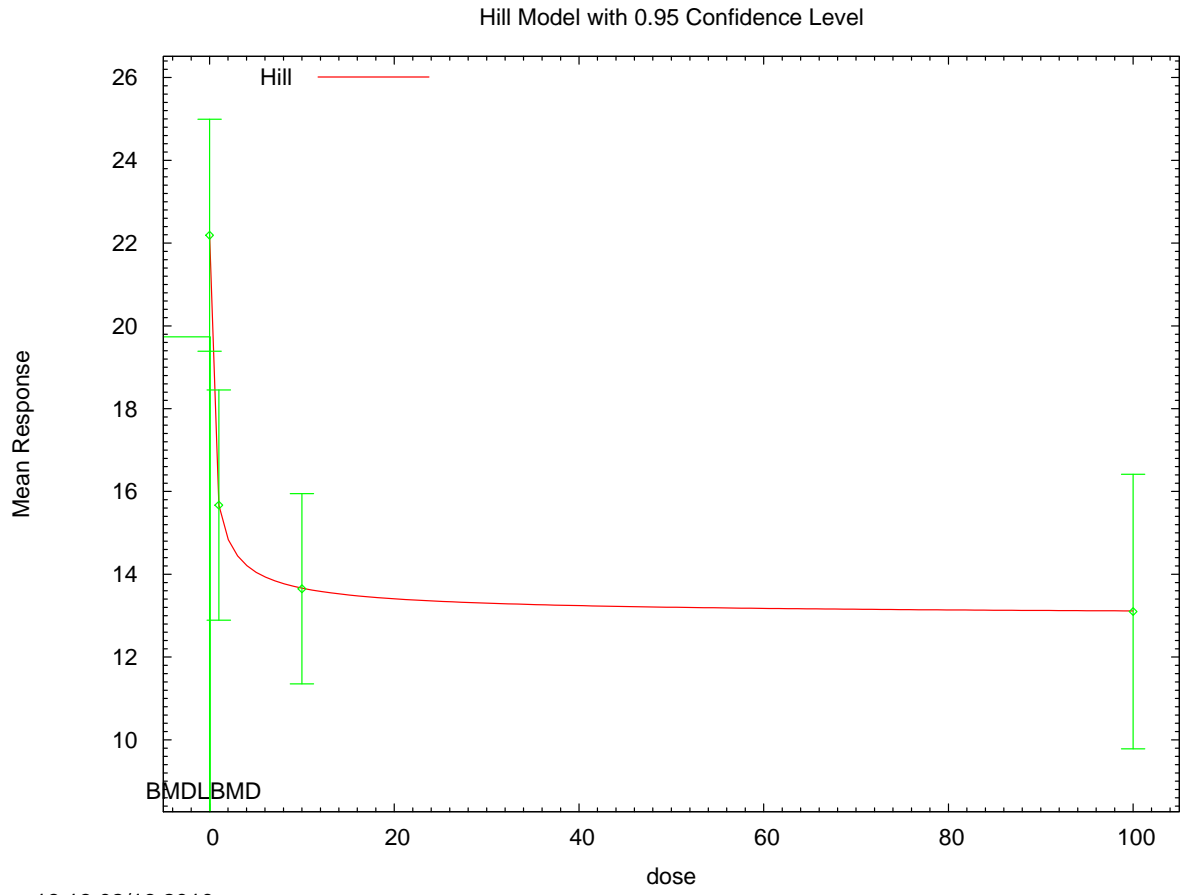
G.3.28. Li et al. ([1997](#)): FSH

G.3.28.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	8	<0.0001	1,095.240	1.340E+04	1.060E+04	
Exponential (M3)	8	<0.0001	1,095.240	1.340E+04	1.060E+04	power hit bound (*d* = 1)
Exponential (M4)	7	<0.0001	1,061.243	1.031E+03	4.015E+02	
Exponential (M5)	7	<0.0001	1,061.243	1.031E+03	4.015E+02	power hit bound (*d* = 1)
Hill	7	<0.0001	1,059.547	6.645E+02	error	*n* lower bound hit (*n* = 1)
Linear	8	<0.0001	1,078.221	5.287E+03	3.602E+03	
Polynomial, 8-degree	9	<0.0001	1,155.670	error	error	
Power [b]	**8**	**<0.0001**	**1,078.221**	**5.287E+03**	**3.602E+03**	**power bound hit (power = 1)**
Hill, unrestricted	6	0.001	1,039.902	2.809E+00	6.602E−01	unrestricted (*n* = 0.291)
Power, unrestricted [c]	7	0.002	1,037.821	2.508E+00	2.525E−01	unrestricted (power = 0.279)

[a] Nonconstant variance model selected (*p* = <0.0001).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.28.2. *Output for Selected Model: Power*

Li et al. ([1997](#)): FSH

```
 =======================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\72_Li_1997_FSH_Pwr_1.(d)
        Gnuplot Plotting File:  C:\1\72_Li_1997_FSH_Pwr_1.plt
                                        Tue Feb 16 20:07:31 2010
 =======================================================================

 Figure 3: FSH in female S-D rats 24hr after dosing, 22 day old rats
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is restricted to be greater than or equal to 1
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 10
```

```
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                            lalpha =        9.8191
                               rho =             0
                           control =       22.1591
                             slope =       26.1213
                             power =      0.264963



            Asymptotic Correlation Matrix of Parameter Estimates


            ( *** The model parameter(s)  -power
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                   lalpha           rho        control          slope

      lalpha            1         -0.99          -0.29         -0.023

         rho        -0.99             1            0.2          0.023

     control        -0.29           0.2              1          -0.35

       slope       -0.023         0.023          -0.35              1




                              Parameter Estimates


                                                     95.0% Wald
Confidence Interval
      Variable          Estimate         Std. Err.     Lower Conf. Limit
Upper Conf. Limit
        lalpha           3.5473           1.23656               1.12369
5.9709
           rho          1.26137          0.244246              0.782659
1.74009
       control          88.9479           12.9114               63.6419
114.254
         slope        0.0188972        0.00351723             0.0120035
0.0257908
         power                1                NA


NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.




        Table of Data and Estimated Values of Interest
```

```
 Dose        N    Obs Mean    Est Mean   Obs Std Dev  Est Std Dev   Scaled
 Res.
 ------      ---  --------    --------   -----------  -----------   ---------
 -


     0       10     23.9        88.9        29.6          99.9        -2.06
     3       10     22.2        89          48.5          99.9        -2.12
    10       10     85.2        89.1        94.3         100          -0.124
    30       10     73.3        89.5        48.5         100          -0.511
   100       10    126          90.8       159          101           1.1
   300       10    132          94.6       116          104           1.14
  1000       10    117         108          51.2        113           0.25
  3000       10    304         146         154          136           3.68
 1e+004      10    347         278         151          205           1.06
 3e+004      10    455         656         286          352          -1.8
```

Model Descriptions for likelihoods calculated

Model A1:   Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2

Model A2:   Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma(i)^2

Model A3:   Yij = Mu(i) + e(ij)
         Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model R: Yi = Mu + e(i)
         Var{e(i)} = Sigma^2

                    Likelihoods of Interest

            Model   Log(likelihood)   # Param's   AIC
             A1   -535.687163   11   1093.374327
             A2   -496.367061   20   1032.734122
             A3   -502.709623   12   1029.419246
           fitted   -535.110448   4   1078.220896
             R   -574.835246   2   1153.670492

                    Explanation of Tests

 Test 1: Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2: Are Variances Homogeneous? (A1 vs A2)
 Test 3: Are variances adequately modeled? (A2 vs. A3)
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

```
   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              156.936          18          <.0001
   Test 2              78.6402           9          <.0001
   Test 3              12.6851           8          0.1232
   Test 4              64.8016           8          <.0001
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different
model

                  Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

            BMD = 5286.67

            BMDL = 3601.91

G.3.28.3. *Figure for Selected Model: Power*

Power Model with 0.95 Confidence Level

20:07 02/16 2010

2
3
4   **G.3.28.4.** *Output for Additional Model Presented: Power, Unrestricted*

5   Li et al. ([1997](#)): FSH

6
7
```
8   =======================================================================
9          Power Model. (Version: 2.15;   Date: 04/07/2008)
10         Input Data File: C:\1\72_Li_1997_FSH_Pwr_U_1.(d)
11         Gnuplot Plotting File:  C:\1\72_Li_1997_FSH_Pwr_U_1.plt
12                                        Tue Feb 16 20:07:33 2010
13  =======================================================================
14
15  Figure 3: FSH in female S-D rats 24hr after dosing, 22 day old rats
16  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18     The form of the response function is:
19
20     Y[dose] = control + slope * dose^power
21
22
23     Dependent variable = Mean
24     Independent variable = Dose
```

```
The power is not restricted
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 10
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                     Default Initial Parameter Values
                          lalpha =        9.8191
                             rho =             0
                         control =       22.1591
                           slope =       26.1213
                           power =      0.264963


          Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho        control         slope          power

     lalpha            1        -0.99          -0.69         -0.15           0.28

        rho        -0.99            1           0.65          0.11          -0.26

    control        -0.69         0.65              1         -0.17          0.024

      slope        -0.15         0.11          -0.17             1          -0.93

      power         0.28        -0.26          0.024         -0.93              1




                              Parameter Estimates


                                                        95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
          lalpha        3.72156          1.13117               1.5045
5.93861
             rho        1.17032         0.223249             0.732758
1.60788
         control        15.7412          6.97367              2.07307
29.4094
           slope         24.963          6.42976              12.3609
37.5651
           power        0.278637        0.0312355            0.217417
0.339857




    Table of Data and Estimated Values of Interest
```

```
   Dose        N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
   ------      ---   --------     --------   -----------  -----------  ---------
 -


      0    10      23.9         15.7         29.6         32.3        0.796
      3    10      22.2         49.6         48.5         63.2        -1.38
     10    10      85.2         63.2         94.3         72.7         0.96
     30    10      73.3         80.1         48.5         83.6       -0.259
    100    10       126          106          159         98.4        0.654
    300    10       132          138          116          115       -0.164
   1000    10       117          187         51.2          137        -1.62
   3000    10       304          248          154          162         1.1
  1e+004    10       347          341          151          195       0.0999
  3e+004    10       455          457          286          232      -0.0271
```

Model Descriptions for likelihoods calculated

Model A1:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model R: Yi = Mu + e(i)
          Var{e(i)} = Sigma^2

                   Likelihoods of Interest

          Model   Log(likelihood)   # Param's   AIC
           A1   -535.687163   11   1093.374327
           A2   -496.367061   20   1032.734122
           A3   -502.709623   12   1029.419246
        fitted   -513.910636   5   1037.821272
           R   -574.835246   2   1153.670492

                  Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

                   Tests of Interest
```

```
     Test     -2*log(Likelihood Ratio)  Test df         p-value

     Test 1              156.936          18            <.0001
     Test 2              78.6402           9            <.0001
     Test 3              12.6851           8            0.1232
     Test 4               22.402           7            0.002165

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


                   Benchmark Dose Computation

Specified effect =              1

Risk Type       =      Estimated standard deviations from the control mean

Confidence level =          0.95

            BMD = 2.50839


            BMDL = 0.252541
```

1   **G.3.28.5.** *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

20:07 02/16 2010

2
3
4

G.3.29. Li et al. ([2006](#)): Estradiol, 3-Day

2 **G.3.29.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.147	269.146	3.044E+02	1.108E+02	
Exponential (M3)	2	0.147	269.146	3.044E+02	1.108E+02	power hit bound ($d = 1$)
Exponential (M4)	1	0.341	268.212	error	error	
Exponential (M5)	0	N/A	270.212	error	error	
Hill	0	N/A	270.212	error	error	
Linear[b]	**2**	**0.151**	**269.084**	**3.471E+02**	**1.082E+02**	
Polynomial, 3-degree	2	0.151	269.084	3.471E+02	1.082E+02	
Power	2	0.151	269.084	3.471E+02	1.082E+02	power bound hit (power = 1)
Hill, unrestricted	0	N/A	270.266	1.059E+17	1.059E+17	unrestricted ($n = 0.025$)
Power, unrestricted	1	0.327	268.266	3.727E+14	error	unrestricted (power = 0.012)

[a] Constant variance model selected ($p = 0.4372$).
[b] Best-fitting model, BMDS output presented in this appendix.

3
4

5 **G.3.29.2.** *Output for Selected Model: Linear*

6 Li et al. ([2006](#)): Estradiol, 3-Day
7
8

```
9    =========================================================================
10          Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
11          Input Data File: C:\1\31_Li_2006_Estra_LinearCV_1.(d)
12          Gnuplot Plotting File:  C:\1\31_Li_2006_Estra_LinearCV_1.plt
13                                          Tue Feb 16 18:13:56 2010
14    =========================================================================
15
16   Figure 3, 3-day estradiol
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the response function is:
20
21     Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
22
23
24     Dependent variable = Mean
25     Independent variable = Dose
26     rho is set to 0
27     Signs of the polynomial coefficients are not restricted
28     A constant variance model is fit
29
30     Total number of dose groups = 4
31     Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                      Default Initial Parameter Values
                            alpha =      267.211
                              rho =            0    Specified
                           beta_0 =      16.4428
                           beta_1 =    0.0468351



            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -rho
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                    alpha        beta_0        beta_1

      alpha             1    -2.6e-013     -4.5e-015

     beta_0    -2.6e-013            1         -0.68

     beta_1    -4.5e-015        -0.68             1




                              Parameter Estimates


                                                    95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
          alpha          264.303            59.1              148.469
380.137
         beta_0          16.4428         3.50431              9.57445
23.3111
         beta_1        0.0468351        0.062677            -0.0760095
0.16968




      Table of Data and Estimated Values of Interest

   Dose        N    Obs Mean      Est Mean    Obs Std Dev  Est Std Dev    Scaled
Res.
  ------      ---   --------      --------    -----------  -----------  ---------
-

      0        10        10.2          16.4          12.2         16.3       -1.22
      2        10        19.9          16.5            20         16.3       0.656
     50        10        24.7          18.8          14.6         16.3        1.16
    100        10        18.1          21.1          17.6         16.3      -0.591
```

```
  Model Descriptions for likelihoods calculated


  Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

  Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

            Model     Log(likelihood)   # Param's      AIC
            A1          -129.653527           5      269.307054
            A2          -128.294657           8      272.589314
            A3          -129.653527           5      269.307054
         fitted         -131.541911           3      269.083823
            R           -131.819169           2      267.638338


                    Explanation of Tests

  Test 1:  Do responses and/or variances differ among Dose levels?
           (A2 vs. R)
  Test 2:  Are Variances Homogeneous? (A1 vs A2)
  Test 3:  Are variances adequately modeled? (A2 vs. A3)
  Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
  (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test     -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              7.04902           6            0.3163
   Test 2              2.71774           3            0.4372
   Test 3              2.71774           3            0.4372
   Test 4              3.77677           2            0.1513

The p-value for Test 1 is greater than .05.  There may not be a
diffence between responses and/or variances among the dose levels
Modelling the data with a dose/response curve may not be appropriate

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
```
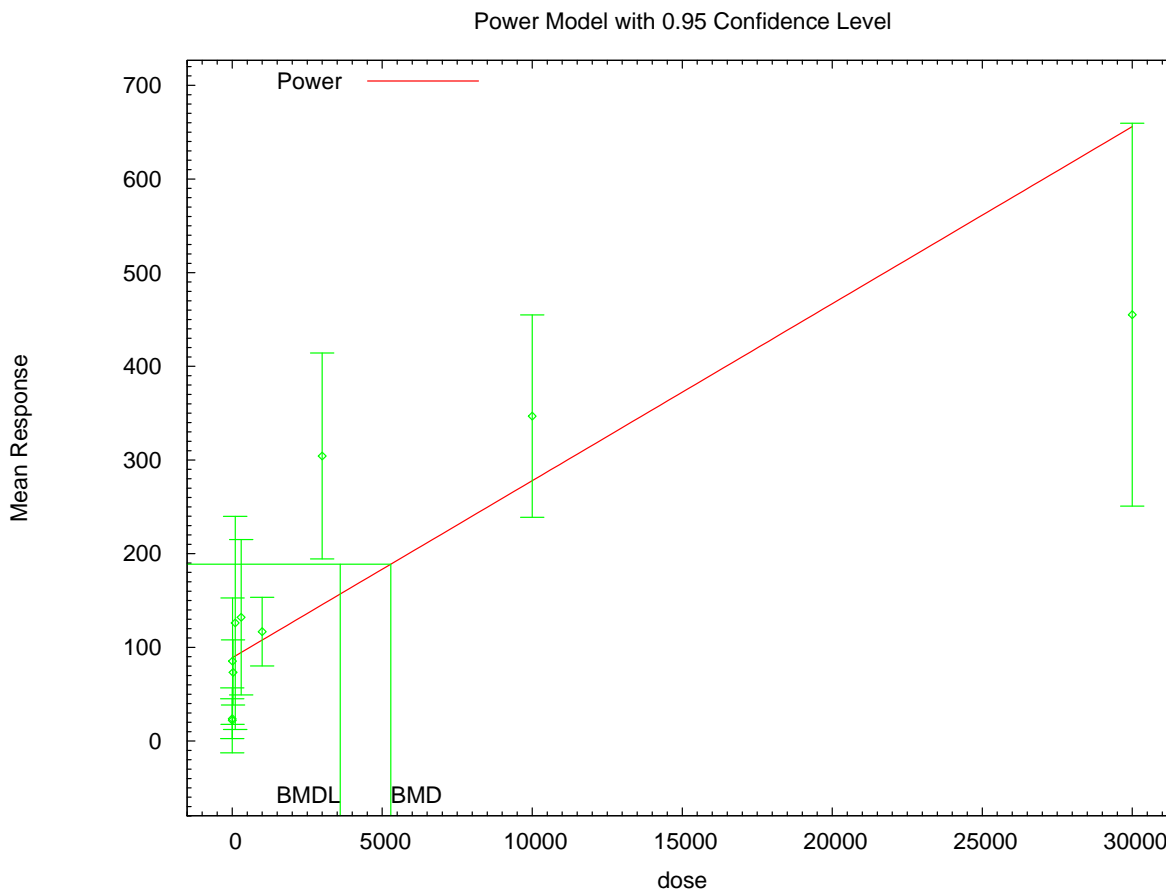
```
 1    to be appropriate here
 2
 3   The p-value for Test 4 is greater than .1.  The model chosen seems
 4   to adequately describe the data
 5
 6
 7                 Benchmark Dose Computation
 8
 9   Specified effect =                1
10
11   Risk Type         =      Estimated standard deviations from the control mean
12
13   Confidence level =         0.95
14
15           BMD =            347.12
16
17
18           BMDL =           108.173
19
20
```

G.3.29.3. *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

18:13 02/16 2010

1 **G.3.30. Li et al. ([2006](#)): Progesterone, 3-Day**

2 **G.3.30.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	<0.001	330.234	5.252E+01	error	
Exponential (M3)	2	<0.001	330.234	5.252E+01	error	power hit bound (*d* = 1)
Exponential (M4)[b]	**1**	**0.384**	**315.734**	**1.353E−01**	**8.351E−02**	
Exponential (M5)	0	N/A	317.734	5.225E−01	7.503E−02	
Hill	1	0.386	315.729	1.135E−02	1.161E−05	*n* lower bound hit (*n* = 1)
Linear	2	<0.001	331.121	7.765E+01	5.264E+01	
Polynomial, 3-degree	2	<0.001	331.121	7.765E+01	5.264E+01	
Power	2	<0.001	331.121	7.765E+01	5.264E+01	power bound hit (power = 1)
Power, unrestricted	1	0.405	315.670	1.066E−63	1.066E−63	unrestricted (power = 0.009)

[a] Nonconstant variance model selected (*p* = 0.0013).
[b] Best-fitting model, BMDS output presented in this appendix.

3
4
5 **G.3.30.2.** *Output for Selected Model: Exponential (M4)*

6 Li et al. ([2006](#)): Progesterone, 3-Day
7

```
8    =====================================================================
9         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
10        Input Data File: C:\1\32_Li_2006_Progest_Exp_1.(d)
11        Gnuplot Plotting File:
12                                        Tue Feb 16 18:14:31 2010
13   =====================================================================
14
15   Figure 4, 3-day progesterone
16  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18     The form of the response function by Model:
19        Model 2:     Y[dose] = a * exp{sign * b * dose}
20        Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
21        Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
22        Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
23
24      Note: Y[dose] is the median response for exposure = dose;
25           sign = +1 for increasing trend in data;
26           sign = -1 for decreasing trend.
27
28        Model 2 is nested within Models 3 and 4.
29        Model 3 is nested within Model 5.
30        Model 4 is nested within Model 5.
31
32
```

```
1    Dependent variable = Mean
2    Independent variable = Dose
3    Data are assumed to be distributed: normally
4    Variance Model: exp(lnalpha +rho *ln(Y[dose]))
5    The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
6
7    Total number of dose groups = 4
8    Total number of records with missing values = 0
9    Maximum number of iterations = 250
10   Relative Function Convergence has been set to: 1e-008
11   Parameter Convergence has been set to: 1e-008
12
13   MLE solution provided: Exact
14
15
16                    Initial Parameter Values
17
18               Variable            Model 4
19               --------            --------
20                 lnalpha             11.3313
21                    rho            -1.44835
22                      a             64.8274
23                      b           0.0456906
24                      c            0.166844
25                      d                   1
26
27
28
29                    Parameter Estimates
30
31               Variable            Model 4
32               --------            -------
33                 lnalpha              14.074
34                    rho            -2.27065
35                      a             61.7474
36                      b             2.13327
37                      c            0.318566
38                      d                   1
39
40
41           Table of Stats From Input Data
42
43     Dose      N        Obs Mean     Obs Std Dev
44     -----    ---       ----------   -------------
45        0      10        61.74          11.1
46        2      10        30.56          40.48
47       50      10        16.93          33.3
48      100      10        11.36          43.75
49
50
51            Estimated Values of Interest
52
53     Dose      Est Mean      Est Std     Scaled Residual
54     ------    ----------    ---------    ----------------
55        0        61.75        10.55         -0.002085
56        2        20.26        37.38          0.8713
57       50        19.67        38.66         -0.224
```

```
       100              19.67           38.66              -0.6801


   Other models for which likelihoods are calculated:

     Model A1:          Yij = Mu(i) + e(ij)
               Var{e(ij)} = Sigma^2

     Model A2:          Yij = Mu(i) + e(ij)
               Var{e(ij)} = Sigma(i)^2

     Model A3:          Yij = Mu(i) + e(ij)
               Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

     Model  R:          Yij = Mu + e(i)
               Var{e(ij)} = Sigma^2


                         Likelihoods of Interest

                   Model     Log(likelihood)     DF        AIC
                   -------   ----------------    ----   ------------
                     A1          -159.6327         5      329.2653
                     A2          -151.8128         8      319.6255
                     A3          -152.4882         6      316.9763
                      R          -165.6989         2      335.3978
                      4          -152.8668         5      315.7335


   Additive constant for all log-likelihoods =    -36.76.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                         Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 6a: Does Model 4 fit the data? (A3 vs 4)



                         Tests of Interest

     Test          -2*log(Likelihood Ratio)        D. F.        p-value
    --------       ------------------------       ------     --------------
     Test 1                 27.77                    6         0.0001037
     Test 2                 15.64                    3         0.001344
     Test 3                 1.351                    2         0.5089
    Test 6a                 0.7572                   1         0.3842



   The p-value for Test 1 is less than .05.  There appears to be a
```

difference between response and/or variances among the dose
levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous
variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled
variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems
to adequately describe the data.

Benchmark Dose Computations:

   Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

   Confidence Level = 0.950000

                BMD =   0.135296

               BMDL =   0.0835054

1 **G.3.30.3.** *Figure for Selected Model: Exponential (M4)*

Exponential_beta Model 4 with 0.95 Confidence Level

18:14 02/16 2010

2
3
4 **G.3.30.4.** *Output for Additional Model Presented: Hill, Unrestricted*

5 Li et al. (2006): Progesterone, 3-Day

6
7
```
8    ====================================================================
9           Hill Model. (Version: 2.14;  Date: 06/26/2008)
10          Input Data File: C:\1\32_Li_2006_Progest_Hill_U_1.(d)
11          Gnuplot Plotting File:  C:\1\32_Li_2006_Progest_Hill_U_1.plt
12                                          Tue Feb 16 18:14:41 2010
13   ====================================================================
14
15  Figure 4, 3-day progesterone
16  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18     The form of the response function is:
19
20     Y[dose] = intercept + v*dose^n/(k^n + dose^n)
21
22
23     Dependent variable = Mean
24     Independent variable = Dose
25     Power parameter is not restricted
26     The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))
```

```
    Total number of dose groups = 4
    Total number of records with missing values = 0
    Maximum number of iterations = 250
    Relative Function Convergence has been set to: 1e-008
    Parameter Convergence has been set to: 1e-008




                      Default Initial Parameter Values
                            lalpha =      7.08699
                               rho =            0
                         intercept =      61.7404
                                 v =     -50.3835
                                 n =      1.43997
                                 k =       1.6159



            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -k
                    have been estimated at a boundary point, or have been
    specified by the user,
                    and do not appear in the correlation matrix )

                     lalpha          rho     intercept            v              n

        lalpha            1        -0.99       -0.097         0.84           NA

           rho        -0.99            1         0.13        -0.81           NA

     intercept       -0.097         0.13            1        -0.43           NA

             v         0.84        -0.81        -0.43            1           NA

             n           NA           NA           NA           NA
    NA



    NA - This parameter's variance has been estimated as zero or less.
    THE MODEL HAS PROBABLY NOT CONVERGED!!!




                               Parameter Estimates


                                                        95.0% Wald
    Confidence Interval
         Variable         Estimate        Std. Err.     Lower Conf. Limit
    Upper Conf. Limit
         lalpha          13.9863               NA                   NA
    NA
            rho         -2.25026               NA                   NA
    NA
       intercept         61.7404               NA                   NA
    NA
```

```
              v        -42.1239              NA                    NA
NA
              n         2.02774              NA                    NA
NA
              k          1e-013              NA

At least some variance estimates are negative.
THIS USUALLY MEANS THE MODEL HAS NOT CONVERGED!
Try again from another starting point.




     Table of Data and Estimated Values of Interest

 Dose      N    Obs Mean    Est Mean  Obs Std Dev  Est Std Dev   Scaled
Res.
 ------    ---  --------    --------  -----------  -----------   ---------
-

    0      10     61.7        61.7        11.1         10.5      9.74e-008
    2      10     30.6        19.6        40.5         38.3         0.905
   50      10     16.9        19.6        33.3         38.3        -0.222
  100      10     11.4        19.6        43.7         38.3        -0.683




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                  Likelihoods of Interest

          Model    Log(likelihood)   # Param's      AIC
           A1       -159.632675          5       329.265349
           A2       -151.812765          8       319.625529
           A3       -152.488175          6       316.976349
         fitted     -152.873643          5       315.747285
           R        -165.698875          2       335.397750



                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
```

```
        (A2 vs. R)
  Test 2:  Are Variances Homogeneous? (A1 vs A2)
  Test 3:  Are variances adequately modeled? (A2 vs. A3)
  Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
  (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)


                    Tests of Interest


    Test    -2*log(Likelihood Ratio)  Test df       p-value


    Test 1             27.7722          6        0.0001037
    Test 2             15.6398          3         0.001344
    Test 3             1.35082          2          0.5089
    Test 4             0.770936         1          0.3799


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data


The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here


The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data



          Benchmark Dose Computation


Specified effect =               1


Risk Type        =      Estimated standard deviations from the control mean


Confidence level =              0.95


            BMD =    5.81703e-014


            BMDL =   5.81703e-014
```

1   **G.3.30.5.** *Figure for Additional Model Presented: Hill, Unrestricted*

Hill Model with 0.95 Confidence Level

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G.3.31. Markowski et al. ([2001](#)): FR10 Run Opportunities

G.3.31.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)[b]	**2**	**0.248**	**117.557**	**1.653E+02**	**5.025E+01**	
Exponential (M3)	2	0.248	117.557	1.653E+02	5.025E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.412	117.445	4.742E+01	1.729E−01	
Exponential (M5)	0	N/A	118.918	3.178E+01	3.967E−05	
Hill	0	N/A	118.918	2.348E+01	6.728E−06	
Linear	2	0.190	118.089	2.081E+02	1.051E+02	
Polynomial, 3-degree	2	0.190	118.089	2.081E+02	1.051E+02	
Power	2	0.190	118.089	2.081E+02	1.051E+02	power bound hit (power = 1)
Power, unrestricted	1	0.238	118.164	9.153E+01	5.911E−07	unrestricted (power = 0.237)

[a] Constant variance model selected (*p* = 0.1719).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.31.2. *Output for Selected Model: Exponential (M2)*

Markowski et al. ([2001](#)): FR10 Run Opportunities

```
=====================================================================
        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
        Input Data File: C:\1\33_Mark_2001_FR10opp_ExpCV_1.(d)
        Gnuplot Plotting File:
                                    Tue Feb 16 18:15:26 2010
=====================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the response function by Model:
     Model 2:    Y[dose] = a * exp{sign * b * dose}
     Model 3:    Y[dose] = a * exp{sign * (b * dose)^d}
     Model 4:    Y[dose] = a * [c-(c-1) * exp{-b * dose}]
     Model 5:    Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

   Note: Y[dose] is the median response for exposure = dose;
         sign = +1 for increasing trend in data;
         sign = -1 for decreasing trend.

     Model 2 is nested within Models 3 and 4.
     Model 3 is nested within Model 5.
     Model 4 is nested within Model 5.
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.


Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


MLE solution provided: Exact


                      Initial Parameter Values

                  Variable              Model 2
                  --------              --------
                    lnalpha               3.5321
                       rho(S)                  0
                        a                 6.98169
                        b              0.00309891
                        c                       0
                        d                       1


   (S) = Specified




                      Parameter Estimates

                  Variable              Model 2
                  --------              -------
                    lnalpha              3.64823
                       rho                     0
                        a                11.9443
                        b              0.0044262
                        c                      0
                        d                      1


          Table of Stats From Input Data

   Dose      N         Obs Mean      Obs Std Dev
   -----     ---       ----------    -------------
       0      7          13.29          8.65
      20      4          11.25          5.56
      60      6           5.75          3.53
     180      7              7          6.01



               Estimated Values of Interest

     Dose       Est Mean       Est Std     Scaled Residual
```

```
    ------    ----------    ---------    ----------------
       0        11.94         6.197           0.5745
      20        10.93         6.197           0.1025
      60         9.158        6.197          -1.347
     180         5.385        6.197           0.6897




  Other models for which likelihoods are calculated:

    Model A1:          Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma^2

    Model A2:          Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma(i)^2

    Model A3:          Yij = Mu(i) + e(ij)
                 Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

    Model  R:          Yij = Mu + e(i)
                 Var{e(ij)} = Sigma^2



                          Likelihoods of Interest

                   Model      Log(likelihood)      DF        AIC
                  -------    ----------------     ----    ------------
                    A1         -54.38526            5       118.7705
                    A2         -51.88568            8       119.7714
                    A3         -54.38526            5       118.7705
                     R         -57.45429            2       118.9086
                     2         -55.77871            3       117.5574



   Additive constant for all log-likelihoods =      -22.05.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                           Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)
   Test 4:  Does Model 2 fit the data? (A3 vs. 2)



                           Tests of Interest

    Test          -2*log(Likelihood Ratio)         D. F.          p-value
   --------       ------------------------        ------       --------------
    Test 1                   11.14                   6             0.08423
    Test 2                   4.999                   3             0.1719
    Test 3                   4.999                   3             0.1719
    Test 4                   2.787                   2             0.2482
```

```
     The p-value for Test 1 is greater than .05.  There may not be a
     diffence between responses and/or variances among the dose levels
     Modelling the data with a dose/response curve may not be appropriate.

     The p-value for Test 2 is greater than .1.  A homogeneous
     variance model appears to be appropriate here.

     The p-value for Test 3 is greater than .1.  The modeled
     variance appears to be appropriate here.

     The p-value for Test 4 is greater than .1.  Model 2 seems
     to adequately describe the data.


  Benchmark Dose Computations:

     Specified Effect = 1.000000

           Risk Type = Estimated standard deviations from control

     Confidence Level = 0.950000

                 BMD =      165.284

                BMDL =      50.2488
```

1 **G.3.31.3.** *Figure for Selected Model: Exponential (M2)*

Exponential_beta Model 2 with 0.95 Confidence Level

18:15 02/16 2010

2
3
4

1 **G.3.32. Markowski et al. (2001): FR2 Revolutions**

2 **G.3.32.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.192	217.636	1.627E+02	5.807E+01	
Exponential (M3)	2	0.192	217.636	1.627E+02	5.807E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.298	217.415	4.668E+01	1.965E−01	
Exponential (M5)	0	N/A	218.532	3.308E+01	1.193E+01	
Hill[b]	**0**	**N/A**	**218.532**	**2.364E+01**	**7.336E+00**	***n* upper bound hit (*n* = 18)**
Linear	2	0.150	218.129	1.989E+02	1.025E+02	
Polynomial, 3-degree	2	0.150	218.129	1.989E+02	1.025E+02	
Power	2	0.150	218.129	1.989E+02	1.025E+02	power bound hit (power = 1)
Power, unrestricted[c]	1	0.160	218.302	9.101E+01	1.800E−13	unrestricted (power = 0.272)

[a] Constant variance model selected (*p* = 0.1092).
[b] Best-fitting model, BMDS output presented in this appendix..
[c] Alternate model, BMDS output also presented in this appendix.

3
4
5 **G.3.32.2.** *Output for Selected Model: Hill*

6 Markowski et al. (2001): FR2 Revolutions
7
8
9
```
      ==========================================================================
10          Hill Model. (Version: 2.14;  Date: 06/26/2008)
11          Input Data File: C:\1\34_Mark_2001_FR2rev_HillCV_1.(d)
12          Gnuplot Plotting File:  C:\1\34_Mark_2001_FR2rev_HillCV_1.plt
13                                         Tue Feb 16 18:16:03 2010
14      ==========================================================================
15
16   Table 3
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the response function is:
20
21     Y[dose] = intercept + v*dose^n/(k^n + dose^n)
22
23
24     Dependent variable = Mean
25     Independent variable = Dose
26     rho is set to 0
27     Power parameter restricted to be greater than 1
28     A constant variance model is fit
29
30     Total number of dose groups = 4
31     Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                     Default Initial Parameter Values
                            alpha =      2598.74
                              rho =            0   Specified
                        intercept =       119.29
                                v =       -62.79
                                n =      1.80602
                                k =        35.85



            Asymptotic Correlation Matrix of Parameter Estimates


            ( *** The model parameter(s)  -rho
                   have been estimated at a boundary point, or have been
specified by the user,
                   and do not appear in the correlation matrix )


                    alpha    intercept           v            n            k

      alpha             1   -8.1e-009    4.5e-008      -3e-005       3e-005

  intercept    -8.1e-009            1       -0.81     -0.00013      -0.0022

          v     4.5e-008        -0.81           1       0.0002       0.0014

          n        -3e-005     -0.00013      0.0002            1           -1

          k         3e-005      -0.0022      0.0014           -1            1




                           Parameter Estimates


                                                    95.0% Wald
Confidence Interval
        Variable         Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
          alpha          2183.85          630.425             948.245
3419.46
        intercept         119.29          17.6629             84.6713
153.909
              v         -56.5223          21.9082            -99.4615
-13.5831
              n               18          8854.08            -17335.7
17371.7
              k          21.6708          855.263            -1654.61
1697.95




     Table of Data and Estimated Values of Interest
```

```
   Dose       N    Obs Mean    Est Mean   Obs Std Dev  Est Std Dev   Scaled
  Res.
  ------     ---   --------    --------   -----------  -----------   ---------
  -

     0        7      119         119        69.9         46.7      2.74e-008
    20        4      109         108          61         46.7      8.42e-010
    60        6     56.5        62.8        31.2         46.7        -0.329
   180        7     68.1        62.8        33.2         46.7         0.304


Degrees of freedom for Test A3 vs fitted <= 0




 Model Descriptions for likelihoods calculated


 Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

            Model     Log(likelihood)   # Param's     AIC
            A1        -104.165520         5        218.331040
            A2        -101.140174         8        218.280349
            A3        -104.165520         5        218.331040
          fitted      -104.266162         5        218.532324
            R         -107.599268         2        219.198536


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)   Test df       p-value

   Test 1            12.9182            6          0.04435
   Test 2            6.05069            3           0.1092
```

```
     Test 3                6.05069          3             0.1092
     Test 4                0.201283         0             NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

NA - Degrees of freedom for Test 4 are less than or equal to 0.  The Chi-
Square
     test for fit is not valid


         Benchmark Dose Computation

Specified effect =              1

Risk Type        =      Estimated standard deviations from the control mean

Confidence level =         0.95

           BMD =        23.6366

          BMDL =       7.33648
```
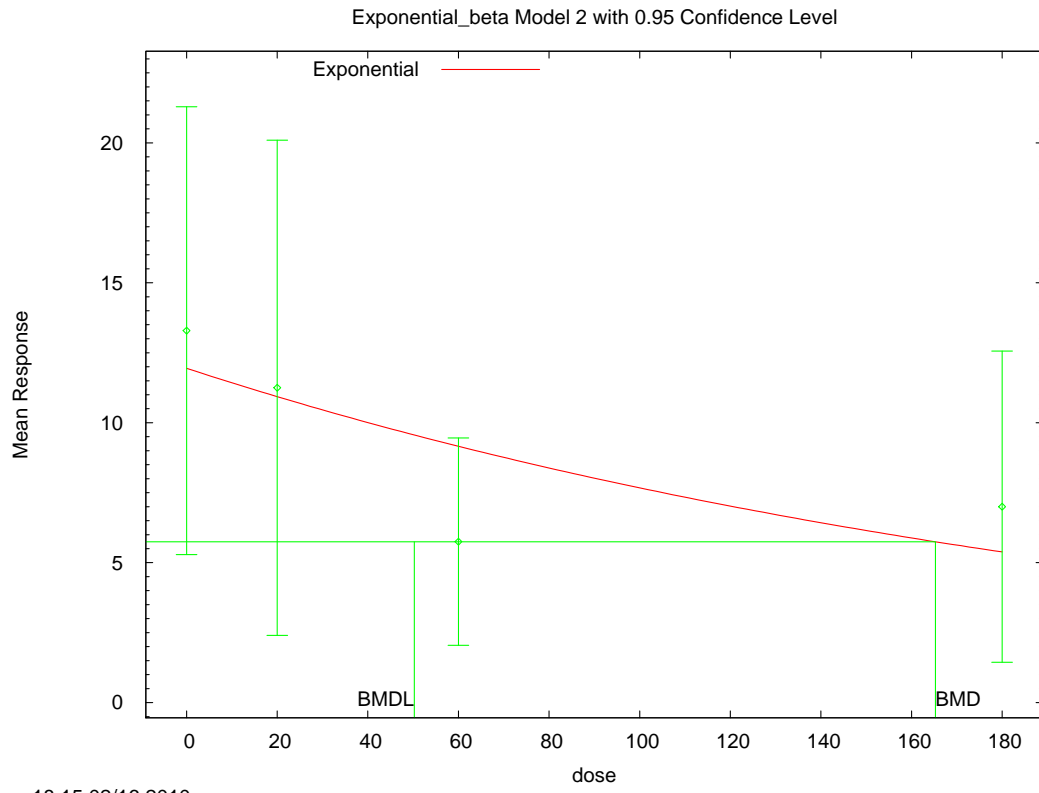
1   **G.3.32.3.** *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

18:16 02/16 2010

2
3
4   **G.3.32.4.** *Output for Additional Model Presented: Power, Unrestricted*

5   Markowski et al. ([2001](#)): FR2 Revolutions

6
7
8   ```
     ==
9   Power Model. (Version: 2.15; Date: 04/07/2008)
10   Input Data File: C:\1\34_Mark_2001_FR2rev_PowerCV_U_1.(d)
11   Gnuplot Plotting File: C:\1\34_Mark_2001_FR2rev_PowerCV_U_1.plt
12   Tue Feb 16 18:16:04 2010
13   ==
14
15   Table 3
16   ~~~~~~
17
18   The form of the response function is:
19
20   Y[dose] = control + slope * dose^power
21
22
23   Dependent variable = Mean
     ```

```
Independent variable = Dose
rho is set to 0
The power is not restricted
A constant variance model is fit


Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                     Default Initial Parameter Values
                            alpha =      2598.74
                              rho =            0    Specified
                          control =       119.29
                            slope =     -1.79436
                            power =     0.708231



            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -rho
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                    alpha       control        slope        power

      alpha             1     9.7e-009     -1.9e-008     -1.6e-008

    control      9.7e-009            1         -0.49         -0.28

      slope     -1.9e-008        -0.49            1          0.96

      power     -1.6e-008        -0.28         0.96            1




                              Parameter Estimates


                                                      95.0% Wald
Confidence Interval
        Variable        Estimate       Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha            2351         678.674              1020.82
3681.17
          control        120.074        18.0837              84.6305
155.517
          slope         -14.1965        22.2073              -57.722
29.329
          power          0.27229       0.301344            -0.318334
0.862913
```

```
     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean    Obs Std Dev   Est Std Dev   Scaled
 Res.
 ------     ---  --------     --------    -----------   -----------   ---------
 -

     0      7      119          120          69.9          48.5       -0.0428
    20      4      109           88          61            48.5        0.846
    60      6      56.5         76.8         31.2          48.5       -1.02
   180      7      68.1         61.7         33.2          48.5        0.352




 Model Descriptions for likelihoods calculated


 Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                  Likelihoods of Interest

            Model     Log(likelihood)   # Param's      AIC
             A1        -104.165520           5      218.331040
             A2        -101.140174           8      218.280349
             A3        -104.165520           5      218.331040
           fitted      -105.151136           4      218.302271
             R         -107.599268           2      219.198536



                  Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                  Tests of Interest

   Test     -2*log(Likelihood Ratio)   Test df        p-value

   Test 1            12.9182              6           0.04435
   Test 2            6.05069              3           0.1092
```

```
   Test 3                6.05069           3             0.1092
   Test 4                1.97123           1             0.1603


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data


The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here



The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data



                 Benchmark Dose Computation

Specified effect =              1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =         0.95

           BMD = 91.0145


           BMDL = 1.8e-013

```

1 **G.3.32.5.** *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

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G.3.33. Markowski et al. ([2001](#)): FR5 Run Opportunities

G.3.33.1. *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	2	0.149	133.830	9.491E+01	4.324E+01	
Exponential (M3)	2	0.149	133.830	9.491E+01	4.324E+01	power hit bound (*d* = 1)
Exponential (M4)	1	0.303	133.087	2.961E+01	9.356E+00	
Exponential (M5)	0	N/A	134.032	2.871E+01	1.226E+01	
Hill[b]	**1**	**0.939**	**132.032**	**2.214E+01**	**1.117E+01**	***n* upper bound hit (*n* = 18)**
Linear	2	0.091	134.825	1.349E+02	8.118E+01	
Polynomial, 3-degree	2	0.091	134.825	1.349E+02	8.118E+01	
Power	2	0.091	134.825	1.349E+02	8.118E+01	power bound hit (power = 1)
Power, unrestricted[c]	1	0.133	134.281	3.721E+01	1.439E−07	unrestricted (power = 0.336)

[a] Constant variance model selected (*p* = 0.2262).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

G.3.33.2. *Output for Selected Model: Hill*

Markowski et al. ([2001](#)): FR5 Run Opportunities

```
 =======================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\35_Mark_2001_FR5opp_HillCV_1.(d)
        Gnuplot Plotting File:  C:\1\35_Mark_2001_FR5opp_HillCV_1.plt
                                        Tue Feb 16 18:16:39 2010
 =======================================================================

 Table 3
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          alpha =      77.4849
                            rho =            0    Specified
                      intercept =        26.14
                              v =       -13.34
                              n =      2.36002
                              k =      35.0654



           Asymptotic Correlation Matrix of Parameter Estimates


           ( *** The model parameter(s)  -rho     -n
                  have been estimated at a boundary point, or have been
  specified by the user,
                  and do not appear in the correlation matrix )


                  alpha     intercept            v            k


      alpha           1     -3.6e-009     9.8e-009     3.6e-008

  intercept   -3.6e-009             1        -0.81        -0.51

          v    9.8e-009         -0.81            1         0.36

          k    3.6e-008         -0.51         0.36            1




                              Parameter Estimates


                                              95.0% Wald
Confidence Interval
      Variable       Estimate       Std. Err.    Lower Conf. Limit
Upper Conf. Limit
         alpha        64.5863        18.6445             28.0438
101.129
       intercept        26.14        3.03753             20.1865
32.0935
             v       -13.1569         3.7676            -20.5413
-5.77257
             n             18             NA
             k        21.5963        2.68136             16.3409
26.8517


NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.




       Table of Data and Estimated Values of Interest
```

```
 Dose         N    Obs Mean      Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------       ---   --------      --------   -----------  -----------   ---------
-


    0         7     26.1          26.1         12.3         8.04       1.02e-008
   20         4     23.5          23.5         7.04         8.04      -1.39e-007
   60         6     12.8            13         6.17         8.04       -0.0558
  180         7     13.1            13         7.14         8.04        0.0517




Model Descriptions for likelihoods calculated


Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
   Model A3 uses any fixed variance parameters that
   were specified by the user

Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

          Model      Log(likelihood)   # Param's      AIC
           A1         -62.013133           5       134.026266
           A2         -59.839035           8       135.678070
           A3         -62.013133           5       134.026266
        fitted        -62.016024           4       132.032049
           R          -67.530040           2       139.060081


                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
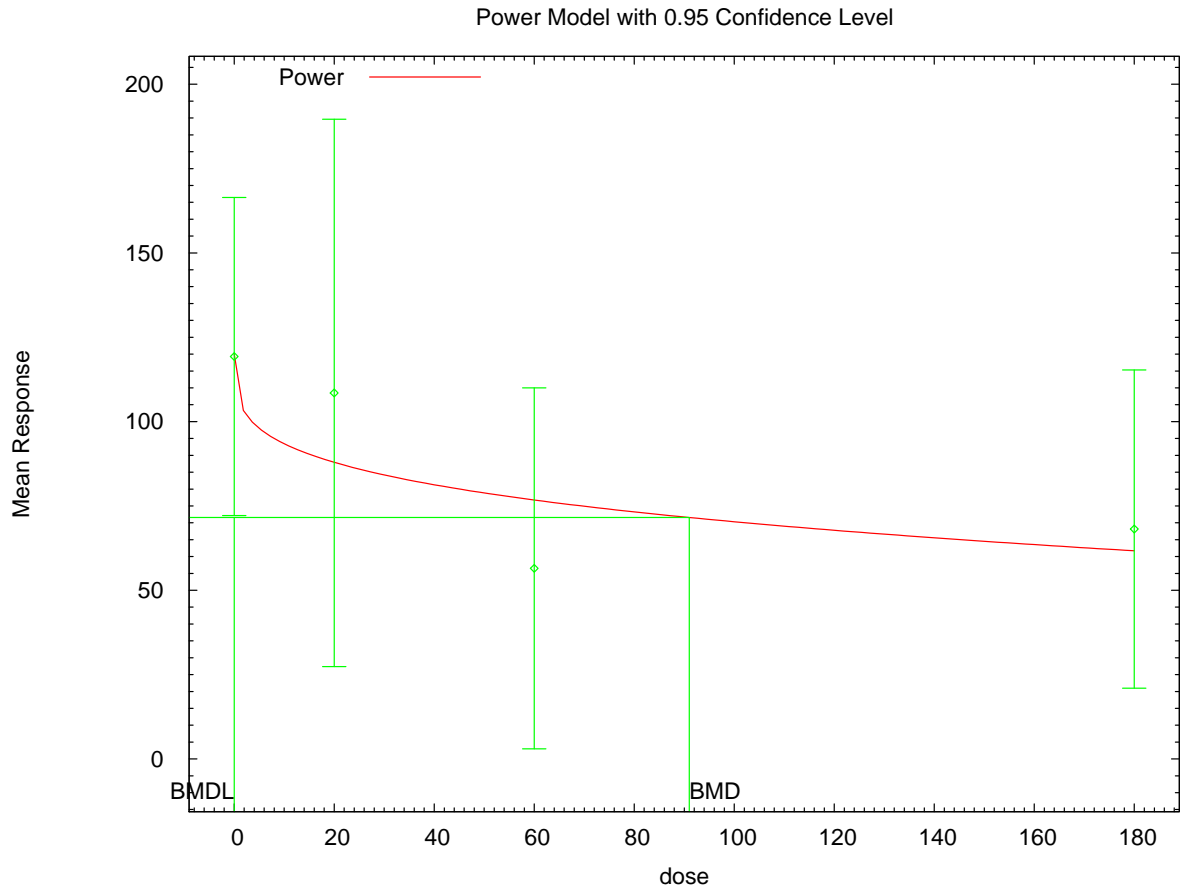(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              15.382           6          0.01748
   Test 2              4.3482           3          0.2262
   Test 3              4.3482           3          0.2262
```

```
   Test 4            0.0057833        1          0.9394

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

Risk Type       =    Estimated standard deviations from the control mean

Confidence level =         0.95

         BMD =        22.144

        BMDL =        11.165
```

1   **G.3.33.3.** *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

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2
3
4   **G.3.33.4.** *Output for Additional Model Presented: Power, Unrestricted*

5   Markowski et al. ([2001](#)): FR5 Run Opportunities

6
7
8
```
       ====================================================================
9             Power Model. (Version: 2.15;  Date: 04/07/2008)
10            Input Data File: C:\1\35_Mark_2001_FR5opp_PwrCV_U_1.(d)
11            Gnuplot Plotting File:  C:\1\35_Mark_2001_FR5opp_PwrCV_U_1.plt
12                                       Tue Feb 16 18:16:40 2010
       ====================================================================
13
14
15     Table 3
16    ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18        The form of the response function is:
19
20        Y[dose] = control + slope * dose^power
21
22
23        Dependent variable = Mean
24        Independent variable = Dose
```

```
rho is set to 0
The power is not restricted
A constant variance model is fit


Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                           alpha =       77.4849
                             rho =             0   Specified
                         control =         26.14
                           slope =      -0.39517
                           power =      0.725538



           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                   alpha        control         slope          power

     alpha             1       7.4e-009       4.3e-008       4.8e-008

   control      7.4e-009             1          -0.51          -0.34

     slope      4.3e-008         -0.51             1           0.97

     power      4.8e-008         -0.34          0.97              1




                              Parameter Estimates


                                                       95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
          alpha         70.9323         20.4764              30.7993
111.065
        control         26.3567         3.13032              20.2213
32.492
          slope        -2.49841         3.16984             -8.71118
3.71437
          power        0.336003        0.242031            -0.138368
0.810375




     Table of Data and Estimated Values of Interest
```

```
 Dose        N    Obs Mean     Est Mean    Obs Std Dev   Est Std Dev   Scaled
Res.
------       ---  --------     --------    -----------   -----------   ---------
-

    0         7     26.1         26.4         12.3          8.42        -0.0681
   20         4     23.5         19.5         7.04          8.42         0.945
   60         6     12.8         16.5         6.17          8.42        -1.07
  180         7     13.1         12.1         7.14          8.42         0.341
```

Model Descriptions for likelihoods calculated

Model A1:   Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2

Model A2:   Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma(i)^2

Model A3:   Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2
   Model A3 uses any fixed variance parameters that
   were specified by the user

Model R: Yi = Mu + e(i)
         Var{e(i)} = Sigma^2

                    Likelihoods of Interest

```
            Model     Log(likelihood)   # Param's      AIC
             A1         -62.013133          5       134.026266
             A2         -59.839035          8       135.678070
             A3         -62.013133          5       134.026266
          fitted        -63.140714          4       134.281428
             R          -67.530040          2       139.060081
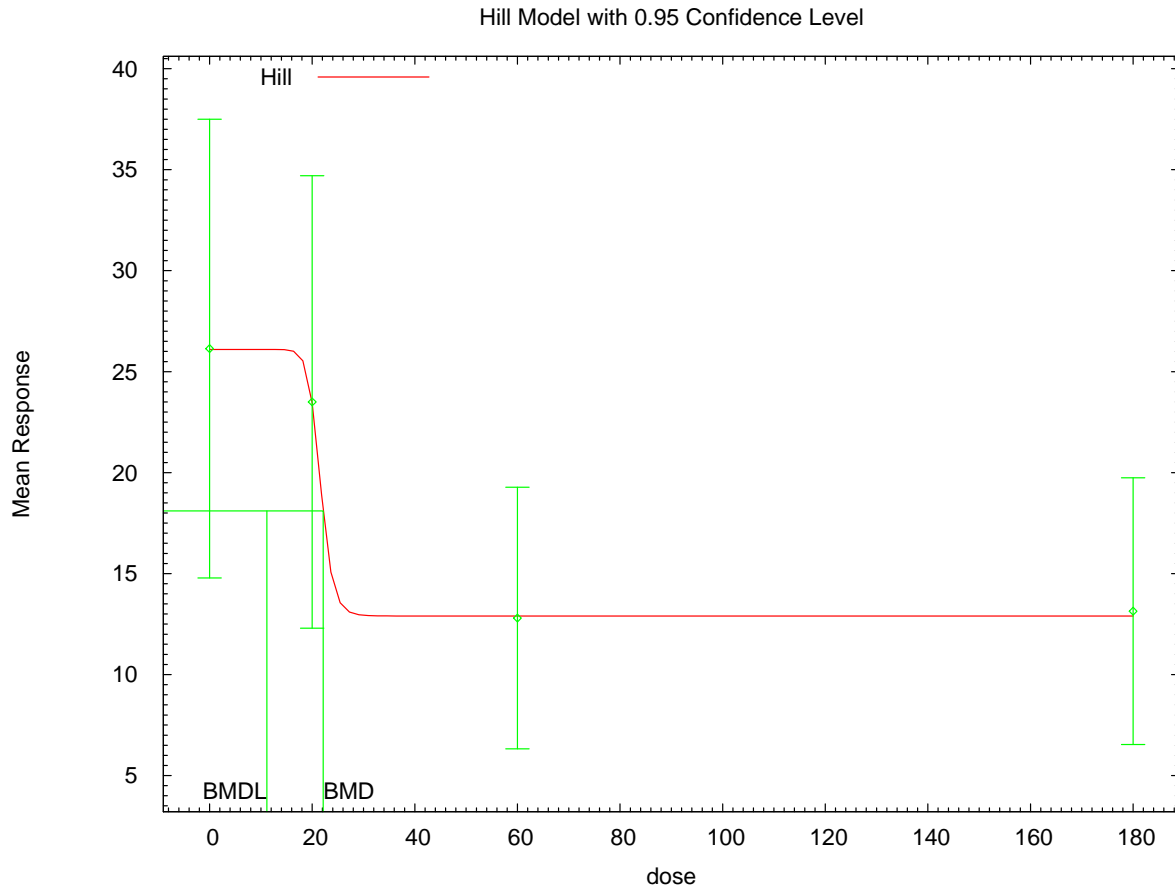```

                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

```
  Test     -2*log(Likelihood Ratio)   Test df        p-value

  Test 1              15.382             6           0.01748
  Test 2              4.3482             3           0.2262
  Test 3              4.3482             3           0.2262
```

```
   Test 4                2.25516          1            0.1332
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

                  Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

            BMD = 37.2131

            BMDL = 1.43926e-007

1   **G.3.33.5.** *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

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2
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G.3.34. Miettinen et al. ([2006](#)): Cariogenic Lesions, Pups

G.3.34.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	3	0.345	162.699	7.505E+01	4.086E+01	power bound hit (power = 1)
Logistic	3	0.315	162.909	8.991E+01	5.250E+01	
Log-logistic[a]	**3**	**0.506**	**161.767**	**3.130E+01**	**1.054E+01**	**slope bound hit (slope = 1)**
Log-probit	3	0.257	163.393	1.390E+02	6.729E+01	slope bound hit (slope = 1)
Multistage, 4-degree	3	0.345	162.699	7.505E+01	4.086E+01	final ß = 0
Probit	3	0.299	163.031	9.941E+01	6.208E+01	
Weibull	3	0.345	162.699	7.505E+01	4.086E+01	power bound hit (power = 1)
Gamma, unrestricted	2	0.797	161.805	1.591E−02	1.335E−240	unrestricted (power = 0.184)
Log-logistic, unrestricted[b]	2	0.723	161.998	3.713E−01	error	unrestricted (slope = 0.403)
Log-probit, unrestricted	2	0.726	161.987	5.098E−01	error	unrestricted (slope = 0.25)
Weibull, unrestricted	2	0.761	161.897	1.174E−01	error	unrestricted (power = 0.281)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.3.34.2. *Output for Selected Model: Log-Logistic*

Miettinen et al. ([2006](#)): Cariogenic Lesions, Pups

```
 =====================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\36_Miet_2006_Cariogenic_LogLogistic_1.(d)
         Gnuplot Plotting File:
C:\1\36_Miet_2006_Cariogenic_LogLogistic_1.plt
                                         Tue Feb 16 18:17:16 2010
 =====================================================================

 Table 2 converting the percentage into the number of animals, and control is
Control II from the study. Dose is in ng per kg and is from Table 1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
```

```
Total number of observations = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =     0.595238
                      intercept =     -5.52519
                          slope =            1


         Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                background    intercept

background              1        -0.64

 intercept          -0.64            1




                             Parameter Estimates

                                                    95.0% Wald
Confidence Interval
       Variable          Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
     background        0.658158              *                *
*
      intercept        -5.64068              *                *
*
          slope               1              *                *
*

* - Indicates that this value is not calculated.




                         Analysis of Deviance Table

        Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model       -77.6769           5
    Fitted model      -78.8837           2        2.41374        3
0.4911
```

```
Reduced model        -83.2067          1        11.0597        4
0.0259

           AIC:          161.767


                         Goodness  of  Fit
                                                        Scaled
       Dose     Est._Prob.    Expected    Observed     Size    Residual
     ------------------------------------------------------------------------
       0.0000     0.6582       27.643      25.000        42      -0.860
      30.0000     0.6911       20.041      23.000        29       1.189
     100.0000     0.7477       18.693      19.000        25       0.141
     300.0000     0.8345       20.027      20.000        24      -0.015
    1000.0000     0.9249       29.596      29.000        32      -0.400

   Chi^2 = 2.33     d.f. = 3       P-value = 0.5062


       Benchmark Dose Computation

   Specified effect =          0.1

   Risk Type        =      Extra risk

   Confidence level =          0.95

              BMD =        31.2951

              BMDL =       10.5354
```

1 **G.3.34.3.** *Figure for Selected Model: Log-Logistic*

Log-Logistic Model with 0.95 Confidence Level

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2
3
4 **G.3.34.4.** *Output for Additional Model Presented: Log-Logistic, Unrestricted*

5 Miettinen et al. (2006): Cariogenic Lesions, Pups
6
7
```
8   ====================================================================
9           Logistic Model. (Version: 2.12; Date: 05/16/2008)
10          Input Data File: C:\1\36_Miet_2006_Cariogenic_LogLogistic_U_1.(d)
11          Gnuplot Plotting File:
12  C:\1\36_Miet_2006_Cariogenic_LogLogistic_U_1.plt
13                                      Tue Feb 16 18:17:18 2010
14  ====================================================================
15
16   Table 2 converting the percentage into the number of animals, and control is
17   Control II from the study. Dose is in ng per kg and is from Table 1
18   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
19
20      The form of the probability function is:
21
22      P[response] = background+(1-background)/[1+EXP(-intercept-
23   slope*Log(dose))]
24
```

```
Dependent variable = DichEff
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


                  Default Initial Parameter Values
                      background =     0.595238
                       intercept =    -1.68849
                           slope =     0.382632


          Asymptotic Correlation Matrix of Parameter Estimates

                background      intercept          slope

background            1          -0.41           0.24

 intercept        -0.41              1          -0.96

    slope          0.24          -0.96              1



                            Parameter Estimates

                                               95.0% Wald
Confidence Interval
       Variable       Estimate       Std. Err.    Lower Conf. Limit
Upper Conf. Limit
    background       0.597778            *                 *
*
      intercept     -1.79836             *                 *
*
         slope       0.402606            *                 *
*

* - Indicates that this value is not calculated.




                        Analysis of Deviance Table

     Model        Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
   Full model        -77.6769           5
  Fitted model       -77.9988           3      0.643944      2
0.7247
```

```
Reduced model           -83.2067          1          11.0597        4
0.0259

          AIC:           161.998


                         Goodness  of  Fit
                                                          Scaled
     Dose      Est._Prob.    Expected    Observed    Size    Residual
   ------------------------------------------------------------------------
     0.0000      0.5978        25.107      25.000       42      -0.034
    30.0000      0.7564        21.936      23.000       29       0.460
   100.0000      0.8045        20.112      19.000       25      -0.561
   300.0000      0.8480        20.351      20.000       24      -0.200
  1000.0000      0.8905        28.495      29.000       32       0.286

 Chi^2 = 0.65     d.f. = 2       P-value = 0.7227


   Benchmark Dose Computation

Specified effect =             0.1

Risk Type        =       Extra risk

Confidence level =             0.95

          BMD =        0.371315

          Benchmark dose computation failed.  Lower limit includes zero.
```

1   **G.3.34.5.** *Figure for Additional Model Presented: Log-Logistic, Unrestricted*

Log-Logistic Model

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2
3
4

1 **G.3.35. Murray et al. ([1979](#)): Fertility in F2 Generation**

2 **G.3.35.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	0	N/A	61.729	7.016E+00	1.698E+00	
Logistic	1	0.072	60.497	4.007E+00	2.836E+00	
Log-logistic	0	N/A	61.729	7.902E+00	1.584E+00	
Multistage, 1-degree	1	0.053	61.644	2.380E+00	1.320E+00	
Multistage, 2-degree[a]	**1**	**0.094**	**59.935**	**4.548E+00**	**1.635E+00**	
Probit	1	0.070	60.613	3.707E+00	2.615E+00	
Weibull	0	N/A	61.729	8.115E+00	1.698E+00	
Log-probit, unrestricted	0	N/A	61.729	6.373E+00	1.503E+00	unrestricted (slope = 2.306)

[a] Best-fitting model, BMDS output presented in this appendix.

3
4

5 **G.3.35.2.** *Output for Selected Model: Multistage, 2-Degree*

6 Murray et al. ([1979](#)): Fertility in F2 Generation

```
9  ====================================================================
10         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
11         Input Data File: C:\1\Murray_1979_fert_index_f2_Multi2_1.(d)
12         Gnuplot Plotting File:  C:\1\Murray_1979_fert_index_f2_Multi2_1.plt
13                                         Tue Feb 16 20:08:06 2010
14  ====================================================================

16  Table 1 but expressed as number of dams who do not produce offspring
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

19    The form of the probability function is:

21    P[response] = background + (1-background)*[1-EXP(
22               -beta1*dose^1-beta2*dose^2)]

24    The parameter betas are restricted to be positive


27    Dependent variable = DichEff
28    Independent variable = Dose

30  Total number of observations = 3
31  Total number of records with missing values = 0
32  Total number of parameters in model = 3
33  Total number of specified parameters = 0
34  Degree of polynomial = 2
```

```
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                       Background =    0.0624181
                          Beta(1) =            0
                          Beta(2) =    0.00532688



           Asymptotic Correlation Matrix of Parameter Estimates


           ( *** The model parameter(s)  -Beta(1)
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                  Background        Beta(2)


Background                1           -0.44

   Beta(2)            -0.44               1




                              Parameter Estimates


                                                     95.0% Wald
Confidence Interval
       Variable          Estimate         Std. Err.      Lower Conf. Limit
Upper Conf. Limit
     Background         0.0772201              *                *
*
         Beta(1)                0              *                *
*
         Beta(2)        0.00509404             *                *
*

* - Indicates that this value is not calculated.




                           Analysis of Deviance Table


      Model        Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -25.8194          3
    Fitted model       -27.9673          2        4.29584        1
0.03821
    Reduced model      -34.0009          1        16.363         2
0.0002798

          AIC:          59.9347
```

```
                        Goodness  of  Fit
                                                         Scaled
      Dose     Est._Prob.    Expected    Observed    Size    Residual
   ------------------------------------------------------------------
     0.0000     0.0772       2.471       4.000        32      1.013
     1.0000     0.0819       1.638       0.000        20     -1.336
    10.0000     0.4455       8.911       9.000        20      0.040

 Chi^2 = 2.81      d.f. = 1        P-value = 0.0936



    Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =           0.95

          BMD =       4.54787

          BMDL =      1.63487

          BMDU =      6.79105

Taken together, (1.63487, 6.79105) is a 90    % two-sided confidence
interval for the BMD
```

1   **G.3.35.3.** *Figure for Selected Model: Multistage, 2-Degree*

Multistage Model with 0.95 Confidence Level

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2
3
4   **G.3.36. National Toxicology Program (1982): Toxic Hepatitis, Male Mice**

5   **G.3.36.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	1	0.026	113.097	1.552E+01	5.155E+00	
Logistic	2	0.093	110.712	1.769E+01	1.383E+01	
Log-logistic	1	0.027	113.093	1.499E+01	6.628E+00	
Log-probit	1	0.027	113.111	1.360E+01	7.237E+00	
Multistage, 3-degree[a]	**1**	**0.028**	**112.555**	**1.488E+01**	**4.676E+00**	
Probit	2	0.088	110.696	1.564E+01	1.261E+01	
Weibull	1	0.026	113.056	1.619E+01	4.903E+00	

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.36.2. *Output for Selected Model: Multistage, 3-Degree*

National Toxicology Program ([1982](#)): Toxic Hepatitis, Male Mice

```
=====================================================================
       Multistage Model. (Version: 3.0;  Date: 05/16/2008)
       Input Data File: C:\1\37_NTP_1982_ToxHep_Multi3_1.(d)
       Gnuplot Plotting File:  C:\1\37_NTP_1982_ToxHep_Multi3_1.plt
                                      Tue Feb 16 18:17:51 2010
=====================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
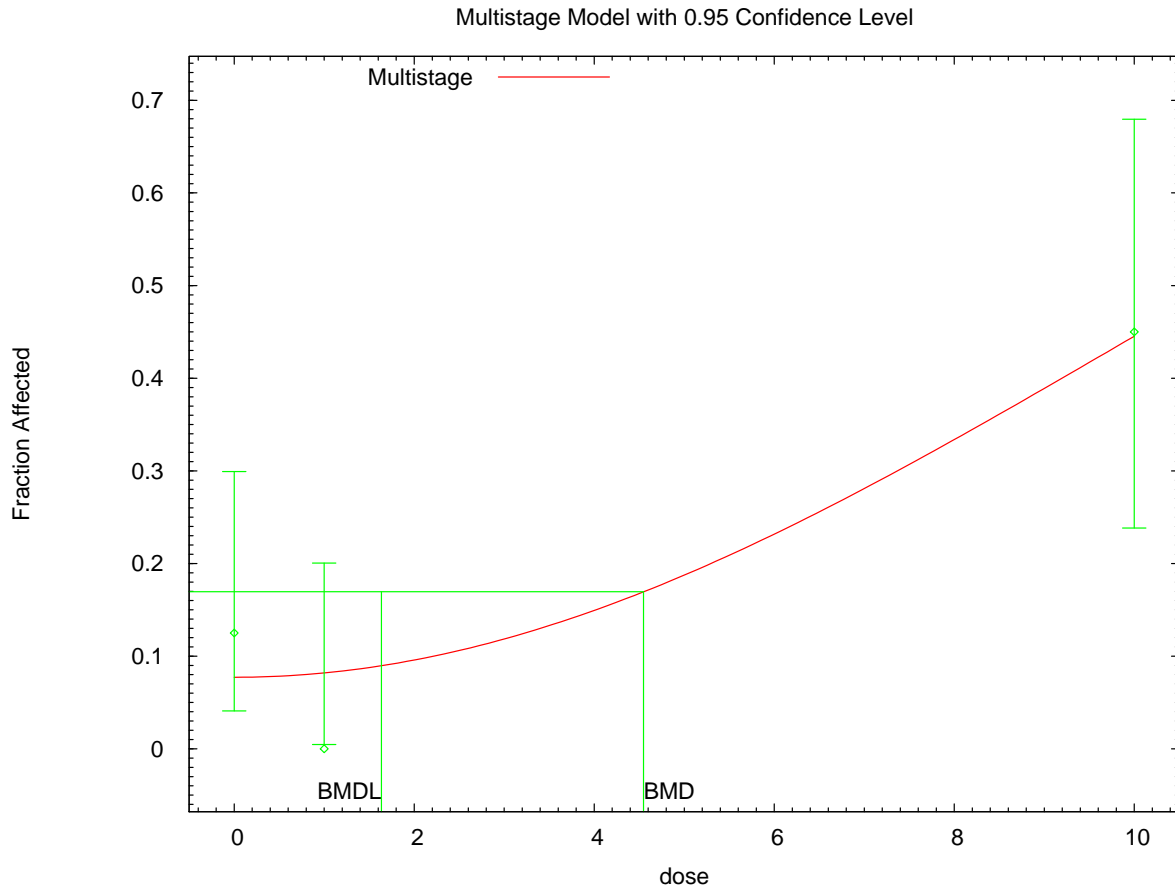
   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008




                  Default Initial Parameter Values
                     Background =    0.0525767
                        Beta(1) =   0.00243254
                        Beta(2) =           0
                        Beta(3) = 5.29052e-006




          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -Beta(2)
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

             Background      Beta(1)      Beta(3)

 Background            1        -0.69         0.66
```

```
   Beta(1)          -0.69              1          -0.98

   Beta(3)           0.66            -0.98             1




                            Parameter Estimates

                                                  95.0% Wald
Confidence Interval
       Variable          Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
     Background         0.0383474             *                *
*
        Beta(1)        0.00605732             *                *
*
        Beta(2)                 0             *                *
*
        Beta(3)      4.60855e-006             *                *
*

* - Indicates that this value is not calculated.




                         Analysis of Deviance Table

        Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -51.0633           4
   Fitted model        -53.2776           3       4.42854       1
0.03534
   Reduced model       -121.743           1       141.358       3        <.0001

          AIC:          112.555




                            Goodness  of  Fit
                                                            Scaled
     Dose      Est._Prob.     Expected     Observed     Size     Residual
   ----------------------------------------------------------------------
    0.0000      0.0383        2.799        1.000         73      -1.097
    1.4000      0.0465        2.278        5.000         49       1.847
    7.1000      0.0803        3.937        3.000         49      -0.492
   71.0000      0.8798       43.990       44.000         50       0.004

 Chi^2 = 4.86      d.f. = 1       P-value = 0.0275



   Benchmark Dose Computation

Specified effect =          0.1

Risk Type       =      Extra risk

Confidence level =          0.95

          BMD =       14.8848
```

```
 1
 2              BMDL =          4.67636
 3
 4              BMDU =          28.8293
 5
 6  Taken together, (4.67636, 28.8293) is a 90     % two-sided confidence
 7  interval for the BMD
 8
 9
```

10 **G.3.36.3.** *Figure for Selected Model: Multistage, 3-Degree*

Multistage Model with 0.95 Confidence Level

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11
12
13

G.3.37. National Toxicology Program (2006): Alveolar Metaplasia

2 **G.3.37.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	4	<0.001	340.127	2.240E+00	1.791E+00	power bound hit (power = 1)
Logistic	4	<0.001	358.346	4.997E+00	4.149E+00	
Log-logistic[a]	**4**	**0.409**	**312.970**	**6.644E−01**	**5.041E−01**	**slope bound hit (slope = 1)**
Log-probit	4	<0.001	340.296	3.291E+00	2.517E+00	slope bound hit (slope = 1)
Multistage, 5-degree	4	<0.001	340.127	2.240E+00	1.791E+00	final ß = 0
Probit	4	<0.001	362.181	5.656E+00	4.810E+00	
Weibull	4	<0.001	340.127	2.240E+00	1.791E+00	power bound hit (power = 1)
Gamma, unrestricted	3	0.407	314.135	2.211E−02	8.081E−04	unrestricted (power = 0.297)
Log-logistic, unrestricted[b]	3	0.739	312.487	3.062E−01	7.972E−02	unrestricted (slope = 0.785)
Log-probit, unrestricted	3	0.727	312.543	3.316E−01	8.968E−02	unrestricted (slope = 0.471)
Weibull, unrestricted	3	0.586	313.176	9.000E−02	1.341E−02	unrestricted (power = 0.465)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

3
4
5 **G.3.37.2.** *Output for Selected Model: Log-Logistic*

6 National Toxicology Program (2006): Alveolar Metaplasia
7
8
```
9    =====================================================================
10         Logistic Model. (Version: 2.12; Date: 05/16/2008)
11         Input Data File: C:\1\40_NTP_2006_AlvMeta_LogLogistic_1.(d)
12         Gnuplot Plotting File:  C:\1\40_NTP_2006_AlvMeta_LogLogistic_1.plt
13                                         Tue Feb 16 18:19:30 2010
14    =====================================================================
15
16    0
17 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19    The form of the probability function is:
20
21    P[response] = background+(1-background)/[1+EXP(-intercept-
22 slope*Log(dose))]
23
24
25    Dependent variable = DichEff
26    Independent variable = Dose
27    Slope parameter is restricted as slope >= 1
28
29    Total number of observations = 6
```

```
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




   User has chosen the log transformed model


                  Default Initial Parameter Values
                     background =    0.0377358
                      intercept =     -2.03745
                          slope =          1



         Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -slope
                  have been estimated at a boundary point, or have been
   specified by the user,
                  and do not appear in the correlation matrix )

              background    intercept

   background           1         -0.4

    intercept        -0.4            1




                            Parameter Estimates

                                                95.0% Wald
   Confidence Interval
        Variable         Estimate        Std. Err.      Lower Conf. Limit
   Upper Conf. Limit
       background      0.0448753              *                  *
   *
        intercept      -1.78837              *                  *
   *
           slope             1               *                  *
   *

   * - Indicates that this value is not calculated.




                          Analysis of Deviance Table

        Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
        Full model       -152.615        6
      Fitted model       -154.485        2        3.7393       4
   0.4424
     Reduced model       -216.802        1        128.374      5        <.0001

          AIC:           312.97
```

```
                         Goodness  of  Fit
                                                         Scaled
     Dose     Est._Prob.    Expected    Observed    Size    Residual
    --------------------------------------------------------------------
     0.0000     0.0449        2.378       2.000       53     -0.251
     2.1400     0.2966       16.017      19.000       54      0.889
     7.1400     0.5647       29.928      33.000       53      0.851
    15.7000     0.7366       38.301      35.000       52     -1.039
    32.9000     0.8531       45.214      45.000       53     -0.083
    71.4000     0.9262       48.162      46.000       52     -1.147

 Chi^2 = 3.98     d.f. = 4      P-value = 0.4088


   Benchmark Dose Computation

Specified effect =          0.1

Risk Type        =     Extra risk

Confidence level =          0.95

            BMD =       0.664411

            BMDL =      0.504109
```

1 **G.3.37.3.** *Figure for Selected Model: Log-Logistic*

Log-Logistic Model with 0.95 Confidence Level

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2
3
4 **G.3.37.4.** *Output for Additional Model Presented: Log-Logistic, Unrestricted*

5 National Toxicology Program (2006): Alveolar Metaplasia
6
7
```
8   ========================================================================
9           Logistic Model. (Version: 2.12; Date: 05/16/2008)
10          Input Data File: C:\1\40_NTP_2006_AlvMeta_LogLogistic_U_1.(d)
11          Gnuplot Plotting File:  C:\1\40_NTP_2006_AlvMeta_LogLogistic_U_1.plt
12                                         Tue Feb 16 18:19:31 2010
13  ========================================================================
14
15   0
16  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18     The form of the probability function is:
19
20     P[response] = background+(1-background)/[1+EXP(-intercept-
21  slope*Log(dose))]
22
23
24     Dependent variable = DichEff
```

```
Independent variable = Dose
Slope parameter is not restricted
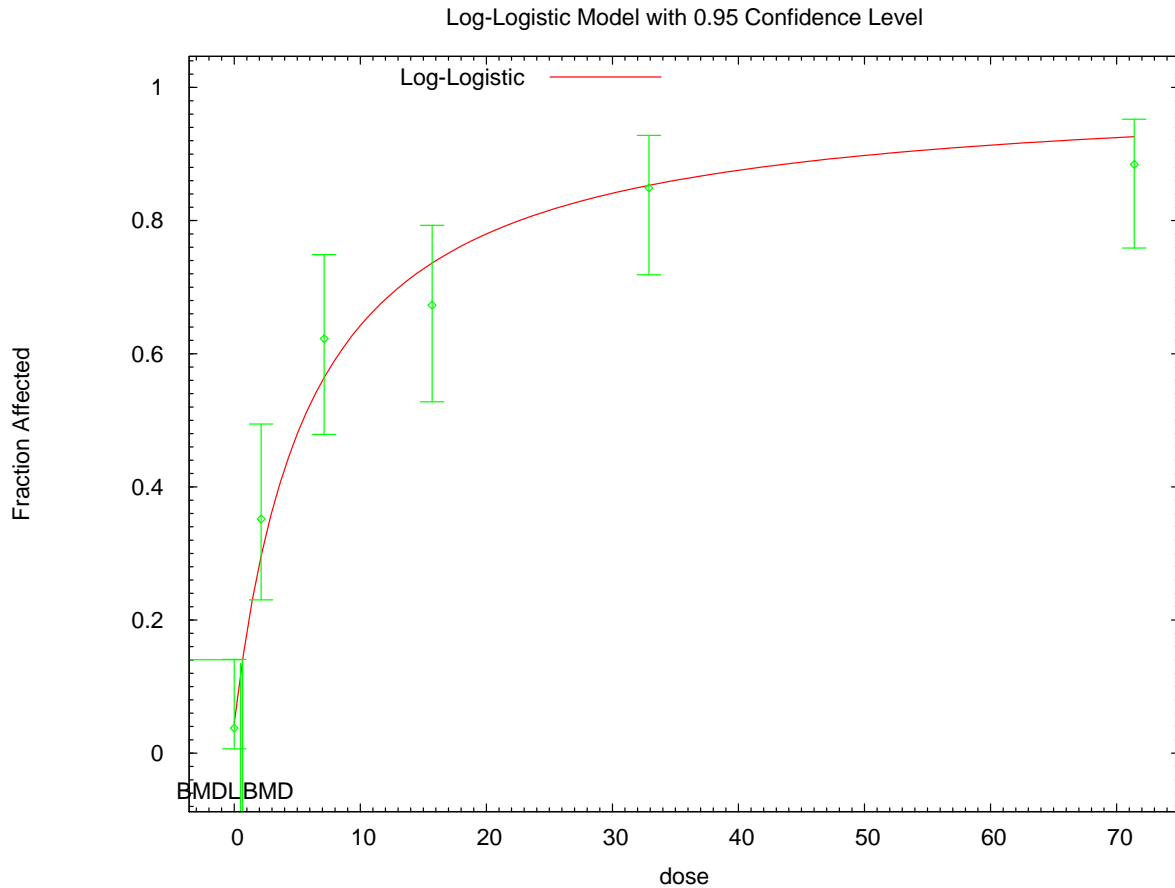
Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


              Default Initial Parameter Values
                   background =    0.0377358
                    intercept =    -1.26694
                        slope =    0.784484


        Asymptotic Correlation Matrix of Parameter Estimates

               background      intercept        slope

background             1          -0.24          0.11

 intercept         -0.24              1           -0.9

    slope           0.11           -0.9              1




                         Parameter Estimates

                                              95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
      background        0.0375286              *                  *
*
       intercept        -1.26811              *                  *
*
          slope        0.785033              *                  *
*

* - Indicates that this value is not calculated.




                     Analysis of Deviance Table

       Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model       -152.615          6
    Fitted model       -153.244          3        1.2566       3
0.7395
    Reduced model      -216.802          1       128.374       5        <.0001
```

```
         AIC:            312.487


                         Goodness  of  Fit
                                                        Scaled
        Dose    Est._Prob.    Expected    Observed    Size    Residual
    ----------------------------------------------------------------------
       0.0000    0.0375       1.989       2.000        53       0.008
       2.1400    0.3631      19.609      19.000        54      -0.172
       7.1400    0.5845      30.980      33.000        53       0.563
      15.7000    0.7205      37.468      35.000        52      -0.763
      32.9000    0.8207      43.498      45.000        53       0.538
      71.4000    0.8934      46.455      46.000        52      -0.204

   Chi^2 = 1.26     d.f. = 3       P-value = 0.7388


      Benchmark Dose Computation

   Specified effect =          0.1

   Risk Type        =      Extra risk

   Confidence level =          0.95

             BMD =       0.306194

             BMDL =      0.0797223
```

1   **G.3.37.5.** *Figure for Additional Model Presented: Log-Logistic, Unrestricted*

Log-Logistic Model with 0.95 Confidence Level

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2
3
4

G.3.38. National Toxicology Program (2006): Eosinophilic Focus, Liver

G.3.38.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	4	0.367	330.457	5.676E+00	4.532E+00	power bound hit (power = 1)
Logistic	4	0.167	333.343	1.258E+01	1.071E+01	
Log-logistic	3	0.117	334.148	4.727E+00	2.867E+00	
Log-probit	4	0.084	334.683	1.078E+01	8.514E+00	
Multistage, 5-degree	3	0.313	331.771	6.568E+00	4.666E+00	
Probit[a]	**4**	**0.187**	**332.962**	**1.196E+01**	**1.031E+01**	
Weibull	4	0.367	330.457	5.675E+00	4.532E+00	power bound hit (power = 1)
Log-probit, unrestricted	3	0.087	334.849	4.750E+00	1.757E+00	unrestricted (slope = 0.643)

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.38.2. *Output for Selected Model: Probit*

National Toxicology Program (2006): Eosinophilic Focus, Liver

```
  ========================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\1\45_NTP_2006_LivEosFoc_Probit_1.(d)
         Gnuplot Plotting File:  C:\1\45_NTP_2006_LivEosFoc_Probit_1.plt
                                         Tue Feb 16 18:25:56 2010
  ========================================================================
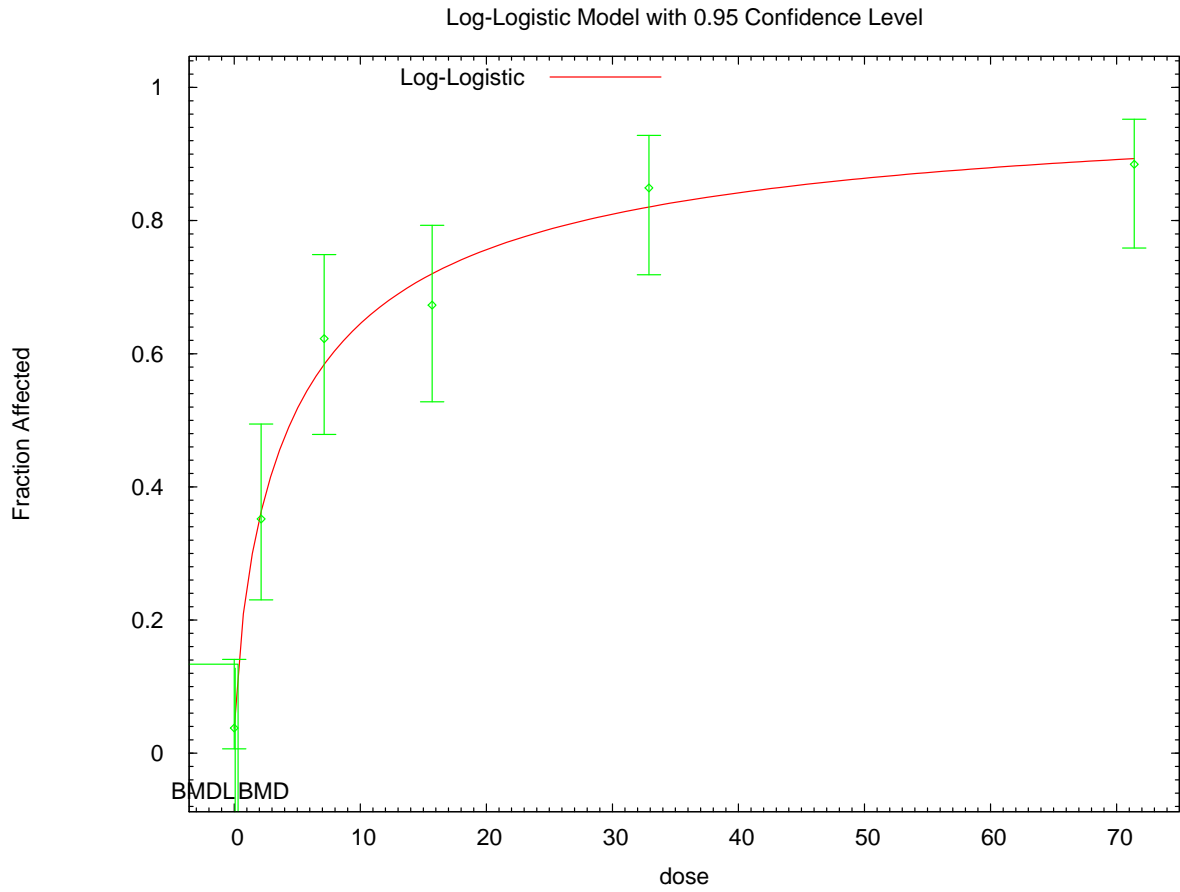
  0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = CumNorm(Intercept+Slope*Dose),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

```
                    Default Initial (and Specified) Parameter Values
                        background =            0    Specified
                         intercept =      -1.11935
                            slope =    0.0279665


                 Asymptotic Correlation Matrix of Parameter Estimates

                 ( *** The model parameter(s)  -background
                        have been estimated at a boundary point, or have been
specified by the user,
                        and do not appear in the correlation matrix )


                    intercept        slope

   intercept                1        -0.69

       slope           -0.69             1



                              Parameter Estimates

                                                      95.0% Wald
Confidence Interval
         Variable         Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
         intercept        -1.06148         0.109177            -1.27546
-0.847497
          slope         0.0269279         0.00327788            0.0205034
0.0333525




                              Analysis of Deviance Table

        Model        Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model          -161.07          6
    Fitted model        -164.481          2         6.8221        4
0.1456
    Reduced model        -202.816          1        83.4925        5        <.0001

          AIC:          332.962



                              Goodness  of  Fit
                                                                   Scaled
       Dose      Est._Prob.    Expected    Observed    Size      Residual
      -------------------------------------------------------------------
       0.0000      0.1442        7.645       3.000       53       -1.816
       2.1400      0.1577        8.517       8.000       54       -0.193
       7.1400      0.1924       10.195      14.000       53        1.326
      15.7000      0.2615       13.860      17.000       53        0.982
      32.9000      0.4303       22.807      22.000       53       -0.224
      71.4000      0.8054       42.688      42.000       53       -0.239
```

```
 1
 2   Chi^2 = 6.16        d.f. = 4         P-value = 0.1873
 3
 4
 5     Benchmark Dose Computation
 6
 7  Specified effect =              0.1
 8
 9  Risk Type         =        Extra risk
10
11  Confidence level =             0.95
12
13           BMD =           11.9584
14
15          BMDL =           10.3075
16
```

17 **G.3.38.3.** *Figure for Selected Model: Probit*

Probit Model with 0.95 Confidence Level

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1   **G.3.39. National Toxicology Program ([2006](#)): Fatty Change Diffuse, Liver**

2   **G.3.39.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	4	0.668	252.294	4.224E+00	3.166E+00	
Logistic	4	0.005	269.825	1.092E+01	9.292E+00	
Log-logistic	4	0.292	255.082	4.697E+00	3.153E+00	
Log-probit	4	0.118	257.548	6.236E+00	5.204E+00	slope bound hit (slope = 1)
Multistage, 5-degree	4	0.808	251.545	4.021E+00	3.250E+00	
Probit	4	0.005	269.430	1.052E+01	9.068E+00	
Weibull[a]	**4**	**0.679**	**252.218**	**4.252E+00**	**3.174E+00**	
Log-probit, unrestricted	4	0.282	255.258	4.581E+00	3.193E+00	unrestricted (slope = 0.824)

[a] Best-fitting model, BMDS output presented in this appendix.

3
4

5   **G.3.39.2.** *Output for Selected Model: Weibull*

6   National Toxicology Program ([2006](#)): Fatty Change Diffuse, Liver
7
8
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```
 ==========================================================================
         Weibull Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
         Input Data File: C:\1\47_NTP_2006_LivFatDiff_Weibull_1.(d)
         Gnuplot Plotting File:  C:\1\47_NTP_2006_LivFatDiff_Weibull_1.plt
                                         Tue Feb 16 18:26:57 2010
 ==========================================================================

 NTP_liver_fatty_change_diffuse
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
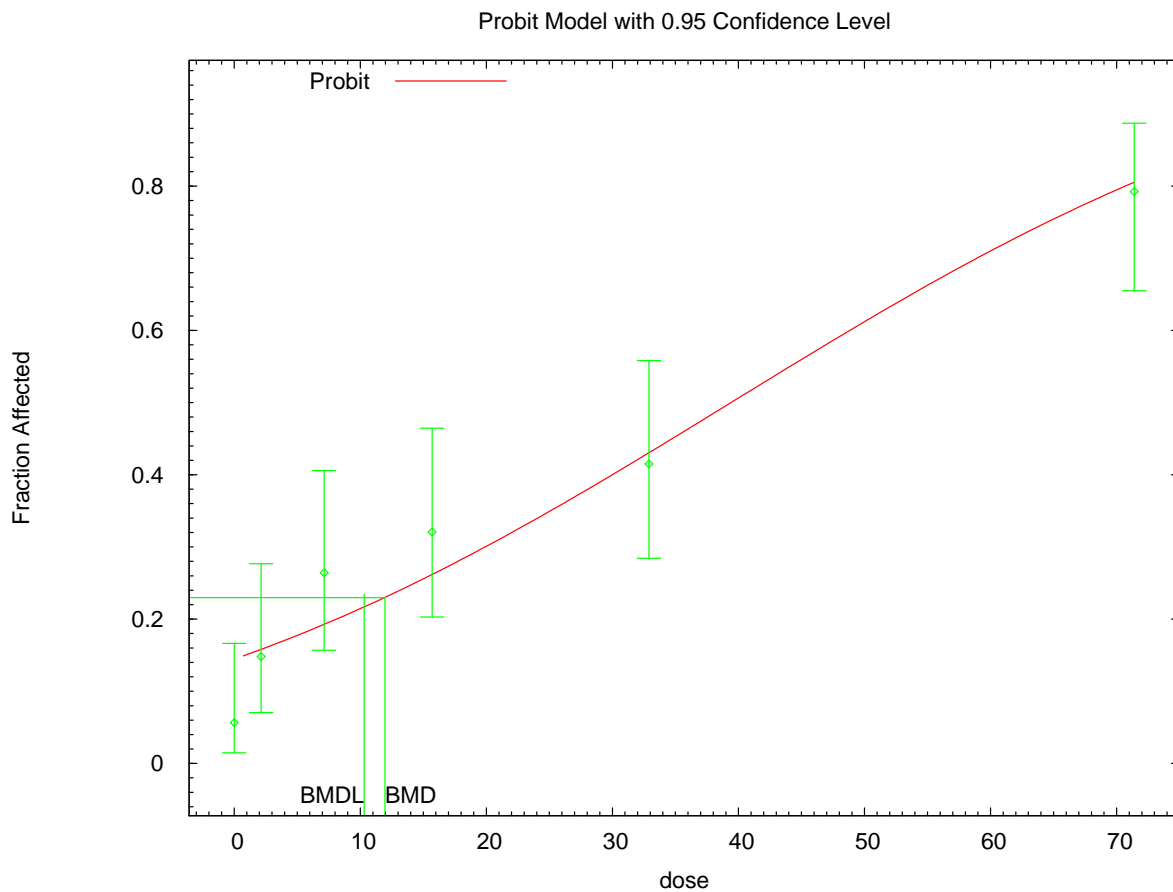
   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]


   Dependent variable = DichEff
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

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35

```
                    Default Initial (and Specified) Parameter Values
                       Background =  0.00925926
                            Slope =  0.00962604
                            Power =    1.28042



              Asymptotic Correlation Matrix of Parameter Estimates

              ( *** The model parameter(s)  -Background
                    have been estimated at a boundary point, or have been
specified by the user,
                    and do not appear in the correlation matrix )

                        Slope        Power

        Slope            1          -0.97

        Power         -0.97            1




                             Parameter Estimates

                                                      95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
        Background             0             NA
           Slope      0.0223474      0.00951041           0.0037073
0.0409874
           Power       1.07133        0.122134            0.831952
1.31071


NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.




                         Analysis of Deviance Table

        Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
        Full model        -122.992        6
     Fitted model         -124.109        2       2.23388      4
0.6928
     Reduced model        -204.846        1      163.708       5        <.0001


          AIC:          252.218




                              Goodness  of  Fit
                                                             Scaled
       Dose      Est._Prob.    Expected    Observed     Size      Residual
     ----------------------------------------------------------------------
       0.0000      0.0000       0.000       0.000        53       0.000
       2.1400      0.0492       2.659       2.000        54      -0.414
       7.1400      0.1677       8.889      12.000        53       1.144
```

```
 15.7000      0.3475        18.420      17.000        53        -0.409
 32.9000      0.6107        32.365      30.000        53        -0.666
 71.4000      0.8851        46.909      48.000        53         0.470

 Chi^2 = 2.31      d.f. = 4        P-value = 0.6785


    Benchmark Dose Computation

Specified effect =            0.1

Risk Type       =       Extra risk

Confidence level =           0.95

          BMD =        4.25219

          BMDL =       3.17375
```

G.3.39.3. *Figure for Selected Model: Weibull*

Weibull Model with 0.95 Confidence Level

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1　**G.3.40. National Toxicology Program ([2006](#)): Gingival Hyperplasia, Squamous, 2 Years**

2　**G.3.40.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	4	0.012	318.867	2.295E+01	1.417E+01	power bound hit (power = 1)
Logistic	4	0.008	320.908	3.594E+01	2.564E+01	
Log-logistic[a]	**4**	**0.015**	**317.969**	**1.838E+01**	**1.044E+01**	**slope bound hit (slope = 1)**
Log-probit	4	0.003	323.633	4.313E+01	2.794E+01	slope bound hit (slope = 1)
Multistage, 5-degree	4	0.012	318.867	2.295E+01	1.417E+01	final ß = 0
Probit	4	0.008	320.687	3.436E+01	2.425E+01	
Weibull	4	0.012	318.867	2.295E+01	1.417E+01	power bound hit (power = 1)
Gamma, unrestricted	3	0.651	307.529	2.480E−01	5.096E−09	unrestricted (power = 0.199)
Log-logistic, unrestricted[b]	3	0.675	307.416	3.710E−01	1.505E−07	unrestricted (slope = 0.265)
Log-probit, unrestricted	3	0.688	307.354	4.688E−01	8.851E−07	unrestricted (slope = 0.156)
Weibull, unrestricted	3	0.663	307.471	3.076E−01	3.210E−08	unrestricted (power = 0.23)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

3
4
5　**G.3.40.2.** *Output for Selected Model: Log-Logistic*

6　National Toxicology Program ([2006](#)): Gingival Hyperplasia, Squamous, 2 Years
7
8
```
9   ==========================================================================
10          Logistic Model. (Version: 2.12; Date: 05/16/2008)
11          Input Data File: C:\1\42_NTP_2006_GingHypSq_LogLogistic_1.(d)
12          Gnuplot Plotting File:  C:\1\42_NTP_2006_GingHypSq_LogLogistic_1.plt
13                                          Tue Feb 16 18:20:29 2010
14   ==========================================================================
15
16   [insert study notes]
17   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the probability function is:
20
21     P[response] = background+(1-background)/[1+EXP(-intercept-
22   slope*Log(dose))]
23
24
25     Dependent variable = DichEff
26     Independent variable = Dose
27     Slope parameter is restricted as slope >= 1
28
29     Total number of observations = 6
```

```
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


              Default Initial Parameter Values
                   background =    0.0188679
                    intercept =      -4.5509
                        slope =            1



        Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -slope
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

              background    intercept

background             1        -0.71

 intercept         -0.71             1




                          Parameter Estimates

                                              95.0% Wald
Confidence Interval
      Variable          Estimate         Std. Err.      Lower Conf. Limit
Upper Conf. Limit
     background         0.117717              *                  *
*
      intercept         -5.10866              *                  *
*
          slope                1              *                  *
*

* - Indicates that this value is not calculated.




                       Analysis of Deviance Table

      Model        Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
       Full model        -149.95          6
     Fitted model       -156.985          2      14.0696         4
0.007076
    Reduced model       -162.631          1      25.3627         5
0.0001186
```

```
AIC:                317.969


                        Goodness  of  Fit
                                                     Scaled
      Dose     Est._Prob.    Expected    Observed    Size    Residual
     ------------------------------------------------------------------
      0.0000     0.1177        6.239       1.000       53     -2.233
      2.1400     0.1290        6.965       7.000       54      0.014
      7.1400     0.1542        8.174      14.000       53      2.216
     15.7000     0.1942       10.292      13.000       53      0.940
     32.9000     0.2641       13.995      15.000       53      0.313
     71.4000     0.3837       20.335      16.000       53     -1.225

   Chi^2 = 12.38     d.f. = 4        P-value = 0.0147


      Benchmark Dose Computation

   Specified effect =            0.1

   Risk Type         =       Extra risk

   Confidence level =           0.95

                 BMD =        18.3832

                BMDL =        10.4359
```

1   **G.3.40.3.** *Figure for Selected Model: Log-Logistic*

Log-Logistic Model with 0.95 Confidence Level

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2
3
4   **G.3.40.4.** *Output for Additional Model Presented: Log-Logistic, Unrestricted*

5   National Toxicology Program (2006): Gingival Hyperplasia, Squamous, 2 Years

6
7
8   ```
     ==
9   Logistic Model. (Version: 2.12; Date: 05/16/2008)
10   Input Data File: C:\1\42_NTP_2006_GingHypSq_LogLogistic_U_1.(d)
11   Gnuplot Plotting File:
12   C:\1\42_NTP_2006_GingHypSq_LogLogistic_U_1.plt
13   Tue Feb 16 18:20:29 2010
14   ==
15
16   [insert study notes]
17   ~~~~~~
18
19   The form of the probability function is:
20
21   P[response] = background+(1-background)/[1+EXP(-intercept-
22   slope*Log(dose))]
23
24
     ```

```
Dependent variable = DichEff
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


             Default Initial Parameter Values
                 background =    0.0188679
                  intercept =     -2.04571
                      slope =     0.299277


        Asymptotic Correlation Matrix of Parameter Estimates

              background      intercept          slope

background            1           -0.3           0.12

 intercept         -0.3              1          -0.91

    slope          0.12          -0.91              1




                        Parameter Estimates

                                              95.0% Wald
Confidence Interval
      Variable          Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
    background        0.0185126              *                  *
*
      intercept        -1.93464              *                  *
*
         slope        0.264795              *                  *
*

* - Indicates that this value is not calculated.




                     Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -149.95         6
   Fitted model        -150.708        3         1.5163        3
0.6785
```

```
  Reduced model          -162.631           1          25.3627         5
0.0001186

            AIC:            307.416


                            Goodness  of  Fit
                                                            Scaled
     Dose      Est._Prob.    Expected    Observed     Size    Residual
    ------------------------------------------------------------------
    0.0000      0.0185        0.981       1.000        53       0.019
    2.1400      0.1659        8.959       7.000        54      -0.717
    7.1400      0.2105       11.155      14.000        53       0.959
   15.7000      0.2447       12.972      13.000        53       0.009
   32.9000      0.2806       14.873      15.000        53       0.039
   71.4000      0.3219       17.059      16.000        53      -0.311

 Chi^2 = 1.53     d.f. = 3       P-value = 0.6750


   Benchmark Dose Computation

Specified effect =              0.1

Risk Type        =        Extra risk

Confidence level =             0.95

           BMD =        0.370958

          BMDL =    1.50494e-007
```
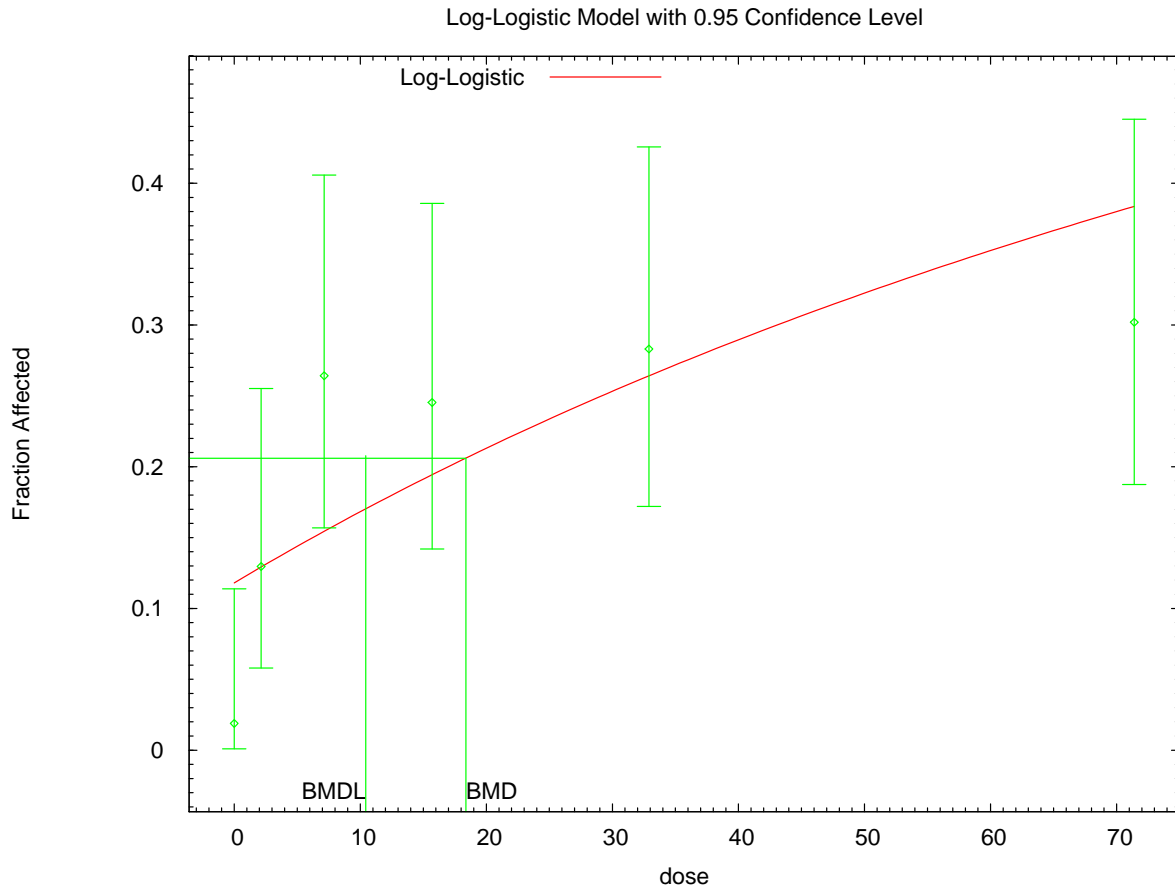
1   **G.3.40.5.** *Figure for Additional Model Presented: Log-Logistic, Unrestricted*

Log-Logistic Model with 0.95 Confidence Level

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2
3
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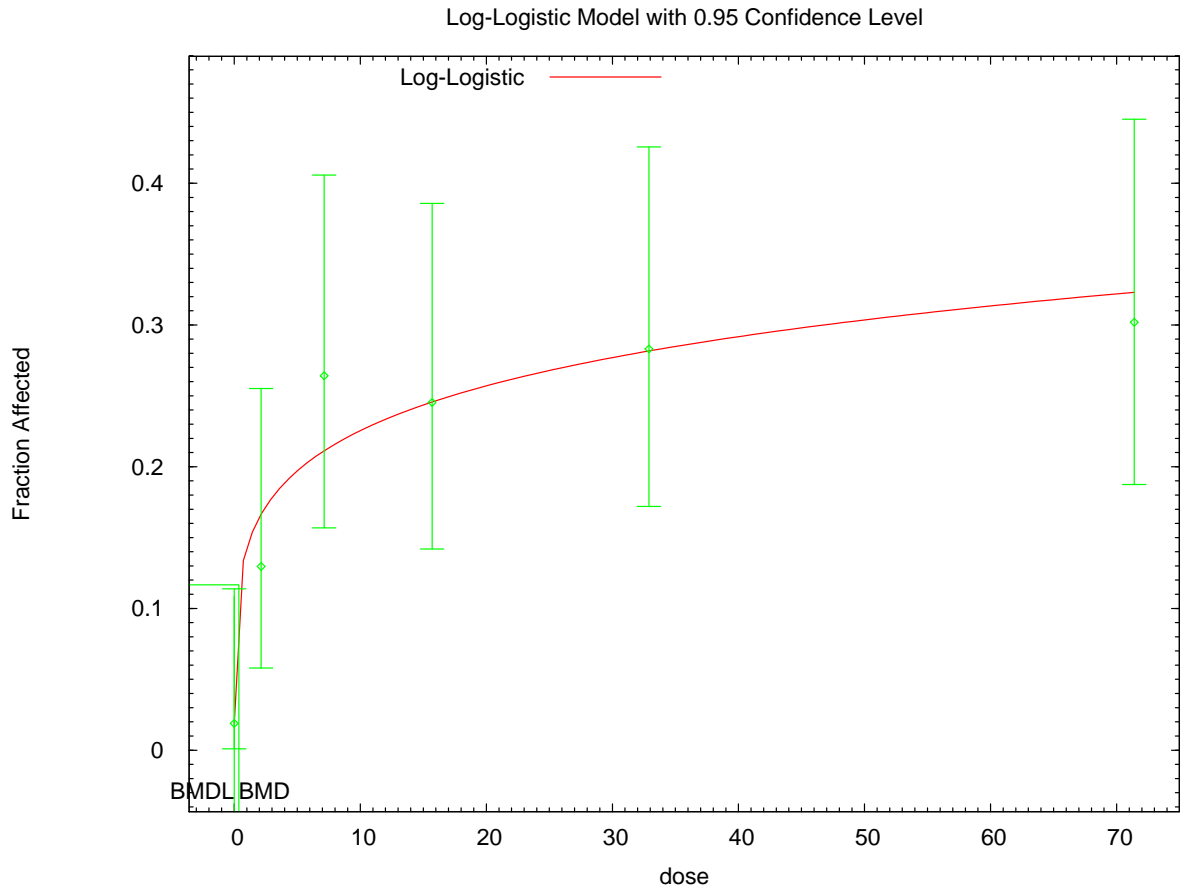
G.3.41. National Toxicology Program ([2006](#)): Hepatocyte Hypertrophy, 2 Years

2 **G.3.41.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	4	<0.001	290.365	1.647E+00	1.340E+00	power bound hit (power = 1)
Logistic	4	<0.001	310.492	4.315E+00	3.650E+00	
Log-logistic	5	0.010	278.082	6.978E−01	5.454E−01	slope bound hit (slope = 1)
Log-probit	4	<0.001	297.168	2.930E+00	2.267E+00	slope bound hit (slope = 1)
Multistage, 5-degree[a]	**4**	**<0.001**	**290.365**	**1.647E+00**	**1.340E+00**	**final ß = 0**
Probit	4	<0.001	313.841	4.564E+00	3.923E+00	
Weibull	4	<0.001	290.365	1.647E+00	1.340E+00	power bound hit (power = 1)
Gamma, unrestricted	4	0.029	275.042	error	error	unrestricted (power = 0.478)
Log-logistic, unrestricted	4	0.005	280.068	6.672E−01	2.939E−01	unrestricted (slope = 0.984)
Log-probit, unrestricted	4	0.006	279.204	7.167E−01	3.322E−01	unrestricted (slope = 0.594)
Weibull, unrestricted	4	0.019	275.967	3.709E−01	1.315E−01	unrestricted (power = 0.64)

[a] Best-fitting model, BMDS output presented in this appendix.

3
4

5 **G.3.41.2.** *Output for Selected Model: Multistage, 5-Degree*

6 National Toxicology Program ([2006](#)): Hepatocyte Hypertrophy, 2 Years
7
8

```
9   ====================================================================
10          Multistage Model. (Version: 3.0;  Date: 05/16/2008)
11          Input Data File: C:\1\43_NTP_2006_HepHyper_Multi5_1.(d)
12          Gnuplot Plotting File:  C:\1\43_NTP_2006_HepHyper_Multi5_1.plt
13                                         Tue Feb 16 18:21:00 2010
14   ====================================================================
15
16   [insert study notes]
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the probability function is:
20
21     P[response] = background + (1-background)*[1-EXP(
22                 -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-
23   beta5*dose^5)]
24
25     The parameter betas are restricted to be positive
26
27
28     Dependent variable = DichEff
29     Independent variable = Dose
30
```

```
Total number of observations = 6
Total number of records with missing values = 0
Total number of parameters in model = 6
Total number of specified parameters = 0
Degree of polynomial = 5


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                 Default Initial Parameter Values
                    Background =    0.232262
                      Beta(1) =    0.045074
                      Beta(2) =           0
                      Beta(3) =           0
                      Beta(4) =           0
                      Beta(5) = 2.59945e-010



         Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -Beta(2)    -Beta(3)    -Beta(4)
-Beta(5)
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

              Background      Beta(1)

Background            1         -0.64

   Beta(1)        -0.64             1




                            Parameter Estimates

                                               95.0% Wald
Confidence Interval
       Variable       Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
     Background      0.0541647             *                  *
*
        Beta(1)      0.0639585             *                  *
*
        Beta(2)             0              *                  *
*
        Beta(3)             0              *                  *
*
        Beta(4)             0              *                  *
*
        Beta(5)             0              *                  *
*
```

```
* - Indicates that this value is not calculated.



                         Analysis of Deviance Table

         Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
        Full model      -129.986         6
       Fitted model     -143.183         2        26.3932      4
2.6361629e-005
      Reduced model     -219.97          1        179.968      5         <.0001


             AIC:          290.365



                            Goodness  of  Fit
                                                            Scaled
        Dose      Est._Prob.    Expected    Observed    Size    Residual
       -------------------------------------------------------------------
        0.0000      0.0542        2.871       0.000       53      -1.742
        2.1400      0.1752        9.458      19.000       54       3.416
        7.1400      0.4009       21.248      19.000       53      -0.630
       15.7000      0.6535       34.635      42.000       53       2.126
       32.9000      0.8847       46.887      41.000       53      -2.532
       71.4000      0.9902       52.479      52.000       53      -0.667


 Chi^2 = 26.48     d.f. = 4        P-value = 0.0000


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type       =      Extra risk

Confidence level =          0.95

          BMD =        1.64733

          BMDL =       1.34007

          BMDU =        2.0581

Taken together, (1.34007, 2.0581 ) is a 90     % two-sided confidence
interval for the BMD
```

1   **G.3.41.3.** *Figure for Selected Model: Multistage, 5-Degree*

Multistage Model with 0.95 Confidence Level
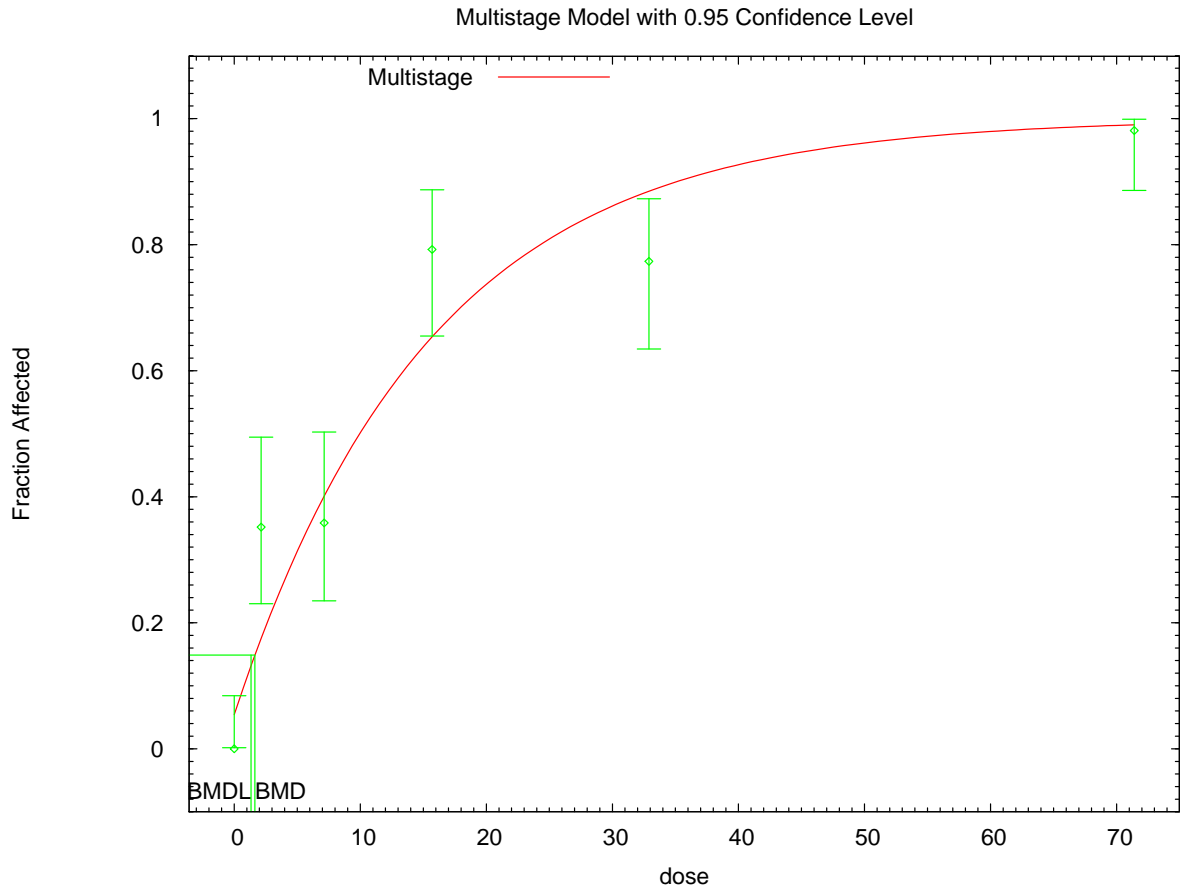
18:21 02/16 2010

2
3

1 **G.3.42. National Toxicology Program ([2006](#)): Necrosis, Liver**

2 **G.3.42.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Logistic	4	0.397	238.314	3.484E+01	2.842E+01	negative intercept (intercept = −2.601)
Log-logistic	4	0.810	235.265	1.791E+01	1.194E+01	slope bound hit (slope = 1)
Log-probit	4	0.290	239.107	3.205E+01	2.382E+01	slope bound hit (slope = 1)
Multistage, 5-degree	4	0.763	235.581	2.019E+01	1.419E+01	final ß = 0
Probit	4	0.445	237.888	3.266E+01	2.637E+01	
Weibull	4	0.763	235.581	2.019E+01	1.419E+01	power bound hit (power = 1)
Gamma, unrestricted	3	0.869	236.344	1.114E+01	3.487E+00	unrestricted (power = 0.599)
Log-logistic, unrestricted	3	0.833	236.483	1.112E+01	3.581E+00	unrestricted (slope = 0.695)
Log-probit, unrestricted[a]	**3**	**0.768**	**236.742**	**1.061E+01**	**3.498E+00**	**unrestricted (slope = 0.367)**
Weibull, unrestricted	3	0.856	236.393	1.117E+01	3.554E+00	unrestricted (power = 0.64)

[a] Best-fitting model, BMDS output presented in this appendix.

3
4
5 **G.3.42.2.** *Output for Selected Model: Log-Probit, Unrestricted*

6 National Toxicology Program ([2006](#)): Necrosis, Liver
7
8
```
9   ====================================================================
10        Probit Model. (Version: 3.1;  Date: 05/16/2008)
11        Input Data File: C:\1\50_NTP_2006_LivNec_LogProbit_U_1.(d)
12        Gnuplot Plotting File:  C:\1\50_NTP_2006_LivNec_LogProbit_U_1.plt
13                                   Tue Feb 16 18:34:31 2010
14   ====================================================================
15
16  NTP_liver_necrosis
17 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19    The form of the probability function is:
20
21    P[response] = Background
22               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
23
24    where CumNorm(.) is the cumulative normal distribution function
25
26
27    Dependent variable = DichEff
28    Independent variable = Dose
29    Slope parameter is not restricted
30
```

```
Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


                  Default Initial (and Specified) Parameter Values
                       background =    0.0188679
                        intercept =    -1.98094
                            slope =    0.316942


          Asymptotic Correlation Matrix of Parameter Estimates

                  background      intercept         slope

background              1          -0.69           0.59


 intercept          -0.69              1          -0.97


    slope            0.59          -0.97              1




                              Parameter Estimates


                                                    95.0% Wald
Confidence Interval
       Variable        Estimate         Std. Err.      Lower Conf. Limit
Upper Conf. Limit
     background       0.0228339        0.0230818          -0.0224057
0.0680734
      intercept        -2.14844         0.527256            -3.18184
-1.11503
          slope        0.367034         0.139055            0.0944904
0.639577




                         Analysis of Deviance Table


     Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -114.813         6
    Fitted model       -115.371         3         1.1157         3
0.7733
   Reduced model       -127.98          1        26.3331         5      <.0001

          AIC:          236.742



                              Goodness   of   Fit
                                                              Scaled
```

```
      Dose      Est._Prob.    Expected    Observed    Size      Residual
  ------------------------------------------------------------------------
     0.0000      0.0228        1.210       1.000        53       -0.193
     2.1400      0.0529        2.858       4.000        54        0.694
     7.1400      0.0979        5.187       4.000        53       -0.549
    15.7000      0.1475        7.819       8.000        53        0.070
    32.9000      0.2116       11.215      10.000        53       -0.409
    71.4000      0.2968       15.729      17.000        53        0.382


 Chi^2 = 1.14      d.f. = 3         P-value = 0.7678



    Benchmark Dose Computation

 Specified effect =          0.1

 Risk Type       =      Extra risk

 Confidence level =         0.95

           BMD =       10.6107

           BMDL =       3.49791
```

1   **G.3.42.3.** *Figure for Selected Model: Log-Probit, Unrestricted*

LogProbit Model with 0.95 Confidence Level
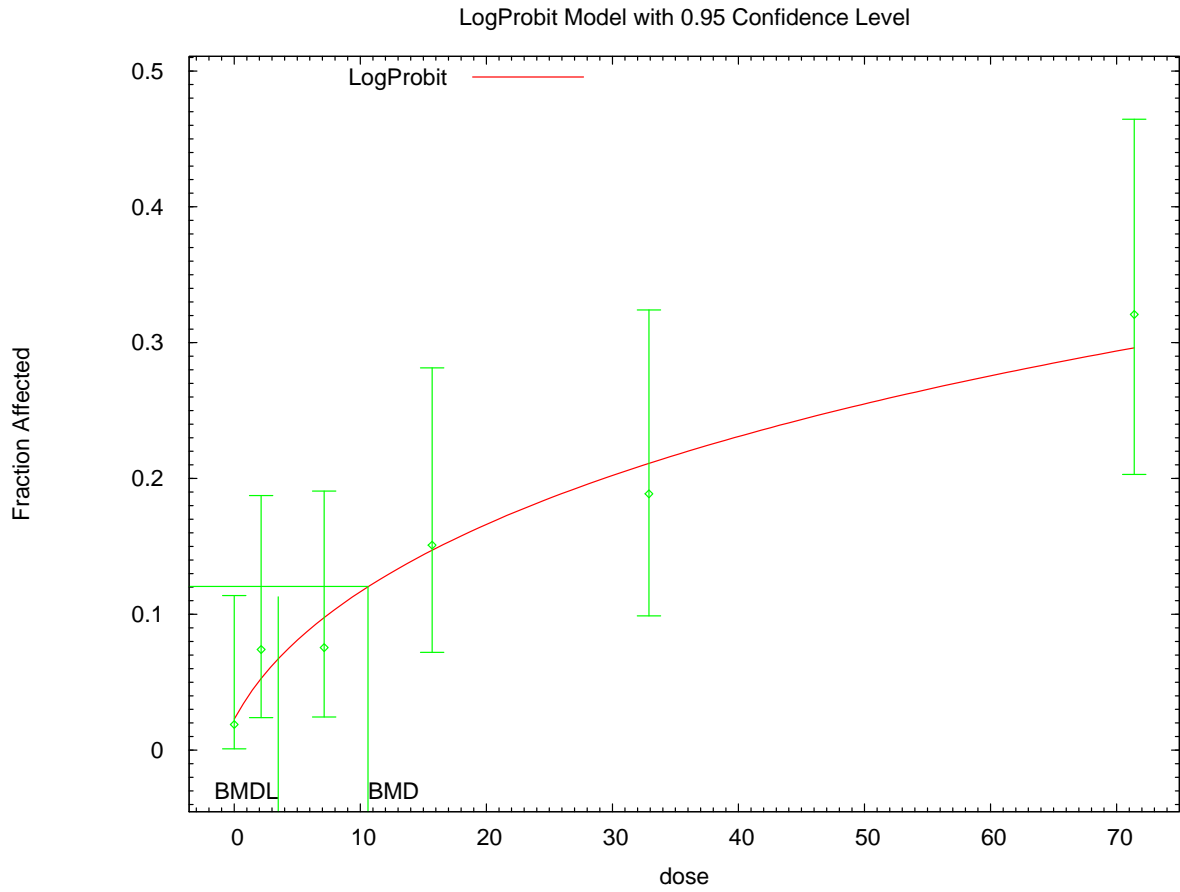
18:34 02/16 2010

2
3
4

1 **G.3.43. National Toxicology Program (2006): Oval Cell Hyperplasia**

2 **G.3.43.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	3	0.072	199.446	8.970E+00	5.499E+00	
Logistic	4	0.069	199.875	9.792E+00	8.245E+00	
Log-logistic	3	0.039	202.012	9.708E+00	7.247E+00	
Log-probit	3	0.068	200.421	9.968E+00	7.758E+00	
Multistage, 5-degree	2	0.066	198.641	5.424E+00	3.514E+00	
Probit[a]	**4**	**0.112**	**198.166**	**9.103E+00**	**7.701E+00**	
Weibull[b]	3	0.075	198.690	7.712E+00	4.692E+00	

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

3
4

5 **G.3.43.2.** *Output for Selected Model: Probit*

6 National Toxicology Program (2006): Oval Cell Hyperplasia
7
8
```
9   ==========================================================================
10         Probit Model. (Version: 3.1;  Date: 05/16/2008)
11         Input Data File: C:\1\53_NTP_2006_OvalHyper_Probit_1.(d)
12         Gnuplot Plotting File:  C:\1\53_NTP_2006_OvalHyper_Probit_1.plt
13                                     Tue Feb 16 19:51:52 2010
14   ==========================================================================
15
16    0
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the probability function is:
20
21     P[response] = CumNorm(Intercept+Slope*Dose),
22
23     where CumNorm(.) is the cumulative normal distribution function
24
25
26     Dependent variable = DichEff
27     Independent variable = Dose
28     Slope parameter is not restricted
29
30     Total number of observations = 6
31     Total number of records with missing values = 0
32     Maximum number of iterations = 250
33     Relative Function Convergence has been set to: 1e-008
34     Parameter Convergence has been set to: 1e-008
35
```

```
                    Default Initial (and Specified) Parameter Values
                         background =             0   Specified
                          intercept =     -1.92612
                             slope =    0.0670004


                Asymptotic Correlation Matrix of Parameter Estimates

                 ( *** The model parameter(s)  -background
                       have been estimated at a boundary point, or have been
        specified by the user,
                       and do not appear in the correlation matrix )

                     intercept          slope

         intercept             1            -0.8

            slope          -0.8             1




                                   Parameter Estimates


                                                        95.0% Wald
        Confidence Interval
             Variable         Estimate         Std. Err.       Lower Conf. Limit
        Upper Conf. Limit
             intercept       -1.82129           0.16954           -2.15359
        -1.489
               slope       0.0767832      0.00835175           0.060414
        0.0931523




                                Analysis of Deviance Table

            Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
           Full model        -92.4898          6
          Fitted model       -97.0832          2       9.18683        4
        0.0566
         Reduced model       -210.191          1       235.402        5        <.0001

              AIC:           198.166



                                   Goodness  of  Fit
                                                                       Scaled
            Dose      Est._Prob.    Expected    Observed     Size      Residual
          ------------------------------------------------------------------------
           0.0000       0.0343        1.817       0.000        53       -1.372
           2.1400       0.0488        2.633       4.000        54        0.864
           7.1400       0.1015        5.379       3.000        53       -1.082
          15.7000       0.2690       14.258      20.000        53        1.779
          32.9000       0.7596       40.256      38.000        53       -0.725
          71.4000       0.9999       52.993      53.000        53        0.082
```

```
Chi^2 = 7.50        d.f. = 4        P-value = 0.1119


    Benchmark Dose Computation

Specified effect =              0.1

Risk Type        =        Extra risk

Confidence level =              0.95

          BMD =          9.1026

          BMDL =         7.7011
```

G.3.43.3. *Figure for Selected Model: Probit*

Probit Model with 0.95 Confidence Level

19:51 02/16 2010
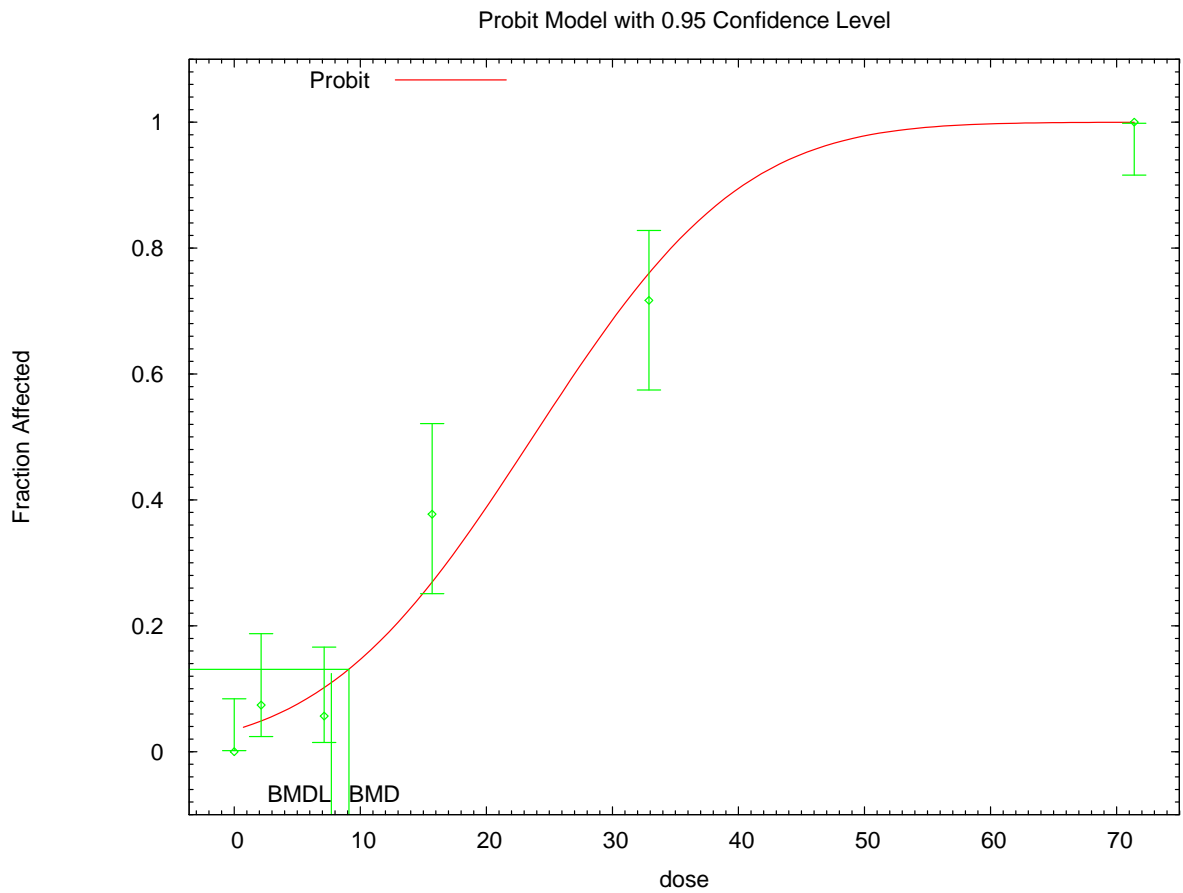
G.3.43.4. *Output for Additional Model Presented: Weibull*

National Toxicology Program ([2006](#)): Oval Cell Hyperplasia

```
   ====================================================================
         Weibull Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
         Input Data File: C:\1\53_NTP_2006_OvalHyper_Weibull_1.(d)
         Gnuplot Plotting File:  C:\1\53_NTP_2006_OvalHyper_Weibull_1.plt
                                       Tue Feb 16 19:51:53 2010
   ====================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose^power)]


   Dependent variable = DichEff
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




                    Default Initial (and Specified) Parameter Values
                        Background =   0.00925926
                             Slope =    0.0044452
                             Power =      1.63009



         Asymptotic Correlation Matrix of Parameter Estimates

               Background        Slope        Power

Background              1        -0.63         0.61

    Slope          -0.63            1        -0.99

    Power           0.61        -0.99            1




                              Parameter Estimates

                                                    95.0% Wald
Confidence Interval
      Variable         Estimate       Std. Err.    Lower Conf. Limit
Upper Conf. Limit
```

```
      Background         0.021258        0.0198428         -0.0176332
0.0601492
         Slope         0.0028715        0.00303327        -0.0030736
0.0088166
         Power          1.76359         0.309457           1.15706
2.37011



                        Analysis of Deviance Table

      Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
    Full model       -92.4898          6
   Fitted model      -96.3448          3       7.70998      3
0.0524
  Reduced model      -210.191          1       235.402      5         <.0001

         AIC:          198.69


                           Goodness  of  Fit
                                                           Scaled
     Dose      Est._Prob.    Expected    Observed    Size    Residual
   ------------------------------------------------------------------
    0.0000      0.0213        1.127       0.000       53     -1.073
    2.1400      0.0320        1.725       4.000       54      1.760
    7.1400      0.1073        5.685       3.000       53     -1.192
   15.7000      0.3234       17.138      20.000       53      0.840
   32.9000      0.7490       39.698      38.000       53     -0.538
   71.4000      0.9953       52.750      53.000       53      0.501

 Chi^2 = 6.92      d.f. = 3       P-value = 0.0746


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =       Extra risk

Confidence level =           0.95

         BMD =        7.71171

         BMDL =       4.69152
```

1   **G.3.43.5.** *Figure for Additional Model Presented: Weibull*

Weibull Model with 0.95 Confidence Level
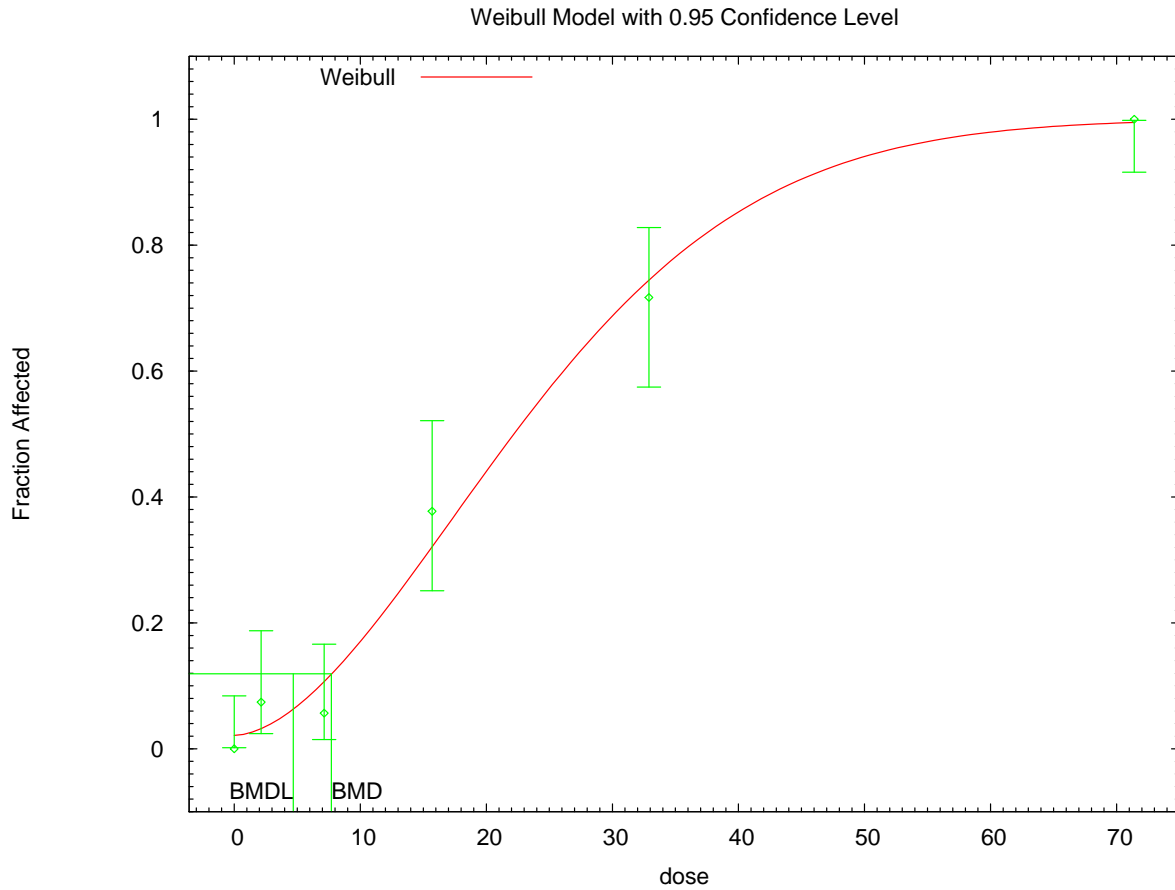
19:51 02/16 2010

2
3
4   **G.3.44. National Toxicology Program (2006): Pigmentation, Liver**

5   **G.3.44.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	3	0.385	197.655	1.547E+00	8.055E−01	
Logistic	4	<0.001	203.517	2.259E+00	1.872E+00	
Log-logistic	3	0.978	195.600	2.212E+00	1.452E+00	
Log-probit[a]	**3**	**0.980**	**195.450**	**2.072E+00**	**1.399E+00**	
Multistage, 5-degree	3	0.210	199.850	9.396E−01	7.079E−01	final ß = 0
Probit	4	<0.001	210.309	2.259E+00	1.916E+00	
Weibull	3	0.290	198.489	1.280E+00	7.518E−01	

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.44.2. *Output for Selected Model: Log-Probit*

National Toxicology Program ([2006](#)): Pigmentation, Liver

```
====================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\1\54_NTP_2006_Pigment_LogProbit_1.(d)
         Gnuplot Plotting File:  C:\1\54_NTP_2006_Pigment_LogProbit_1.plt
                                         Tue Feb 16 19:52:19 2010
====================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = Background
                 + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




   User has chosen the log transformed model


                   Default Initial (and Specified) Parameter Values
                      background =    0.0754717
                       intercept =     -1.91144
                           slope =      1.07385


           Asymptotic Correlation Matrix of Parameter Estimates

               background     intercept        slope

background             1         -0.45         0.35

 intercept         -0.45             1         -0.94

     slope          0.35         -0.94             1




                         Parameter Estimates
```

```
                                                      95.0% Wald
Confidence Interval
       Variable        Estimate       Std. Err.      Lower Conf. Limit
Upper Conf. Limit
      background       0.0735956       0.0343284          0.00631316
0.140878
       intercept       -2.19294        0.400053           -2.97703
-1.40885
          slope        1.25068         0.169731           0.918012
1.58335




                    Analysis of Deviance Table

      Model      Log(likelihood)  # Param's  Deviance  Test d.f.  P-value
    Full model       -94.6177          6
   Fitted model      -94.7248          3       0.214232      3
0.9753
  Reduced model      -210.717          1       232.198       5        <.0001

       AIC:           195.45



                          Goodness  of  Fit
                                                           Scaled
     Dose      Est._Prob.     Expected    Observed    Size   Residual
   ------------------------------------------------------------------
    0.0000      0.0736         3.901       4.000       53     0.052
    2.1400      0.1729         9.338       9.000       54    -0.122
    7.1400      0.6338        33.591      34.000       53     0.117
   15.7000      0.9023        47.822      48.000       53     0.082
   32.9000      0.9863        52.275      52.000       53    -0.325
   71.4000      0.9992        52.959      53.000       53     0.202

 Chi^2 = 0.18     d.f. = 3        P-value = 0.9801


   Benchmark Dose Computation

Specified effect =          0.1

Risk Type        =      Extra risk

Confidence level =          0.95

          BMD =       2.07241

          BMDL =      1.39932
```

1 **G.3.44.3.** *Figure for Selected Model: Log-Probit*

LogProbit Model with 0.95 Confidence Level

19:52 02/16 2010
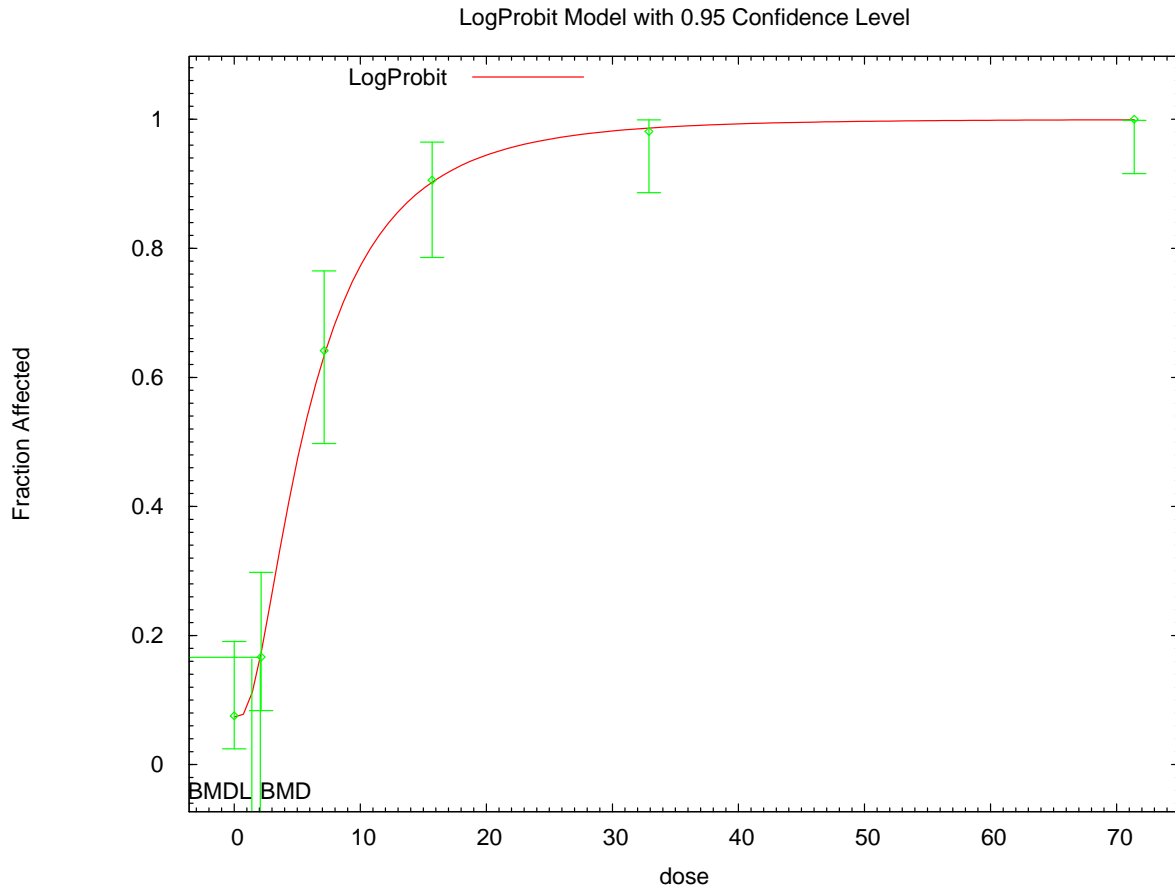
2
3
4 **G.3.45. National Toxicology Program (2006): Toxic Hepatopathy**

5 **G.3.45.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 p-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	4	0.772	185.634	4.668E+00	3.317E+00	
Logistic	4	0.012	198.445	7.070E+00	5.925E+00	
Log-logistic	3	0.362	190.061	5.676E+00	4.040E+00	
Log-probit	3	0.378	189.858	6.061E+00	4.079E+00	
Multistage, 5-degree[a]	**4**	**0.577**	**186.521**	**4.163E+00**	**2.701E+00**	**final ß = 0**
Probit	4	0.019	197.159	6.784E+00	5.712E+00	
Weibull	4	0.745	185.657	4.454E+00	3.159E+00	

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.45.2. *Output for Selected Model: Multistage, 5-Degree*

National Toxicology Program ([2006](#)): Toxic Hepatopathy

```
    ====================================================================
           Multistage Model. (Version: 3.0;  Date: 05/16/2008)
           Input Data File: C:\1\55_NTP_2006_ToxHepa_Multi5_1.(d)
           Gnuplot Plotting File:  C:\1\55_NTP_2006_ToxHepa_Multi5_1.plt
                                         Tue Feb 16 19:52:49 2010
    ====================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-
beta5*dose^5)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 6
 Total number of specified parameters = 0
 Degree of polynomial = 5


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                        Background =            0
                           Beta(1) =            0
                           Beta(2) =            0
                           Beta(3) =            0
                           Beta(4) =            0
                           Beta(5) = 5.40983e+010


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(3)    -Beta(4)
-Beta(5)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )
```

```
                    Beta(1)        Beta(2)

   Beta(1)             1          -0.91

   Beta(2)          -0.91             1




                              Parameter Estimates


                                                        95.0% Wald
Confidence Interval
        Variable          Estimate         Std. Err.      Lower Conf. Limit
Upper Conf. Limit
     Background              0                *                 *
*
         Beta(1)         0.019656            *                 *
*
         Beta(2)         0.00135796          *                 *
*
         Beta(3)             0               *                 *
*
         Beta(4)             0               *                 *
*
         Beta(5)             0               *                 *
*


* - Indicates that this value is not calculated.




                         Analysis of Deviance Table


        Model      Log(likelihood)   # Param's   Deviance   Test d.f.   P-value
      Full model      -89.8076          6
     Fitted model     -91.2606          2        2.90597        4
0.5737
    Reduced model    -218.207           1        256.799        5        <.0001

          AIC:         186.521




                             Goodness  of  Fit
                                                              Scaled
     Dose      Est._Prob.    Expected    Observed    Size    Residual
    -------------------------------------------------------------------------
    0.0000     0.0000         0.000       0.000       53      0.000
    2.1400     0.0471         2.545       2.000       54     -0.350
    7.1400     0.1891        10.021       8.000       53     -0.709
   15.7000     0.4745        25.146      30.000       53      1.335
   32.9000     0.8796        46.616      45.000       53     -0.682
   71.4000     0.9998        52.987      53.000       53      0.113

 Chi^2 = 2.89     d.f. = 4        P-value = 0.5771



  Benchmark Dose Computation
```

```
Specified effect =              0.1

Risk Type        =       Extra risk

Confidence level =              0.95

            BMD =        4.16294

           BMDL =        2.70063

           BMDU =        6.00186

Taken together, (2.70063, 6.00186) is a 90     % two-sided confidence
interval for the BMD
```

G.3.45.3. *Figure for Selected Model: Multistage, 5-Degree*

Multistage Model with 0.95 Confidence Level
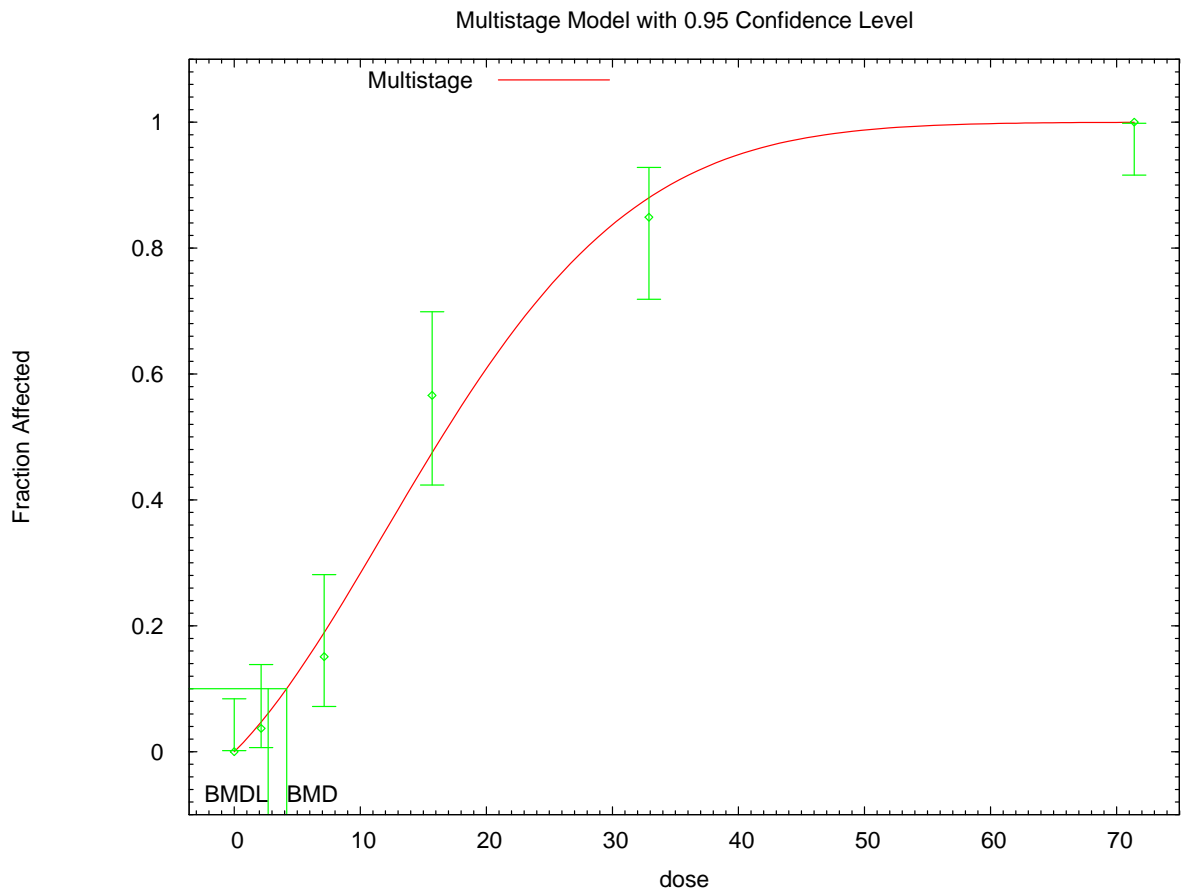
19:52 02/16 2010

G.3.46. Ohsako et al. (2001): Ano-Genital Length, PND 120

2   **G.3.46.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	3	0.019	171.804	5.650E+02	3.785E+02	
Exponential (M3)	3	0.019	171.804	5.650E+02	3.785E+02	power hit bound (*d* = 1)
Exponential (M4)	2	0.117	168.204	2.854E+01	1.054E+01	
Exponential (M5)	1	0.049	169.789	2.948E+01	1.135E+01	
Hill[b]	**2**	**0.148**	**167.727**	**3.722E+01**	**9.752E+00**	***n* lower bound hit (*n* = 1)**
Linear	3	0.018	171.954	5.852E+02	4.047E+02	
Polynomial, 4-degree	3	0.018	171.954	5.852E+02	4.047E+02	
Power	3	0.018	171.954	5.852E+02	4.047E+02	power bound hit (power = 1)
Hill, unrestricted[c]	1	0.055	169.600	5.101E+01	3.066E+00	unrestricted (*n* = 0.502)
Power, unrestricted	2	0.151	167.689	6.200E+01	2.291E+00	unrestricted (power = 0.252)

[a] Constant variance model selected (*p* = 0.165).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

3
4
5   **G.3.46.2.** *Output for Selected Model: Hill*

6   Ohsako et al. (2001): Ano-Genital Length, PND 120
7
8
```
9    =====================================================================
10          Hill Model. (Version: 2.14;  Date: 06/26/2008)
11          Input Data File: C:\1\56_Ohsako_2001_Anogen_HillCV_1.(d)
12          Gnuplot Plotting File:  C:\1\56_Ohsako_2001_Anogen_HillCV_1.plt
13                                       Tue Feb 16 19:53:25 2010
14    =====================================================================
15
16   Figure 7
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the response function is:
20
21     Y[dose] = intercept + v*dose^n/(k^n + dose^n)
22
23
24     Dependent variable = Mean
25     Independent variable = Dose
26     rho is set to 0
27     Power parameter restricted to be greater than 1
28     A constant variance model is fit
29
30     Total number of dose groups = 5
```

```
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                         alpha =      7.27386
                           rho =            0   Specified
                     intercept =       28.905
                             v =      -5.1065
                             n =      1.40226
                             k =      33.9669



          Asymptotic Correlation Matrix of Parameter Estimates


          ( *** The model parameter(s)  -rho     -n
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                   alpha    intercept            v            k

      alpha            1   -2.2e-009    -2.4e-008    -7.2e-009

  intercept    -2.2e-009           1        -0.66         -0.5

          v    -2.4e-008       -0.66            1        -0.11

          k    -7.2e-009        -0.5        -0.11            1




                           Parameter Estimates


                                            95.0% Wald
Confidence Interval
       Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
          alpha        7.08444           1.3634              4.41223
9.75666
       intercept       28.9809         0.745637              27.5195
30.4423
              v       -4.79692         0.983318             -6.72418
-2.86965
              n              1               NA
              k        29.8628          24.4463             -18.0511
77.7767


NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

```
     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev  Scaled
Res.
------      ---  --------     --------   -----------  -----------  ---------
-

    0     12      28.9          29         3.13         2.66      -0.0988
 12.5     10      27.9         27.6         2.5         2.66       0.442
   50     10      25.2          26         3.21         2.66      -0.963
  200     10        26         24.8        2.85         2.66       1.42
  800     12      23.8         24.4        1.56         2.66      -0.726




Model Descriptions for likelihoods calculated


Model A1:         Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2

Model A2:         Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma(i)^2

Model A3:         Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
         Var{e(i)} = Sigma^2


                 Likelihoods of Interest

          Model      Log(likelihood)   # Param's      AIC
          A1          -77.952340           6       167.904680
          A2          -74.703868          10       169.407736
          A3          -77.952340           6       167.904680
        fitted        -79.863340           4       167.726680
          R           -89.824703           2       183.649405


                 Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                 Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df      p-value

  Test 1           30.2417             8        0.0001916
```

```
Test 2                6.49694        4            0.165
Test 3                6.49694        4            0.165
Test 4                3.822          2            0.1479
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

          Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

          BMD =   37.2249

          BMDL =   9.75249

G.3.46.3. *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

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G.3.46.4. *Output for Additional Model Presented: Hill, Unrestricted*

Ohsako et al. (2001): Ano-Genital Length, PND 120

```
=====================================================================
        Hill Model. (Version: 2.14;   Date: 06/26/2008)
        Input Data File: C:\1\56_Ohsako_2001_Anogen_HillCV_U_1.(d)
        Gnuplot Plotting File:  C:\1\56_Ohsako_2001_Anogen_HillCV_U_1.plt
                                    Tue Feb 16 19:53:26 2010
=====================================================================

 Figure 7
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
```

```
rho is set to 0
Power parameter is not restricted
A constant variance model is fit


Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          alpha =      7.27386
                            rho =            0    Specified
                      intercept =       28.905
                              v =      -5.1065
                              n =      1.40226
                              k =      33.9669



          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                  alpha     intercept           v           n           k

     alpha            1     2.1e-009     -1.8e-008    -1.7e-008    1.6e-008

 intercept     2.1e-009            1         0.012       0.0075       -0.13

         v    -1.8e-008        0.012             1         0.98       -0.99

         n    -1.7e-008       0.0075          0.98            1       -0.97

         k     1.6e-008        -0.13         -0.99        -0.97           1




                              Parameter Estimates

                                                        95.0% Wald
Confidence Interval
      Variable         Estimate       Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         alpha          7.06785         1.36021             4.40189
9.73381
      intercept         28.9608        0.755363            27.4803
30.4413
             v         -6.94236         12.2514            -30.9547
17.07
             n         0.501942        0.915162            -1.29174
2.29563
```

```
                   k          131.957         1071.9         -1968.92
2232.84



     Table of Data and Estimated Values of Interest

 Dose        N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------      ---   --------     --------   -----------  -----------   ---------
-

    0    12      28.9          29           3.13         2.66        -0.0727
 12.5   10      27.9         27.3           2.5          2.66         0.72
   50   10      25.2         26.3          3.21          2.66        -1.37
  200   10        26         25.1          2.85          2.66         1.04
  800   12      23.8           24          1.56          2.66        -0.287



Model Descriptions for likelihoods calculated


Model A1:        Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
         Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:        Yi = Mu + e(i)
         Var{e(i)} = Sigma^2


                    Likelihoods of Interest

          Model       Log(likelihood)   # Param's      AIC
          A1          -77.952340              6     167.904680
          A2          -74.703868             10     169.407736
          A3          -77.952340              6     167.904680
       fitted         -79.800035              5     169.600070
          R           -89.824703              2     183.649405


                    Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

```
                        Tests of Interest

    Test      -2*log(Likelihood Ratio)   Test df        p-value

    Test 1              30.2417              8         0.0001916
    Test 2              6.49694              4           0.165
    Test 3              6.49694              4           0.165
    Test 4              3.69539              1          0.05456

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1.  You may want to try a different
model


         Benchmark Dose Computation

Specified effect =              1

Risk Type        =      Estimated standard deviations from the control mean

Confidence level =          0.95

          BMD =        51.0107

          BMDL =       3.06631
```
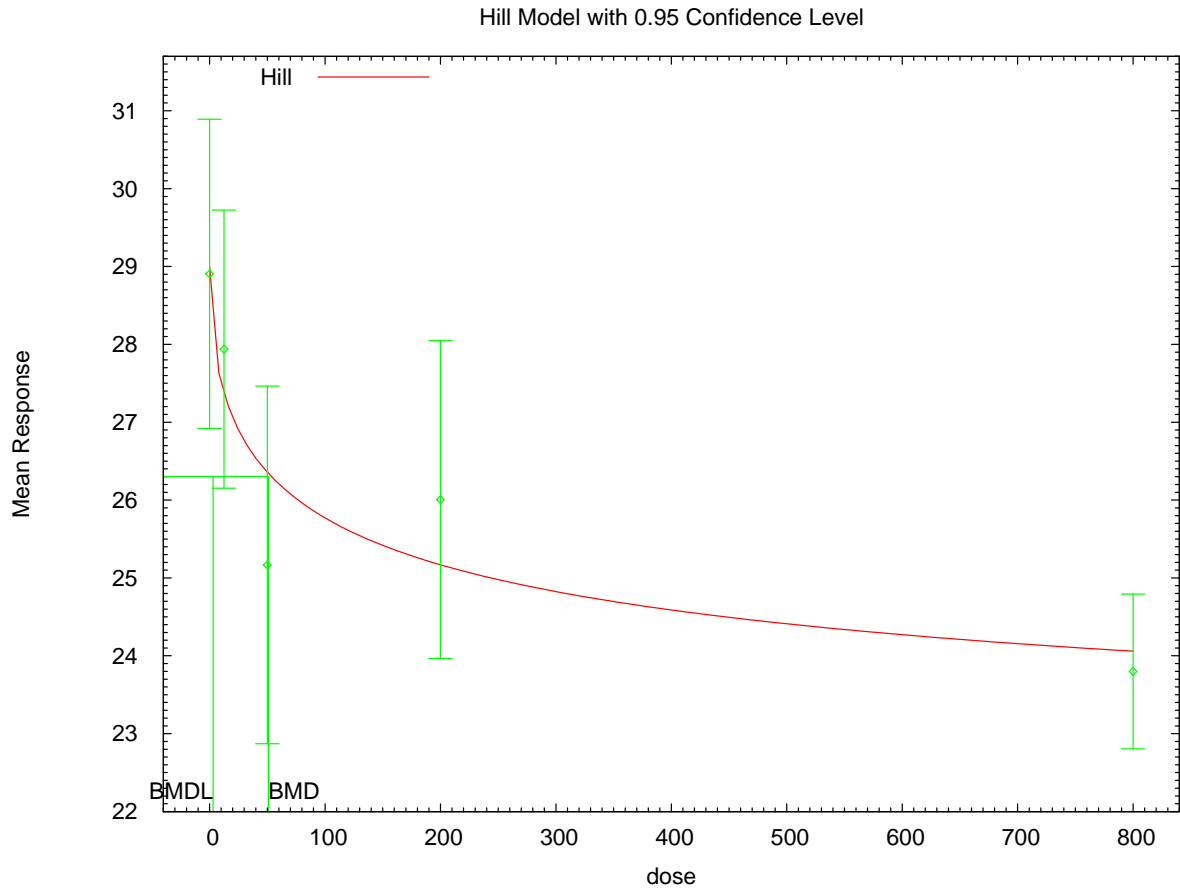
1 **G.3.46.5.** *Figure for Additional Model Presented: Hill, Unrestricted*

Hill Model with 0.95 Confidence Level

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1 **G.3.47. Sewall et al. ([1995](#)): T4 In Serum**

2 **G.3.47.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	3	0.424	205.966	5.762E+01	3.783E+01	
Exponential (M3)	3	0.424	205.966	5.762E+01	3.783E+01	power hit bound ($d = 1$)
Exponential (M5)	2	0.611	206.152	2.523E+01	8.442E+00	power hit bound ($d = 1$)
Hill[b]	**2**	**0.702**	**205.875**	**2.071E+01**	**5.164E+00**	*n* **lower bound hit (***n* **= 1)**
Linear	3	0.332	206.584	6.788E+01	4.858E+01	
Polynomial, 4-degree	3	0.332	206.584	6.788E+01	4.858E+01	
Power	3	0.332	206.584	6.788E+01	4.858E+01	power bound hit (power = 1)
Hill, unrestricted[c]	1	0.844	207.205	1.657E+01	1.903E+00	unrestricted ($n = 0.427$)
Power, unrestricted	2	0.983	205.200	1.658E+01	1.820E+00	unrestricted (power = 0.403)

[a] Constant variance model selected ($p = 0.4078$).
[b] Best-fitting model, BMDS output presented in this appendix.
[c] Alternate model, BMDS output also presented in this appendix.

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4
5 **G.3.47.2.** *Output for Selected Model: Hill*

6 Sewall et al. ([1995](#)): T4 In Serum
7
8
9
10
11
12
13
14

```
      ==========================================================================
             Hill Model. (Version: 2.14;  Date: 06/26/2008)
             Input Data File: C:\1\58_Sewall_1995_T4_HillCV_1.(d)
             Gnuplot Plotting File:  C:\1\58_Sewall_1995_T4_HillCV_1.plt
                                              Tue Feb 16 19:54:30 2010
      ==========================================================================

 Figure 1, Saline noninitiated
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function is:

    Y[dose] = intercept + v*dose^n/(k^n + dose^n)


    Dependent variable = Mean
    Independent variable = Dose
    rho is set to 0
    Power parameter restricted to be greater than 1
    A constant variance model is fit

    Total number of dose groups = 5
    Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                      Default Initial Parameter Values
                            alpha =      33.0913
                              rho =            0    Specified
                        intercept =      30.6979
                                v =     -12.2937
                                n =     0.695384
                                k =      24.6674



           Asymptotic Correlation Matrix of Parameter Estimates


           ( *** The model parameter(s)  -rho     -n
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                   alpha    intercept           v            k

      alpha            1    1.2e-008    4.1e-008    -2.4e-008

   intercept    1.2e-008           1        0.14        -0.66

         v     4.1e-008        0.14           1        -0.76

         k    -2.4e-008       -0.66       -0.76            1




                             Parameter Estimates


                                                   95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
          alpha         29.8807         6.29941             17.5341
42.2274
       intercept        29.9609         1.64749             26.7319
33.1899
            v          -14.2338         4.35645            -22.7723
-5.69537
            n                 1              NA
            k           33.2198         37.0852            -39.4658
105.905


NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.




     Table of Data and Estimated Values of Interest
```

```
  Dose        N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------       ---   --------     --------   -----------  -----------   ---------
-

     0        9      30.7          30         4.66         5.47         0.404
   3.5        9      27.9         28.6        7.17         5.47        -0.399
  10.7        9      25.9         26.5        6.81         5.47        -0.328
    35        9      23.6         22.7        5.38         5.47         0.493
   125        9      18.4         18.7        4.12         5.47        -0.171




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

            Model     Log(likelihood)   # Param's       AIC
            A1          -98.583448          6        209.166896
            A2          -96.590204         10        213.180407
            A3          -98.583448          6        209.166896
          fitted        -98.937315          4        205.874631
            R          -109.013252          2        222.026503


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1             24.8461            8            0.001651
   Test 2             3.98649            4            0.4078
```

```
   Test 3                 3.98649          4            0.4078
   Test 4                 0.707735         2            0.702
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance
model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

         Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

           BMD =   20.7117

          BMDL =   5.16405

1   **G.3.47.3.** *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

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2
3
4   **G.3.47.4.** *Output for Additional Model Presented: Hill, Unrestricted*

5   Sewall et al. (1995): T4 In Serum

6
7
8   ```
     ==
9   Hill Model. (Version: 2.14;   Date: 06/26/2008)
10   Input Data File: C:\1\58_Sewall_1995_T4_HillCV_U_1.(d)
11   Gnuplot Plotting File: C:\1\58_Sewall_1995_T4_HillCV_U_1.plt
12   Tue Feb 16 19:54:31 2010
13   ==
14
15   Figure 1, Saline noninitiated
16   ~~~~~~
17
18   The form of the response function is:
19
20   Y[dose] = intercept + v*dose^n/(k^n + dose^n)
21
22
23   Dependent variable = Mean
24   Independent variable = Dose
     ```

```
rho is set to 0
Power parameter is not restricted
A constant variance model is fit


Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                         alpha =      33.0913
                           rho =            0    Specified
                     intercept =      30.6979
                             v =     -12.2937
                             n =     0.695384
                             k =      24.6674



            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -rho
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                  alpha    intercept          v            n            k

      alpha           1      -0.0004       0.0059       0.0048      -0.0059

  intercept     -0.0004            1       -0.026        -0.44         0.07

          v      0.0059       -0.026            1         0.77           -1

          n      0.0048        -0.44         0.77            1        -0.82

          k     -0.0059         0.07           -1        -0.82            1




                             Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable        Estimate       Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha         29.4396         6.20653              17.2751
41.6042
       intercept        30.6757         1.77521              27.1963
34.155
              v        -141.324          1202.4             -2497.98
2215.33
              n        0.426599        0.262207           -0.0873175
0.940515
```

```
               k            31487          770429        -1.47853e+006
1.5415e+006




      Table of Data and Estimated Values of Interest

 Dose        N    Obs Mean     Est Mean    Obs Std Dev  Est Std Dev   Scaled
Res.
 ------      ---  --------     --------    -----------  -----------   --------
-

    0        9     30.7         30.7          4.66         5.43        0.0123
   3.5       9     27.9         27.8          7.17         5.43        0.0279
  10.7       9     25.9         26.1          6.81         5.43       -0.137
   35        9     23.6         23.3          5.38         5.43        0.132
  125        9     18.4         18.5          4.12         5.43       -0.0354




Model Descriptions for likelihoods calculated


Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                    Likelihoods of Interest

          Model      Log(likelihood)   # Param's      AIC
           A1          -98.583448           6      209.166896
           A2          -96.590204          10      213.180407
           A3          -98.583448           6      209.166896
         fitted        -98.602701           5      207.205403
           R          -109.013252           2      222.026503



                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
```

```
                         Tests of Interest


     Test     -2*log(Likelihood Ratio)  Test df         p-value


     Test 1                  24.8461          8           0.001651
     Test 2                  3.98649          4             0.4078
     Test 3                  3.98649          4             0.4078
     Test 4                0.0385071          1             0.8444


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data


The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here



The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here


The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data



          Benchmark Dose Computation

Specified effect =               1

Risk Type        =       Estimated standard deviations from the control mean

Confidence level =            0.95

           BMD =         16.5689

          BMDL =        1.90347
```

1   **G.3.47.5.** *Figure for Additional Model Presented: Hill, Unrestricted*

Hill Model with 0.95 Confidence Level

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2
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4

1 **G.3.48. Shi et al. ([2007](#)): Estradiol 17B, PE9**

2 **G.3.48.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	3	0.001	395.701	1.729E+01	8.956E+00	
Exponential (M3)	3	0.001	395.701	1.729E+01	8.956E+00	power hit bound ($d = 1$)
Exponential (M4)[a]	**2**	**0.494**	**383.635**	**5.559E−01**	**2.236E−01**	
Exponential (M5)	2	0.494	383.635	5.559E−01	2.236E−01	power hit bound ($d = 1$)
Hill	2	0.773	382.743	4.434E−01	error	*n* lower bound hit ($n = 1$)
Linear	3	0.001	397.484	2.243E+01	1.523E+01	
Polynomial, 4-degree	3	0.001	397.484	2.243E+01	1.523E+01	
Power	3	0.001	397.484	2.243E+01	1.523E+01	power bound hit (power = 1)
Hill, unrestricted	1	0.874	384.251	3.998E−01	error	unrestricted ($n = 0.616$)
Power, unrestricted	2	0.506	383.589	3.409E−01	5.002E−03	unrestricted (power = 0.155)

[a] Best-fitting model, BMDS output presented in this appendix.

3
4

5 **G.3.48.2.** *Output for Selected Model: Exponential (M4)*

6 Shi et al. ([2007](#)): Estradiol 17B, PE9
7
8
```
9   =====================================================================
10          Exponential Model. (Version: 1.61;  Date: 7/24/2009)
11          Input Data File: C:\1\59_Shi_2007_Estradiol_Exp_1.(d)
12          Gnuplot Plotting File:
13                                      Tue Feb 16 19:55:06 2010
14   =====================================================================
15
16   Figure 4 PE9 only
17 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19    The form of the response function by Model:
20       Model 2:     Y[dose] = a * exp{sign * b * dose}
21       Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
22       Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
23       Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
24
25     Note: Y[dose] is the median response for exposure = dose;
26           sign = +1 for increasing trend in data;
27           sign = -1 for decreasing trend.
28
29       Model 2 is nested within Models 3 and 4.
30       Model 3 is nested within Model 5.
31       Model 4 is nested within Model 5.
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


MLE solution provided: Exact


                    Initial Parameter Values

                    Variable          Model 4
                    --------          --------
                      lnalpha           2.65881
                          rho          0.913414
                            a               108
                            b          0.136287
                            c          0.340136
                            d                 1




                    Parameter Estimates

                    Variable          Model 4
                    --------          -------
                      lnalpha           1.81331
                          rho           1.12126
                            a           100.526
                            b           1.53823
                            c          0.431796
                            d                 1


          Table of Stats From Input Data

     Dose      N        Obs Mean      Obs Std Dev
     -----    ---      ----------    -------------
        0     10         102.9           41.41
    0.143     10         86.19           19.58
    0.714     10         63.33           29.36
     7.14     10          48.1           18.82
     28.6     10         38.57           22.59



                 Estimated Values of Interest

      Dose      Est Mean       Est Std     Scaled Residual
     ------    ----------     ---------    ----------------
```

```
      0           100.5         32.83              0.2245
   0.143           89.25        30.71             -0.3147
   0.714           62.45        25.14              0.1108
    7.14           43.41         20.5              0.723
    28.6           43.41         20.5             -0.7458




   Other models for which likelihoods are calculated:

      Model A1:         Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma^2

      Model A2:         Yij = Mu(i) + e(ij)
                 Var{e(ij)} = Sigma(i)^2

      Model A3:         Yij = Mu(i) + e(ij)
                 Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

      Model  R:         Yij = Mu + e(i)
                 Var{e(ij)} = Sigma^2



                           Likelihoods of Interest

                 Model      Log(likelihood)      DF         AIC
                 -------    ----------------     ----    ------------
                   A1         -188.3615            6        388.7231
                   A2          -183.667           10        387.3339
                   A3         -186.1132            7        386.2263
                    R         -203.3606            2        410.7211
                    4         -186.8176            5        383.6352



   Additive constant for all log-likelihoods =      -45.95.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                           Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 6a: Does Model 4 fit the data? (A3 vs 4)



                           Tests of Interest

    Test          -2*log(Likelihood Ratio)         D. F.         p-value
    --------      ------------------------         ------      --------------
    Test 1                   39.39                    8           < 0.0001
    Test 2                   9.389                    4            0.05208
    Test 3                   4.892                    3            0.1798
```

```
   Test 6a                                1.409              2                0.4944
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose
levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous
variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled
variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems
to adequately describe the data.

Benchmark Dose Computations:

   Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

   Confidence Level = 0.950000

                BMD =   0.555948

               BMDL =   0.223612

1   **G.3.48.3.** *Figure for Selected Model: Exponential (M4)*

Exponential_beta Model 4 with 0.95 Confidence Level

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G.3.49. Smialowicz et al. ([2008](#)): PFC per 10^6 Cells

G.3.49.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	3	0.048	903.586	8.234E+01	4.833E+01	
Exponential (M3)	3	0.048	903.586	8.234E+01	4.833E+01	power hit bound ($d = 1$)
Exponential (M4)	2	0.019	905.578	8.032E+01	6.220E+00	
Exponential (M5)	2	0.019	905.578	8.032E+01	6.220E+00	power hit bound ($d = 1$)
Hill	2	0.026	904.975	1.617E+01	2.214E+00	*n* lower bound hit ($n = 1$)
Linear	3	0.016	905.992	1.450E+02	1.102E+02	
Polynomial, 4-degree	2	<0.0001	1,198.471	1.375E+03	3.331E+01	
Power[a]	3	0.016	905.992	1.450E+02	1.102E+02	power bound hit (power = 1)
Hill, unrestricted	1	0.183	901.442	8.297E+00	4.172E−01	unrestricted ($n = 0.266$)
Power, unrestricted[b]	**2**	**0.446**	**899.282**	**7.676E+00**	**4.087E−01**	**unrestricted (power = 0.249)**

[a] Alternate model, BMDS output also presented in this appendix.
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.49.2. *Output for Selected Model: Power, Unrestricted*

Smialowicz et al. ([2008](#)): PFC per 10^6 Cells

```
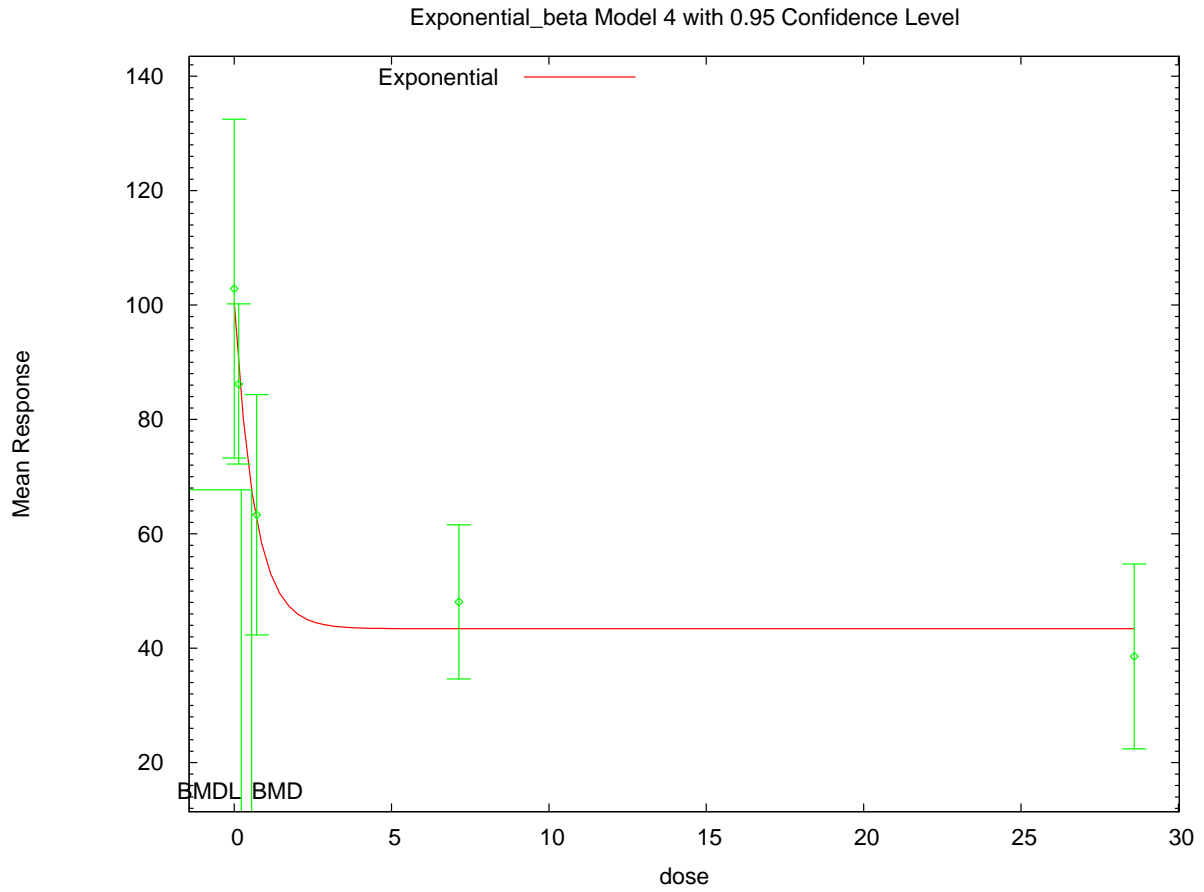   =====================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\60_Smial_2008_PFCcells_PwrCV_U_1.(d)
         Gnuplot Plotting File:  C:\1\60_Smial_2008_PFCcells_PwrCV_U_1.plt
                                     Tue Feb 16 19:55:53 2010
   =====================================================================

 Anti Response to SRBCs, PFC per 10to6 cells, Table 4
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The power is not restricted
   A constant variance model is fit

   Total number of dose groups = 5
```

```
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




                      Default Initial Parameter Values
                              alpha =       232385
                                rho =            0    Specified
                            control =         1491
                              slope =     -384.362
                              power =     0.215085



              Asymptotic Correlation Matrix of Parameter Estimates


               ( *** The model parameter(s)  -rho
                     have been estimated at a boundary point, or have been
   specified by the user,
                     and do not appear in the correlation matrix )

                      alpha       control         slope          power

       alpha             1    -1.5e-009     -8.2e-009      -1.1e-008

     control     -1.5e-009            1         -0.79          -0.65

       slope     -8.2e-009        -0.79             1           0.96

       power     -1.1e-008        -0.65          0.96              1




                              Parameter Estimates


                                                      95.0% Wald
   Confidence Interval
         Variable        Estimate        Std. Err.     Lower Conf. Limit
   Upper Conf. Limit
           alpha          220294          38061.1             145696
   294893
          control         1470.38          124.07            1227.21
   1713.55
            slope        -282.777          145.113           -567.193
   1.64025
            power        0.248621         0.0856348          0.0807799
   0.416462




      Table of Data and Estimated Values of Interest

    Dose      N    Obs Mean     Est Mean   Obs Std Dev   Est Std Dev   Scaled
   Res.
   ------    ---   --------     --------   -----------   -----------   ---------
   -
```

```
     0    15  1.49e+003    1.47e+003          716          469          0.17
  1.07    14  1.13e+003    1.18e+003          171          469         -0.429
  10.7    15        945          961          516          469         -0.129
   107    15        677          567          465          469          0.91
   321     8        161          283          117          469         -0.735
```

Model Descriptions for likelihoods calculated

Model A1:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:   Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model R: Yi = Mu + e(i)
          Var{e(i)} = Sigma^2

                    Likelihoods of Interest

           Model   Log(likelihood)   # Param's   AIC
            A1   -444.832859   6   901.665718
            A2   -425.402825   10   870.805651
            A3   -444.832859   6   901.665718
         fitted   -445.641102   4   899.282205
            R   -463.753685   2   931.507371

                    Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

  Test   -2*log(Likelihood Ratio) Test df   p-value

  Test 1   76.7017   8   <.0001
  Test 2   38.8601   4   <.0001
  Test 3   38.8601   4   <.0001
  Test 4   1.61649   2   0.4456

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
```

```
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  Consider running a
non-homogeneous variance model

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data



              Benchmark Dose Computation

Specified effect =              1

Risk Type       =     Estimated standard deviations from the control mean

Confidence level =         0.95

           BMD = 7.67564


           BMDL = 0.408661
```

1   **G.3.49.3.** *Figure for Selected Model: Power, Unrestricted*

Power Model with 0.95 Confidence Level

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2
3
4   **G.3.49.4.** *Output for Additional Model Presented: Power*

5   Smialowicz et al. (2008): PFC per 10^6 Cells

6
7
8
9
```
   ====================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\60_Smial_2008_PFCcells_PwrCV_1.(d)
         Gnuplot Plotting File:  C:\1\60_Smial_2008_PFCcells_PwrCV_1.plt
                                      Tue Feb 16 19:55:53 2010
   ====================================================================

 Anti Response to SRBCs, PFC per 10to6 cells, Table 4
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function is:

    Y[dose] = control + slope * dose^power


    Dependent variable = Mean
    Independent variable = Dose
```

```
rho is set to 0
The power is restricted to be greater than or equal to 1
A constant variance model is fit

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          alpha =        232385
                            rho =             0   Specified
                        control =          1491
                          slope =      -2925.99
                          power =     -0.136613



          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -rho     -power
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

                    alpha        control         slope

     alpha              1     3.6e-009      -1.2e-008

   control     3.6e-009             1          -0.53

     slope    -1.2e-008         -0.53              1




                              Parameter Estimates

                                                       95.0% Wald
Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         alpha           250878          43345.1               165923
335833
       control          1176.24          72.2586              1034.61
1317.86
         slope         -3.45384         0.592114             -4.61436
-2.29332
         power                1               NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

```
       Table of Data and Estimated Values of Interest

  Dose        N    Obs Mean     Est Mean    Obs Std Dev   Est Std Dev    Scaled
  Res.
  ------      ---  --------     --------    -----------   -----------    ---------
  -


     0    15  1.49e+003   1.18e+003         716           501            2.43
  1.07    14  1.13e+003   1.17e+003         171           501          -0.325
  10.7    15         945   1.14e+003         516           501           -1.5
   107    15         677        807         465           501             -1
   321     8         161       67.6         117           501          0.528




  Model Descriptions for likelihoods calculated


  Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

  Model  R:        Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                    Likelihoods of Interest

             Model     Log(likelihood)    # Param's      AIC
              A1         -444.832859          6       901.665718
              A2         -425.402825         10       870.805651
              A3         -444.832859          6       901.665718
           fitted        -449.996183          3       905.992366
              R          -463.753685          2       931.507371


                    Explanation of Tests

  Test 1:  Do responses and/or variances differ among Dose levels?
           (A2 vs. R)
  Test 2:  Are Variances Homogeneous? (A1 vs A2)
  Test 3:  Are variances adequately modeled? (A2 vs. A3)
  Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
  (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

    Test    -2*log(Likelihood Ratio)  Test df        p-value

    Test 1              76.7017            8           <.0001
```

```
Test 2                38.8601          4            <.0001
Test 3                38.8601          4            <.0001
Test 4                10.3266          3            0.01598
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. Consider running a
non-homogeneous variance model

The p-value for Test 3 is less than .1. You may want to consider a
different variance model

The p-value for Test 4 is less than .1. You may want to try a different
model

                     Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

              BMD = 145.02

           BMDL = 110.161

```

1 **G.3.49.5.** *Figure for Additional Model Presented: Power*

Power Model with 0.95 Confidence Level



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**G.3.50. Smialowicz et al. (2008): PFC per Spleen**

2 **G.3.50.1.** *Summary Table of BMDS Modeling Results*

| Model | Degrees of freedom | $\chi^2$ *p*-value | AIC | BMD (ng/kg-day) | BMDL (ng/kg-day) | Notes |
|---|---|---|---|---|---|---|
| Exponential (M2) | 3 | 0.133 | 377.395 | 1.320E+02 | 8.431E+01 | |
| Exponential (M3) | 3 | 0.133 | 377.395 | 1.320E+02 | 8.431E+01 | power hit bound (*d* = 1) |
| Exponential (M4) | 3 | 0.133 | 377.395 | 1.320E+02 | 8.184E+01 | |
| Exponential (M5) | 2 | 0.061 | 379.395 | 1.320E+02 | 8.184E+01 | power hit bound (*d* = 1) |
| Hill | 2 | 0.069 | 379.150 | 1.401E+02 | error | *n* lower bound hit (*n* = 1) |
| Linear | 3 | 0.044 | 379.895 | 2.151E+02 | 1.704E+02 | |
| Polynomial, 4-degree | 3 | 0.044 | 379.895 | 2.151E+02 | 1.704E+02 | |
| Power[a] | 3 | 0.044 | 379.895 | 2.151E+02 | 1.704E+02 | power bound hit (power = 1) |
| Hill, unrestricted | 2 | <0.0001 | 441.885 | 7.545E−23 | error | unrestricted (*n* = 0.038) |
| **Power, unrestricted[b]** | **2** | **0.230** | **376.738** | **9.374E+01** | **2.088E+01** | **unrestricted (power = 0.418)** |

[a] Alternate model, BMDS output also presented in this appendix.
[b] Best-fitting model, BMDS output presented in this appendix.

3
4
5 **G.3.50.2.** *Output for Selected Model: Power, Unrestricted*

6 Smialowicz et al. (2008): PFC per Spleen
7
8
```
9   ===
10   Power Model. (Version: 2.15; Date: 04/07/2008)
11   Input Data File: C:\1\61_Smial_2008_PFCspleen_Pwr_U_1.(d)
12   Gnuplot Plotting File: C:\1\61_Smial_2008_PFCspleen_Pwr_U_1.plt
13   Tue Feb 16 19:56:26 2010
14   ===
15
16   Anti Response to SRBCs - PFC x 10 to the 4 per spleen, Table 4
17   ~~~~~~
18
19   The form of the response function is:
20
21   Y[dose] = control + slope * dose^power
22
23
24   Dependent variable = Mean
25   Independent variable = Dose
26   The power is not restricted
27   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
28
29   Total number of dose groups = 5
30   Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                      Default Initial Parameter Values
                            lalpha =      4.76607
                               rho =            0
                           control =         27.8
                             slope =     -7.21601
                             power =     0.213905


          Asymptotic Correlation Matrix of Parameter Estimates

                     lalpha         rho       control       slope        power

      lalpha              1       -0.98          0.25       -0.27        -0.23

         rho          -0.98           1         -0.31        0.28         0.23

     control           0.25       -0.31             1       -0.81        -0.74

       slope          -0.27        0.28         -0.81           1         0.99

       power          -0.23        0.23         -0.74        0.99            1




                               Parameter Estimates


                                                          95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
          lalpha        0.747155          1.0244             -1.26063
2.75494
             rho         1.36972        0.357098              0.66982
2.06962
         control         25.1733         2.93169              19.4273
30.9193
           slope        -1.98465         1.82113               -5.554
1.5847
           power        0.417867        0.141932             0.139686
0.696048



     Table of Data and Estimated Values of Interest

 Dose        N    Obs Mean      Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
 ------      ---  --------      --------   -----------  -----------   ---------
 -

    0        15       27.8          25.2         13.4         13.2       0.769
```

```
1    1.07    14        21       23.1        13.6        12.5       -0.639
2    10.7    15      17.6       19.8         9.4        11.2       -0.768
3     107    15      12.6       11.2         8.7        7.59        0.721
4     321     8         3       3.04         3.1        3.11      -0.0353
5
6
7
8    Model Descriptions for likelihoods calculated
9
10
11   Model A1:          Yij = Mu(i) + e(ij)
12            Var{e(ij)} = Sigma^2
13
14   Model A2:          Yij = Mu(i) + e(ij)
15            Var{e(ij)} = Sigma(i)^2
16
17   Model A3:          Yij = Mu(i) + e(ij)
18            Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
19      Model A3 uses any fixed variance parameters that
20      were specified by the user
21
22   Model  R:          Yi = Mu + e(i)
23            Var{e(i)} = Sigma^2
24
25
26                       Likelihoods of Interest
27
28             Model      Log(likelihood)    # Param's      AIC
29              A1          -190.565019           6      393.130038
30              A2          -181.476284          10      382.952569
31              A3          -181.900030           7      377.800059
32           fitted         -183.369059           5      376.738118
33              R          -204.636496           2      413.272993
34
35
36                      Explanation of Tests
37
38   Test 1:  Do responses and/or variances differ among Dose levels?
39           (A2 vs. R)
40   Test 2:  Are Variances Homogeneous? (A1 vs A2)
41   Test 3:  Are variances adequately modeled? (A2 vs. A3)
42   Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
43   (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)
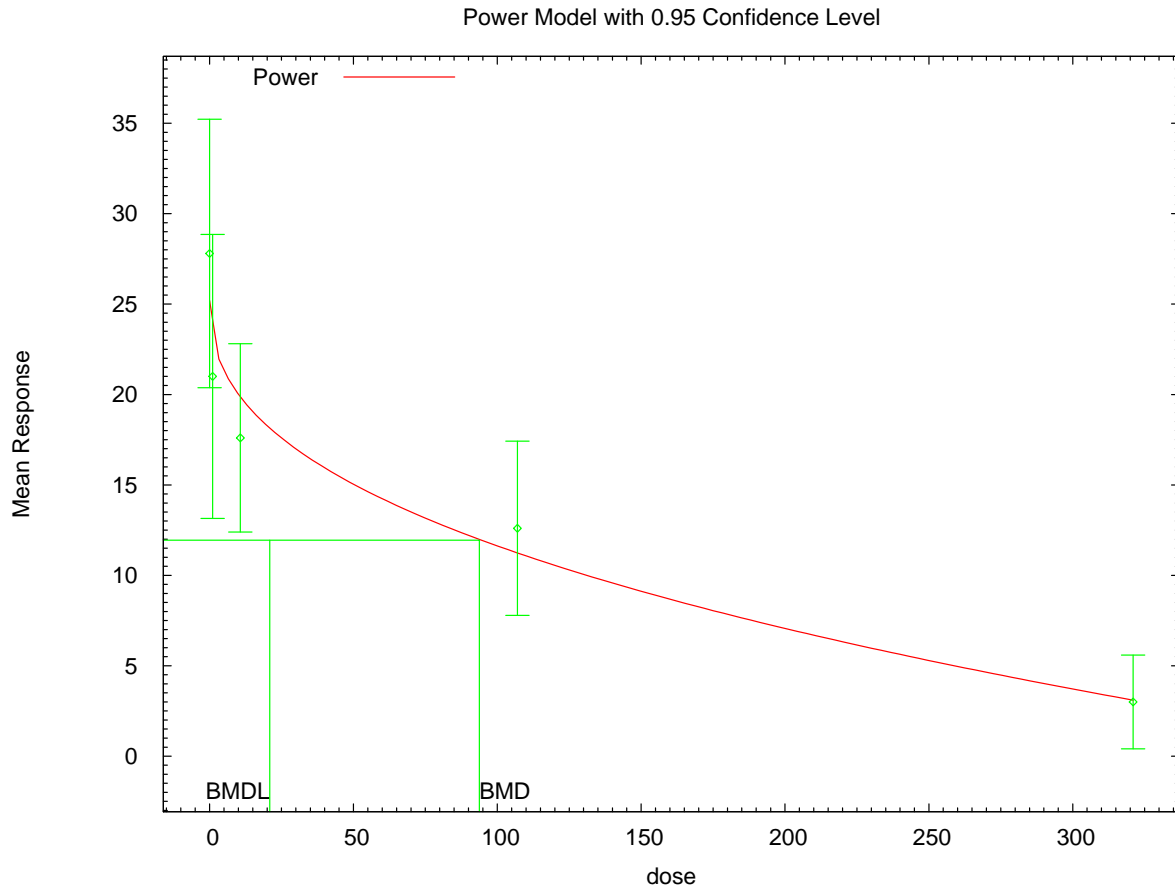44
45                      Tests of Interest
46
47     Test    -2*log(Likelihood Ratio)  Test df       p-value
48
49    Test 1              46.3204          8            <.0001
50    Test 2              18.1775          4          0.001139
51    Test 3              0.84749          3            0.8381
52    Test 4              2.93806          2            0.2301
53
54   The p-value for Test 1 is less than .05.  There appears to be a
55   difference between response and/or variances among the dose levels
56   It seems appropriate to model the data
57
```

```
1    The p-value for Test 2 is less than .1.  A non-homogeneous variance
2    model appears to be appropriate
3
4    The p-value for Test 3 is greater than .1.  The modeled variance appears
5     to be appropriate here
6
7    The p-value for Test 4 is greater than .1.  The model chosen seems
8    to adequately describe the data
9
10
11                   Benchmark Dose Computation
12
13   Specified effect =              1
14
15   Risk Type       =      Estimated standard deviations from the control mean
16
17   Confidence level =          0.95
18
19              BMD = 93.7416
20
21
22            BMDL = 20.8758
23
24
```

1 **G.3.50.3.** *Figure for Selected Model: Power, Unrestricted*

Power Model with 0.95 Confidence Level

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2
3
4 **G.3.50.4.** *Output for Additional Model Presented: Power*

5 Smialowicz et al. ([2008](#)): PFC per Spleen

6
7
8
9
10
11
12
13

```
 ========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\61_Smial_2008_PFCspleen_Pwr_1.(d)
         Gnuplot Plotting File:  C:\1\61_Smial_2008_PFCspleen_Pwr_1.plt
                                        Tue Feb 16 19:56:25 2010
 ========================================================================

 Anti Response to SRBCs - PFC x 10 to the 4 per spleen, Table 4
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the response function is:

    Y[dose] = control + slope * dose^power


    Dependent variable = Mean
    Independent variable = Dose
```

14
15
16
17
18
19
20
21
22
23
24

```
The power is restricted to be greater than or equal to 1
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          lalpha =        4.76607
                             rho =              0
                         control =           27.8
                           slope =       -54.5244
                           power =      -0.136501



           Asymptotic Correlation Matrix of Parameter Estimates

             ( *** The model parameter(s)  -power
                   have been estimated at a boundary point, or have been
specified by the user,
                   and do not appear in the correlation matrix )

                  lalpha            rho          control          slope

     lalpha            1          -0.98             0.16          -0.48

        rho        -0.98              1            -0.25           0.54

    control         0.16          -0.25                1          -0.88

      slope        -0.48           0.54            -0.88              1




                              Parameter Estimates

                                                          95.0% Wald
Confidence Interval
        Variable         Estimate         Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          lalpha         0.474614          1.09569              -1.6729
2.62213
             rho          1.48709         0.385029             0.732449
2.24173
         control          21.3571          1.69233              18.0402
24.674
           slope       -0.0574184       0.00632057           -0.0698064
-0.0450303
           power                1               NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

```
      Table of Data and Estimated Values of Interest

 Dose        N    Obs Mean    Est Mean   Obs Std Dev   Est Std Dev   Scaled
Res.
 ------      ---  --------    --------   -----------   -----------   ---------
-

    0     15      27.8        21.4        13.4          12.3          2.02
 1.07    14        21        21.3        13.6          12.3        -0.0898
 10.7    15      17.6        20.7         9.4          12.1         -1.01
  107    15      12.6        15.2         8.7           9.6         -1.05
  321     8         3        2.93         3.1          2.82         0.0745



Model Descriptions for likelihoods calculated


Model A1:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:          Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:          Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                  Likelihoods of Interest

          Model      Log(likelihood)    # Param's       AIC
           A1         -190.565019            6        393.130038
           A2         -181.476284           10        382.952569
           A3         -181.900030            7        377.800059
         fitted       -185.947278            4        379.894555
            R         -204.636496            2        413.272993


                  Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                  Tests of Interest
```

```
     Test    -2*log(Likelihood Ratio)  Test df        p-value

     Test 1               46.3204          8            <.0001
     Test 2               18.1775          4          0.001139
     Test 3               0.84749          3            0.8381
     Test 4                8.0945          3            0.0441
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
 to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different
model

                  Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

             BMD = 215.073

           BMDL = 170.412

1 **G.3.50.5.** *Figure for Additional Model Presented: Power*

Power Model with 0.95 Confidence Level

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G.3.51. Smith et al. ([1976](#)): Cleft Palate in Pups

G.3.51.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	3	0.4203	69.78	6.184E+02	2.205E+02	
Logistic	4	0.5057	68.90	9.754E+02	7.256E+02	
Log-logistic [a]	**3**	**0.4194**	**69.82**	**6.816E+02**	**1.842E+02**	
Log-probit	3	0.4132	69.89	7.341E+02	3.927E+02	
Multistage, 5th degree	3	0.4528	69.43	4.829E+02	2.277E+02	
Probit	4	0.5721	68.33	8.688E+02	6.580E+02	
Weibull	3	0.43	69.68	5.908E+02	2.223E+02	
Gamma, unrestricted	3	0.4203	69.78	6.184E+02	1.227E+02	
Log-logistic, unrestricted	3	0.4194	69.82	6.816E+02	1.705E+02	
Log-probit, unrestricted	3	0.4133	69.89	7.341E+02	1.767E+02	
Weibull, unrestricted	3	0.43	69.68	5.908E+02	1.432E+02	

[a] Best-fitting model, BMDS output presented in this appendix.

G.3.51.2. *Output for Selected Model: Log-Logistic*

```
=====================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File:
C:\USEPA\BMDS21\1a\76_Smith_1976_cleft_palate_LogLogistic_1.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\1a\76_Smith_1976_cleft_palate_LogLogistic_1.plt
                                  Thu Sep 01 12:46:35 2011
 =====================================================================
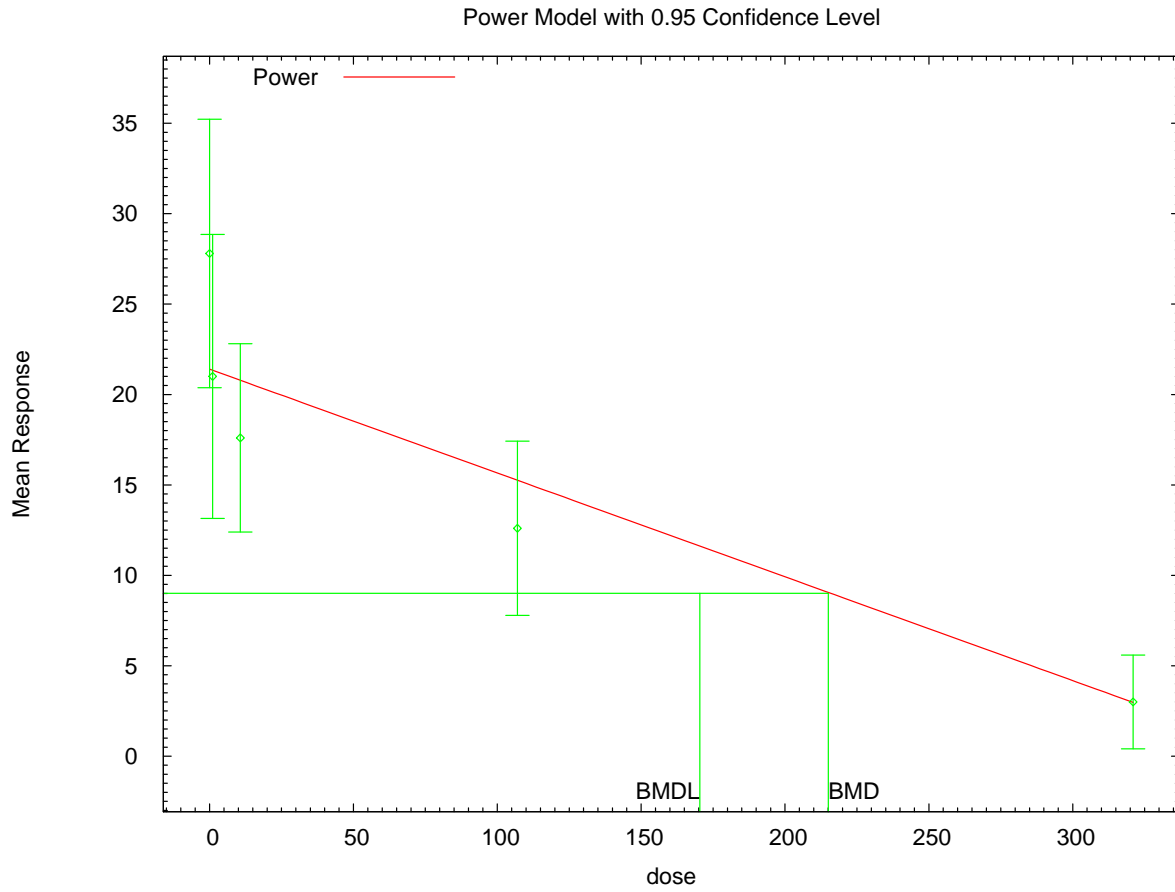
 Table 3 cleft palate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
```

```
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                  Default Initial Parameter Values
                      background =          0
                       intercept =    -7.91888
                           slope =          1



         Asymptotic Correlation Matrix of Parameter Estimates

              background      intercept        slope

background            1          -0.18          0.17

 intercept        -0.18              1            -1

    slope          0.17             -1             1




                          Parameter Estimates

                                              95.0% Wald
Confidence Interval
      Variable         Estimate      Std. Err.     Lower Conf. Limit
Upper Conf. Limit
      background       0.0262471           *                 *
*
       intercept       -15.6136           *                 *
*
          slope         2.05633           *                 *
*


* - Indicates that this value is not calculated.




                       Analysis of Deviance Table

     Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model      -29.9486         6
    Fitted model     -31.9094         3       3.92153       3
0.2701
  Reduced model      -52.2767         1      44.6562        5         <.0001

        AIC:          69.8188



                          Goodness  of  Fit
                                                        Scaled
     Dose     Est._Prob.   Expected    Observed    Size      Residual
    -------------------------------------------------------------------------
```

```
1      0.0000      0.0262        0.892      0.000          34      -0.957
2      1.0000      0.0262        1.076      2.000          41       0.903
3     10.0000      0.0263        0.499      0.000          19      -0.716
4    100.0000      0.0283        0.482      1.000          17       0.758
5   1000.0000      0.2175        4.132      4.000          19      -0.074
6   3000.0000      0.7085        9.918     10.000          14       0.048
7
8    Chi^2 = 2.83      d.f. = 3       P-value = 0.4194
9
10
11     Benchmark Dose Computation
12
13   Specified effect =           0.1
14
15   Risk Type       =      Extra risk
16
17   Confidence level =           0.95
18
19            BMD =       681.581
20
21            BMDL =      184.164
22
23
```

24 **G.3.51.3.** *Figure for Selected Model: Log-Logistic*

Log-Logistic Model with 0.95 Confidence Level

G.3.52. Sparschu et al. ([1971](#)): Fetal Body Weight, Male

2 **G.3.52.1.** *Summary Table of BMDS Modeling Results*

Model[a]	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	3	0.0001	-246.49	6.665E+02	4.188E+02	
Exponential (M3)	3	0.0001	-246.49	6.665E+02	4.188E+02	
Exponential (M4)	2	0.0002	-247.97	5.744E+02	3.197E+02	
Exponential (M5)[b]	**1**	**<0.0001**	**-246.36**	**5.459E+02**	**1.296E+02**	
Hill	1	<0.0001	-246.90	5.105E+02	error	
Linear	3	<0.0001	-245.45	7.248E+02	4.607E+02	
Polynomial, 3-degree	3	<0.0001	-245.45	7.248E+02	4.607E+02	
Power	3	<0.0001	-245.45	7.248E+02	4.607E+02	
Hill, unrestricted	1	<0.0001	-246.90	5.105E+02	error	
Power, unrestricted	2	<0.0001	-245.65	6.812E+02	3.949E+02	

[a] Modeled variance model presented ($p < 0.0001$) ; variance not appropriately captured (*p*-test 3 = 0.008).
[b] Best-fitting model, BMDS output presented in this appendix.

3

4 **G.3.52.2.** *Output for Selected Model: Exponential (M5)*

```
5   ==========================================================================
6           Exponential Model. (Version: 1.61;  Date: 7/24/2009)
7           Input Data File:
8   C:\USEPA\BMDS21\1a\74_Sparschu_1971_pup_bw_male_Exp_1.(d)
9           Gnuplot Plotting File:
10                                      Thu Sep 01 12:56:10 2011
11   ==========================================================================
12
13   Table 4 males
14   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
15
16     The form of the response function by Model:
17        Model 2:     Y[dose] = a * exp{sign * b * dose}
18        Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
19        Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
20        Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
21
22      Note: Y[dose] is the median response for exposure = dose;
23            sign = +1 for increasing trend in data;
24            sign = -1 for decreasing trend.
25
26        Model 2 is nested within Models 3 and 4.
27        Model 3 is nested within Model 5.
28        Model 4 is nested within Model 5.
29
30
31      Dependent variable = Mean
```

```
1    Independent variable = Dose
2    Data are assumed to be distributed: normally
3    Variance Model: exp(lnalpha +rho *ln(Y[dose]))
4    The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
5
6    Total number of dose groups = 5
7    Total number of records with missing values = 0
8    Maximum number of iterations = 250
9    Relative Function Convergence has been set to: 1e-008
10   Parameter Convergence has been set to: 1e-008
11
12   MLE solution provided: Exact
13
14
15                    Initial Parameter Values
16
17                    Variable          Model 5
18                    --------          --------
19                     lnalpha          -4.28192
20                        rho           1.66816
21                         a            4.347
22                         b            0.000395512
23                         c            0.312859
24                         d                     1
25
26
27
28                    Parameter Estimates
29
30                    Variable          Model 5
31                    --------          -------
32                     lnalpha          16.7441
33                        rho          -13.5393
34                         a            4.04428
35                         b            0.00167144
36                         c            0.859252
37                         d            1.18216
38
39
40          Table of Stats From Input Data
41
42      Dose      N        Obs Mean     Obs Std Dev
43      -----    ---      ----------   -------------
44         0    117         4.03           0.37
45        30     55         4.14           0.26
46       125     66         3.85           0.35
47       500     39         3.86           0.61
48      2000      3         2.72           0.25
49
50
51          Estimated Values of Interest
52
53      Dose     Est Mean     Est Std     Scaled Residual
54      ------   ----------   ---------   ----------------
55         0       4.044       0.3372         -0.458
56        30       4.028       0.3465          2.398
57       125       3.962       0.3878         -2.336
```

```
        500          3.729         0.5845            1.404
       2000          3.484         0.9255           -1.43



   Other models for which likelihoods are calculated:

     Model A1:        Yij = Mu(i) + e(ij)
               Var{e(ij)} = Sigma^2

     Model A2:        Yij = Mu(i) + e(ij)
               Var{e(ij)} = Sigma(i)^2

     Model A3:        Yij = Mu(i) + e(ij)
               Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

     Model  R:        Yij = Mu + e(i)
               Var{e(ij)} = Sigma^2


                        Likelihoods of Interest

                 Model      Log(likelihood)     DF        AIC
                 -------    ----------------    ----    -----------
                  A1          126.4055           6       -240.8109
                  A2          145.7666          10       -271.5331
                  A3          137.4206           7       -260.8413
                   R          101.5293           2       -199.0587
                   5          129.1813           6       -246.3626


   Additive constant for all log-likelihoods =    -257.3.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                        Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 7a: Does Model 5 fit the data? (A3 vs 5)



                        Tests of Interest

     Test        -2*log(Likelihood Ratio)        D. F.        p-value
   --------      ------------------------        ------     --------------
    Test 1                  88.47                  8          < 0.0001
    Test 2                  38.72                  4          < 0.0001
    Test 3                  16.69                  3          0.0008177
   Test 7a                  16.48                  1          < 0.0001
```

```
The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose
levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1.  A non-homogeneous
variance model appears to be appropriate.

The p-value for Test 3 is less than .1.  You may want to
consider a different variance model.

The p-value for Test 7a is less than .1.  Model 5 may not adequately
describe the data; you may want to consider another model.


Benchmark Dose Computations:

   Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

   Confidence Level = 0.950000

                BMD =      545.876

               BMDL =      129.551
```

1 **G.3.52.3.** *Figure for Selected Model: Exponential (M5)*

Exponential_beta Model 5 with 0.95 Confidence Level

2   12:56 09/01 2011
3
4

G.3.53. Sparschu et al. (1971): Fetal Body Weight, Female

G.3.53.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 p-Value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2) [b]	**3**	**0.0278**	**-229.517**	**1.033E+03**	**6.479E+02**	
Exponential (M3)	3	0.0278	-229.517	1.033E+03	6.479E+02	
Exponential (M4)	2	0.0147	-228.188	1.057E+03	5.759E+02	
Exponential (M5)	2	0.0147	-228.188	1.057E+03	5.759E+02	
Hill	2	0.0151	-228.244	1.073E+03	5.800E+02	
Linear	3	0.0245	-229.239	1.050E+03	6.749E+02	
Polynomial, 3-degree	3	0.0245	-229.239	1.050E+03	6.749E+02	
Power	2	0.0025	-224.657	1.860E+03	5.877E+02	
Hill, unrestricted	1	0.0038	-226.278	1.073E+03	5.828E+02	
Power, unrestricted	2	0.0146	-228.180	1.077E+03	6.192E+02	

[a] Modeled variance model presented ($p = 0.001$); variance not appropriately captured (p-test 3 = 0.005).
[b] Best-fitting model, BMDS output presented in this appendix.

G.3.53.2. *Output for Selected Model: Exponential (M2)*

```
=====================================================================
       Exponential Model. (Version: 1.61;  Date: 7/24/2009)
       Input Data File:
C:\USEPA\BMDS21\1a\75_Sparschu_1971_pup_bw_male_Exp_1.(d)
       Gnuplot Plotting File:
                                 Thu Sep 01 13:43:52 2011
=====================================================================

 Table 4 females
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:    Y[dose] = a * exp{sign * b * dose}
      Model 3:    Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:    Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:    Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


    Dependent variable = Mean
```

```
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                 Initial Parameter Values

                 Variable          Model 2
                 --------          --------
                  lnalpha              -7.22746
                     rho               4.02075
                       a               3.75712
                       b           0.000140769
                       c                     0
                       d                     1




                 Parameter Estimates

                 Variable          Model 2
                 --------          -------
                  lnalpha            10.6901
                     rho            -9.26779
                       a             3.89584
                       b          0.000100525
                       c                   0
                       d                   1



         Table of Stats From Input Data

    Dose      N        Obs Mean     Obs Std Dev
    -----    ---       ----------   -------------
        0    129        3.89           0.39
       30     60        3.98           0.35
      125     58        3.71           0.37
      500     54        3.78           0.54
     2000      4        2.69           0.19



            Estimated Values of Interest

    Dose      Est Mean      Est Std     Scaled Residual
    ------   ----------    ---------    ----------------
        0       3.896        0.3842         -0.1727
       30       3.884        0.3896          1.907
      125       3.847        0.4072         -2.566
```

```
       500          3.705         0.4849                 1.139
      2000          3.186         0.9753                -1.018



   Other models for which likelihoods are calculated:

     Model A1:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma^2

     Model A2:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = Sigma(i)^2

     Model A3:        Yij = Mu(i) + e(ij)
              Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

     Model  R:        Yij = Mu + e(i)
              Var{e(ij)} = Sigma^2


                            Likelihoods of Interest

                    Model      Log(likelihood)     DF         AIC
                    -------    ----------------    ----    -----------
                      A1          123.0729          6       -234.1458
                      A2          132.131          10        -244.262
                      A3          123.3163          7       -232.6326
                       R          100.5646          2       -197.1292
                       2          118.7583          4       -229.5166


   Additive constant for all log-likelihoods =     -280.3.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.



                            Explanation of Tests

   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)
   Test 4:  Does Model 2 fit the data? (A3 vs. 2)



                            Tests of Interest

     Test        -2*log(Likelihood Ratio)        D. F.        p-value
     --------    ------------------------        ------    --------------
     Test 1                      63.13             8         < 0.0001
     Test 2                      18.12             4          0.001171
     Test 3                      17.63             3          0.0005244
     Test 4                      9.116             3           0.02779



   The p-value for Test 1 is less than .05.  There appears to be a
```

```
difference between response and/or variances among the dose
levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1.  A non-homogeneous
variance model appears to be appropriate.

The p-value for Test 3 is less than .1.  You may want to
consider a different variance model.

The p-value for Test 4 is less than .1.  Model 2 may not adequately
describe the data; you may want to consider another model.


Benchmark Dose Computations:

   Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

   Confidence Level = 0.950000

                BMD =      1032.78

               BMDL =      647.855
```

1 **G.3.53.3.** *Figure for Selected Model: Exponential (M2)*

Exponential_beta Model 2 with 0.95 Confidence Level

2   13:43 09/01 2011
3
4

G.3.54. Toth et al. (1979): Amyloidosis

G.3.54.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	2	0.022	150.666	2.296E+02	1.460E+02	power bound hit (power = 1)
Logistic	2	0.013	152.187	4.088E+02	3.125E+02	
Log-logistic[a]	**2**	**0.028**	**149.984**	**1.759E+02**	**9.729E+01**	**slope bound hit (slope = 1)**
Log-probit	2	0.007	153.479	4.402E+02	2.965E+02	slope bound hit (slope = 1)
Multistage, 3-degree	2	0.022	150.666	2.296E+02	1.460E+02	final ß = 0
Probit	2	0.014	152.040	3.846E+02	2.911E+02	
Weibull	2	0.022	150.666	2.296E+02	1.460E+02	power bound hit (power = 1)
Gamma, unrestricted	2	0.917	140.208	7.687E−01	7.637E−04	unrestricted (power = 0.187)
Log-logistic, unrestricted[b]	2	0.847	140.370	8.465E−01	1.565E−03	unrestricted (slope = 0.238)
Log-probit, unrestricted	2	0.811	140.458	8.545E−01	2.334E−03	unrestricted (slope = 0.135)
Weibull, unrestricted	2	0.882	140.287	8.179E−01	1.140E−03	unrestricted (power = 0.212)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

G.3.54.2. *Output for Selected Model: Log-Logistic*

Toth et al. (1979): Amyloidosis

```
    ==========================================================================
           Logistic Model. (Version: 2.12; Date: 05/16/2008)
           Input Data File: C:\1\62_Toth_1979_Amy1yr_LogLogistic_1.(d)
           Gnuplot Plotting File:  C:\1\62_Toth_1979_Amy1yr_LogLogistic_1.plt
                                           Tue Feb 16 19:56:59 2010
    ==========================================================================

  Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
   Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




User has chosen the log transformed model


                  Default Initial Parameter Values
                      background =           0
                       intercept =     -6.90711
                           slope =           1



          Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -slope
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

               background     intercept

background              1         -0.47

 intercept          -0.47             1




                              Parameter Estimates


                                               95.0% Wald
Confidence Interval
      Variable         Estimate       Std. Err.     Lower Conf. Limit
Upper Conf. Limit
      background      0.0848984            *                 *
*
       intercept      -7.36716            *                 *
*
           slope             1            *                 *
*

* - Indicates that this value is not calculated.




                         Analysis of Deviance Table


      Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -68.017         4
     Fitted model      -72.9918         2        9.9496       2
0.00691
    Reduced model      -82.0119         1        27.99        3        <.0001

        AIC:          149.984
```

```
                           Goodness  of  Fit
                                                        Scaled
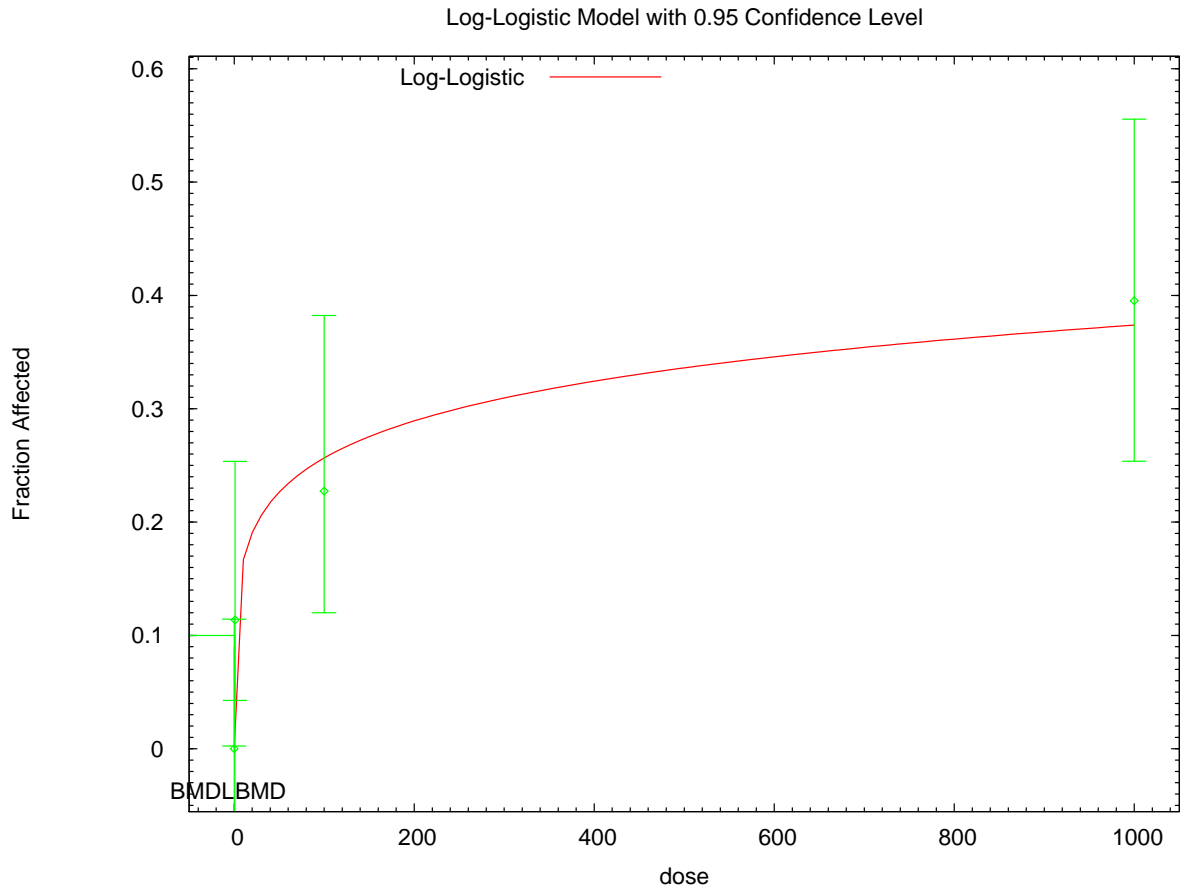      Dose      Est._Prob.    Expected    Observed    Size    Residual
    ---------------------------------------------------------------------
      0.0000      0.0849        3.226       0.000       38     -1.878
      1.0000      0.0855        3.761       5.000       44      0.668
    100.0000      0.1393        6.128      10.000       44      1.686
   1000.0000      0.4392       18.884      17.000       43     -0.579


  Chi^2 = 7.15      d.f. = 2        P-value = 0.0280



    Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =       Extra risk

Confidence level =           0.95

          BMD =        175.903

          BMDL =        97.2899
```

1 **G.3.54.3.** *Figure for Selected Model: Log-Logistic*

Log-Logistic Model with 0.95 Confidence Level

19:56 02/16 2010

2
3
4 **G.3.54.4.** *Output for Additional Model Presented: Log-Logistic, Unrestricted*

5 Toth et al. (1979): Amyloidosis

6
7
8
```
=====================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\1\62_Toth_1979_Amy1yr_LogLogistic_U_1.(d)
        Gnuplot Plotting File:  C:\1\62_Toth_1979_Amy1yr_LogLogistic_U_1.plt
                                        Tue Feb 16 19:57:00 2010
=====================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted
```

```
   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008




   User has chosen the log transformed model


                   Default Initial Parameter Values
                      background =            0
                       intercept =     -2.10894
                           slope =     0.227921


          Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -background
                  have been estimated at a boundary point, or have been
   specified by the user,
                  and do not appear in the correlation matrix )

                 intercept        slope

    intercept             1       -0.89

       slope       -0.89             1




                              Parameter Estimates

                                                   95.0% Wald
   Confidence Interval
         Variable          Estimate        Std. Err.      Lower Conf. Limit
   Upper Conf. Limit
       background                 0             *                  *
   *
         intercept       -2.15753              *                  *
   *
           slope        0.238304               *                  *
   *

   * - Indicates that this value is not calculated.




                         Analysis of Deviance Table

        Model        Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
        Full model        -68.017          4
     Fitted model       -68.1848          2       0.33571      2
   0.8455
     Reduced model      -82.0119          1         27.99      3        <.0001
```

```
         AIC:              140.37


                        Goodness   of   Fit
                                                        Scaled
      Dose      Est._Prob.    Expected    Observed    Size    Residual
   ------------------------------------------------------------------
     0.0000      0.0000        0.000       0.000        38      0.000
     1.0000      0.1036        4.560       5.000        44      0.218
   100.0000      0.2573       11.321      10.000        44     -0.456
  1000.0000      0.3749       16.119      17.000        43      0.277


 Chi^2 = 0.33      d.f. = 2        P-value = 0.8471


   Benchmark Dose Computation

 Specified effect =          0.1

 Risk Type        =      Extra risk

 Confidence level =          0.95

           BMD =        0.846547

          BMDL =      0.00156534
```

1 **G.3.54.5.** *Figure for Additional Model Presented: Log-Logistic, Unrestricted*

Log-Logistic Model with 0.95 Confidence Level

19:57 02/16 2010

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G.3.55. Toth et al. ([1979](#)): Skin Lesions

2 **G.3.55.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Gamma	2	0.009	159.223	1.181E+02	8.308E+01	power bound hit (power = 1)
Logistic[a]	**2**	**0.002**	**162.974**	**2.709E+02**	**2.147E+02**	
Log-logistic	2	0.029	156.567	6.750E+01	4.057E+01	slope bound hit (slope = 1)
Log-probit	2	0.001	164.598	2.446E+02	1.626E+02	slope bound hit (slope = 1)
Multistage, 3-degree	2	0.009	159.223	1.181E+02	8.308E+01	final ß = 0
Probit	2	0.003	162.684	2.522E+02	2.015E+02	
Weibull	2	0.009	159.223	1.181E+02	8.308E+01	power bound hit (power = 1)
Gamma, unrestricted	2	0.882	147.287	error	error	unrestricted (power = 0.251)
Log-logistic, unrestricted[b]	2	0.630	147.969	1.137E+00	5.477E−02	unrestricted (slope = 0.351)
Log-probit, unrestricted	2	0.558	148.218	1.096E+00	6.847E−02	unrestricted (slope = 0.202)
Weibull, unrestricted	2	0.762	147.581	1.077E+00	4.080E−02	unrestricted (power = 0.3)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

3
4
5 **G.3.55.2.** *Output for Selected Model: Logistic*

6 Toth et al. ([1979](#)): Skin Lesions
7
8
```
9   ======================================================================
10          Logistic Model. (Version: 2.12; Date: 05/16/2008)
11          Input Data File: C:\1\63_Toth_1979_SkinLes_Logistic_1.(d)
12          Gnuplot Plotting File:  C:\1\63_Toth_1979_SkinLes_Logistic_1.plt
13                                          Tue Feb 16 19:57:29 2010
14   ======================================================================
15
16   Table 2
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the probability function is:
20
21     P[response] = 1/[1+EXP(-intercept-slope*dose)]
22
23
24     Dependent variable = DichEff
25     Independent variable = Dose
26     Slope parameter is not restricted
27
28     Total number of observations = 4
29     Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                       background =            0   Specified
                        intercept =     -2.53484
                            slope =   0.00299511



           Asymptotic Correlation Matrix of Parameter Estimates


           ( *** The model parameter(s)  -background
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                  intercept           slope

  intercept              1          -0.67


     slope          -0.67               1




                              Parameter Estimates


                                              95.0% Wald
Confidence Interval
        Variable         Estimate         Std. Err.     Lower Conf. Limit
Upper Conf. Limit
        intercept        -1.91768           0.26892          -2.44475
-1.39061
          slope        0.00230499       0.000419329          0.00148312
0.00312686




                        Analysis of Deviance Table


        Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -71.5177          4
     Fitted model       -79.487           2       15.9387      2
0.0003459
    Reduced model       -95.8498          1       48.6642      3       <.0001


          AIC:          162.974




                             Goodness  of  Fit
                                                              Scaled
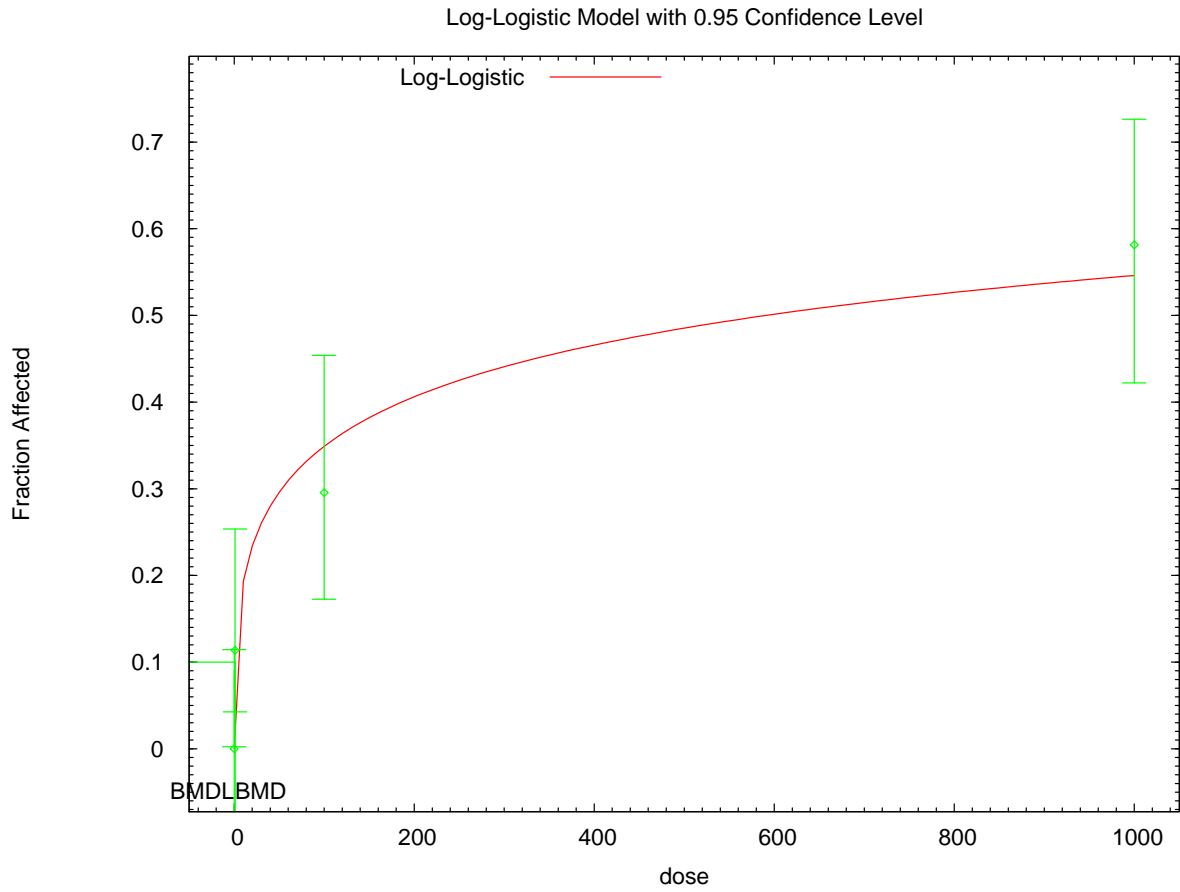      Dose      Est._Prob.    Expected    Observed     Size     Residual
   -------------------------------------------------------------------------
     0.0000      0.1281        4.869       0.000        38       -2.363
     1.0000      0.1284        5.649       5.000        44       -0.292
```

```
 1      100.0000      0.1561        6.870    13.000            44          2.546
 2     1000.0000      0.5956       25.612    25.000            43         -0.190
 3
 4    Chi^2 = 12.19     d.f. = 2         P-value = 0.0023
 5
 6
 7      Benchmark Dose Computation
 8
 9   Specified effect =            0.1
10
11   Risk Type        =       Extra risk
12
13   Confidence level =           0.95
14
15              BMD =        270.917
16
17              BMDL =        214.66
18
19
```

20 ## G.3.55.3. *Figure for Selected Model: Logistic*

Logistic Model with 0.95 Confidence Level

19:57 02/16 2010

21
22
23

G.3.55.4. *Output for Additional Model Presented: Log-Logistic, Unrestricted*

Toth et al. (1979): Skin Lesions

```
 =====================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\63_Toth_1979_SkinLes_LogLogistic_U_1.(d)
         Gnuplot Plotting File:  C:\1\63_Toth_1979_SkinLes_LogLogistic_U_1.plt
                                        Tue Feb 16 20:01:56 2010
 =====================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = DichEff
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                   Default Initial Parameter Values
                       background =            0
                        intercept =      -2.14055
                            slope =       0.332409



           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

               intercept         slope

   intercept           1          -0.9

      slope         -0.9             1
```

```
                          Parameter Estimates


                                                    95.0% Wald
Confidence Interval
       Variable          Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
      background              0               *                *
*
       intercept         -2.24241            *                *
*
         slope          0.350932             *                *
*


* - Indicates that this value is not calculated.



                       Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.  P-value
     Full model      -71.5177          4
    Fitted model     -71.9844          2       0.93345      2
0.6271
   Reduced model     -95.8498          1       48.6642      3        <.0001


         AIC:          147.969



                          Goodness  of  Fit
                                                          Scaled
     Dose      Est._Prob.    Expected    Observed    Size    Residual
    -------------------------------------------------------------------
    0.0000      0.0000        0.000       0.000       38      0.000
    1.0000      0.0960        4.224       5.000       44      0.397
  100.0000      0.3483       15.327      13.000       44     -0.736
 1000.0000      0.5453       23.448      25.000       43      0.475

 Chi^2 = 0.93      d.f. = 2       P-value = 0.6295



   Benchmark Dose Computation

Specified effect =          0.1

Risk Type       =      Extra risk

Confidence level =          0.95

         BMD =         1.1374

        BMDL =       0.0547689
```

1   **G.3.55.5.** *Figure for Additional Model Presented: Log-Logistic, Unrestricted*

Log-Logistic Model with 0.95 Confidence Level

20:01 02/16 2010

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G.3.56. van Birgelen et al. ([1995](#)): Hepatic Retinol

2 **G.3.56.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	4	<0.0001	164.340	2.912E+02	error	
Exponential (M3)	4	<0.0001	164.340	2.912E+02	error	power hit bound (*d* = 1)
Exponential (M4)[a]	**3**	**<0.0001**	**148.052**	**1.151E+02**	**7.098E+01**	
Exponential (M5)	3	<0.0001	148.052	1.151E+02	7.098E+01	power hit bound (*d* = 1)
Hill	3	0.044	128.757	1.314E+01	error	*n* lower bound hit (*n* = 1)
Linear	4	<0.0001	178.734	7.815E+02	5.997E+02	
Polynomial, 5-degree	0	N/A	283.606	2.481E+03	error	
Power	4	<0.0001	178.734	7.815E+02	5.997E+02	power bound hit (power = 1)
Hill, unrestricted	2	0.269	125.273	5.561E+00	error	unrestricted (*n* = 0.571)
Power, unrestricted[b]	3	0.025	129.990	4.205E−01	8.504E−03	unrestricted (power = 0.118)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

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4
5 **G.3.56.2.** *Output for Selected Model: Exponential (M4)*

6 van Birgelen et al. ([1995](#)): Hepatic Retinol
7
8
9
```
       =====================================================================
10        Exponential Model. (Version: 1.61;  Date: 7/24/2009)
11        Input Data File: C:\1\65_VanB_1995a_HepRet_Exp_1.(d)
12        Gnuplot Plotting File:
13                                         Tue Feb 16 20:03:05 2010
14       =====================================================================
15
16    Tbl3, hepatic retinol
17    ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19     The form of the response function by Model:
20        Model 2:     Y[dose] = a * exp{sign * b * dose}
21        Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
22        Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
23        Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]
24
25      Note: Y[dose] is the median response for exposure = dose;
26           sign = +1 for increasing trend in data;
27           sign = -1 for decreasing trend.
28
29        Model 2 is nested within Models 3 and 4.
30        Model 3 is nested within Model 5.
```

```
Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


                    Initial Parameter Values

                Variable           Model 4
                --------           --------
                  lnalpha             -1.16065
                     rho              1.53688
                       a               15.645
                       b            0.00625117
                       c             0.0365247
                       d                     1



                    Parameter Estimates

                Variable           Model 4
                --------           -------
                  lnalpha            -0.882225
                     rho              1.82707
                       a              10.5294
                       b            0.00720346
                       c             0.0688661
                       d                     1



            Table of Stats From Input Data

     Dose      N        Obs Mean      Obs Std Dev
     -----    ---       ----------    ------------
         0     8          14.9          8.768
        14     8           8.4          3.394
        26     8           8.2          2.263
        47     8           5.1          0.8485
       320     8           2.2          0.8485
      1024     8           0.6          0.5657



                    Estimated Values of Interest
```

```
        Dose      Est Mean      Est Std    Scaled Residual
       ------    ----------    ---------   ----------------
           0         10.53        5.526             2.237
          14         9.589        5.073            -0.6628
          26         8.855        4.717            -0.3926
          47         7.714        4.159            -1.778
         320         1.703        1.046             1.343
        1024        0.7313       0.4833            -0.7681



   Other models for which likelihoods are calculated:

     Model A1:         Yij = Mu(i) + e(ij)
               Var{e(ij)} = Sigma^2

     Model A2:         Yij = Mu(i) + e(ij)
               Var{e(ij)} = Sigma(i)^2

     Model A3:         Yij = Mu(i) + e(ij)
               Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

     Model  R:         Yij = Mu + e(i)
               Var{e(ij)} = Sigma^2


                           Likelihoods of Interest

                   Model     Log(likelihood)     DF        AIC
                   -------   -----------------   ----   ------------
                    A1          -87.1567          7      188.3134
                    A2          -47.28742        12      118.5748
                    A3          -55.32422         8      126.6484
                     R          -109.967          2      223.934
                     4          -69.02619         5      148.0524


   Additive constant for all log-likelihoods =    -44.11.  This constant
added to the
   above values gives the log-likelihood including the term that does not
   depend on the model parameters.


                           Explanation of Tests
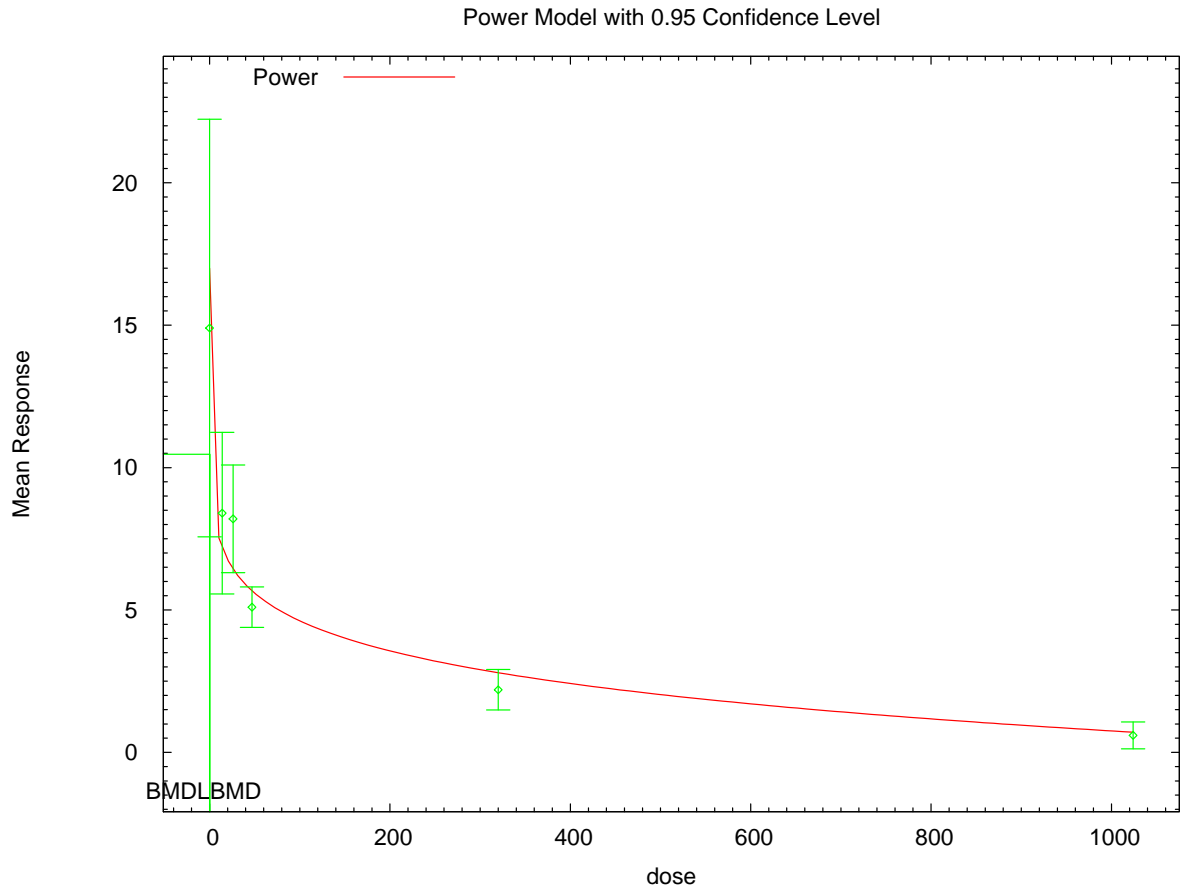
   Test 1:  Does response and/or variances differ among Dose levels? (A2 vs.
R)
   Test 2:  Are Variances Homogeneous? (A2 vs. A1)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)

   Test 6a: Does Model 4 fit the data? (A3 vs 4)


                           Tests of Interest

     Test        -2*log(Likelihood Ratio)        D. F.         p-value
   --------      ----------------------         ------      --------------
```

```
    Test 1                              125.4          10          < 0.0001
    Test 2                              79.74           5          < 0.0001
    Test 3                              16.07           4          0.002922
  Test 6a                               27.4           3          < 0.0001


    The p-value for Test 1 is less than .05.  There appears to be a
    difference between response and/or variances among the dose
    levels, it seems appropriate to model the data.

    The p-value for Test 2 is less than .1.  A non-homogeneous
    variance model appears to be appropriate.

    The p-value for Test 3 is less than .1.  You may want to
    consider a different variance model.

    The p-value for Test 6a is less than .1.  Model 4 may not adequately
    describe the data; you may want to consider another model.


 Benchmark Dose Computations:

    Specified Effect = 1.000000

          Risk Type = Estimated standard deviations from control

    Confidence Level = 0.950000

                 BMD =      115.128

                 BMDL =      70.981
```

1 **G.3.56.3.** *Figure for Selected Model: Exponential (M4)*

Exponential_beta Model 4 with 0.95 Confidence Level

20:03 02/16 2010

2
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4 **G.3.56.4.** *Output for Additional Model Presented: Power, Unrestricted*

5 van Birgelen et al. (1995): Hepatic Retinol
6
7

```
8   =====================================================================
9           Power Model. (Version: 2.15;  Date: 04/07/2008)
10          Input Data File: C:\1\65_VanB_1995a_HepRet_Pwr_U_1.(d)
11          Gnuplot Plotting File:  C:\1\65_VanB_1995a_HepRet_Pwr_U_1.plt
12                                          Tue Feb 16 20:03:11 2010
13  =====================================================================
14
15   Tbl3, hepatic retinol
16  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
17
18     The form of the response function is:
19
20     Y[dose] = control + slope * dose^power
21
22
23     Dependent variable = Mean
24     Independent variable = Dose
```

```
    The power is not restricted
    The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

    Total number of dose groups = 6
    Total number of records with missing values = 0
    Maximum number of iterations = 250
    Relative Function Convergence has been set to: 1e-008
    Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          lalpha =       2.76506
                             rho =             0
                         control =          14.9
                           slope =      -3.78637
                           power =      0.191713


        Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho        control         slope          power

      lalpha           1         -0.8         -0.047         0.042          0.065

         rho        -0.8            1         -0.085       -0.0029          -0.11

     control      -0.047       -0.085              1         -0.95          -0.81

       slope       0.042      -0.0029          -0.95             1           0.96

       power       0.065        -0.11          -0.81          0.96              1




                             Parameter Estimates

                                                      95.0% Wald
Confidence Interval
       Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
         lalpha        -1.02622        0.389164           -1.78897
-0.263475
            rho         1.68421        0.199212            1.29376
2.07466
        control         16.9577         2.21133            12.6235
21.2918
          slope        -7.19097         1.99708           -11.1052
-3.27676
          power        0.117935       0.0225396          0.0737578
0.162111




    Table of Data and Estimated Values of Interest
```

```
 Dose        N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------      ---   --------    --------   -----------  -----------   ---------
-

    0        8       14.9          17        8.77         6.49       -0.896
   14        8        8.4        7.14        3.39         3.13        1.14
   26        8        8.2         6.4        2.26         2.86        1.78
   47        8        5.1        5.63       0.849         2.57       -0.588
  320        8        2.2        2.76       0.849         1.41        -1.12
 1024        8        0.6       0.672       0.566        0.428       -0.475



Model Descriptions for likelihoods calculated


Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                   Likelihoods of Interest

          Model     Log(likelihood)   # Param's      AIC
           A1         -87.156698           7       188.313395
           A2         -47.287416          12       118.574833
           A3         -55.324218           8       126.648436
        fitted        -59.994980           5       129.989960
            R        -109.967018           2       223.934036


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                   Tests of Interest

  Test     -2*log(Likelihood Ratio)  Test df        p-value

  Test 1             125.359            10           <.0001
  Test 2             79.7386             5           <.0001
```

```
   Test 3                16.0736           4            0.002922
   Test 4                9.34152           3            0.02508
```

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1. You may want to consider a
different variance model

The p-value for Test 4 is less than .1. You may want to try a different
model

                     Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

           BMD = 0.420475

           BMDL = 0.00850422

1   **G.3.56.5.** *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

20:03 02/16 2010

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G.3.57. van Birgelen et al. (1995): Hepatic Retinol Palmitate

2 **G.3.57.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	4	<0.0001	467.446	error	error	
Exponential (M3)	4	<0.0001	467.446	error	error	power hit bound (d = 1)
Exponential (M4)	3	<0.0001	454.087	error	error	
Exponential (M5)	3	<0.0001	454.087	error	error	power hit bound (d = 1)
Hill	3	<0.0001	563.579	error	error	
Linear[a]	**4**	**<0.0001**	**488.446**	**1.420E+03**	**9.889E+02**	
Polynomial, 5-degree	0	N/A	573.977	error	error	
Power	4	<0.0001	488.446	1.420E+03	9.889E+02	power bound hit (power = 1)
Hill, unrestricted	3	<0.0001	522.322	2.418E−12	2.418E−12	unrestricted (n = 0.452)
Power, unrestricted[b]	3	0.348	408.062	3.765E−02	1.208E−05	unrestricted (power = 0.054)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

3
4
5 **G.3.57.2.** *Output for Selected Model: Linear*

6 van Birgelen et al. (1995): Hepatic Retinol Palmitate
7
8
9
```
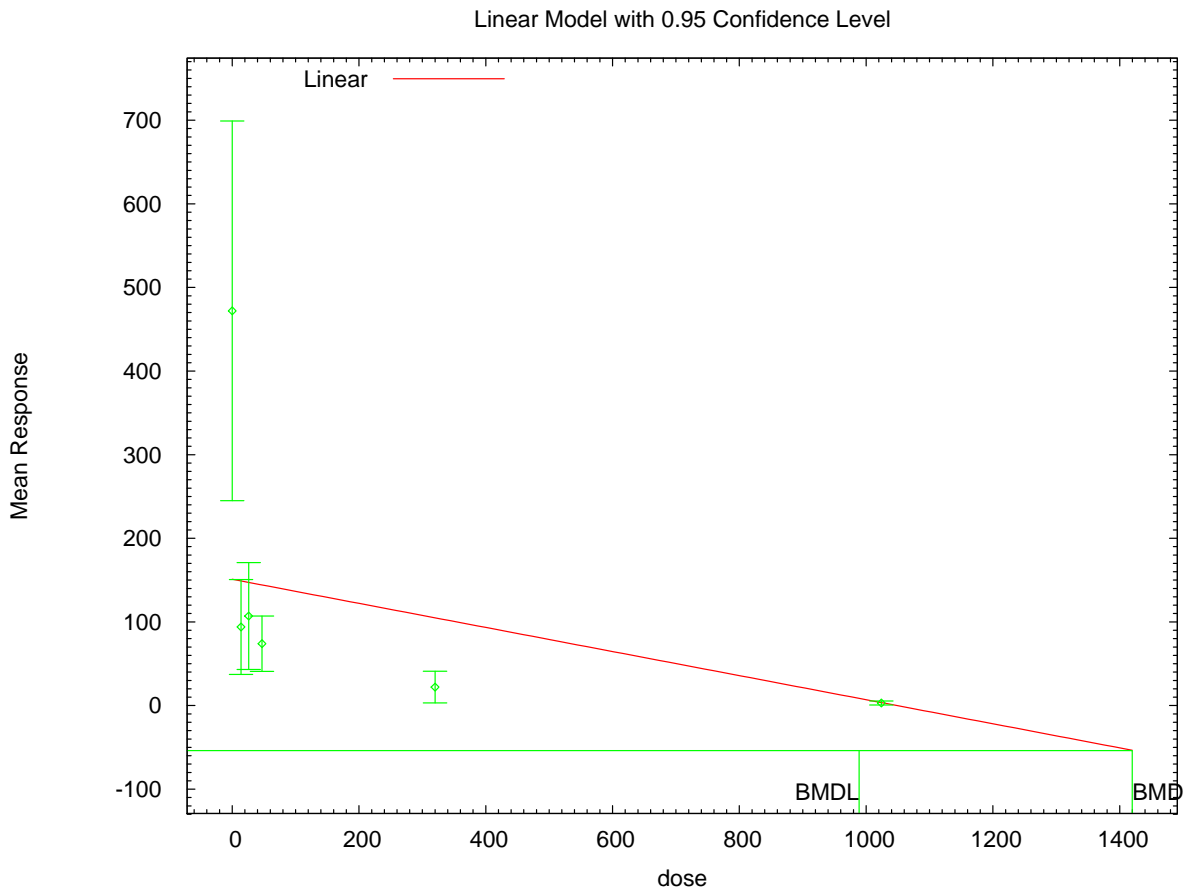      =====================================================================
10           Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
11           Input Data File: C:\1\66_VanB_1995a_HepRetPalm_Linear_1.(d)
12           Gnuplot Plotting File:  C:\1\66_VanB_1995a_HepRetPalm_Linear_1.plt
13                                       Tue Feb 16 20:03:46 2010
14      =====================================================================
15
16   Tbl3, hepatic retinol palmitate
17   ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19      The form of the response function is:
20
21      Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
22
23
24      Dependent variable = Mean
25      Independent variable = Dose
26      Signs of the polynomial coefficients are not restricted
27      The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
28
29      Total number of dose groups = 6
30      Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                      Default Initial Parameter Values
                             lalpha =      9.57332
                                rho =            0
                            beta_0 =      177.506
                            beta_1 =     -0.204775



          Asymptotic Correlation Matrix of Parameter Estimates

                     lalpha          rho         beta_0         beta_1

     lalpha               1        -0.95        -0.017          0.022

        rho           -0.95            1       0.00019        -0.0048

     beta_0          -0.017      0.00019             1             -1

     beta_1           0.022      -0.0048            -1              1




                             Parameter Estimates

                                                        95.0% Wald
Confidence Interval
        Variable         Estimate        Std. Err.      Lower Conf. Limit
Upper Conf. Limit
          lalpha       -0.723216         0.638291             -1.97424
0.527811
             rho         2.26615         0.140196              1.99137
2.54093
          beta_0         150.535         31.5457              88.7064
212.363
          beta_1       -0.143931        0.0308317             -0.20436
-0.0835018



     Table of Data and Estimated Values of Interest

  Dose       N    Obs Mean     Est Mean    Obs Std Dev   Est Std Dev   Scaled
 Res.
 ------     ---   --------     --------    -----------   -----------   ---------
 -

      0      8       472          151          272           204          4.45
     14      8        94          149         67.9           201         -0.766
     26      8       107          147         76.4           199         -0.567
     47      8        74          144         39.6           194         -1.02
    320      8        22          104         22.6           135         -1.73
   1024      8         3         3.15         2.83          2.56         -0.166
```

```
Model Descriptions for likelihoods calculated


Model A1:          Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma^2

Model A2:          Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma(i)^2

Model A3:          Yij = Mu(i) + e(ij)
            Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
      Model A3 uses any fixed variance parameters that
      were specified by the user

Model  R:          Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                   Likelihoods of Interest

           Model      Log(likelihood)    # Param's      AIC
           A1         -250.554817            7       515.109634
           A2         -196.755746           12       417.511491
           A3         -197.383174            8       410.766347
        fitted        -240.223107            4       488.446215
           R          -276.789644            2       557.579287



                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                   Tests of Interest

  Test     -2*log(Likelihood Ratio)  Test df        p-value

  Test 1             160.068            10           <.0001
  Test 2             107.598             5           <.0001
  Test 3             1.25486             4            0.869
  Test 4             85.6799             4           <.0001

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
```

to be appropriate here

The p-value for Test 4 is less than .1. You may want to try a different
model

                   Benchmark Dose Computation

Specified effect =   1

Risk Type   =   Estimated standard deviations from the control mean

Confidence level =   0.95

           BMD =   1419.81

           BMDL =   988.945

G.3.57.3. *Figure for Selected Model: Linear*

Linear Model with 0.95 Confidence Level

20:03 02/16 2010

G.3.57.4. *Output for Additional Model Presented: Power, Unrestricted*

van Birgelen et al. (1995): Hepatic Retinol Palmitate

```
====================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\1\66_VanB_1995a_HepRetPalm_Pwr_U_1.(d)
        Gnuplot Plotting File:  C:\1\66_VanB_1995a_HepRetPalm_Pwr_U_1.plt
                                        Tue Feb 16 20:03:50 2010
====================================================================

 Tbl3, hepatic retinol palmitate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the response function is:

  Y[dose] = control + slope * dose^power


  Dependent variable = Mean
  Independent variable = Dose
  The power is not restricted
  The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

  Total number of dose groups = 6
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                        lalpha =      9.57332
                           rho =            0
                       control =          472
                         slope =     -315.054
                         power =    0.0586881


        Asymptotic Correlation Matrix of Parameter Estimates

               lalpha          rho       control        slope        power

   lalpha           1        -0.95         0.29        -0.31         -0.3

      rho       -0.95            1         -0.4         0.39         0.29

  control        0.29         -0.4            1        -0.98        -0.82

    slope       -0.31         0.39        -0.98            1         0.91

    power        -0.3         0.29        -0.82         0.91            1
```

```
                        Parameter Estimates


                                                     95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          lalpha       0.0734958        0.849559           -1.59161
1.7386
             rho        1.80632         0.194602            1.42491
2.18774
         control        465.497          86.914             295.149
635.845
           slope        -318.06         82.4127            -479.586
-156.534
           power       0.0540573        0.0117709          0.0309869
0.0771278




     Table of Data and Estimated Values of Interest

  Dose        N    Obs Mean      Est Mean    Obs Std Dev  Est Std Dev   Scaled
Res.
 ------      ---   --------      --------    ----------   -----------   --------
-

    0         8       472          465          272          266         0.069
   14         8        94         98.7         67.9         65.6        -0.201
   26         8       107         86.2         76.4         58.1         1.01
   47         8        74         73.8         39.6         50.5        0.0086
  320         8        22         31.1         22.6         23.1        -1.11
 1024         8         3         2.86         2.83         2.68        0.145




 Model Descriptions for likelihoods calculated


 Model A1:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:         Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:         Yi = Mu + e(i)
          Var{e(i)} = Sigma^2



                    Likelihoods of Interest

         Model      Log(likelihood)   # Param's      AIC
          A1          -250.554817          7       515.109634
```

```
        A2           -196.755746         12      417.511491
        A3           -197.383174          8      410.766347
    fitted           -199.031154          5      408.062307
         R           -276.789644          2      557.579287


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                    Tests of Interest

   Test     -2*log(Likelihood Ratio)  Test df        p-value

   Test 1          160.068             10            <.0001
   Test 2          107.598              5            <.0001
   Test 3          1.25486              4             0.869
   Test 4          3.29596              3            0.3482

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


                    Benchmark Dose Computation

Specified effect =              1

Risk Type        =      Estimated standard deviations from the control mean

Confidence level =         0.95

           BMD = 0.0376489


           BMDL = 1.20769e-005
```

1 **G.3.57.5.** *Figure for Additional Model Presented: Power, Unrestricted*

Power Model with 0.95 Confidence Level

20:03 02/16 2010

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1 **G.3.58. White et al. ([1986](#)): CH50**

2 **G.3.58.1.** *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	χ^2 *p*-value	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Notes
Exponential (M2)	5	0.001	391.472	4.480E+02	2.844E+02	
Exponential (M3)	5	0.001	391.472	4.480E+02	2.844E+02	power hit bound (*d* = 1)
Exponential (M4)	4	0.001	392.128	3.126E+02	1.140E+02	
Exponential (M5)	4	0.001	392.128	3.126E+02	1.140E+02	power hit bound (*d* = 1)
Hill[a]	**4**	**0.001**	**391.223**	**2.042E+02**	**3.585E+01**	***n* lower bound hit (*n* = 1)**
Linear	5	<0.0001	396.430	8.065E+02	5.899E+02	
Polynomial, 6-degree	3	<0.0001	643.059	9.600E+02	error	
Power	5	<0.0001	396.430	8.065E+02	5.899E+02	power bound hit (power = 1)
Hill, unrestricted[b]	3	0.058	381.943	9.677E−01	1.900E−01	unrestricted (*n* = 0.211)
Power, unrestricted	4	0.131	379.574	7.186E−01	1.157E−02	unrestricted (power = 0.188)

[a] Best-fitting model, BMDS output presented in this appendix.
[b] Alternate model, BMDS output also presented in this appendix.

3

4

5 **G.3.58.2.** *Output for Selected Model: Hill*

6 White et al. ([1986](#)): CH50
7

8

```
9    =======================================================================
10         Hill Model. (Version: 2.14;  Date: 06/26/2008)
11         Input Data File: C:\1\71_White_1986_CH50_Hill_1.(d)
12         Gnuplot Plotting File:  C:\1\71_White_1986_CH50_Hill_1.plt
13                                        Tue Feb 16 20:06:45 2010
14    =======================================================================
15
16  [insert study notes]
17  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
18
19    The form of the response function is:
20
21    Y[dose] = intercept + v*dose^n/(k^n + dose^n)
22
23
24    Dependent variable = Mean
25    Independent variable = Dose
26    Power parameter restricted to be greater than 1
27    The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))
28
29    Total number of dose groups = 7
30    Total number of records with missing values = 0
```

```
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                          lalpha =      5.60999
                             rho =            0
                       intercept =           91
                               v =          -74
                               n =    0.0969998
                               k =           10



           Asymptotic Correlation Matrix of Parameter Estimates


           ( *** The model parameter(s)  -n
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                 lalpha         rho    intercept            v            k

     lalpha           1       -0.99         0.19         0.13        -0.22

        rho       -0.99           1         -0.2        -0.14         0.23

  intercept        0.19        -0.2            1         0.33         -0.7

          v        0.13       -0.14         0.33            1        -0.86

          k       -0.22        0.23         -0.7        -0.86            1




                              Parameter Estimates


                                                        95.0% Wald
Confidence Interval
        Variable        Estimate        Std. Err.    Lower Conf. Limit
Upper Conf. Limit
         lalpha         4.34761          1.59601              1.21948
7.47574
            rho        0.381496         0.413764            -0.429467
1.19246
      intercept         71.6585          5.38454               61.105
82.212
              v        -62.7464          14.9646             -92.0765
-33.4163
              n               1               NA
              k         441.016          460.151             -460.864
1342.9


NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

```
      Table of Data and Estimated Values of Interest

  Dose       N     Obs Mean     Est Mean    Obs Std Dev   Est Std Dev    Scaled
Res.
 ------      ---   --------     --------    -----------   -----------    ---------
-

     0       8         91         71.7          14.1          19.9           2.75
    10       8         54         70.3          8.49          19.8          -2.33
    50       8         63         65.3          11.3          19.5          -0.329
   100       8         56         60.1          25.5          19.2          -0.598
   500       8         41         38.3            17          17.6           0.43
  1000       8         32         28.1            17          16.6           0.661
  2000       8         17         20.2            17          15.6          -0.589
```

Model Descriptions for likelihoods calculated

```
Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2
```

                    Likelihoods of Interest

```
          Model      Log(likelihood)   # Param's       AIC
           A1         -181.340979          8       378.681959
           A2         -175.820265         14       379.640529
           A3         -181.238690          9       380.477380
         fitted       -190.611743          5       391.223485
           R          -212.367055          2       428.734109
```

                    Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

```
                        Tests of Interest

    Test     -2*log(Likelihood Ratio)  Test df       p-value

    Test 1              73.0936             12          <.0001
    Test 2              11.0414              6          0.0871
    Test 3              10.8369              5          0.05471
    Test 4              18.7461              4          0.0008815

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is less than .1.  You may want to consider a
different variance model

The p-value for Test 4 is less than .1.  You may want to try a different
model



         Benchmark Dose Computation

Specified effect =             1

Risk Type       =      Estimated standard deviations from the control mean

Confidence level =         0.95

           BMD =        204.214

          BMDL =        35.8504
```

1   **G.3.58.3.** *Figure for Selected Model: Hill*

Hill Model with 0.95 Confidence Level

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2
3
4   **G.3.58.4.** *Output for Additional Model Presented: Hill, Unrestricted*

5   White et al. (1986): CH50

6
7
8   ===
9   Hill Model. (Version: 2.14; Date: 06/26/2008)
10   Input Data File: C:\1\71_White_1986_CH50_Hill_U_1.(d)
11   Gnuplot Plotting File: C:\1\71_White_1986_CH50_Hill_U_1.plt
12   Tue Feb 16 20:06:46 2010
13   ===
14
15   [insert study notes]
16   ~~~~~~
17
18   The form of the response function is:
19
20   Y[dose] = intercept + v*dose^n/(k^n + dose^n)
21
22
23   Dependent variable = Mean
24   Independent variable = Dose

```
Power parameter is not restricted
The variance is to be modeled as Var(i) = exp(lalpha  + rho * ln(mean(i)))
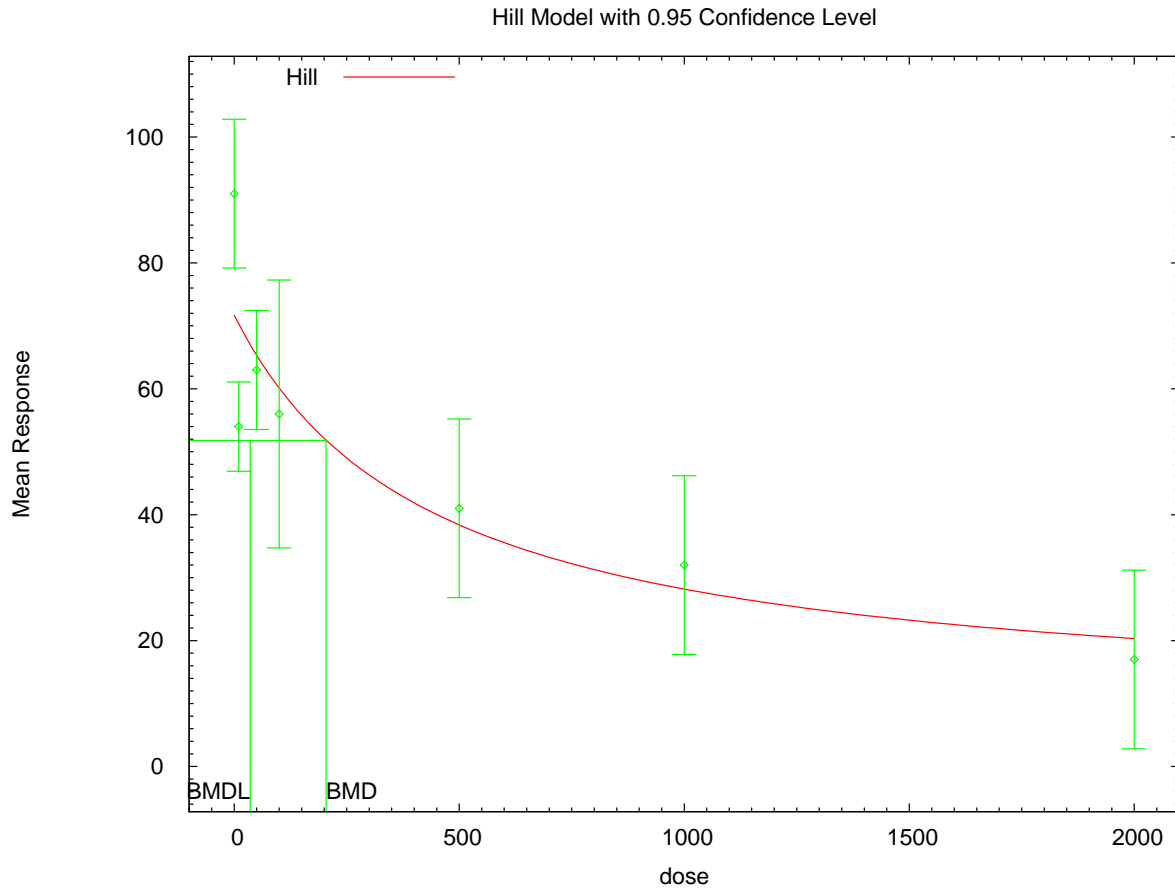
Total number of dose groups = 7
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008




                    Default Initial Parameter Values
                        lalpha =       5.60999
                           rho =             0
                     intercept =            91
                             v =           -74
                             n =     0.0969998
                             k =            10


          Asymptotic Correlation Matrix of Parameter Estimates

                   lalpha         rho     intercept           v            n
 k

     lalpha            1          -1         0.17        0.22        -0.42
-0.022

        rho           -1           1        -0.17       -0.22         0.42
0.019

  intercept         0.17       -0.17            1        0.16        -0.58
0.0069

          v         0.22       -0.22         0.16           1        -0.048
-0.91

          n        -0.42        0.42        -0.58       -0.048           1
-0.35

          k       -0.022       0.019       0.0069       -0.91        -0.35
1




                              Parameter Estimates


                                                   95.0% Wald
Confidence Interval
        Variable       Estimate      Std. Err.    Lower Conf. Limit
Upper Conf. Limit
          lalpha        6.62767        2.14235            2.42875
10.8266
             rho      -0.266376       0.555274           -1.35469
0.821941
       intercept         89.579        5.61106            78.5815
100.576
```

```
                    v          -458.615        402.837            -1248.16
330.93
                    n           0.210614      0.0503369            0.111956
0.309273
                    k        9.00638e+006    4.61231e+007       -8.13933e+007
9.94061e+007




      Table of Data and Estimated Values of Interest

  Dose        N      Obs Mean     Est Mean    Obs Std Dev  Est Std Dev   Scaled
Res.
 ------      ---     --------     --------    -----------  -----------   ---------
-

    0        8          91         89.6          14.1         15.1         0.266
   10        8          54         65.4          8.49         15.8        -2.04
   50        8          63         56.3          11.3         16.1         1.18
  100        8          56         51.5          25.5         16.3         0.777
  500        8          41         37.9           17          16.9         0.516
 1000        8          32         30.8           17          17.4         0.191
 2000        8          17         22.9           17          18.1        -0.927




 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

 Model  R:        Yi = Mu + e(i)
          Var{e(i)} = Sigma^2


                    Likelihoods of Interest

          Model     Log(likelihood)    # Param's       AIC
           A1        -181.340979            8        378.681959
           A2        -175.820265           14        379.640529
           A3        -181.238690            9        380.477380
         fitted      -184.971691            6        381.943382
            R        -212.367055            2        428.734109


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
```

```
            (A2 vs. R)
   Test 2:  Are Variances Homogeneous? (A1 vs A2)
   Test 3:  Are variances adequately modeled? (A2 vs. A3)
   Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
   (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)


                    Tests of Interest


     Test    -2*log(Likelihood Ratio)  Test df       p-value


     Test 1              73.0936           12          <.0001
     Test 2              11.0414            6          0.0871
     Test 3              10.8369            5          0.05471
     Test 4               7.466            3          0.05844


The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data


The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate


The p-value for Test 3 is less than .1.  You may want to consider a
different variance model


The p-value for Test 4 is less than .1.  You may want to try a different
model



          Benchmark Dose Computation

Specified effect =               1

Risk Type        =      Estimated standard deviations from the control mean

Confidence level =           0.95

           BMD =       0.967689

          BMDL =       0.189992
```

1   **G.3.58.5.** *Figure for Additional Model Presented: Hill, Unrestricted*

Hill Model with 0.95 Confidence Level

20:06 02/16 2010

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4   **G.4.   REFERENCES**

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APPENDIX H

Endpoints Excluded From Reference Dose Derivation Based on Toxicological Relevance

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NOTICE

THIS DOCUMENT IS AN AGENCY/INTERAGENCY REVIEW DRAFT. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH

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APPENDIX H. ENDPOINTS EXCLUDED FROM REFERENCE DOSE DERIVATION BASED ON TOXICOLOGICAL RELEVANCE

The National Academy of Sciences committee commented on the low dose model predictions and the need to discuss the biological significance of the noncancer health effects modeled in the 2003 Reassessment. In selecting point of departure (POD) candidates from the animal bioassays for derivation of the reference dose (RfD), U.S. Environmental Protection Agency (EPA) had to consider the toxicological relevance of the identified endpoint(s) from any given study. Often endpoints/effects may be sensitive, but lack general toxicological significance due to not being clearly adverse (defined in the Integrated Risk Information System glossary as a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge), being an adaptive response, or not being clearly linked to downstream functional or pathological alterations. It is standard EPA RfD derivation policy not to base a reference value on endpoints that are not adverse or not obvious precursors to an adverse effect. For select studies, a rationale for lack of toxicological relevance of particular endpoints reported is listed here. These endpoints were not considered for derivation of the RfD.

H.1. BURLESON ET AL. (1996)

Burleson et al. (1996) analyzed the effect of a TCDD on viral host resistance following a single gavage dose of TCDD by measuring mortality mediated by influenza virus challenge in B6C3F$_1$ female mice. The study authors found that TCDD at ≥10 ng/kg-day increased influenza-induced mortality. The experimental design calls for a 30% mortality in untreated animals (15% was achieved); mortality, itself, is not a direct result of TCDD exposure. None of the other immunologically-relevant measures were affected by TCDD treatment in this study, and no other effects were reported. The interpretation of these results with respect to humans is problematic. Furthermore, the findings were not reproduced by Nohara et al. (2002) using the same experimental design (see Section 2.4.2). Therefore, this endpoint is not considered relevant as a POD candidate.

H.2. DEVITO ET AL. (1994)

Devito et al. (1994) assessed the activity of CYP1A1 and CYP1A2, the amount of phosphorylation of phosphotyrosyl proteins (pp32, pp34, and pp38), and the levels of estrogen receptor in the liver, uterus, lung and skin tissue of female $B6C3F_1$ mice administered TCDD for 5 days a week for 13 weeks. The authors hypothesized that these measurements may be sensitive biomarkers for exposure to TCDD. Body weights were also recorded weekly. Induction of CY1A1 and CYP1A2, as well as increased phosphorylated forms of pp32, pp34, and pp38 were sensitive indicators of TCDD exposure, with statistically significant changes seen at 1.07 ng/kg-day. EROD activity in the ling, skin, and liver was also observed with significant increases at this dose. However, the authors did not find a change in rat body or terminal organ weights, nor did they note any pathology in the animals at this dose level. The role of CYPs and phosphorylated pp32, pp34, and pp38 in TCDD-mediated toxicity is unknown, and changes in the activity or function of these proteins are not considered adverse. Therefore, these endpoints are not considered suitable as PODs.

H.3. HASSOUN ET AL. (2003; 2002; 2000; 1998)

In multiple studies by Hassoun et al. (2003; 2002; 2000; 1998), various indicators of oxidative stress were measured in hepatic and brain tissue of female $B6C3F_1$ mice and Sprague-Dawley rats following 13 or 30 weeks of TCDD gavage dosing (5 days a week). Biomarkers for oxidative stress included production superoxide anion, lipid peroxidation, and DNA single-strand breaks. The authors report a statistically significant effect on several oxidative stress markers as a result of TCDD exposure, the lowest dose producing an effect being 0.32 ng/kg-day (1998). In this study, all oxidative stress markers were significantly affected, but no other indicators of brain pathology were assessed. Thus, it is impracticable to link the markers of oxidative stress to a toxicological outcome in the brain, and this study and its endpoints are not considered relevant POD candidates.

H.4. HONG ET AL. (1989)

Hong et al. (1989) studied the immunotoxicity of TCDD in female adult rhesus monkeys administered 0.12 or 0.67 ng/kg-day TCDD in feed for 4 years. Additionally, offspring from exposed mothers were examined. In adult monkeys, an increased number of T lymphocytes

1   were observed in the 0.67 ng/kg-day dose group, but there was not a proportional increase in

2   each of the T cells subsets. Macrophage depletion in the 0.12, and 0.67 ng/kg-day groups

3   resulted in the absence of amplification in a mixed lymphocyte response assay, compared to a

4   fivefold amplification in control monkeys. In the offspring, there was an immune

5   hyperresponsiveness to tetanus toxoid immunization which correlated with TCDD tissue levels.

6   Although a thorough immunological investigation, in the absence of any relevant

7   immunotoxicity endpoints or functional decrements of immune function following TCDD

8   exposure, there are no suitable endpoints for consideration as candidate PODs in this study.

9

10 **H.5. KITCHIN AND WOODS (1979)**

11   Kitchin and Woods (1979) administered female Sprague-Dawley rats a single gavage

12 dose of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and measured cytochrome P450 (CYP)

13 levels and benzo[*a*]pyrene hydroxylase (BPH) activity as a marker of hepatic microsomal

14 cytochrome P448-mediated enzyme activity. They found a statistically significant increase in

15 BPH at doses ≥2 ng/kg and a significant increase in cytochrome P450 levels at doses

16 ≥600 ng/kg. Aryl hydrocarbon hydrolase and 7-ethoxyresorufin-O-deethylase (EROD) were

17 both significantly increased 3 months after exposure; however the elevation did not maintain

18 statistical significance at 6 months. No other indicators of hepatic effects were analyzed. CYP

19 induction alone is not considered a significant toxicologically adverse effect given that CYPs are

20 induced as a means of hepatic processing of xenobiotic agents. Additionally, the role of CYP

21 induction in hepatotoxicity and carcinogenicity of TCDD is unknown, and CYP induction is not

22 considered a relevant POD without obvious pathological significance.

23

24 **H.6. LATCHOUMYCANDANE ET AL. (2003)**

25   Latchoumycandane et al. (2003) examined the induction of oxidative stress in epididymal

26 sperm of male Wistar rats. The activities of antioxidant enzymes including superoxide dismutase

27 (SOD), catalase (CAT), glutathione reductase (GRX), and glutathione peroxidase (GPX), as well

28 as the oxidative stress indicators hydrogen peroxide (H_2O_2) and lipid peroxidation (LPX) were

29 measured in epididymal sperm, caput epididymis, corpus epididymis, and cauda epididymis

30 following gavage dosing of 0, 100, 1,000, and 10,000 ng/kg-day TCDD for 4 consecutive days.

31 No significant changes in epididymal sperm counts were evident at any dose tested compared to

1   control. SOD, CAT, GRX, and GPX activities were significantly decreased at doses

2    $\geq$1,000 ng/kg-day in epididymal sperm. H_2O_2 and LPX were significantly increased at all doses

3   tested. SOD, CAT, GRX, and GPX activities were significantly decreased only at the highest

4   dose in the caput epididymis and corpus epididymis, but were significantly decreased at all doses

5   tested in the cauda epididymis. Conversely, H_2O_2 and LPX were significantly increased only at

6   the highest dose in the caput epididymis and corpus epididymis, but were significantly increased

7   at all doses tested in the cauda epididymis. Although several oxidative stress indicators were

8   significantly changed in this study, sperm count was not altered, and no other indices of sperm

9   function were assessed; it is unfeasible to link the markers of oxidative stress to a

10   TCDD-induced toxicological outcome. Therefore, these endpoints are not considered relevant as

11   POD candidates.

12

13   **H.7. LUCIER ET AL. (1986)**

14   Because TCDD had been detected in the soil of contaminated locations, determining the

15   bioavailability of TCDD from ingested soil may be important to the calculation of safe exposure

16   levels. Lucier et al. (1986) fed adult female Sprague-Dawley rats TCDD contaminated soil or

17   gave them TCDD in corn oil at various doses and compared the effects of TCDD on biochemical

18   parameters from liver tissue. They found that equivalent doses of TCDD in corn oil and soil

19   produced similar increases in hepatic aryl hydrocarbon hydroxylase activity (AHH) and UDP

20   glucuronyltransferase activity. They determined that AHH was statistically induced 1.8-fold at

21   15 ng/kg in corn oil and 40 ng/kg in soil. Cytochrome P450 was significantly increased at higher

22   doses. No clinical signs of acute toxicity or changes in body weight were observed. The

23   association between AHH activity and TCDD-mediated hepatotoxicity is unknown and no

24   adverse endpoints were measured. Thus, this endpoint is not suitable as a POD candidate.

25

26   **H.8. MALLY AND CHIPMAN (2002)**

27   Mally and Chipman (2002) evaluated the effect of TCDD on gap junctions,

28   hypothesizing that as a nongenotoxic carcinogen, TCDD may induce tumor formation by

29   disturbing tissue homeostasis. Female F344 rats were dosed with TCDD by oral gavage for

30   either 3 consecutive days or 2 days a week for 28 days. Gap junction connexin (Cx) plaque

31   expression and hepatocyte proliferation was measured. The study authors report a decrease in

1 Cx32 plaque number and area in the liver of rats exposed to 0.7 ng/kg-day and higher, however

2 they did not find an associated increase in hepatocyte proliferation. No clinical signs of toxicity

3 were observed, and histological examination of the liver revealed no abnormalities. In the

4 absence of additional indicators of hepatotoxicity, a decrease in Cx32 plaque formation is not

5 clearly linked to TCDD-mediated hepatotoxicity or hepatocarcinogenicity, nor is it considered an

6 adverse effect. This endpoint is not considered a toxicologically relevant POD.

7

8 **H.9. SEWALL ET AL. (1993)**

9 Sewall et al. (1993) investigated alterations in the epidermal growth factor receptor

10 (EGFR) pathway in a two-stage initiation promotion model of TCDD hepatic cancer. EGFR

11 signaling has been implicated in the altered cell growth induction by tumor promoters. Female

12 Sprague-Dawley rats were administered TCDD biweekly by oral gavage for 30 weeks following

13 initiation by a single dose of diethylnitrosamine (DEN). A group also received TCDD without

14 prior DEN initiation. Livers were harvested and fixed from sacrificed animals and sections

15 tested for EGFR binding, autophosphorylation, immunolocalization, and hepatic cell

16 proliferation. The authors report a significant dose-dependent decrease in plasma membrane

17 EGFR maximum binding capacity in TCDD-exposed rats beginning at 3.5 ng/kg-day. However,

18 at this same dose, the authors note a statistically significant decrease in cell proliferation (as

19 measured by DNA replication labeling), with increases in proliferation only occurring at higher

20 doses (125 ng/kg-day). No other indicators of hepatic toxicity or tumorigenicity were assessed.

21 The role of EGFR in TCDD-mediated hepatotoxicity and hepatocarcinogenicity is unknown, and

22 as such, this endpoint cannot be unequivocally linked to TCDD-induced hepatic effects nor

23 labeled as adverse. Thus, it is not suitable as a POD candidate.

24

25 **H.10. SLEZAK ET AL. (2000)**

26 Slezak et al. (2000) studied the impact of subchronic TCDD exposure on oxidative stress

27 in various organs of B6C3F$_1$ female mice. The oxidative stress indicators superoxide anion

28 (SA), lipid peroxidation (TBARS), ascorbic acid (AA), and total glutathione (GSH) were

29 measured in liver, lung, kidney, and spleen following gavage dosing for 13 weeks (5 days a

30 week). Tissue TCDD concentrations also were measured. Significant TCDD-induced changes

31 in the liver included decreased SA and GSH at 0.15 ng/kg-day, increased GSH at

1   0.45 ng/kg-day, increased SA and AA at 15 and 150 ng/kg-day, and increased GSH and TBARS

2   at 150 ng/kg-day. Unlike the liver, there was no significant increase in SA in the lung, but SA

3   was significantly decreased at 0.45, 15, and 150 ng/kg-day. Lung GSH and AA were decreased

4   at 0.15 ng/kg-day, while AA was increased at 15 and 150 ng/kg-day. In the kidney, SA was

5   increased at 15 and 150 ng/kg-day. Renal GSH, like the liver and the lung, was decreased at

6   0.15 ng/kg-day with this trend continuing at 0.45 and 1.5 ng/kg-day, and AA levels were lower at

7   all doses except 1.5 ng/kg-day. In the spleen, SA was unchanged, GSH was increased at

8   150 ng/kg-day, and AA was decreased at 0.15, 1.5, and 150 ng/kg-day. Although several

9   oxidative stress indicators were significantly changed in this study, no other indices of liver,

10   lung, kidney, or spleen pathology were measured, and it is unfeasible to link the markers of

11   oxidative stress to a TCDD-induced toxicological outcome in the organs assessed. Therefore,

12   these endpoints are not considered relevant as POD candidates.

13

14   **H.11. SUGITA-KONISHI ET AL. (2003)**

15   Sugita-Konishi et al. (2003) investigated the change in host resistance of mice offspring

16   lactationally exposed to TCDD. Pregnant C57BL/6NCji mice were administered TCDD via

17   drinking water from parturition to weaning of the offspring (17 days). One group of offspring

18   was then infected with *Listeria monocytogenes* and blood and spleen samples were collected

19   various time points post infection. Uninfected, TCDD exposed offspring were weighed and their

20   spleens and thymuses removed for assay of cellular content and protein expression. TCDD

21   exposure caused a statistically-significant decrease in relative spleen weight and a

22   statistically-significant increase in thymic CD4+ cells in the high-dose group (11.3 ng/kg-day).

23   Offspring infected with *Listeria* following TCDD exposure exhibited a statistically significant

24   increase in serum tumor necrosis factor alpha 2 days after infection in both sexes in the low-

25   (1.14 ng/kg-day) and high-dose groups. The authors conclude that exposure to TCDD disrupted

26   the host resistance of the offspring at the lowest dose tested, despite the primary immune

27   parameters being unaffected. Without an obvious association between TCDD and immune

28   function, however, this endpoint is not suitable for identification of a

29   lowest-observed-adverse-effect level (LOAEL). Thus, the LOAEL for this study is

30   11.3 ng/kg-day, and the no-observed-adverse-effect level is 1.14 ng/kg-day.

31

H.12. TRITSCHER ET AL. (1992)

Tritscher et al. (1992) performed an initiation-promotion study in female Sprague-Dawley rats. Rats were initiated with an i.p. injection of diethylnitrosamine (DEN) or saline, followed 2 weeks later by promotion with biweekly administration of TCDD via gavage for 30 weeks. Hepatic cytochrome P450 levels (CYP1A1 and CYP1A2) and EROD activity were quantified, and immunohistochemical detection of CYP1A1 and CYP1A2 in liver was also conducted. Liver TCDD concentrations were also analyzed. A dose-response trend for increased liver CYP1A1 and CYP1A2 protein was observed in initiated and noninitiated rats as assessed by microsomal quanitification and immunihistochemical staining. A strong relationship between liver TCDD concentration and CYP1A1 and CYP1A2 protein levels and EROD activity was also observed in DEN/TCDD-treated rats. CYP induction alone is not considered a significant toxicologically adverse effect given that CYPs are induced as a means of hepatic processing of xenobiotic agents. Additionally, the role of CYP induction in the hepatotoxicity and carcinogenicity of TCDD is unknown, and CYP induction is not considered a relevant POD without obvious pathological significance.

H.13. VANDEN HEUVEL ET AL. (1994)

Vanden Heuvel et al. (1994) analyzed changes in hepatic messenger ribonucleic acid (mRNA) following a single administration of TCDD to female Sprague-Dawley rats by oral gavage. Four days after treatment, animals were sacrificed and livers were excised. Using reverse transcriptase-polymerase chain reaction on hepatic ribonucleic acid, they compared levels of "dioxin responsive" mRNA's (CYP1A1, uridine diphosphate [UDP]-glucuronosyltransferase I, plasminogen activator inhibitor 2, and transforming growth factor α) at various doses of TCDD and at control (baseline) levels. They determined that CYP1A1 elicited the most sensitive response to TCDD, with a statistically significant increase (threefold) in mRNA from rat livers exposed to 1 ng/kg-day TCDD. Induction of CYP1A1 expression is not considered an adverse effect, as the role of CYP1A1 in TCDD-mediated carcinogenicity is unsettled. Therefore, in the absence of other indicators of hepatoxicity, increases in liver CYP1A1 cannot be considered toxicologically relevant for a POD candidate.

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APPENDIX I

Literature Search Terms

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National Center for Environmental Assessment
Office of Research and Development
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CONTENTS—Appendix I: Literature Search Terms

APPENDIX I.   LITERATURE SEARCH TERMS

The U.S. Environmental Protection Agency (EPA) has developed a literature database of peer reviewed studies on 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) toxicity, including in vivo mammalian dose response studies and epidemiologic studies for use in quantitative TCDD dose-response assessment and supporting qualitative discussions. An initial literature search for studies published since the 2003 Reassessment was conducted by the U.S. Department of Energy's Argonne National Laboratory (ANL) through an Interagency Agreement with EPA. ANL used the online National Library of Medicine database (PubMed) and identified studies published between the year 2000 and October 31, 2008.

EPA published the initial literature search results in the Federal Register on November 24, 2008 (73 FR 70999; November 24, 2008) and invited the public to review the list and submit additional peer reviewed in vivo mammalian dose response studies for TCDD, including epidemiologic studies that were absent from the list (U.S. EPA, 2008). Submissions were accepted by the EPA through an electronic docket, email and hand delivery, and were evaluated for use in TCDD dose-response assessment.

This appendix contains the search terms utilized by ANL in conducting the literature search.

LITERATURE SEARCH TERMS

1746-01-6	anamnestic response	behavioral
2,3,7,8-TCDD; TCDD	anemia	behavioral abnormalities
dioxin	animal, animal stud	benchmark (see BMC, BMD, others)
absorbed, absorbed dose	antibody	benign
absorbed, absorption	antigen	bicuspid
accident	antigen presenting cell	bicuspid valve
acetylcholine	antigenic	bile
acetylcholinesterase	aorta	bile, biliary
acute	apoptosis	bile, biliary
acute myocardial infarction	arcuate nucleus	biliary
adenocarcinoma	area under curve	binding
adenoma	artery	bioaccumulation
adipose	atheromatous plaque	bioavailability, bioavailable
administered	atria	bioavailable, bioavailability
administered, administered dose	atrioventricular	biochem, biochemical
adrenal	atrioventricular fistula	biological half-life
adrenal (gland, cortex)	atrioventricular node	biotransformation
adverse	atrioventricular opening	blind
age	atrioventricular valve	blood
agent orange	atrium	blood cells
agonist	atrophy	blood concentration
Ah, aryl hydrocarbon, Ah receptor	AUC, area under the curve	blood pressure
AhR, arylhydrocarbon receptor	autoimmune	blood, blood concentration
alveolar	B cell	BMC, benchmark concentration
alveolar duct	B-cell	BMD, benchmark dose
alveoli	beagle	BMDL
AMI	behavior	BMR, benchmark response

body burden	cardio (myopathy), cardiovascular, CV	cohort
body weight	cardiogenic	colitis
bolus	cardiogenic plate	colon
bone	cardiomyopathy	compartment
bowel	cardiovascular	concentration, peak
brain	cardiovascular disease	conjugate
brain aromatase	case report	contaminant, contamination, contaminated
brain stem	CD4	control
brain tissue	CD8	COPD
brain tissues	cell, cell line, cell proliferation	COPD, chronic obstructive pulm disease
brainstem	cell-mediated immune response	coplanar, coplanar PCB(s)
breast milk	central nervous system	cornea
breast milk, lactation, milk	cerebellar	corneal
bronchi	cerebral	coronary
bronchial	cerebrum	cortical
bronchial tree	chloracne	cortical asymmetry
bronchiole	cholesterol	cortical cells
CA, cancer, carcino, carcinogen	chordae tendineae	cortical thickness
cancer	chronic	count
carcinogen	chronic lymphocytic leukemia	critical
carcinogenesis	chronic obstructive pulmonary disease	culture, tissue culture
carcinogenic	cirrhosis	cuspid
carcinoma	cirrhotic	cutaneous
cardiac	cleft	CV
cardiac arrest	clinical	CVD
cardiac cycle	cognition	CVD (CV), cardiovascular disease
cardiac notch	cognitive	CYP, cytochrome P450
cardio	cognitive abnormalities	cytochrome, CYP (1A1, 1A2)

LITERATURE SEARCH TERMS (continued)

cytokine	disposition	endometriosis
dam	distribute, distributed, distribution	endometriosis
deficit	DLC, dioxin-like compound	enterohepatic
defoliant	dog	enzyme
degeneration	dorsal raphe nuclei	epidemiol, epidemiologic
delayed-type hypersensitivity reaction	dose response, dose-response	epidermal
dendrite	dose, dose metric, dose-dependent	epidermis
dendritic	dose, dose-dependent	equilibrium
dentition	dose-dependent	ER
depot	duodenum	EROD
depot	dysplasia	EROD, ethoxyresorufin-o-deethylase
dermal	ED, effective dose	estrogen
dermal, dermis, transdermal	edema	estrogen receptor
dermal, transdermal, skin	effect, effect level	estrogen, ER, estrogen receptor
dermis	eliminate, eliminated, elimination	ethoxyresorufin-O-deethylase
developing	embryo	excrete(d), excretion
developmental	embryo, embryotox(ic), embryonic	excrete, excreted, excretion
developmental, developmental effect	embryonic	eye
diabetes	embryotoxic	fat
diabetic	endo, endocrine, endocrine disrupt(or/ion)	fat, fatty
dialysis	endocarditis	fate
diaphragm	endocrine	fatty
diastole	endocrine disrupter	fecal
diet, dietary	endocrine disrupting	fecal, feces
dietary, ingestion	endocrine disruption	feces
differentiation, cell differentiation	endocrine disruptor	fecundity (2 spellings?)
diffusion, permeability	endocrinology	FEL, frank effect, frank effect level
disease	endometrial	female

fertility	gestation	heart disease
fetal	gestation, gestational, gestational day, GD	heart murmur
fetal, feto, fetotox, fetotoxic, fetus	gestational	hematology
fetotoxic	gestational day	hematopoiesis
fetus	GI	hemoglobin
FEV	glia	hemopoeisis
fish	glial cells	hemopoeisis, hematopoiesis / poeitic
foci	glomerular	hemopoeitic
food consumption	glomerulus	hemorragic
forced expiratory volume	glucagon	hemorrhage
forebrain	gonadotropin	hemorrhage, hemorragic
fraction	granule neuroblast	hemotoxin
fraction, ratio	gravid	hepatic
function	growth hormone	hepatic enzyme
furan, furans	gut	hepatic, hepato(cyte), hepatotox(ic)(ity)
gastritis	haematology	hepatic, liver
gastrointestinal	haematopoiesis	hepatocyte
gastrointestinal, GI, gut	haemopoeisis	hepatoma
gastrointestine	haemopoeitic	hepatotoxicity
gastrointestine, gastrointestinal, GI, gut	half-life, half life, half-lives	hepatoxic
gavage	half-life, half-lives	herbicide
gavage, bolus	hamster	high blood pressure
GD	hamster (Syrian golden)	high density lipoprotein
gender	HDL	high-density lipoprotein
genotox, genotoxicity	HDL, high-density lipoprotein	hippocampus
genotoxic	health	histologic, histopathologic, histopath
genotoxicity	heart	Hodgkins (2 spellings)
gerbil	heart attack	hormone, hormone

LITERATURE SEARCH TERMS (continued)

hospital	immune suppression	inhal, inhalation
human	immune system	inhibition
human, human stud	immune, immuno, immunological	injection
humoral immune response	immunocompromised	instillation
hydronephrosis	immunoglobulin	instillation, tracheal instillation
hydroxylate(ion)	immunologic	insulin
hyperglycemia	immunological	interleukin
hyperglycemia, hypoglycemia	immunology	intermediate
hyperglycemic	immunosuppression	intermediate, reactive intermediate
hyperplasia	immunosuppressive	intestinal
hyperplasia, hypertrophy	immunotox, immunotoxicity	intestine
hypersensitivity reaction	immunotoxic	intraperitoneal, ip
hypersensitized	immunotoxicity	intravenous, iv
hypertension	implantation	involuntary muscle
hypertrophy	impurity, impurities, impure	IP, intraperitoneal
hypertrophys	in vitro, in vivo	islets of Langerhorn
hypoglycemia	individual	IV, intravenous
hypoglycemic	induce(d), inducible, induction	jaw
hypotension	induce(d), inducible, induction, induc	jejunum
hypothalamus	infant	keratitis, keratitic, keratin(ized), kerat
hypothalamus-preoptic area	infection	kidney
IL	infertility	kinetic
IL 5, interleukin 5	inflammation	Kupffer
ileitis	inflammatory	lactat(ion), lactate, lactational
ileum	inflammatory lesion	lactation
immune	inflammatory, inflammation	lactational
immune regulation	influenza	large intestine
immune response	ingestion	LC, lethal concentration

LD, lethal dose	macrophage	mitral regurgitation
LDL	major histocompatibility complex	mitral valve
LDL, low-density lipoprotein	male	MOA, mode (mechanism) of action
lesion	malignancy	model
lethality	malignant	molar
leukemia	malignant, malignancy	monkey (rhesus)
leukemia, leukemic	mammal	mortality
leukemic	mammary	motor development
lipid	mammary gland	mouse (incl. Swiss)
lipophilic	mammary, mammary gland	MR
lipophilic, lipophilicity	man	MROD
lipophilicity	mandible	Mrp, multidrug resistance-assoc protein
liver	marker	mucosa
liver enzyme	mating behavior	mucosa, mucosal, oral mucosa
LOAEL, LOEL	mechanism, mechanistic (see MOA)	mucosal
lobes	median raphe nuclei	muscosa
low blood pressure	men	muscosal
low density lipoprotein	metabolic	muta, mutagen, mutation
low-density lipoprotein	metabolism, metabolite, metabolize	mutagen
low-dose	metabolite	mutation
lung	metaplasia	myeloid leukemia
lymph node	methoxyresorufin-O-deethylase	myocardial
lymph, lymphatic	MHC	myocardial infarction
lymphocyte	MI	myocardium
lymphoid	mice (several strains)	myocyte
lymphoid organs	microsome, microsomal	nasal
lymphoma	mink	nasal (turbinates)
macaque	mitral	nasal turbinates

LITERATURE SEARCH TERMS (continued)

natural killer	neutrophil	papilloma
neocortical	NK	paraventricular nucleus
neonatal	NOAEL, NOEL	parent
neoplasia	nonca, noncancer, noncarcinogenic	parenteral
neoplasm	non-Hodgkins lymphoma (4 spellings)	partition, partitionong
neoplasm, neoplast, neoplastic, neoplasia	NTS	pathol, pathology
neoplastic	nuclear receptor	pathway
nephron	nucleus of solitary tract	patient
nerve	occupational	PB, physiol, physiologically based
nerve conductance	ocular	PBPK
nerve conduction	olfactory bulb	PCB, polychlorinated biphenyl
nerves	oncogen	PD, pharmacodynamic
neural	oncogene	peak
neural activity	oncogenic	peak, peak dose
neuro, neurologic	optic	people
neuroblast	oral	percent
neuroblastoma	oral mucosa	pericardium
neurochemical	organ	perinatal
neurodevelopment	osteo	peripheral nervous system
neurological	osteoblast	peripheral neuropathy
neuropathy	osteosarcoma	person
neuropeptides	ovary	pesticide
neuropsychological	palate	physiological
neurotox, neurotoxic, neurotoxicity	palate, palat	pig, guinea pig (Hartley)
neurotoxic	pancreas	pituitary
neurotoxicity	pancreatic	pituitary hormone
neurotransmitters	pancreatitis	PK, pharmacokinetic
neurotrophic factor	papillary muscle	plasma

PND	pulmonary valve	rhabdomyosarcoma
PND, postnatal day	pulmonary vein	risk, risk analysis, risk assessment
POD, point of departure	pulmonary, transpulmonary	rodent
polymorphism, polymorph	pup	ROS
polyneuropathy	pup survival	sarcoma
POP, persistent organic pollutant	rabbit	SCC
population	rat (several strains)	SCC, squamous cell carcinoma
porphyrin, porphyria	rate	sensitive, sensitivity
postnatal	rate, time, time-dependent	sequestration
postnatal day	ratio, fraction	serum
potency, potent	reactive (intermediate)	sex
pregnancy	reactive oxygen species	sex ratio
pregnant	receptor, receptor mediated	sheep red blood cells
pregnant, pregnancy	red blood cells	short term
prenatal	regenerate, regeneration, regen	sight
preoptic area	regeneration	signal, signaling
primate	renal	skeletal
product, production	repro, reproductive, reprotox	skeleton
profile	reproduction	skin
progesterone	reproductive	skin
proliferation	reprotoxic	small intestine
promotion, promoter, promote, promoting	respiration	smooth muscle
public	respiratory	soft tissue sarcoma
pulmonary	respiratory, respired air	somatic sensory cortex
pulmonary artery	respired air	species
pulmonary edema	response	sperm
pulmonary embolism	retina	sperm abnormality
pulmonary epithelium	retinal	sperm count

spleen	TEF, toxic equivalency factor	time
sprayed area	TEQ, toxic equivalent	time, time-dependent
squamous cell carcinoma	teratogen	time, time-weighted
SRBC	teratogen, teratogenic(ity)	tissue
SRBC, sheep red blood cell	teratogenic	tissue, target tissue
steady state	teratogenicity	TK, toxicokinetics
stomach	testes	tooth
storage, stored	testes, testicular, testic	toxic, toxicity, toxico, toxicological
strain	testicular	trachea
subacute	testosterone	transcutaneous
subchronic	TG	transdermal
subcutaneous, sc	TG, triglyceride	transduction
substantia negra	TH	transformation
superior vena cava	TH, thyroid hormone	transpire(d) air
superoxide anion	threshold	transpulmonary
superoxide dismutase	thymi	tricuspid
suprachiasmatic nucleus	thymic atrophy	tricuspid valve
susceptible, susceptibility	thymocyte	triglyceride
synapse	thymus	triiodothyronine
synaptic	thymus involution	TSH
system	thymus, thymic, thym	TSH, thyroid stimulating hormone
systole	thyroid	tubular
T cell	thyroid function	tubule
T3	thyroid hormone	tumor
T4	thyroid stimulating hormone	tumor, tumorigenic
T-cell	thyroid, thyroid function	tumorigenic
TD, toxicodynamics	thyroxine	turbinates
teeth	thyroxine, T4; T3, triiodothyronine	uncertainty

urinary, urine	ventricle	vulnerable
urine, urinary	ventricular	vulnerable plaque
uterine	ventromedial hypothalamus	wasting syndrome
uterus	vision	WBC
uterus, uterine	visual cognition	weight
variability	visual motion	white blood cell
vascular	visual, visual acuity	white blood cells
vascular disease	vital capacity	women
vehicle	vitamin A	worker
vein	vitamin D	

I.1.   REFERENCES

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