APPENDIX A

Dioxin Workshop Report

NOTICE

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

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Summary of U.S. EPA Dioxin Workshop

February 18−20, 2009

Cincinnati, Ohio

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

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

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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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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.

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/.

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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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.

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 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
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- 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.

References

Baccarelli, A., P. Mocarelli, D.G. Patterson et al. 2002. Immunologic effects of dioxin: New results from Seveso and comparison with other studies. Environ. Health Perspect. 110(12):1169-1173.

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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)

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- 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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Patandin, S., C.I. Lanting, P.G.H. Mulder, E.R. Boersma, P.J.J. Sauer and N. Weisglas-Kuperus. 1999. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J. Pediatr. 134:33–41.

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Vreugdenhil, H.J., C.I. Lanting, P.G. Mulder, E.R. Boersma and N. Weisglas-Kuperus. 2002. Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age. J. Pediatr. 140:48–56.

Wang S.L., P.H. Su, S.B. Jong, Y.L. Guo, W.L. Chou and O. Päpke. 2005. *In utero* exposure to dioxins and polychlorinated biphenyls and its relations to thyroid function and growth hormone in newborns. Environ. Health Perspect. 113:1645–1650.

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

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

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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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

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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

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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.

[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 **Session 5: Quantitative Uncertainty Analysis of Dose-Response (Hall of Mirrors)**

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 B

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

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 B. EVALUATION OF CANCER AND NONCANCER EPIDEMIOLOGICAL STUDIES FOR INCLUSION IN TCDD DOSE-RESPONSE ASSESSMENT

B.1. EVALUATION OF CANCER STUDIES

B.1.1. NIOSH Cohort Studies

Table B-1. Fingerhut et al., 1991—All cancer sites, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.

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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. Since this study used duration of exposure as the exposure metric, dose-response relationships cannot be quantified.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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 B-2. Steenland et al., 1999—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Exposure scores 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. 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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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. (2001). Therefore, this study was considered for further dose-response analyses.

Table B-3. Steenland et al., 2001—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
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.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied Am J Epidem, 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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.

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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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, criterion has been satisfied and it is recommended that this study be considered for dose-response analysis.

Table B-4. Cheng et al., 2006—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. This is the same data set used in the Steenland et al., (2001) 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 with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 inter-individual 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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Risk Analysis, 2006; 4:1059–1071. 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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Cumulative serum lipid concentrations were estimated for each worker. No other dioxin-like compounds were assessed in this analysis.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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. These data were considered for further dose-response analyses.

Table B-5. Collins et al., 2009—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Vital status complete for all but two workers.

2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
Response	Consideration not 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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. The authors used these serum 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. Exposure levels were not provided.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate 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 for soft tissue sarcomas for which a positive association has been demonstrated.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. This study has the largest number of serum samples obtained from a specific plant.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria not satisfied. While the cohort did have sufficient follow-up, no evaluation of possible latent effects was presented.

Conclusion	Study is not suitable for further evaluation or dose-response modeling since an exposure-response relationship was not demonstrated. The evaluation of exposure metrics and latency considerations should be expanded beyond that presented in the paper. Previous analyses of these same workers found positive associations between cancer mortality and TCDD (Steenland et al., 2001). The reasons for the discrepancy in the findings from the two papers may be due to Steenland et al.'s use of nonlinear exposure metrics, incorporation of a 15-year lag interval, or differences in the TCDD exposure estimates themselves.

B.1.2. BASF Cohort Studies

Table B-6. Zober et al., 1990—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 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 biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. See above discussion of underascertainment in mortality for some of the cohort members. Although it is likely that other co-exposures occurred (e.g., among firefighters), confounding could only occur if these co-exposures were associated with both the endpoint and exposure (TCDD) being considered.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Int Arch Occup Envir 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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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.

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3 **Table B-7. Ott and Zober, 1996—All cancer sites combined**
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1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.

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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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 a fair number of 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. Therefore, quantitative dose-response analyses were considered for these data.

B.1.3. The Hamburg Cohort

Table B-8. Manz et al., 1991—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Smoking data were similar between exposed and nonexposed cohort based on independent samples. Occupational exposure for which individual data are lacking unlikely to explain dose-response with TCDD.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Lance,t 1991, 338:959–964. The authors discussed potential for misclassification using death certificates, healthy worker effect and their 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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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 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 B-9. Flesch-Janys et al., 1995; Flesch-Janys et al., 1996 erratum—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Medical records used to identify deaths over the period 1952–1992.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
Response	Consideration satisfied. Dose-response relationship observed across 6 exposure categories, with the cohort of gas supply workers used as the referent.
4. Consideration	Consideration satisfied. Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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 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 B-10. Flesch-Janys et al., 1998—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
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 co-exposures (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 with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 sub-sample suggesting little bias from lack of smoking data.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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 B-11. Becher et al., 1998—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Risks adjusted for exposures to TEQ, β-hexachlorbenzene, 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 with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 PCDD/Fs other than dioxin due to high correlations with β-HCH, and inability to characterize risks associated with exposures in children.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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.

B.1.4. The Seveso Cohort Studies

Table B-12. Bertazzi et al., 2001—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.

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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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 B-13. Pesatori et al., 2003—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Mortality appears to be well captured from the vital statistics registries in the region (99% complete).
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
Response	Consideration not satisfied. While excesses of mortality were observed for several health conditions in Zone A, a dose-response pattern was not observed across Zones A, B and R. Among men, excess mortality observed in zone A included chronic ischemic disease, and chronic obstructive pulmonary diseases. Among females, an excess in Zone A was observed with hypertension.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate statistical power.

Response	Consideration satisfied. Only 39 deaths observed among men in Zone A; 39 deaths observed among their female counterparts. Among females, only 3 deaths from hypertension observed in Zone A, and only 4 deaths observed among males for chronic obstructive pulmonary disease.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Occup Env 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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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 B-14. Consonni et al., 2008—All cancer sites combined, site-specific analyses

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.

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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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 B-15. Baccarelli et al., 2006—Site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.

Response	Consideration satisfied. Polymerase chain reaction (PCR) 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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
Response	Consideration was 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-Hodgin's lymphoma is uncertain.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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's lymphoma.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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's lymphoma. Given the speculative nature of this endpoint and lack of demonstrated adverse effect, dose-response analyses for this outcome were not conducted.

Table B-16. Warner et al., 2002—Breast cancer incidence

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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), discussed important strengths of the study including characterization of TCDD using serum collected near the time of the accident.

2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. Serum was used to estimate TCDD levels in 981 of 1271 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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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.

B.1.5. The Chapaevsk Study

Table B-17. Revich et al., 2001—All cancer sites combined, and site-specific analyses

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 studied on the basis of information in the official medical statistics.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. Given that this is an ecological study, bias may be present.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration cannot be evaluated. 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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration not satisfied. No individual-level exposure estimates were used.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
Response	Criteria not 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 death registrations between regions. The authors do acknowledge, however, that new investigations being undertaken would characterize exposure using serum-based measures.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. It is a cross-sectional study that compares mortality rates between regions. No individual-level exposure data available.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria not satisfied. No individual-level exposure estimates were used in the study.
Conclusion	These cancer data are cross-sectional in nature and not appropriate for a dose-response analysis.

B.1.6. The Air Force Health ("Ranch Hands") Study

Table B-18. Akhtar et al., 2004—All cancer sites combined and site-specific analyses

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. The risk estimates were adjusted for a number of factors measured on an individual level including smoking. However, analyses are unable to distinguish between exposure to TCDD and 2,4-D as both were used in equal parts in the formulation of Agent Orange.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. TCDD exposures at the end of duty were estimated by back-extrapolating 1987 serum values.
Conclusion	The major limitation of the study is the inability to isolate effects of TCDD from other chemicals used in the formulation of the herbicides. This limitation precludes dose-response modeling of the TCDD and cancer outcomes data.

Table B-19. Michalek and Pavuk, 2008—All cancer sites combined

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. Information collected from repeated physical examinations allowed for the adjustment of risk factors such as smoking. Agent Orange was a 50% mixture of 2,4-D and TCDD; therefore, potential for confounding by other coexposures is likely.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.

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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. TCDD exposures at the end of duty were estimated by back-extrapolating 1987 serum values.
Conclusion	Ranch Hand veterans were exposed to other contaminants in the herbicides that were mixed, thereby making it difficult to determine independent effects of TCDD on cancer. In particular, 2,4-D has been shown to be associated with some cancers, notable cancer of the prostate. In our view, this limitation precludes dose-response modeling of TCDD and cancer using data from this cohort.

B.1.7. Other Studies of Potential Relevance to Dose-Response Modeling

Table B-20. 't Mannetje et al., 2005—All cancer sites combined, site specific analyses

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. National records for death registrations through the New Zealand Health Information Service (NZHIS). 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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Exposure measures were limited to duration of employment and exposed/unexposed.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
Response	Criteria not satisfied Occup Env 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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. This study used duration of exposure, at an individual level, as a surrogate measure of TCDD.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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 B-21. McBride et al., 2009b—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
Response	Consideration not satisfied. There was no examination of dose-response effects.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.

Response	Criteria not satisfied. TCDD exposures were not quantified.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria not satisfied. Effective dose could not be estimated given the lack of individual-level exposure data.
Conclusion	The study lacks the quantification of exposures at an individual level precluded dose-response analysis.

Table B-22. McBride et al., 2009a—All cancer sites combined, site-specific analysis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Workers lost to follow-up were an unlikely source of bias especially for internal analyses. 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 with evidence of an exposure-response relationship.
Response	Consideration not satisfied. 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's Lymphoma.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied.

1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Published in J Occup Environ Med 51:1049-1056. This paper discussed the 22% of the cohort lost to follow-up, differences in cohort definitions between sprayers and producers, and the potential for other exposures during employment at the plant.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined.
Response	Criteria satisfied. Effective dose could be estimated from serum-derived cumulative exposure estimates.
Conclusion	Given that no dose-response associations were found, the data are not suited to dose-response analysis.

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3 **Table B-23. Hooiveld et al., 1998—All cancer sites combined, site-specific**
4 **analysis**
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1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
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 fort lung cancer as well.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Am J Epidemiol, 1998, 147:891–901. The authors address potential limitations of estimating TCDD exposure from a sub-sample of surviving workers, lack of smoking data, the healthy worker effect, and relevance of other occupational exposures.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure 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.

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B.2. EVALUATION OF NONCANCER STUDIES

B.2.1. NIOSH Cohort

Table B-24. Steenland et al., 1999—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.

Response	Criteria not satisfied. Exposure scores assigned at an individual level based on job-exposure matrix (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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
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.

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3 **Table B-25. Collins et al., 2009—Mortality (noncancer)**
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1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Vital status complete for all but two workers.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.

Response	Consideration satisfied. The authors used these serum 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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. This study has the greatest number of serum samples obtained from a specific plant.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
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.

B.2.2. BASF Cohort

Table B-26. Ott and Zober, 1996—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Mortality ascertainment appeared to be fairly complete.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.

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 with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
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, no dose-response analyses of these data are recommended.

B.2.3. Hamburg Cohort

Table B-27. Flesch-Janys et al., 1995; Flesch-Janys et al., 1996 erratum—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Medical records used to identify deaths over the period 1952–1992.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. Exposure based on half-life estimates from individuals with repeated serum measures. Other dioxin-like compounds 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.

B.2.4. The Seveso Women's Health Study

Table B-28. Eskenazi et al., 2002a—Menstrual cycle characteristics

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
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 resulted in a reduced odds of scanty menstrual flow. No association was noted with these two outcomes among postmenarcheal women. A decreased risk of irregular cycles was observed with higher TCDD levels.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.

Response	Criteria 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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response had to be a nonfatal endpoint.
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 (13 years).
Conclusion	This study meets all of the criteria and considerations for further dose-response analysis. The determination of the relevant time interval over which TCDD dose should be considered is uncertain .

Table B-29. Eskenazi et al., 2002b—Endometriosis

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration not satisfied. Results of a pilot study showed that ultrasounds had excellent specificity and sensitivity for ovarian endometriosis.

2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. More than half of the women were classified as 'uncertain' with respect to endometriosis disease status.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Criteria 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 are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration not satisfied. Only a total of 19 cases of endometriosis were identified.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
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 using laparoscopy. Finally, young women may have been underrepresented due to cultural difficulties in examining women who had never been sexually active.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
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	The lack of a statistically significant association coupled with a large number of women for which endometriosis disease status was "uncertain", precludes the use of these data to conduct dose-response analysis.

Table B-30. Eskenazi et al., 2003—Birth outcomes

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration not satisfied. Outcomes were identified through self-reported questionnaires. Women were found to over-report birth weight, and have a tendency to 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 biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. See above.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. There was no association between spontaneous abortions and $\log_{10}$TCDD, or with births small for gestational age. An inverse association with birth weight was noted in first eight years following the accident as were the number of births small for gestational age; however, none achieved statistical significance at $p < 0.05$.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Criteria 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 are large enough to yield precise estimates of risk and ensure adequate 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 post-explosion.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.

Response	Criteria not satisfied. TCDD exposures were extrapolated to 1976 values. However, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis.
Conclusion	The findings of the study are somewhat limited due to the reliance on self-reported information for pregnancy outcomes, and lack of paternal exposures. The findings were not statistically significant. Taken together, quantitative dose-response analyses for this study population is not recommended.

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3 **Table B-31. Warner et al., 2004—Age at menarche**
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1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
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.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Criteria 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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.

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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not 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 found. There may be some misclassification of age at menarche based on self-report, and biologically, the most relevant dose as suggested by animal studies occurs in utero. Additionally, it is difficult to identify the relevant time interval over which TCDD dose should be considered for dose-response analysis. For these reasons, these data are not suited to a dose-response analysis.

Table B-32. Eskenazi et al., 2005—Age at menopause

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Data obtained from the questionnaire allow for the potential confounding influence of several potential confounders to be controlled for.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration not satisfied. Although 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). 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.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Criteria 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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Environ Health Perspect, 113:858–862 (2005). Authors highlight this is first study to look at relationship between dioxin and age at menopause. Other limitations of the study include lowest exposure group (≤ 20.4 ppt) includes exposures level that are far higher than background, and age at menopause was based on retrospective recall. Strength of study is ability to characterize TCDD using serum measures.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
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 findings do not provide strong support for a dose-response relationship. As such, they are not well suited to a quantitative dose-response analysis.

Table B-33. Warner et al., 2007—Ovarian function

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 pre-ovulatory 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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
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 wit the odds of ovulation.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Criteria 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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. The women may not have been exposed at critical period (prenatally).
Conclusion	No association between TCDD levels and ovarian function was found. There may be some misclassification of period of the cycle based on self-report, and biologically, the most relevant dose as suggested by animal studies occurs in utero. For these reasons, these data are not suited to a dose-response analysis.

Table B-34. Eskenazi et al., 2007—Uterine leiomyoma

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.

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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
Response	Consideration satisfied, but inversely. An inverse dose-response pattern with the percentage of women diagnosed (current & 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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.

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 unknown.
Conclusion	The data suggest an inverse (protective) effect between fibroids and exposure to TCDD. As such, these data are not suited to further dose-response analyses.

B.2.5. Other Seveso Noncancer Studies

Table B-35. Mocarelli et al., 2008—Semen quality

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.

Response	Criteria satisfied. Involved males, < 16 years old at time of accident.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
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, quantitative dose-response analyses for this outcome were conducted.

Table B-36. Mocarelli et al., 2000—Sex ratio

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. Statistically significant findings achieved.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria not satisfied. The Lancet, 2000, 355:1858–1863. There is no discussion on the strengths and limitations of this study.

2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
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. 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 unknown.
Conclusion	The data from this study demonstrate a positive dose-response relationship with 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. Using the initial exposures in a dose-response model would yield LOAELs that are too high to be relevant to factor into the RfD calculation. Dose-response analysis for this outcome is, therefore, was not conducted.

Table B-37. Baccarelli et al., 2008—Neonatal thyroid function

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 of which Seveso if a part of.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied for component of the study based on plasma dioxin measures. 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.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.

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 are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied for exposure metric that was based on 'place of residence'. For plasma based estimate of maternal TCDD there were only 51 mother-child pairs. Only seven children in total were found to have b-TSH levels in excess of 5 uU/ml; this implies limited statistical power involving this health outcome.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
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 breastfeeding before b-TSH measurement was available.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria satisfied. Maternal TCDD levels were estimated at the time of delivery based on plasma samples, and the critical window of exposure can be defined as the 9 month gestation period.
Conclusion	The data provide an opportunity for quantitative dose-response analyses.

Table B-38. Alaluusua et al., 2004—Oral hygiene

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.

Response	Consideration satisfied. Additional risk factor information was collected on questionnaires. These factors were considered as adjustment factors. Findings potentially susceptible to participation biases.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Criteria satisfied. Despite small numbers, statistically significant findings were achieved.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Environmental Health Perspectives, 2004, 112(13)1313–1318. 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. 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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
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, quantitative dose-response analysis for this outcome was conducted.

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3 **Table B-39. Bertazzi et al., 2001—Mortality (Noncancer)**
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1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied for some causes of death, but not others. 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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
Response	Consideration not satisfied for most causes of death. An exception was the dose-response relationship was observed for chronic obstructive pulmonary disease across Zones A, and B.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. A total of 494 non-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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.

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. Critieria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
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 a quantitative dose-response analysis. 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 B-40. Consonni et al., 2008—Mortality (Noncancer)

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied for some causes of death, but not others. 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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration not satisfied. Lack of individual-level data precludes an examination of these uncertainties.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.

Response	Consideration satisfied for some causes of death but not others. For example, 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
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 a quantitative dose-response analysis. 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 B-41. Baccarelli et al., 2005—Chloracne

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
Response	Consideration satisfied. Chloracne cases identified using standardized criteria.
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. Authors discussed implications of differential elimination rates by age and body growth.

5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate 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.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
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 a strength of the study 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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria satisfied. TCDD was estimated in both chloracne cases and control using serum measures.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
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 B-42. Baccarelli et al, 2002 and 2004—Immunological effects

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Both exposure and outcome were objectively and accurately measured.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
Response	Consideration satisfied. Plasma IgG levels were inversely related with TCDD.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
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 association between IgG and TCDD was observed, however, because the relationship can not be described in terms of clinical relevance with respect to a specific health outcome, it is our view that these data are not suited to dose-response modeling.

B.2.6. Chapaevsk Study

Table B-43. Revich et al., 2001—Mortality (noncancer) and reproductive health

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 studied on the basis of information in the official medical statistics
2. Consideration	Risk estimates are not susceptible to biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. It is an ecological study.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.

Response	Consideration cannot be evaluated. 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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration not satisfied. No individual-level exposure estimates were used.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied. Population-based data over several years were used to make ecological comparisons.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Published in Chemosphere, 2001, 43(4–7):951–966.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. It is a cross-sectional study that compares mortality rates between regions. No individual-level exposure data available.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. No exposure estimates were used in the study.
Conclusion	These cancer data are cross-sectional in nature and not appropriate for a dose-response analysis.

B.2.7. Air Force Health ("Ranch Hands") Study

Table B-44. Michalek and Pavuk, 2008—Diabetes

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. Adjustment was made for a number of risk factors related to diabetes (e.g., BMI, family history, smoking). However, Agent Orange was a 50% mixture of 2,4-D and TCDD; therefore, potential for confounding by other coexposures is likely.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.

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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. TCDD estimates were derived using serum samples. However, Ranch Hand veterans were exposed to other compounds in the herbicides, such as 2,4-D.
3. Criteria	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria satisfied. TCDD levels at the end of service were estimated. Extrapolation was done using a half-life of 7.6 years. Exposures were grouped into comparison, background, low and high. This allows for a shape of the dose-response curve to be evaluated. A continuous measure of TCDD was also examined ($\log_{10}$TCDD).
Conclusion	Ranch Hand veterans were exposed to other contaminants in the herbicides that were mixed, thereby making it difficult to determine independent effects of TCDD on diabetes. In our view, this limitation precludes dose-response modeling of TCDD and diabetes using data from this cohort.

B.2.8. Other Noncancer Studies of Dioxin

Table B-45. McBride et al., 2009a—Mortality (Noncancer)

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.

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 biases from confounding exposures or from study design or statistical analysis.
Response	Consideration satisfied. Workers lost to follow-up were an unlikely source of bias especially for internal analyses. 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 with evidence of an exposure-response relationship.
Response	Consideration not satisfied. There was no cause of death among those considered for which a dose-response trend was observed across four exposure categories of TCDD.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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.
5. Consideration	Study size and follow-up are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration not satisfied.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
Response	Criteria satisfied. Published in J Occup Environ Med, 2009, 51:1049–1056. The other studies in the cohort highlight the 22% of the cohort lost to follow-up, the limited size of the cohort tissue sarcomas, differences in cohort definitions between sprayers and producers, and the potential for other exposures during employment at the plant.
2. Criteria	Exposure must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
Response	Criteria not satisfied. Dichotomous exposure assessment did not allow individual estimates of dose to be developed. However, 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 noted. As a result, the data are not suited to dose-response analysis.

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Table B-46. McBride et al., 2009b—Mortality (noncancer)

1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
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 with evidence of an exposure-response relationship.
Response	Consideration not satisfied. Because no individual exposure estimates were available for these analyses, dose-response could not be evaluated.
4. Consideration	Exposure assessment methodology is clear and adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
Response	Consideration satisfied. 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 are large enough to yield precise estimates of risk and ensure adequate statistical power.
Response	Consideration satisfied.
1. Criteria	Study is published in the peer-reviewed scientific literature and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.
Response	Criteria not satisfied. Exposures were not quantified. The dichotomous exposure measure was based on exposure to TCDD, chlorinated dioxins and phenoxy herbicides.
3. Critiera	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.

Response	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. As a result, the data are not suited to dose-response analysis.

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3 **Table B-47. Ryan et al., 2002—Sex ratio**
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1. Consideration	Methods used to ascertain health outcomes identified were unbiased, highly sensitive, and specific.
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 biases from confounding exposures or from study design or statistical analysis.
Response	Consideration not satisfied. See above.
3. Consideration	Study demonstrates an association between TCDD and adverse health effect with evidence of an exposure-response relationship.
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 adequately characterizes individual-level exposures. The limitations and uncertainties in the exposure assessment are considered.
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 are large enough to yield precise estimates of risk and ensure adequate 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 and has an appropriate discussion of the strengths and limitations.
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 must be primarily TCDD and is properly quantified so that dose-response relationships can be assessed.

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	The effective dose and oral exposure can be reasonably estimated and the measures of exposure are consistent with the current biological understanding of dose. The reported dose is consistent with a toxicologically relevant dose. Latency and appropriate window(s) of exposure examined. Response has to be a nonfatal endpoint.
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	The data are not suitable for dose-response modeling. Risk estimates have not been derived in relation to TCDD exposure levels. There exist uncertainties 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 should not be used for quantitative dose-response modeling, the much lower M/F birth ratio among exposed fathers is consistent with the finding by Mocarelli et al, and lends support to those findings.

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APPENDIX C

Kinetic Modeling

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 C. KINETIC MODELING

C.1. LITERATURE SEARCH STRATEGY AND RESULTS—IDENTIFYING RECENT PUBLICATIONS FOR UPDATING 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 2004–2005 and Emond and colleagues described in 2004–2006. 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 *Reassessment of Health Risks From Dioxin and Related Compounds* (2003 Reassessment, U.S. EPA, 2003). English-only references from 2003 to May 2009 were searched using bibliographic data bases relevant to health effects and toxicology of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (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 C.1.3.

C.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 C.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

The PUBMED data base was used for the supplemental search.

C.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.

C.1.2.1. *Chemical Search Terms—DIALOG Search*

- CASRN: 1746-01-6
- 2,3,7,8-tetrachlorodibenzo-*p*-dioxin
- 2,3,7,8-TCDD

C.1.2.2. *Primary Search Terms (Species)—DIALOG Search*

- Guinea pig(s)
- Human(s)
- Monkey(s)
- Mouse
- Mice

- Rodent(s)
- Rat(s)

C.1.2.3. *Secondary Search Terms (Toxicology)—DIALOG Search*

1. Absor*
2. ADME
3. Aryl hydrocarbon receptor
4. AhR
5. Bioavail*
6. Biliar*
7. Biotransform*
8. Cytochrome
9. CYP*
10. CYP1A1
11. CYP1A2
12. Diet, dietary, diets
13. Disposit*
14. Distrib*
15. Drink*
16. Elimin*
17. Excret*
18. Epidemiolog*
19. Feces
20. Feed*
21. First order kinetics
22. Food*
23. Gastro*
24. Gavage*
25. Half-life
26. Induct*
27. Ingest*
28. In silico
29. Kinetic*
30. Liver
31. Lymph*
32. Mechanism (1w) action
33. Metabo*
34. Oral*
35. P450
36. Partition coefficient
37. PBPK
38. Pharmacodynamic*
39. Pharmacokinetic*
40. Physiologically based
41. pharmacokinetic
42. Protein bind*
43. Toxicokinetic*
44. Urin*

ADME = absorption, distribution, metabolism, elimination; AhR = aryl hydrocarbon receptor; CYP = cytochrome P450; * = truncated; 1w = terms are within 1 word of each other and in the order specified (see search term 32

C.1.3. Citation Screening Procedures and Result*s*

Initial DIALOG searches resulted in a very large number of citation hits. Therefore, some title and key word restrictions were applied iteratively to screen out less relevant citations (e.g., requiring some search terms in title, requiring 2,3,7,8-TCDD rather than just TCDD). Then, using reference management software, pooled information obtained from the various DIALOG data bases was screened to remove duplicates. Citations then were numbered sequentially (as a unique identifier). Information retrieved included the following (when available): author(s), publication year, title, source document name, volume, and page numbers.

The DIALOG search and duplicate removal procedure produced 775 unique citations. In the next step, all 775 citations were screened for potential applicability to updating parameters in the Aylward and Emond PBPK models. Of these 775 citations, 26 were selected for more detailed review to determine their potential applicability, and full publications were retrieved. Two citations were added from the supplemental search, giving a total of 28 articles identified for further review.

Bibliographic information for the 28 articles selected for full review is provided in the reference list at the end of this section. Table C-1 summarizes the model input parameters potentially addressed by the selected articles.

During 2003 to May 2009, the authors of the two kinetic models under consideration published several articles. For the Emond model, which was first published in 2004 (Emond et al., 2004), two subsequent papers have been published (Emond et al., 2005, 2006). The Aylward model, which originated from the 1995 papers by Carrier et al. (1995a, b), was later updated by the same group (Aylward et al., 2004, 2005). The major change implemented in the last two papers was the description of a desorption process in the digestive tract. The transfer rate described is slow, but for a low body burden of TCDD, this process remains significant. This concept was reported in 2002 by Moser and McLachlan (2002). The major modifications expected to update the Emond model are (1) consideration of the desorption process in the gastrointestinal tract and (2) rearrangement of the elimination constant, which will have a negligible impact on the simulation. These changes are motivated by plausible observations reported in the literature.

Because of the body burden found in humans and the importance of selecting an appropriate dose metric in human risk assessment, the physiological model is an important tool for assessing the kinetics following exposure to TCDD (Kim et al., 2003). Based on the literature identified in this search, the major contributions that should be reviewed with respect to the Aylward and Emond kinetic models are not modes of action or pharmacokinetic mechanisms, but rather information for verifying or improving the accuracy of some model parameters.

Pharmacokinetics typically refers to four distinct steps including absorption, distribution, metabolism, and excretion. Physiologically-based models consider each step. In the model each step is parameterized to reflect better predictions of the real observations. Occasionally, reviewing these models is essential to determine if any key processes or parameters might be

described with better accuracy. This perspective underlies the review of the literature described here. The review indicates TCDD disposition has become recognized as relatively significant since the publication of the Emond and Aylward models. The literature that provides information related to improving these models, however, is limited. For the benefit of this exercise, EPA selected the literature that would likely contribute significantly to model response, or to clarify or confirm different key issues driving the model results. Regarding the two TCDD models, the two major issues that should be evaluated with respect to the recent literature identified are the elimination profile and the induction of CYP1A2.

Reviewing the elimination variation in different species and testing variable elimination with a data set appears to be appropriate. The literature reports that various factors might influence elimination rate. Recent publications report the influence of diverse predictors such age, body fat, or smoking habit on the elimination half-life (Milbrath et al., 2009; Kerger et al., 2006, 2007). Determining whether using the Milbrath et al. information would help account for intraspecies variability in elimination rate in the Emond and Aylward kinetic models would be useful. In 2006, Emond et al. reviewed the influence of body fat mass and CYP1A2 induction on the pharmacokinetics of TCDD. These two factors appear to contribute significantly to elimination and their influences seem to be driven by TCDD body burden. Mullerova and Kopecky (2007) discussed the influence of adipose tissue and the "yo-yo" effects on various diseases that might be influenced by persistent organic pollutant distribution. One group explored the importance of variable elimination and compared these predictions to first-order elimination using the Aylward and Emond models and supported these approaches for risk assessment (Heinzl et al., 2007). Two groups of authors considered a one-compartment model to derive the elimination half-life (Aylward et al., 2009; Nadal et al., 2008). Comparing the half-life they obtained using this approach for a range of body burden to the variable elimination half-life would be interesting.

The second important mechanism driving the distribution and elimination of TCDD is the induction of CYP1A2, identified as the major ligand protein in liver (Diliberto et al., 1997). For that process, authors suggested different aspects that should be investigated, including the importance of the dose metrics in the target tissue and the inducible level of CYP1A2 (Wilkes et al., 2008; Staskal et al., 2005). Other papers address the intraspecies variability of lethal potency in mature species versus the developing fetus (Kransler et al., 2007; Korkalainen et al.,

2004). Still others point out pronounced differences among species (namely, guinea pigs, hamsters, mice, and rats) (Bohonowych and Denison, 2007), as observed in studies of long-term effects of low TCDD dose in liver and in studies comparing hepatic accumulation and clearance of TCDD (Korenaga et al., 2007; Boverhof et al., 2005). The interspecies variation of the binding affinity constant of AhR also has been reported (Connor and Aylward, 2006; Nohara et al., 2006).

The articles identified in this literature review should be adequate to update the Aylward and Emond models, which need to be evaluated according to the same structure of compartments described in the literature by the two model authors.

C.1.4. References Selected for More Detailed Review for Updating the PBPK Models

Aylward, LL; Brunet, RC; Carrier, G; et al. (2004) Concentration-dependent TCDD elimination kinetics in humans: toxicokinetic modeling for moderately to highly exposed adults from Seveso, Italy, and Vienna, Austria, and impact on dose estimates for the NIOSH cohort. J Expo Anal Environ Epidemiol 15(1):51−65.

Aylward, LL; Brunet, RC; Starr, TB; et al. (2005) Exposure reconstruction for the TCDD-exposed NIOSH cohort using a concentration- and age-dependent model of elimination. Risk Anal 25(4):945−956.

Aylward, LL; Bodner, KM; Collins, JJ; et al. (2009) TCDD exposure estimation for workers at a New Zealand 2,4,5-T manufacturing facility based on serum sampling data. J Expo Sci Environ Epidemiol. doi: 10.1038/jes.2009.31.

Bohonowych, JE; Denison, MS. (2007) Persistent binding of ligands to the aryl hydrocarbon receptor. Toxicol Sci 98(1):99–109.

Boverhof, DR; Burgoon, LD; Tashiro, C; et al. (2005) Temporal and dose-dependent hepatic gene expression patterns in mice provide new insights into TCDD-mediated hepatotoxicity. Toxicol Sci 85(2):1048−1063.

Connor, KT; Aylward, LL. (2006) Human response to dioxin: aryl hydrocarbon receptor (AhR) molecular structure, function, and dose-response data for enzyme induction indicate an impaired human AhR. J Toxicol Environ Health B 9(2):147−171.

Heinzl, H; Mittlback, M; Edler, L. (2007) On the translation of uncertainty from toxicokinetic to toxicodynamic models - the TCDD example. Chemosphere 67(9):S365−S374.

Irigaray, P; Mejean, L; Laurent, F. (2005) Behaviour of dioxin in pig adipocytes. Food Chem Toxicol 43(3):457−460.

Kerger, BD; Leung, HW; Scott, P; et al. (2006) Age- and concentration-dependent elimination half-life of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Seveso children. Environ Health Perspect 114(10):1596−1602.

Kerger, BD; Leung, HW; Scott, PK; et al. (2007) Refinements on the age-dependent half-life model for estimating child body burdens of polychlorodibenzodioxins and dibenzofurans. 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.

C.1.5. Brief Descriptions of DIALOG Bibliographic Data Bases Searched

The National Technical Information Service (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 (MITI); laboratories administered by the United Kingdom Department of Industry; the German Federal Ministry of Research and Technology (BMFT); and the French National Center for Scientific Research (CNRS).

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.

BIOSIS Previews® contains citations from Biological Abstracts® (BA) and Biological Abstracts/Reports, Reviews, and Meetings® (BA/RRM) (formerly BioResearch Index®), the major publications of BIOSIS®. These publications constitute the major English-language service providing comprehensive worldwide coverage of research in the biological and biomedical sciences. Biological Abstracts includes approximately 350,000 accounts of original research yearly from nearly 5,000 primary journal and monograph titles. BA/RRM includes an additional 200,000+ citations a year from meeting abstracts, reviews, books, book chapters, notes, letters, and selected reports.

IPA Toxicology provides focused toxicology information on all phases of the development and use of drugs and on professional pharmaceutical practice. The scope of the database ranges from the clinical and practical to the theoretical aspects of toxicology literature. A unique feature of abstracts reporting clinical studies is the inclusion of the study design, number of patients, dosage, dosage forms, and dosage schedule.

Medical Literature, Analysis, and Retrieval System Online (MEDLINE®), produced by the U.S. National Library of Medicine (NLM), is NLM's premier bibliographic database. It contains more than 15 million references to journal articles in life sciences with a concentration on biomedicine. The broad coverage of the database includes basic biomedical research and the clinical sciences since 1950, including nursing, dentistry, veterinary medicine, pharmacy, allied health, and pre-clinical sciences. MEDLINE® also covers life sciences that are vital to biomedical practitioners, researchers, and educators, including some aspects of biology, environmental science, marine biology, and plant and animal science, as well as biophysics and chemistry. MEDLINE® is indexed using NLM's controlled vocabulary, Medical Subject Headings (MeSH®). Approximately 400,000 records are added per year, of which more than 76 percent are in English. MEDLINE® contains AIDSLINE, HealthSTAR, Toxline, In Process (formerly known as Pre-MEDLINE®), In Data Review, and POPLINE.

ToxFile covers the toxicological, pharmacological, biochemical, and physiological effects of drugs and other chemicals. Adverse drug reactions, chemically induced diseases, carcinogenesis, mutagenesis, teratogenesis, environmental pollution, waste disposal, radiation, and food contamination are typical areas of coverage. The databases Environmental Mutagen Information Center (EMIC), Developmental and Reproductive Toxicology (DART), and Toxic Substances Control Act Test Submissions (TSCATS) are included in ToxFile. It is not clearly stated whether the Chemical Carcinogenesis Research Information System (CCRIS), Hazardous Substances Data Bank (HSDB), or Genetic Toxicology Data Bank (GENE-TOX) are included in ToxFile. Consequently, a separate, on-line search was conducted to ensure that these databases were searched.

BIOSIS® Toxicology contains citations from BA and BA/RRM (formerly BioResearch Index®), the major publications of BIOSIS®, that focus on toxicology and related topics. Records are drawn from journal articles, conference papers, monographs and book chapters, notes, letters, and reports, as well as original research. U.S. patent records are also included.

CANCERLIT® is produced by the International Cancer Research DataBank Branch (ICRDB) of the U.S. National Cancer Institute. The database consists of bibliographic records referencing cancer research publications dating from 1963 to 2002. Most records contain abstracts, and all records contain citation information and additional descriptive fields such as document type and language. Beginning with the June 1983 CANCERLIT update, records from the MEDLINE® database dealing with cancer topics have been added to CANCERLIT.

The Registry of Toxic Effects of Chemical Substances (RTECS®) is a comprehensive database of basic toxicity information for over 150,000 chemical substances including prescription and non-prescription drugs, food additives, pesticides, fungicides, herbicides, solvents, diluents, chemical wastes, reaction products of chemical waste, and substances used in both industrial and household situations. Reports of the toxic effects of each compound are cited. In addition to toxic effects and general toxicology reviews, data on skin and/or eye irritation, mutation, reproductive consequences and tumorigenicity are provided. Federal standards and regulations, National Institute for Occupational Safety and Health (NIOSH) recommended exposure limits and information on the activities of EPA, NIOSH, National Toxicology Program (NTP), and Occupational Safety and Health Administration (OSHA) regarding the substance are also included. The toxic effects are linked to literature citations from both published and unpublished governmental reports, and published articles from the scientific literature. The database corresponds to the print version of the RTECS®, formerly known as the Toxic Substances List, which was started in 1971. Originally prepared by the NIOSH, the RTECS® database is now produced and distributed by Symyx Technologies, Inc.

C.2. TOXICOKINETIC MODELING CODE (Emond et al., 2005)

C.2.1. Human Standard Model

C.2.1.1. *Model Code*

PROGRAM: 'Three Compartment PBPK Model for TCDD in Human: Standard Model (Non-Gestation)'

```
!HUM_NON_GEST_ICF_F083109.csl
!*************************************************

INITIAL  !INITIALIZATION OF PARAMETERS
```

```
1
2       !SIMULATION PARAMETERS ====
3     CONSTANT EXP_TIME_ON      =    0.       ! TIME AT WHICH EXPOSURE BEGINS
4     (HOUR)
5     CONSTANT EXP_TIME_OFF     =    6.132e5  ! TIME AT WHICH EXPOSURE ENDS
6     (HOUR)
7     CONSTANT DAY_CYCLE        =   24.0    ! NUMBER OF HOURS BETWEEN DOSES
8     (HOUR)
9     CONSTANT BCK_TIME_ON      =    6.132e5    ! TIME AT WHICH BACKGROUND
10    EXPOSURE BEGINS (HOUR)
11    CONSTANT BCK_TIME_OFF     =    6.132e5    ! TIME AT WHICH BACKGROUND
12    EXPOSURE ENDS (HOUR)
13
14      !EXPOSURE DOSES
15    CONSTANT  MSTOTBCKGR      =    0.0   ! ORAL BACKGROUND EXPOSURE DOSE
16    (NG/KG)
17    CONSTANT  MSTOT           =    1.0E-7     ! ORAL EXPOSURE DOSE (NG/KG)
18    CONSTANT  DOSEIV          =    0.0        ! INJECTED DOSE (NG/KG)
19    CONSTANT  MW              =    322.0      ! MOLECULAR WEIGHT (G/MOL)
20     MSTOT_NM = MSTOT/MW                     ! CONVERTS THE DOSE TO NMOL/KG
21     MSTOT_NMBCKGR = MSTOTBCKGR/MW  !CONVERTS THE BACKGROUND DOSE
22    TO NMOL/KG
23      DOSEIV_NM = DOSEIV/MW                 ! CONVERTS THE INJECTED DOSE TO
24    NMOL/KG
25
26      !INITIAL GUESS OF THE FREE CONCENTRATION IN THE LIGAND
27    (COMPARTMENT INDICATED BELOW) ====
28    CONSTANT CFLLI0       =    0.0              ! LIVER  (NMOL/L)
29
30      !BINDING CAPACITY (AhR) FOR NON LINEAR BINDING (COMPARTMENT
31    INDICATED BELOW) ===
32    CONSTANT LIBMAX       =    0.35          ! LIVER  (NMOL/L)
33
34      ! PROTEIN AFFINITY CONSTANTS (1A2 OR AhR, COMPARTMENT INDICATED
35    BELOW) ===
36    CONSTANT KDLI         =      0.1           ! LIVER (AhR) (NMOL/L) WANG ET AL.. 1997
37    CONSTANT KDLI2        =      40.0          ! LIVER (1A2) (NMOL/L) EMOND ET AL. 2004
38
39      !EXCRETION AND ABSORPTION CONSTANTS
40    CONSTANT KST          =      0.01          ! GASTRIC RATE CONSTANT (HR-1), EMOND
41    ET AL., 2005
42    CONSTANT KABS         =      0.06        ! INTESTINAL ABSORPTION CONSTANT (HR-1),
43    EMOND ET AL. 2005
44
45      !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 PAS_INDUC  =    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; COOPERATIVELY 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_LACK    =     0.0        ! DELAY BEFORE EXPOSURE ENDS
(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_LACK   =     0.0      ! DELAY BEFORE EXPOSURE BEGINS
(MONTH)

    !SET FOR BACKGROUND EXPOSURE==========
    !TIME CONSTANT FOR BACKGROUND EXPOSURE==========
CONSTANT Day_LACK_BG    =   0.0        ! DELAY BEFORE EXPOSURE BEGINS
(HOUR)
CONSTANT Day_PERIOD_BG  =   24.0     ! LENGTH OF EXPOSURE (HOUR)

    !TIME CONSTANT FOR WEEKLY EXPOSURE
CONSTANT WEEK_LACK_BG   =   0.0     ! DELAY BEFORE BACKGROUND
EXPOSURE BEGINS (WEEK)
CONSTANT WEEK_PERIOD_BG =   168.0   !  NUMBER OF HOURS IN THE WEEK
(HOURS)
CONSTANT WEEK_FINISH_BG =   168.0     ! TIME EXPOSURE ENDS (HOURS)

    ! CONSTANT USED IN CARDIAC OUTPUT EQUATION
CONSTANT QCC         =   15.36                ! (L/KG-H),  EMOND ET AL. 2004

    ! COMPARTMENT LIPID EXPRESSED AS THE FRACTION OF TOTAL LIPID
    !Data from Emonds Thesis 2001
CONSTANT F_TOTLIP      =   0.8000          ! ADIPOSE TISSUE (UNITLESS)
CONSTANT B_TOTLIP      =   0.0057          ! BLOOD (UNITLESS)
CONSTANT RE_TOTLIP     =   0.0190          ! REST OF THE BODY (UNITLESS)
CONSTANT LI_TOTLIP     =   0.0670          ! LIVER (UNITLESS)
CONSTANT MEANLIPID     =   974.0

END  ! END OF THE INITIAL SECTION


DYNAMIC ! DYNAMIC SIMULATION SECTION
```

```
  !
ALGORITHM  IALG        =     2       ! GEAR METHOD
CINTERVAL  CINT        =     10.0      ! COMMUNICATION INTERVAL
MAXTERVAL  MAXT        =    1.0e+10    !MAXIMUM INTERVAL CALCULATION
MINTERVAL  MINT        =    1.0E-10    !MINIMUM INTERVAL CALCULATION
VARIABLE   T           =     0.0
CONSTANT   TIMELIMIT   =     1.752e5  !SIMULATION LIMIT TIME (HOUR)
CONSTANT    Y0         =      0.0   ! AGE (YEARS) AT BEGINNING OF SIMULATION
CONSTANT   GROWON      =       1.0    ! INCLUDE BODY WEIGHT AND HEIGHT
GROWTH? (1 = YES, 0 = NO)
  CINTXY  = CINT
  PFUNC   = CINT

  DAY=T/24.0                          ! TIME IN DAYS
  WEEK =T/168.0                       ! TIME IN WEEKS
  MONTH =T/730.0                      ! TIME IN MONTHS
  YEAR=Y0+T/8760.0                    ! TIME IN YEARS
  GYR =Y0 + growon*T/8760.0       ! TIME FOR USE IN GROWTH EQUATION (YEARS)

DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS

    ! CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
    ! NUMBER OF EXPOSURES PER DAY
 DAY_LACK     = EXP_TIME_ON       ! DELAY 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_LACK_BG   = BCK_TIME_ON    !DELAY BEFORE BACKGROUD 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 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,
  ! 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_LACK_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
WEEK_EXPOSURE_BG  =
PULSE(WEEK_LACK_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
MONTH_EXPOSURE_BG =
PULSE(MONTH_LACK_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

MSTTCH_BG =
(DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCK
GR
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_LACK,DAY_PERIOD,DAY_FINISH)
WEEK_EXPOSURE  = PULSE(WEEK_LACK,WEEK_PERIOD,WEEK_FINISH)
MONTH_EXPOSURE = PULSE(MONTH_LACK,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
ELSE
```

```
  ABSMSTT = 0.
END IF

 CYCLETOT=INTEG(CYCLE,0.0)

     ! MASS Balance CHANGE IN THE LUMEN
RMSTT= -(KST+KABS)*MST+ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE
(NMOL/H)
 MST = INTEG(RMSTT,0.)              !AMOUNT REMAINING IN GI TRACT (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
PRCT_remain_GIT  = 100.0*MST/(MSTT+1E-30)

     !IV ABSORTPION SCENARIO ---------
 IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
 EXPIV= IVR * (1.0-STEP(PFUNC))
 IVDOSE = integ(EXPIV,0.0)

     !SYSTEMIC BLOOD COMPARTMENT
     ! MODIFICATION OCT 8 2009
CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM)/(QC+CLURI) !
 CA = CB                          !CONCENTRATION (NMOL/L)

   !CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM-RAURI)/QC !
   ! CA = CB                       ! CONCENTRATION (NMOL/L)

      !URINARY EXCRETION BY KIDNEY
      ! MODIFICATION OCT 8 2009
RAURI = CLURI *CB
  AURI = INTEG(RAURI,0.0)


      !CONCENTRATION UNIT
  PRCT_B = 100.0*CB/(MSTT+1E-30)       ! PERCENT OF DOSE
  CBSNGKGLIADJ = CB*MW/(0.55*B_TOTLIP) !serum concentration in lipid adjust (PG/G
LIPID=PPT)
     CBPPT = CBSNGKGLIADJ
  CBNGKG = CB*MW
```

```
1
2   CBpptRH = CB*MW*10000/(0.55*MEANLIPID) !SERUM CONCENTRATION IN LIPID
3   ADJUST (PG/G LIPID=PPT)
4
5      AUC_CBSNGKGLIADJ=INTEG(CBSNGKGLIADJ,0.0)
6
7         !ADIPOSE TISSUE COMPARTMENT
8   RAFB= QF*(CA-CFB)-PAF*(CFB-CF/PF)       !(NMOL/HR)
9    AFB = INTEG(RAFB,0.0)                  !(NMOL)
10   CFB = AFB/WFB                         !(NMOL/KG)
11        !TISSUE SUBCOMPARTMENT
12  RAF = PAF*(CFB-CF/PF)                  !(NMOL/HR)
13   AF = INTEG(RAF,0.0)                   !(NMOL)
14   CF  = AF/WF                           !(NMOL/KG)
15
16        !POST SIMULATION UNIT CONVERSION
17  CFTOTAL = (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION NMOL/ML
18  PRCT_F = 100.0*CFTOTAL/(MSTT+1E-30)
19  CFNGKG =CFTOTAL*MW
20
21        !REST OF THE BODY COMPARTMENT========
22  RAREB= QRE*(CA-CREB)-PARE*(CREB-CRE/PRE) !(NMOL/HR)
23   AREB = INTEG(RAREB,0.0)               !(NMOL)
24   CREB = AREB/WREB                     !(NMOL/KG)
25        !TISSUE SUBCOMPARTMENT
26  RARE = PARE*(CREB-CRE/PRE)             !(NMOL/HR)
27   ARE = INTEG(RARE,0.0)                 !(NMOL)
28   CRE  = ARE/WRE                       !(NMOL/KG)
29
30        !POST SIMULATION UNIT CONVERSION
31  CRETOTAL = (ARE + AREB)/(WRE + WREB) ! TOTAL CONCENTRATION IN NMOL/ML
32  PRCT_RE = 100.0*CRETOTAL/(MSTT+1E-30) ! PERCENT OF DOSE
33
34        !LIVER COMPARTMENT
35        !TISSUE BLOOD SUBCOMPARTMENT
36  RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM        !(NMOL/HR)
37    ALIB = INTEG(RALIB,0.0)                          !(NMOL)
38   CLIB = ALIB/WLIB
39        !TISSUE SUBCOMPARTMENT
40   RALI =  PALI*(CLIB-CFLLIR)-REXCLI                  !(NMOL/HR)
41    ALI = INTEG(RALI,0.0)           !(NMOL)
42    CLI  = ALI/WLI               !(NMOL/KG)
43
44
45        !FREE TCDD IN LIVER
46        ! MODIFICATION OCTOBER 8 2009
```

```
CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR)) &
      +((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR)*PAS_INDUC)))-CFLLI,CFLLI0) !
CONCENTRATION OF FREE TCDD IN LIVER
   CFLLIR=DIM(CFLLI,0.0)

!MODIFIED FROM:
    !PARAMETER (LIVER_1RMN = 1.0E-30)
    ! CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &      !
+LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR &
    !       +LIVER_1RMN)*PAS_INDUC)))-CFLLI,CFLLI0)
    !   CFLLIR=DIM(CFLLI,0.0)


CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR) !CONC OF TCDD BOUDN TO AhR

!CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !CONC BIND

     !POST SIMULATION UNIT CONVERSION
CLITOTAL = (ALI + ALIB)/(WLI + WLIB)      ! TOTAL CONCENTRATION IN NMOL/ML
PRCT_LI = 100.0*CLITOTAL/(MSTT+1.0E-30)
rec_occ_AHR= 100.0*CFLLIR/(KDLI+CFLLIR+1.0)  ! PERCENT  BOUND TO AhR
OCCUPANCY
PROT_occ_1A2= 100.0*CFLLIR/(KDLI2+CFLLIR)    ! PERCENT  BOUND TO 1A2
OCCUPANCY
CLINGKG= CLITOTAL*MW                    ![NG TCDD/KG]
CBNDLINGKG = CBNDLI*MW

   !FRACTION INCREASE OF INDUCTION OF CYP1A2
fold_ind=CYP1A2_1OUT/CYP1A2_1A2
VARIATIONOFAC =(CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2

   !VARIABLE ELIMINATION BASED ON THE CYP1A2
KBILE_LI_T = Kelv*VARIATIONOFAC!

 REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT RATE OF BILLIARY
EXCRETION OF DIOXIN
   EXCLI = INTEG(REXCLI,0.0)  !TOTAL AMOUNT OF DIOXIN EXCRETED

   !CHEMICAL IN CYP450 (1A2) COMPARTMENT
   !PARAMETER FOR INDUCTION OF CYP1A2

CYP1A2_1KINP = CYP1A2_1KOUT*CYP1A2_1OUTZ ! BASAL RATE OF CYP1A2
PRODUCTION SET EQUAL TO BASAL RATE OF DEGRDATION AT STEADY STATE

   ! MODIFICATION OCTOBER 8 2009
```

```
CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-
30)**HILL &
    /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
     - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ) ! LEVELS OF CYP1A2
! MODEIFIED FROM:
!PARAMETER (CYP1A2_1RMN = 1e-30)
!CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1 + CYP1A2_1EMAX *(CBNDLI &
!    +CYP1A2_1RMN)**HILL/(CYP1A2_1EC50 + (CBNDLI + CYP1A2_1RMN)**HILL) &
!    +CYP1A2_1RMN) - CYP1A2_1KOUT*CYP1A2_1&
!    OUT, CYP1A2_1OUTZ)

! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)
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 IN TERMS OF CONCENTRATION (NG/KG)
  BBNGKG = (AFB+AF+AREB+ARE+ALIB+ALI)*MW/WT0      !

    !COMMAND END OF THE SIMULATION
TERMT (T.GE. TIMELIMIT, 'Time limit has been reached.')

END   ! END OF THE DERIVATIVE SECTION
END   ! END OF THE DYTNAMIC SECTION
END   ! END OF THE PROGRAM
```

C.2.1.2. *Input File*

```
% base file name = "TESTJULY2009.m"
%clear @variable
output @clear
prepare @clear year T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG  CBNDLINGKG
CBNGKG
%output @all
% PARAMETERS FOR SIMULATION
CINT = 1 %0.5
EXP_TIME_ON  =   0.      % TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF = 613200    %324120    % HOUR/YEAR !TIME AT WHICH EXPOSURE
ENDS (HOUR)
DAY_CYCLE   = 24        % NUMBER OF HOURS BETWEEN DOSES (HOUR)
```

```
BCK_TIME_ON  = 613200     %324120     % TIME AT WHICH BACKGROUND
EXPOSURE BEGINS (HOUR)
BCK_TIME_OFF = 613200     %324120     % TIME AT WHICH BACKGROUND
EXPOSURE ENDS (HOUR)
TIMELIMIT    = 613200     %324120      %324120     % SIMULATION TIME LIMIT (HOUR)
MSTOTBCKGR   =   0.       % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 9.97339283634997E-07       % ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV       =   0          %NG/KG
% oral dose oral dose oral dose

MEANLIPID    = 730        %
PAS_INDUC= 1          % INDUCTION INCLUDED? (1=YES, 0=NO)
```

C.2.2. Human Gestational Model

C.2.2.1. *Model Code*

```
PROGRAM:  'Three Compartment PBPK Model for TCDD in Human (Gestation)'
! Parameters were change may 16, 2002
! Come from {8MAI_CHR_PRE-EXP_GD}
! Come from {12_Mouse_GD}file
!*****************************************
!{{IMPORTANT-IMPORTANT-IMPORTANT-IMPORTANT}}
! REDUCTION OF MOTHER AND FETUS COMPARTMENT
! 2M_R_TCDD_JULY2002 ////(JULY 18,2002)////
!TCDD_RED_4Species_2003_4        ////(APR  8 ,2003)////
!TCDD_RED_4Species_2003_9        ////(APR  17 ,2003)////
!TCDD_RED_4Species_2003_12        ////(APR  17 ,2003)////
!*************************************************
!APRIL 18 2003
!TCDD_4C_4SP_2003        ////(APR  18 ,2003)////
! was "Gest 4 species 1.csl"   but update July 2009

!GEST_HUM_0_45Y_4_ICF_afterKKfix_v3_humangestational.csl
!HUM_GESTATIONAL_ICF_F083109.csl
!HUM_GESTATIONAL_ICF_F100709.csl
!*************************************************

 !Legend/Legend/Legend/Legend/Legend/Legend/Legend/Legend/
 !Legend for this PBPK model
 !Mating: control the tenure of exchange between fetus and
    !Mother and also control imitated tissue growth
    !Control: WTFE, WPLA0, QPLAF
    !(for rat, mouse, human, and monkey)
```

```
 !Control transfer from mother to fetus and fetus to mother by TRANSTIME_ON
   !SWITCH_trans = 0 NO TRANSFER
   !SWITCH_trans = 1 TRANSFER OCCURS
 ! These switches are also controlled by mating parameters

INITIAL  !

    !SIMULATION PARAMETERS
CONSTANT PARA_ZERO      = 1e-30
CONSTANT EXP_TIME_ON    = 0.0       !TIME AT WHICH EXPOSURE BEGINS
(HOURS)
CONSTANT EXP_TIME_OFF   = 530.0     !TIME AT WHICH EXPOSURE ENDS (HOURS)
CONSTANT DAY_CYCLE      =  24.0     !NUMBER OF HOURS BETWEEN DOSES
(HOURS)
CONSTANT BCK_TIME_ON    = 0.0       !TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOURS)
CONSTANT BCK_TIME_OFF   = 0.0       !TIME AT WHICH BACKGROUND EXPOSURE
ENDS (HOURS)
CONSTANT TRANSTIME_ON   = 0.0       !CONTROL TRANSFER FROM MOTHER TO
FETUS AT 9 WEEKS OR 1512 HOURS OF GESTATION

    ! INTRAVENOUS SEQUENCY
CONSTANT IV_LACK        = 0.0
CONSTANT IV_PERIOD      = 0.0

    !PREGNANCY PARAMETER
CONSTANT MATTING        = 0.0       !BEGINNING OF MATING (HOUR)
CONSTANT PFETUS         = 4.0       !PARTITION COEFFICIENT
CONSTANT CLPLA_FET      = 1.0e-3    !CLEARANCE TRANSFER FOR MOTHER TO
FETUS (L/HR)

    !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
(NG/KG)
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 (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/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 PAS_INDUC      = 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/ML)
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; COOPERATIVELY LIGAND
BINDING EFFECT CONSTANT (UNITLESS)

  !DIFFUSIONAL PERMEABILITY FRACTION, WANG ET AL (1997)
CONSTANT PAFF            = 0.12      ! ADIPOSE (UNITLESS)
CONSTANT PAREF           = 0.03      ! REST OF THE BODY (UNITLESS)
CONSTANT PALIF           = 0.35      ! LIVER (UNITLESS)
CONSTANT PAPLAF          = 0.3       ! OPTIMIZED PARAMETER

!TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT,
KRISHNAN 2007
CONSTANT QFF             = 0.05      ! ADIPOSE TISSUE BLOOD FLOW FRACTION
(UNITLESS), KRISHNAN 2008
CONSTANT QLIF            = 0.26      ! LIVER (UNITLESS), KRISHNAN 2008

!===FRACTION OF TISSUE BLOOD WEIGHT Wang et al . (1997)
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     !ASSUME HIGHLY VASCULARIZED

! EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY
EXPOSURE
! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LACK       = 0.0       !DELAY BEFORE EXPOSURE ENDS (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_LACK      = 0.0       !DELAY BEFORE EXPOSURE BEGINS
(MONTHS)

!======= CONSTANT FOR BACKGROUND EXPOSURE==========
CONSTANT Day_LACK_BG     = 0.0       ! DELAY BEFORE EXPOSURE BEGINS
(HOURS)
```

```
CONSTANT Day_PERIOD_BG   = 24.0      !LENGTH OF EXPOSURE (HOURS)

! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LACK_BG    = 0.0      !DELAY BEFORE BACKGROUD EXPOSURE
BEGINS (WEEK)
CONSTANT WEEK_PERIOD_BG  = 168.0     ! NUMBER OF HOURS IN THE WEEK
(HOURS)
CONSTANT WEEK_FINISH_BG  = 168.0     !TIME EXPOSURE ENDS (HOURS)


! CONSTANT USED IN CARDIAC OUTPUT EQUATION
CONSTANT QCC          =  15.36    ![L/KG-H], EMOND ET AL. 2004

! COMPARTMENT LIPID EXPRESSED AS THE FRACTION OF TOTAL LIPID
!Data from Emonds Thesis 2001
CONSTANT F_TOTLIP        =    0.8000      ! ADIPOSE TISSUE (UNITLESS)
CONSTANT B_TOTLIP        =    0.0057      ! BLOOD (UNITLESS)
CONSTANT RE_TOTLIP       =    0.0190      ! REST OF THE BODY (UNITLESS)
CONSTANT LI_TOTLIP       =    0.0670      ! LIVER (UNITLESS)
CONSTANT PLA_TOTLIP      =    0.019       ! PLACENTA (UNITLESS)
CONSTANT FETUS_TOTLIP    =    0.019     ! FETUS (UNITLESS)

CONSTANT MEANLIPID       =    974

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    =         100      !SIMULATION LIMIT TIME (HOUR)
CONSTANT    Y0          =         0.0        ! AGE (YEARS) AT BEGINNING OF
SIMULATION
CONSTANT   GROWON       =         1.0      ! INCLUDE BODY WEIGHT AND HEIGHT
GROWTH? (1=YES, 0=NO)

 CINTXY  = CINT
 PFUNC   = CINT

  !TIME TRANSFORMATION
 DAY= T/24.0
 WEEK  =T/168.0
 YEAR=Y0+T/8760.0                        ! TIME IN YEARS
```

```
 1    GYR =Y0 + growon*T/8760.0                  ! TIME FOR USE IN GROWTH EQUATION
 2
 3   DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS
 4
 5   !====== CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
 6   ! NUMBER OF EXPOSURES PER DAY
 7
 8    DAY_LACK        = EXP_TIME_ON    ! DELAY BEFORE EXPOSURE BEGINS (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
15   ! NUMBER OF EXPOSURES PER DAY AND MONTH
16    DAY_FINISH_BG   = CINTXY
17    MONTH_LACK_BG   = BCK_TIME_ON    !DELAY BEFORE BACKGROUND
18   EXPOSURE BEGINS (MONTHS)
19    MONTH_PERIOD_BG  = TIMELIMIT     !BACKGROUND EXPOSURE PERIOD
20   (MONTHS)
21    MONTH_FINISH_BG  = BCK_TIME_OFF   !LENGTH OF BACKGROUND EXPOSURE
22   (MONTHS)
23
24   ! INTRAVENOUS LATE
25    IV_FINISH = CINTXY
26    B = 1-A ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE
27   LIVER
28
29   ! MOTHER BODY WEIGHT GROWTH EQUATION
30   ! MODIFICATION TO ADAPT THIS MODEL AT HUMAN MODEL
31   ! BECAUSE LINEAR DESCRIPTION IS NOT GOOD ENOUGH FOR MOTHER GROWTH
32   ! MOTHER BODY WEIGHT GROWTH
33   ! HUMAN BODY WEIGHT (0 TO 45 YEARS)
34   ! POLYNOMIAL REGRESSION EXPRESSION WRITTEN
35   !APRIL 10 2008, OPTIMIZED WITH DATA OF PELEKIS ET AL. 2001
36   ! POLYNOMIAL REGRESSION EXPRESSION WRITTEN WITH
37   !HUH AND BOLCH 2003 FOR BMI CALCULATION
38
39   ! BODY WEIGHT CALCULATION.  UNIT IN KG FOR GESTATIONAL PORTION
40
41       WT0 = (0.0006*GYR**3 - 0.0912*GYR**2 + 4.32*GYR + 3.652)
42
43    !BODY MASS INDEX CALCULATION
44
45       BH =  -2D-5*GYR**4+4.2D-3*GYR**3.0-0.315*GYR**2.0+9.7465*GYR+72.098
46   !HEIGHT EQUATION FORMULATED FOR USE FROM 0 TO 70 YEARS
```

```
      BHM= (BH/100.0)!HUMAN HEIGHT IN METER (BHM)
      HBMI= WT0/(BHM**2.0) ! HUMAN BODY MASS INDEX (BMI)


!MODIFICATION IN KG
RTESTGEST= T-MATTING ! STARTING TIME FOR FETAL GROWTH
TESTGEST=DIM(RTESTGEST,0.0)
! GROWTH OF FETAL TISSUE
GESTATTION_FE=((4d-15*TESTGEST**4 -3d-11*TESTGEST**3 +1d-7*TESTGEST**2 -
8d-5*TESTGEST +0.0608))
   WTFER= DIM(GESTATTION_FE,0.0) ! FETAL COMPARTMENT WEIGHT
 WTFE= WTFER

!////////////////////////////////////////////////////////////////////
! FAT GROWTH EXPRESSION LINEAR DURING PREGNANCY
! FROM O'FLAHERTY_1992
!////////////////////////////////////////////////////////////////////

WT0GR= WT0*1.0e3    ! MOTHER BODY WEIGHT IN G

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) ! MOTHER FAT
COMPARTMENT GROWTH

!////////////////////////////////////////////////////////////////////
! WPLA PLACENTA GROWTH EXPRESSION, SINGLE EXPONENTIAL WITH OFFSET
! FROM O'FLAHERTY_1992  ! FOR EACH PUP
!////////////////////////////////////////////////////////////////////
!SAME EQUATION THEN THE FORST MODEL. BODY WEIGHT KEPT IN G
!A CORRECTION FOR THE BODY WEIGHT (WTO(KG)*1000 = WTOGR)

WPLA0N_HUMAN= (850*exp(-9.434*(exp(-5.23d-4*(TESTGEST)))))
 WPLA0R = WPLA0N_HUMAN/WT0GR
 WPLA0W = DIM(WPLA0R,0.0) ! PLACENTA WEIGHT
  WPLA0=WPLA0W

!////////////////////////////////////////////////////////////////////
! QPLA PLACENTA GROWTH EXPRESSION, DOUBLE EXPONENTIAL WITH OFFSET
! FROM O'FLAHERTY_1992
!////////////////////////////////////////////////////////////////////

QPLAF_HUMAN= SWITCH_trans*((1d-10*TESTGEST**3.0 -5D-7*TESTGEST**2.0
+0.0017*TESTGEST+1.1937)/QC)
  GEST_QPLAF=DIM(QPLAF_HUMAN,0.0) ! PLACENTA BLOOD FLOW RATE
  QPLAF =GEST_QPLAF

```

```
! LIVER,VOLUME  (HUMAN 0 TO 70 YEARS)
! 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)) !
LIVER VOLUME IN GROWING HUMAN

! VARIABILITY OF REST OF THE BODY DEPENDS ON OTHER ORGAN
 WRE0 = (0.91-(WLIB0*WLI0+WFB0*WF0+ WPLAB0*WPLA0 + WLI0 + WF0 +
WPLA0))/(1+WREB0)
 QREF = 1-(QFF+QLIF+QPLAF)          !REST BODY BLOOD FLOW (ML/HR)
 QTTQF = QFF+QREF+QLIF+QPLAF         ! SUM MUST EQUAL 1

! COMPARTMENT TISSUE BLOOD VOLUME (L) =========
 WF  =  WF0  * WT0                 ! ADIPOSE TISSUE
 WRE =  WRE0 * WT0                   ! REST OF THE BODY
 WLI =  WLI0 * WT0                 ! LIVER
 WPLA=  WPLA0* WT0                   ! PLACENTA

! COMPARTMENT TISSUE VOLUME (L) =========
 WFB  =  WFB0  * WF                ! ADIPOSE TISSUE
 WREB =  WREB0 * WRE                 ! REST OF THE BODY
 WLIB =  WLIB0 * WLI               ! LIVER
 WPLAB = WPLAB0* WPLA                ! PLACANTA

! TOTAL VOLUME OF COMPARTMENT (L)======
WFT =   WF                        ! TOTAL ADIPOSE TISSUE
WRET =  WRE                         ! TOTAL REST OF THE BODY
WLIT =  WLI                       ! TOTAL LIVER TISSUE
WPLAT=  WPLAB                       ! TOTAL PLACENTA TISSUE

! CONSTANT USED IN CARDIAC OUTPUT EQUATION

! UNIT CHANGED ON JULY 14 2009  (L/HR)
QC= QCC*(WT0)**0.75

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)
QPLA = QPLAF*QC                     !PLACENTA TISSUE BLOOD FLOW RATE (L/HR)
QTTQ = QF+QRE+QLI+QPLA     !TOTAL FLOW RATE (L/HR)

! ========= DIFFUSIONAL PERMEABILITY FACTORS FRACTION ORGAN FLOW
=========
PAF  = PAFF*QF                    ! ADIPOSE TISSUE BLOOD FLOW RATE (L/HR)
PARE = PAREF*QRE                    ! REST OF THE BODY BLOOD FLOW RATE (L/HR)
PALI = PALIF*QLI                  ! LIVER TISSUE BLOOD FLOW RATE (L/HR)
PAPLA = PAPLAF*QPLA                 ! PLACENTA TISSUE BLOOD FLOW RATE (L/HR)
```

```
1
2   !************************************
3   ! ABSORPTION SECTION
4   ! ORAL
5   ! INTRAPERITONEAL
6   ! SUBCUTANEOUS
7   ! INTRAVENOUS
8   !************************************
9
10  !BACKGROUND EXPOSURE
11  !EXPOSURE FOR STEADY STATE CONSIDERATION
12  !REPETITIVE EXPOSURE SCENARIO
13
14  MSTOT_NMBCKGR = MSTOTBCKGR/322      !AMOUNT IN NMOL/G
15  MSTTBCKGR =MSTOT_NMBCKGR *WT0
16
17  DAY_EXPOSURE_BG   = PULSE(DAY_LACK_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
18  WEEK_EXPOSURE_BG  =
19  PULSE(WEEK_LACK_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
20  MONTH_EXPOSURE_BG =
21  PULSE(MONTH_LACK_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)
22
23  MSTTCH_BG =
24  (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCK
25  GR
26  MSTTFR_BG = MSTTBCKGR/CINT
27
28  CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG
29
30  ! CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
31
32  IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
33     ABSMSTT_GB= MSTTFR_BG
34  ELSE
35     ABSMSTT_GB = 0.0
36  END IF
37
38  CYCLETOTBG=INTEG(CYCLE_BG,0.0)
39
40  !************************************
41  !MULTIROUTE  EXPOSURE
42  !REPETITIVE EXPOSURE SCENARIO
43  !************************************
44  MSTT= MSTOT_NM * WT0                !AMOUNT IN NMOL
45  DAY_EXPOSURE   = PULSE(DAY_LACK,DAY_PERIOD,DAY_FINISH)
46  WEEK_EXPOSURE  = PULSE(WEEK_LACK,WEEK_PERIOD,WEEK_FINISH)
```

```
MONTH_EXPOSURE = PULSE(MONTH_LACK,MONTH_PERIOD,MONTH_FINISH)

MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT

MSTTFR = MSTT/CINT

CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE

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)


   !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_LACK,IV_PERIOD,IV_FINISH)
```

```
 1
 2     IV_lateT = IV_EXPOSURE *IV_RlateR
 3     IV_late = IV_lateT/CINT
 4
 5    SUMEXPEVENTIV= integ(IV_EXPOSURE,0.0) !NUMBER OF CYCLE GENERATE
 6    DURING SIMULATION
 7
 8         !SYSTEMIC BLOOD COMPARTMENT
 9         ! MODIFICATION OCT 8 2009
10    CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late)/(QC
11    +CLURI) !
12     CA = CB                          ! CONCENTRATION (NMOL/L)
13
14        !CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late-
15    RAURI)/QC !(NMOL/L)
16
17       !URINARY EXCRETION BY KIDNEY
18       ! MODIFICATION OCT 8 2009
19    RAURI = CLURI *CB
20      AURI = INTEG(RAURI,0.0)
21
22       !RAURI = CLURI * CRE
23       !AURI = INTEG(RAURI,0.0)
24
25       !UNIT CONVERSION POST SIMULATION
26    CONSTANT MW=322 !MOLECULAR WEIGHT (NG/NMOL)
27    CONSTANT SERBLO = 0.55
28    CONSTANT UNITCORR = 1.0e3
29
30     CBSNGKGLIADJ = CB*MW/(0.55*B_TOTLIP) !NG SERUM LIPID ADJUSTED/KG
31       AUCBS_NGKGLIADJ=integ(CBSNGKGLIADJ,0.)
32    CBNGKG= CB*MW   !NG/KG
33    PRCT_B = 100.0*CB/(MSTT+1E-30)       !PERCENT OF ORAL DOSE IN BLOOD
34    PRCT_BIV = 100.0*CB/(IV_RlateR+1E-30) ! PERCENT OF IV DOSE IN BLOOD
35
36       !ADIPOSE COMPARMTENT
37       !TISSUE BLOOD SUBCOMPARTMENT
38    RAFB= QF*(CA-CFB)-PAF*(CFB-CF/PF)    !(NMOL/H)
39     AFB = INTEG(RAFB,0.0)              !(NMOL)
40     CFB = AFB/WFB                    !(NMOL/L)
41       !TISSUE SUBCOMPARTMENT
42    RAF = PAF*(CFB-CF/PF)              !(NMOL/H)
43     AF = INTEG(RAF,0.0)              !(NMOL)
44     CF  = AF/WF                     !(NMOL/L)
45
46       !UNIT CONVERSION POST SIMULATION
```

```
CFTOTAL= (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION IN NMOL/ML
PRCT_F = 100.0*CFTOTAL/(MSTT+1E-30) !PERCENT OF ORAL DOSE IN FAT
PRCT_FIV = 100.0*CFTOTAL/(IV_RlateR+1E-30) !PERCENT OF IV DOSE IN FAT
CFNGKG=CFTOTAL*MW ! FAT CONCENTRATION IN NG/KG
AUCF_NGKGH=integ(CFNGKG,0.)


   !REST OF THE BODY COMPARTMENT
   !TISSUE BLOOD SUBCOMPARTMENT
RAREB= QRE *(CA-CREB)-PARE*(CREB-CRE/PRE)      !(NMOL/H)
 AREB = INTEG(RAREB,0.0)                    !(NMOL)
 CREB = AREB/WREB                          !(NMOL/L)
   !TISSUE SUBCOMPARTMENT
RARE = PARE*(CREB - CRE/PRE)                !(NMOL/H)
 ARE = INTEG(RARE,0.0)                     !(NMOL)
 CRE  = ARE/WRE                           !(NMOL/L)
ARETOT = ARE +AREB

   !POST SIMULATION UNIT CONVERSION
CRETOTAL= (ARE + AREB)/(WRE + WREB)          ! TOTAL CONCENTRATION
(NMOL/L)
PRCT_RE = 100.0*CRETOTAL/(MSTT+1E-30) ! PERCENT OF ORAL DOSE IN REST OF
BODY
PRCT_REIV = 100.0*CRETOTAL/(IV_RlateR+1E-30)   ![ PERCENT OF IV DOSE IN REST
OF BODY
CRENGKG=CRETOTAL*MW                          ! REST OF THE BODY CONCENTRATION
(NG/KG)


   !LIVER COMPARTMENT
   !TISSUE BLOOD SUBCOMPARTMENT
 RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM ! (NMOL/HR)
  ALIB = INTEG(RALIB,0.0)                   !(NMOL)
 CLIB = ALIB/WLIB                          !(NMOL/L)
   !TISSUE SUBCOMPARMTENT
 RALI = PALI*(CLIB - CFLLIR)-REXCLI          ! (NMOL/HR)
  ALI = INTEG(RALI,0.0)                     !(NMOL)
 CLI  = ALI/WLI                           !(NMOL/L)

   !FREE TCDD CONCENTRATION IN LIVER
    ! MODIFICATION OCTOBER 8 2009
 CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR)) &
      +((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR)*PAS_INDUC)))-CFLLI,CFLLI0)
   CFLLIR=DIM(CFLLI,0.0) ! FREE TCDD CONCENTRATION IN LIVER
!MODIFIED FROM:
!PARAMETER (LIVER_1RMN = 1.0E-30)
```

```
! CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
!+LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2 + CFLLIR &
!+LIVER_1RMN)*PAS_INDUC)))-CFLLI,CFLLI0)
!CFLLIR=DIM(CFLLI,0.0)

! MODIFICATION OCTOBER 8 2009
CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR) !BOUND CONCENTRATION (NMOL/L)

   !POST SIMULATION UNIT CONVERSION
CLITOTAL= (ALI + ALIB)/(WLI + WLIB) ! TOTAL CONCENTRATION (NMOL/L)
PRCT_LI = 100.0*CLITOTAL/(MSTT+1E-30) ! PERCENT OF ORAL DOSE IN LIVER
PRCT_LIIV = 100.0*CLITOTAL/(IV_RlateR+1E-30) ! PERCENT OF IV DOSE IN LIVER
Rec_occ= CFLLIR/(KDLI+CFLLIR)
CLINGKG=CLITOTAL*MW ! LIVER CONCENTRATION IN NG/KG
  AUCLI_NGKGH=integ(CLINGKG,0.0)
CBNDLINGKG = CBNDLI*MW ! BOUND CONCENTRATION IN NG/KG
  AUCBNDLI_NGKGH =INTEG(CBNDLINGKG,0.0)

   !FRACTION INCREASE OF INDUCTION OF CYP1A2
fold_ind=CYP1A2_1OUT/CYP1A2_1A2
VARIATIONOFAC =(CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2

!VARIABLE ELIMINATION BASED ON THE CYP1A2
! MODIFICATION OCTOBER 8 2009
KBILE_LI_T = Kelv*VARIATIONOFAC! ! DOSE-DEPENDENT EXCRETION RATE
CONSTANT

 REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT BILLIARY EXCRETION
RATE
   EXCLI = INTEG(REXCLI,0.0)

!KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv !


!CHEMICAL IN CYP450 (1A2) COMPARTMENT

CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ ! BASAL PRODCUTION RATE OF
CYP1A2 SET EQUAL TO BASAL DEGREDATION RATE

   ! MODIFICATION OCTOBER 8 2009
CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-
30)**HILL &
    /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
     - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)
!MODIFIED FROM:
!PARAMETER (CYP1A2_1RMN = 1E-30)
```

```
!CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1 + CYP1A2_1EMAX *(CBND&
!LI +CYP1A2_1RMN)**HILL/(CYP1A2_1EC50 + (CBNDLI + CYP1A2_1&
!RMN)**HILL) +CYP1A2_1RMN) - CYP1A2_1KOUT*CYP1A2_1&
!OUT, CYP1A2_1OUTZ)

! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)
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)

   !PLACENTA COMPARTMENT
   !TISSUE BLOOD SUBCOMPARTMENT
RAPLAB= QPLA*(CA - CPLAB)-PAPLA*(CPLAB -CFLPLAR)   ! NMOL/HR)
 APLAB = INTEG(RAPLAB,0.0)                    ! (NMOL)
 CPLAB = APLAB/(WPLAB+1E-30)                    ! (NMOL/ML)
   !TISSUE SUBCOMPARTMENT
RAPLA = PAPLA*(CPLAB-CFLPLAR)-RAMPF + RAFPM       ! (NMOL/HR)
 APLA = INTEG(RAPLA,0.0)                      ! (NMOL)
 CPLA  = APLA/(WPLA+1e-30)                     ! (NMOL/ML)

   ! NEW EQUATION AUGUST 28  2009
PARAMETER (PARA_ZERO = 1.0E-30)
CFLPLA= IMPLC(CPLA-(CFLPLAR*PPLA +(PLABMAX*CFLPLAR/(KDPLA&
   +CFLPLAR+PARA_ZERO)))-CFLPLA,CFLPLA0)
CFLPLAR=DIM(CFLPLA,0.0)

   !POST SIMULATION UNIT CONVERSION
CPLATOTAL = ((APLAB+APLA)/(WPLAB+WPLA))
PRCT_PLA = (CPLATOTAL/(MSTT+1E-30))*100
PRCT_PLAIV = (CPLATOTAL/(IV_RlateR+1E-30))*100

   !FETUS COMPARTMENT
RAFETUS= RAMPF-RAFPM
 AFETUS=INTEG(RAFETUS,0.0)
CFETUS=AFETUS/(WTFE+1.0e-30)
CFETOTAL= CFETUS
CFETUS_v = CFETUS/PFETUS

   !POST SIMULATION UNIT CONVERSION
 CFETUSNGKG = CFETUS*MW                !(NG/KG)
 PRCT_FE = 100.0*CFETOTAL/(MSTT+1E-30)
 PRCT_FEIV = 100.0*CFETOTAL/(IV_RlateR+1E-30)

```

```
   !TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
   !FETAL EXPOSURE ONLY DURING EXPOSURE

IF (T.LT.TRANSTIME_ON) THEN
 SWITCH_trans = 0.0
ELSE
 SWITCH_trans = 1
END IF

   !TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
   ! MODIFICATION 26 SEPTEMBER 2003

RAMPF = (CLPLA_FET*CPLA)*SWITCH_trans
  AMPF=INTEG(RAMPF,0.0)

   !TRANSFER OF DIOXIN FROM FETUS TO PLACENTA
RAFPM = (CLPLA_FET*CFETUS_v)*SWITCH_trans!
 AFPM = INTEG(RAFPM,0.0)

   !CHECK MASS BALANCE ----------
BDOSE= IVDOSE +LYMLUM+LIMLUM
BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB+AFETUS !
BDIFF = BDOSE-BMASSE

   !BODY BURDEN (NMOL)
BODY_BURDEN = AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB

   !BODY BURDEN CONCENTRATION (NG/KG)
 BBNGKG =(AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB)*MW/WT0

! END SIMULATION COMMAND

TERMT (T.GE. TimeLimit, 'Time limit has been reached.')

END   ! END OF THE DERIVATIVE SECTION
END   ! END OF THE DYNAMIC SECTION
END   ! END OF THE PROGRAM
```

C.2.2.2. *Input File*

```
output @clear
prepare @clear T  year CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG  CBNDLINGKG
CBNGKG

CINT = 1   %168 %100              %INTEGRATION TIME
  %EXPOSURE SCENARIO
```

```
EXP_TIME_ON      = 0         % TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     = 401190    %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE        = 24        %NUMBER OF HOURS BETWEEN DOSES (HOUR)
BCK_TIME_ON      = 401190    %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF     = 401190    %TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
IV_LACK          = 401190
IV_PERIOD        = 401190
   %GESTATION CONTROL
MATTING          = 393120    % BEGINNING OF MATING (HOUR) AT 45 YEARS OLD
TIMELIMIT        = 399840    %SIMULATION TIME LIMIT (HOUR)
TRANSTIME_ON     = 394632    % TRANSFER FROM MOTHER TO FETUS AT 1512
HOURS GESTATION
   %EXPOSURE DOSE
MSTOT            = 9.97339283634997E-07      % NG OF TCDD PER KG OF BW
MSTOTBCKGR       = 0.   %0.1     % ORAL BACKGROUND EXPOSURE DOSE (NG/KG)
DOSEIV           = 0.   %10
DOSEIVLATE       = 0.   %10

    % TRANFER MOTHER TO FETUS CLEARANCE
CLPLA_FET        = 0.001 % MOTHER TO FETUS TRANFER CLEARANCE (L/HR)
```

C.2.3. Rat Standard Model

C.2.3.1. *Model Code*

```
        PROGRAM:  'Three Compartment PBPK Model in Rat: Standard Model (Non-
Gestation)'

!Rat_Dioxin_3C June09_2clean_icf_afterKKfix_v3_ratnongest.csl
!RAT_NON_GEST_ICF_F083109.CSL
!RAT_NON_GEST_ICF_F100609.CSL
 !************************************************

INITIAL  ! INITIALIZATION OF PARAMETERS

    !SIMULATION PARAMETERS
CONSTANT PARA_ZERO      =     1d-30
CONSTANT EXP_TIME_ON    =     0.0         ! TIME AT WHICH EXPOSURE BEGINS
(HOURS)
CONSTANT EXP_TIME_OFF   =     900.0        ! TIME AT WHICH EXPOSURE ENDS
(HOURS)
CONSTANT DAY_CYCLE      =     900.0        ! NUMBER OF HOURS BETWEEN DOSES
(HOURS)
```

```
CONSTANT BCK_TIME_ON    =     0.0         ! TIME AT WHICH BACKGROUND
EXPOSURE BEGINS (HOURS)
CONSTANT BCK_TIME_OFF   =     0.0         ! TIME AT WHICH BACKGROUND
EXPOSURE ENDS (HOURS)

CONSTANT MW=322 !MOLECULAR WEIGHT (NG/NMOL)
CONSTANT SERBLO = 0.55
CONSTANT UNITCORR = 1000


   !EXPOSURE DOSES
CONSTANT MSTOTBCKGR     =     0.0         !ORAL BACKGROUND EXPOSURE DOSE
(UG/KG)
CONSTANT MSTOT          =     10      !ORAL EXPOSURE DOSE (UG/KG)
CONSTANT MSTOTsc        =     0.0         !SUBCUTANEOUS EXPOSURE DOSE (UG/KG)
CONSTANT DOSEIV         =     0.0         ! INJECTED DOSE (UG/KG)

   !ORAL DOSE
 MSTOT_NM           =   MSTOT/MW      !AMOUNT IN NMOL/G
 MSTOT_NMBCKGR      =   MSTOTBCKGR/MW  !AMOUNT IN NMOL/G

   !INTRAVENOUS DOSE
 DOSEIV_NM          =   DOSEIV/MW     !AMOUNT IN 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          =    4.0e-2         !LIVER (1A2) (NMOL/ML), EMOND ET AL.
2004

   !EXCRETION AND ABSORPTION CONSTANT [RAT]
CONSTANT KST            =    0.36          ! GASTRIC RATE CONSTANT (HR-1), WANG ET
AL. (1997)
CONSTANT KABS           =    0.48          !INTESTINAL ABSORPTION CONSTANT (HR-
1), WANG ET AL. 1997

   !URINARY ELIMINATION CLEARANCE (ML/HR)
```

```
CONSTANT CLURI        =    0.01        !URINARY CLEARANCE (ML/HR), EMOND ET
AL. 2004

   !INTERSPECIES VARIABLE ELIMINATION
CONSTANT KELV         =    0.15        ! INTERSPECIES VARIABLE ELIMINATION
CONSTANT (1/HOUR) (OPTIMIZED), EMOND ET AL. 2004

   ! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL
FRACTIONS
CONSTANT A            =    0.7         ! LYMPHATIC FRACTION, WANG ET AL. 1997

   !PARTITION COEFFICIENTS
CONSTANT PF           =    100         ! 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

   !PARAMETER FOR INDUCTION OF CYP 1A2 [MOUSE] ===
CONSTANT PAS_INDUC    =    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; COOPERATIVELY 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_LACK      = 0.0              ! DELAY BEFORE EXPOSURE ENDS
(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_LACK     = 0.0              ! DELAY BEFORE EXPOSURE BEGINS
(MONTH)

    !SET FOR BACKGROUND EXPOSURE==========
    !CONSTANT FOR BACKGROUND EXPOSURE==========
CONSTANT Day_LACK_BG    = 0.0              ! DELAY BEFORE EXPOSURE BEGINS
(HOURS)
CONSTANT Day_PERIOD_BG  = 24.0             ! LENGTH OF EXPOSURE (HOURS)

    !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LACK_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                     !CHANGED FOR SIMULATION

    ! CONSTANT USED IN CARDIAC OUTPUT EQUATION
CONSTANT QCCAR =311.4                      !CONSTANT (ML/MIN/KG), WANG ET AL.

    ! COMPARTMENT LIPID EXPRESSED AS THE FRACTION OF TOTAL LIPID
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_LACK     = EXP_TIME_ON              ! DELAY 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_LACK_BG   = BCK_TIME_ON           ! DELAY 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
```

```
1
2         ! BODY WEIGHT GROWTH EQUATION========
3      PARAMETER (BW_RMN = 1.0E-30)
4      WT0= (BW_T0 *(1.0+(0.41*T)/(1402.5+T+BW_RMN)))
5
6         !VARIABILITY OF REST OF THE BODY DEPEND OTHERS ORGAN
7      WRE0 = (0.91 - (WLIB0*WLI0 + WFB0*WF0 + WLI0 + WF0))/(1.0+WREB0) !REST OF
8     THE BODY FRACTION; UPDATED FOR EPA ASSESSMENT
9      QREF = 1.0-(QFF+QLIF)                    !REST OF BODY BLOOD FLOW
10     QTTQF = QFF+QREF+QLIF                     ! SUM MUST EQUAL 1
11
12        !COMPARTMENT VOLUME (G) =========
13     WF  =  WF0  * WT0                       ! ADIPOSE
14     WRE =  WRE0 * WT0                         ! REST OF THE BODY
15     WLI =  WLI0 * WT0                       ! LIVER
16
17        !COMPARTMENT TISSUE BLOOD VOLUME (G) =========
18     WFB  =  WFB0  * WF                       ! ADIPOSE
19     WREB =  WREB0 * WRE                        ! REST OF THE BODY
20     WLIB =  WLIB0 * WLI                      ! LIVER
21
22        !CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT
23      QC= QCCAR*60.0*(WT0/UNITCORR)**0.75
24
25        ! COMPARTMENT BLOOD FLOW (ML/HR)
26     QF  = QFF*QC                            ! ADIPOSE TISSUE BLOOD FLOW RATE
27     QLI = QLIF*QC                           ! LIVER TISSUE BLOOD FLOW RATE
28     QRE = QREF*QC                             ! REST OF THE BODY BLOOD FLOW RATE
29     QTTQ = QF+QRE+QLI                         ! TOTAL FLOW RATE
30
31        !PERMEABILITY ORGAN FLOW (ML/HR)
32    PAF  = PAFF*QF                           ! ADIPOSE
33    PARE = PAREF*QRE                            ! REST OF THE BODY
34    PALI = PALIF*QLI                         ! LIVER TISSUE
35
36        !CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
37        !EXPOSURE + !REPETITIVE EXPOSURE SCENARIO
38     IV= DOSEIV_NM * WT0  !AMOUNT IN NMOL
39     MSTT= MSTOT_NM * WT0 !AMOUNT IN NMOL
40     MSTTBCKGR =MSTOT_NMBCKGR *WT0
41
42        !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIOS
43     DAY_EXPOSURE_BG   =
44    PULSE(DAY_LACK_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
45     WEEK_EXPOSURE_BG  =
46    PULSE(WEEK_LACK_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
```

```
  MONTH_EXPOSURE_BG =
PULSE(MONTH_LACK_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

  MSTTCH_BG =
(DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCK
GR
  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_LACK,DAY_PERIOD,DAY_FINISH)
  WEEK_EXPOSURE  = PULSE(WEEK_LACK,WEEK_PERIOD,WEEK_FINISH)
  MONTH_EXPOSURE = PULSE(MONTH_LACK,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 CYCLE GENERATE 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 OF STAY 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
 PRCT_remain_GIT  = (MST/(MSTT+PARA_ZERO))*100.0

      !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
 PRCT_B = (CB/(MSTT+PARA_ZERO))*100.0
 CBNGKG = CB*MW*UNITCORR ![NG/KG]


CBSNGKGLIADJ= (CB*MW*UNITCORR*(1.0/B_TOTLIP)*(1.0/SERBLO))![NG of TCDD
Serum/Kg OF LIPIP]

      !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
  PRCT_F  = (CFTOTAL/(MSTT+PARA_ZERO))*100.0 ! PRCENT OF DOSE IN FAT
  CFNGKG   = CFTOTAL*MW*UNITCORR          ! CONCENTRATION [NG/KG]
```

```
1
2         !REST OF THE BODY COMPARTMENT
3         ! TISSUE BLOOD SUBCOMPARTMENT
4      RAREB= QRE*(CA-CREB)-PARE*(CREB-CRE/PRE)          !(NMOL/HR)
5        AREB = INTEG(RAREB,0.0)                          !(NMOL)
6        CREB = AREB/WREB                               !(NMOL/ML)
7         ! TISSUE COMPARTMENT
8      RARE = PARE*(CREB - CRE/PRE)                       !(NMOL/HR)
9        ARE = INTEG(RARE,0.0)                          !(NMOL)
10       CRE  = ARE/WRE                                !(NMOL/ML)
11
12       !CONVERSION EQUATION POST SIMULATION
13       CRETOTAL= (ARE + AREB)/(WRE + WREB)             ! TOTAL CONCENTRATION IN
14     NMOL/ML
15       PRCT_RE = (CRETOTAL/(MSTT+PARA_ZERO))*100.0
16       CTREPGG= CRETOTAL*MW*UNITCORR !(PG/ML)
17        AUC_REPPG = integ(CTREPGG,0.0)
18
19       !LIVER COMPARTMENT
20       !TISSUE BLOOD COMPARTMENT
21     RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM   !(NMOL/HR)
22       ALIB = INTeg(RALIB,0.0)                          !(NMOL)
23       CLIB = ALIB/WLIB
24       !TISSUE COMPARTMENT
25     RALI =  PALI*(CLIB-CFLLIR)-REXCLI                  !(NMOL/HR)
26       ALI = integ(RALI,0.0)                          !(NMOL)
27       CLI  = ALI/WLI                               !(NMOL/ML)
28
29
30     PARAMETER (LIVER_1RMN = 1.0E-30)
31     CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
32     +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR &
33     +LIVER_1RMN)*PAS_INDUC)))-CFLLIR,CFLLI0) ! FREE TCDD CONCENTRATION IN
34     LIVER
35     CFLLIR=DIM(CFLLI,0.0)
36
37      CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND
38     CONCENTRATION
39
40        !CONVERSION EQUATION POST SIMULATION
41      CLITOTAL= (ALI + ALIB)/(WLI + WLIB)              ! TOTAL CONCENTRATION IN
42     NMOL/ML
43      PRCT_LI = (CLITOTAL/(MSTT+PARA_ZERO))*100.0
44      rec_occ_AHR= (CFLLIR/(KDLI+CFLLIR+1))*100.0         ! PERCENT OF AhR
45     OCCUPANCY
```

```
 1    PROT_occ_1A2= (CFLLIR/(KDLI2+CFLLIR))*100.0         ! PERCENT OF 1A2
 2  OCCUPANCY
 3    CLINGKG =(CLITOTAL*MW*UNITCORR)
 4    CBNDLINGKG = CBNDLI*MW*UNITCORR
 5      AUCLI_NGKGH=INTEG(CLINGKG,0.0)
 6    CLINGG=CLITOTAL*MW
 7
 8        !VARIABLE ELIMINATION HALF-LIFE BASED ON THE CONCENTRATION OF
 9  CYP1A2
10      KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv ! INDUCED
11  BILIARY EXCRETION RATE CONSTANT
12
13   REXCLI= (KBILE_LI_T*CFLLIR*WLI) ! DOSE-DEPENDENT BILIARY EXCRETION
14  RATE
15     EXCLI = INTEG(REXCLI,0.0)
16
17       !CHEMICAL IN CYP450 (1A2) COMPARTMENT
18    !===PARAMETER FOR INDUCTION OF CYP1A2
19
20   CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ ! BASAL RATE OF CYP1A2
21  PRODUCTION SET EQUAL TO BASAL RATE OF DEGREDATION
22
23
24       ! MODIFICATION ON OCTOBER 6, 2009
25   CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-
26  30)**HILL &
27       /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &-
28        - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)
29
30  ! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
31  SIMULATIONS)
32
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
43  !---------------BODY BURDEN-----------------------
44    BBNGKG =(((AFB+AF+AREB+ARE+ALIB+ALI)*MW)/(WT0/UNITCORR)) !
45  ! ------------ END OF THE SIMULATION COMMAND ----------
46
```

```
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.
```

C.2.3.2. *Input Files*

C.2.3.2.1. *Cantoni et al. (1981).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

%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 AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    = 7560    %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE       = 168
BCK_TIME_ON     = 0.      %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF    = 0.      %TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT       = 7584    %SIMULATION TIME LIMIT (HOUR)
BW_T0           = 125     % BODY WEIGHT AT THE BEGINNING OF THE SIMULATION
(G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT         = 0.01    % EXPOSURE DOSE IN UG/KG
  %MSTOT        = 0.1     % EXPOSURE DOSE IN UG/KG
  MSTOT         = 1       % EXPOSURE DOSE IN UG/KG
```

C.2.3.2.2. *Chu et al. (2007).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Chu et al. 2007
%protocol:  oral exposure daily for 28 days
```

```
%dose levels: 0.0025, 0.025, 0.250, 1.0 ug/kg every day for 28 days
% dose levels = 2.5, 25, 250, 1000 ng/kg every day for 28 days
MAXT          = 0.01
CINT          = 0.1
EXP_TIME_ON    = 0.          %delay before begin exposure (HOUR) 5 weeks after start of
experiment (age = 12 weeks)
EXP_TIME_OFF    = 672.          %TIME EXPOSURE STOP (HOUR); 30 doses, 1 every two
weeks
DAY_CYCLE      = 24.          % once every two weeks
BCK_TIME_ON    = 0.            %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    = 0.           %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT      = 672.         %SIMULATION LIMIT TIME (HOUR)
BW_T0          = 200.         % Body weight at the beginning of the simulation (g);
corresponds to 12 week old female

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT        = 0.0025       % ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT        = 0.025        % ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT        = 0.250        % ORAL EXPOSURE DOSE (UG/KG)
 MSTOT         = 1.0          % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.3.2.3. ***Crofton et al. (2005).***

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Crofton et al. 2005
%protocol:  oral exposure daily for 4 days
%dose levels: 0.0001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, and 10 ug/kg every day for four days
%dose levels: 0.1, 3, 10, 30, 100, 300, 1000, 3000, and 10000 ng/kg every day for four days

MAXT          = 0.01
CINT          = 0.1
EXP_TIME_ON    = 0.          %delay before begin exposure (HOUR) 5 weeks after start of
experiment (age = 12 weeks)
EXP_TIME_OFF    = 96.          %TIME EXPOSURE STOP (HOUR); 30 doses, 1 every two
weeks
DAY_CYCLE      = 24.          % once every two weeks
BCK_TIME_ON    = 0.            %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    = 0.           %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT      = 96.          %SIMULATION LIMIT TIME (HOUR)
BW_T0          = 250          % Body weight at the beginning of the simulation (g); corresponds
to 12 week old female

%EXPOSURE DOSE SCENARIOS (UG/KG)
```

```
 MSTOT          = 0.0001       % ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT         = 0.003        % ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT         = 0.01         % ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT         = 0.03         % ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT         = 0.1          % ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT         = 0.3          % ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT         = 1.           % ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT         = 3.           % ORAL EXPOSURE DOSE (UG/KG)
 MSTOT        = 10.           % ORAL EXPOSURE DOSE (UG/KG)

```

C.2.3.2.4. ***Fattore et al. (2000).***

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Fattore et al. 2000
%built and check in August 7 2009
%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 AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     = 2184     %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE        = 24
BCK_TIME_ON      = 0.       %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF     = 0.       %TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT        = 2184     %SIMULATION TIME LIMIT (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

```

C.2.3.2.5. ***Hassoun et al. (2000).***

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG
```

```
% 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/weeks for 13 weeks
%dose levels equivalent to: 3, 10, 22, 46 100 ng/kg 5 days/weeks for 13 weeks
%dose levels equivalent to: 2.14, 7.14, 15.7, 32.9, 71.4 ng/kg 7 days/weeks for 13 weeks

MAXT          = 0.01
CINT          = 0.1
EXP_TIME_ON     = 0.        %delay before begin exposure (HOUR)
EXP_TIME_OFF    = 2184.     %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE       =  24.
WEEK_PERIOD     = 168.
WEEK_FINISH     = 119.
BCK_TIME_ON     = 0.        %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    = 0.        %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT       = 2184.     %SIMULATION LIMIT TIME (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
```

C.2.3.2.6. ***Kitchin and Woods (1979).***

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Kitchin and Woods 1979
%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 with
estimated 0.2 ng/kg/day background dose
MAXT          =  0.01
CINT          =  0.1
EXP_TIME_ON     =  0.          %delay before begin exposure (HOUR)
EXP_TIME_OFF    =  23.          %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE       =  24.          % once every two weeks
BCK_TIME_ON     =  0.           %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    =  72.          %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT       =  72.          %SIMULATION LIMIT TIME (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)
```

C.2.3.2.7. *Kociba et al. (1976) (13 weeks).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Kociba et al, 1976.
%built and check in August 7 2009
%protocol:  5 days/week exposure for 13 weeks; SD rats
%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            = 0.01
CINT            = 0.1
EXP_TIME_ON     = 0.      %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    = 2184    %TIME AT WHICH EXPOSURE ENDS (HOUR)
WEEK_PERIOD     = 168
WEEK_FINISH     = 119
DAY_CYCLE       =  24
BCK_TIME_ON     = 0.      % TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF    = 0.      %TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT       = 4368    %SIMULATION TIME LIMIT (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
 MSTOT         = 1             % EXPOSURE DOSE IN UG/KG

```

C.2.3.2.8. ***Kociba et al. (1978) (female) (104 weeks).***

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Kociba et al, 1978.
%built and check in August 7 2009
%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 AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    =  17472        %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  24
BCK_TIME_ON     =  0.           %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF    =  0.           %TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT       =  17472        %SIMULATION TIME LIMIT (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

```

C.2.3.2.9. ***Kociba et al. (1978) (male) (104 weeks).***

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Kociba et al, 1978.
%built and check in August 7 2009
%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 AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF   =  17472         %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE      =  24
BCK_TIME_ON    =  0.            %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF   =  0.            %TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT      =  17472         %SIMULATION TIME LIMIT (HOUR)
BW_T0          =  250           % 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
```

C.2.3.2.10. ***Latchoumycandane and Mathur. (2002).***

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Latchoumycandane and Mathur, 2002.
%built and check in August 7 2009
%protocol:  1 time per day for 45 days oral gavage
%dose levels:  0.001, 0.01, 0.1 ug/kg daily for 45 days
%dose levels:  1, 10, 100 ng/kg daily for 45 days

MAXT           = 0.01
CINT           = 0.1
EXP_TIME_ON    = 0.         % TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF   = 1080       % TIME AT WHICH EXPOSURE ENDS(HOUR)
DAY_CYCLE      = 24
BCK_TIME_ON    = 0.         % TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF   = 0.         % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT      = 1104       % SIMULATION TIME LIMIT (HOUR)
BW_T0          = 200        % 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
```

C.2.3.2.11. *Li et al. (1997).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Li et al 1997
% created 1/10/10
% Non-gestational rat model
% dose levels: 3, 10, 30, 100, 300, 1000, 3000, 10000, 30000 nkd one dose via gavage, sacrificed
24 hrs later

MAXT          = 0.1
CINT          = 0.1
EXP_TIME_ON    = 0.            %delay before begin exposure (HOUR)
EXP_TIME_OFF   = 24.           %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE      = 24.
BCK_TIME_ON    = 0.            %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF   = 0.            %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT      = 24.           %SIMULATION LIMIT TIME (HOUR)
BW_T0          = 56.5          % Body weight at the beginning of the simulation (g)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  MSTOT        = 0.003    % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT       = 0.01     % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT       = 0.03     % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT       = 0.1      % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT       = 0.3      % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT       = 1.       % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT       = 3.       % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT       = 10.      % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT       = 30.      % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.3.2.12. *Murray et al. (1979).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Murray et al 1979
%built and check in August 7 2009
%protocol:  dietary exposure for 3 generations (assume 120 day exposure for each)
%dose levels: 0.001 0.01, 0.1 ug/kg/d
%dose levels: 1, 10, 100  ng/kg/d

MAXT          = 0.01
```

```
CINT          =  0.1
EXP_TIME_ON    =  0.            %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF   =  2880          %TIME AT WHICH EXPOSURE ENDS (HOUR);
CORRESPONDS TO 120 DAYS OF EXPOSURE
DAY_CYCLE      =  24.
BCK_TIME_ON    =  0.            %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF   =  0.            %TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT      =  2880          %SIMULATION TIME LIMIT (HOUR)
BW_T0          =  4.5           % BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT         = 0.001       % ORAL EXPOSURE DOSE IN UG/KG
 %MSTOT         = 0.01        % ORAL EXPOSURE DOSE IN UG/KG
 MSTOT          = 0.1         % ORAL EXPOSURE DOSE IN UG/KG

```

C.2.3.2.13. ***NTP (1982) (female) (chronic).***

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% NTP 1982
%built and check in August 7 2009
%protocol: twice weekly gavage for 104 weeks + 3 week observation period
%dose levels:  0.005, 0.025, 0.25 ug/kg biweekly for 104 weeks + 3 week observation period
%dose levels:  5, 25, 250 ng/kg biweekly for 104 weeks + 3 week observation period
%dose levels equivalent to: 1.43, 7.14, 71.4 ng/kg/d (adj)

MAXT           = 0.01
CINT           = 0.1
EXP_TIME_ON     = 0.          %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    = 17472       %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE       = 84
BCK_TIME_ON     = 0.          %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF    = 0.          %TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT       = 17976       %SIMULATION TIME LIMIT (HOUR)
BW_T0           = 250         % BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)

```

```
 %MSTOT          = 0.005       % EXPOSURE DOSE IN UG/KG
 %MSTOT          = 0.025       % EXPOSURE DOSE IN UG/KG
 MSTOT          = 0.25       % EXPOSURE DOSE IN UG/KG
```

C.2.3.2.14. ***NTP (1982) (male) (chronic).***

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% NTP 1982
%built and check in August 7 2009
%protocol: twice weekly gavage for 104 weeks + 3 week observation period
%dose levels:  0.005, 0.025, 0.25 ug/kg biweekly for 104 weeks + 3 week observation period
%dose levels:  5, 25, 250 ng/kg biweekly for 104 weeks + 3 week observation period
%dose levels equivalent to: 1.43, 7.14, 71.4 ng/kg/d (adj)

MAXT             = 0.01
CINT             = 0.1
EXP_TIME_ON      = 0.          %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     = 17472       %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE        = 84
BCK_TIME_ON      = 0.          %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF     = 0.          %TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT        = 17976       %SIMULATION TIME LIMIT (HOUR)
BW_T0            = 350         % BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)


 %MSTOT          = 0.005       % EXPOSURE DOSE IN UG/KG
 %MSTOT          = 0.025       % EXPOSURE DOSE IN UG/KG
 MSTOT          = 0.25       % EXPOSURE DOSE IN UG/KG
```

C.2.3.2.15. ***NTP (2006) 31 weeks.***

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% NTP 2006
%built and check in August 7 2009
```

```
%protocol:  oral exposure for 31 weeks; SD rats
%Rat_Dioxin_3C June09_2clean.csl
%RAT_NON_GEST_ICF_F083109.CSL  (now 09-11-09)
%dose levels:  0.003, 0.010, 0.022, 0.046, 0.1 ug/kg 5 days/week for 31 weeks
%dose levels equivalent to: 3, 10, 22, 46, 100 ng/kg 5 days/week for 31 weeks
%dose levels equivalent to: 2.14, 7.14, 15.7, 32.9, 71.4 ng/kg 7 days/week for 31 weeks

MAXT          = 0.01
CINT          = 0.1
EXP_TIME_ON     = 0.        %delay before begin exposure (HOUR)
EXP_TIME_OFF    = 17640     %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE       =  24
WEEK_PERIOD     = 168
WEEK_FINISH     = 119
BCK_TIME_ON     = 0.        %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    = 0.        %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT       = 5208      %SIMULATION LIMIT TIME (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
```

C.2.3.2.16. ***NTP (2006) 53 weeks.***

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% NTP 2006
%built and check in August 7 2009
%protocol:  oral exposure for 53 weeks; SD rats
%Rat_Dioxin_3C June09_2clean.csl
%RAT_NON_GEST_ICF_F083109.CSL  (now 09-11-09)
%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.        %delay before begin exposure (HOUR)
EXP_TIME_OFF    = 17640     %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE       =  24
```

```
WEEK_PERIOD     = 168
WEEK_FINISH     = 119
BCK_TIME_ON     = 0.        %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    = 0.        %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT       = 8904      %SIMULATION LIMIT TIME (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
```

C.2.3.2.17. ***NTP (2006) 2 year.***

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% NTP 2006
%built and check in August 7 2009
%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 AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF    = 17640     %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE       =  24
WEEK_PERIOD     = 168
WEEK_FINISH     = 119
BCK_TIME_ON     = 0.        %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF    = 0.        %TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT       = 17640     %SIMULATION TIME LIMIT (HOUR)
BW_T0           = 215       % BODY WEIGHT AT THE BEGINNING OF THE SIMULATION
(G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT       = 0.003     % EXPOSURE DOSE IN UG/KG
   %MSTOT       = 0.010                 % EXPOSURE DOSE IN UG/KG
   %MSTOT       = 0.022                 % EXPOSURE DOSE IN UG/KG
```

```
    %MSTOT     = 0.046                    % EXPOSURE DOSE IN UG/KG
    MSTOT     = 0.1              % EXPOSURE DOSE IN UG/KG

```

C.2.3.2.18. *Sewall et al. (1995).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Sewall et al. 1995
%Rat_Dioxin_3C June09_2clean.csl
%RAT_NON_GEST_ICF_F083109.CSL  (now 09-11-09)
%protocol:  gavage every 2 weeks for 30 weeks
%dose levels: 0.049, 0.1498, 0.49, and 1.75 ug/kg every two weeks
%dose levels: 3.5, 10.7, 35, and 125 ng/kg/d or 49, 149.8, 490, and 1750 ng/kg every two weeks

MAXT          =  0.01
CINT          =  0.1
EXP_TIME_ON    =  0.          %delay before begin exposure (HOUR) 5 weeks after start of
experiment (age = 12 weeks)
EXP_TIME_OFF    =  5030          %TIME EXPOSURE STOP (HOUR); 30 doses, 1 every two
weeks
DAY_CYCLE      =  336.          % once every two weeks
BCK_TIME_ON    =  0.            %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    =  0.           %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT      =  5040          %SIMULATION LIMIT TIME (HOUR)
BW_T0          =  250           % Body weight at the beginning of the simulation (g); corresponds
to 12 week old female

%EXPOSURE DOSE SCENARIOS (UG/KG)
  MSTOT          = 0.049       % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.1498        % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 0.49         % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT         = 1.75         % ORAL EXPOSURE DOSE (UG/KG)

```

C.2.3.2.19. *Shi et al. (2007), adult portion.*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Shi et al 2007
%built and check in August 7 2009
%protocol:  gavage once per week for 322 days
%dose levels: 0.001, 0.005, 0.05 and 0.2 ug TCDD:kg body weight by gavage once per week
%dose levels: 1, 5, 50 and 200 ng/kg ng TCDD:kg body weight by gavage once per week
```

```
% dose equivalent adjusted 0.143, 0.714, 7.14 and 28.6 ng/kg/d

MAXT          = 0.0001
CINT          = 0.1
EXP_TIME_ON    = 504.          % TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF   = 7728          %TIME AT WHICH EXPOSURE ENDS (HOUR);
CORRESPONDS TO 322 DAYS OF EXPOSURE
DAY_CYCLE      = 168.
BCK_TIME_ON    = 0.            % TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOUR)
BCK_TIME_OFF   = 0.            % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT      = 7728          %SIMULATION TIME LIMIT (HOUR)
BW_T0          = 4.5           % BODY WEIGHT AT THE BEGINNING OF THE
SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT        = 0.001     % ORAL EXPOSURE DOSE IN UG/KG
  %MSTOT        = 0.005     % ORAL EXPOSURE DOSE IN UG/KG
  %MSTOT        = 0.05      % ORAL EXPOSURE DOSE IN UG/KG
  MSTOT         = 0.2       % ORAL EXPOSURE DOSE IN UG/KG
```

C.2.3.2.20. ***Van Birgelen et al. (1995).***

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Van Birgelen et al. (1995)
%protocol:  daily dietary exposure for 13 weeks
%dose levels: 0.0135, 0.0264, 0.0469, 0.320, 1.024 ug/kg every day for 13 weeks
% dose levels = 13.5, 26.4, 46.9, 320, 1024 ng/kg every day for 13 weeks
MAXT          = 0.01
CINT          = 0.1
EXP_TIME_ON    = 0.           %delay before begin exposure (HOUR)
EXP_TIME_OFF   = 2184.          %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE      = 24.           % once every two weeks
BCK_TIME_ON    = 0.            %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF   = 0.            %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT      = 2184.         %SIMULATION LIMIT TIME (HOUR)
BW_T0          = 150.          % Body weight at the beginning of the simulation (g)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT        = 0.0135       % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT        = 0.0264       % ORAL EXPOSURE DOSE (UG/KG)
  %MSTOT        = 0.0469       % ORAL EXPOSURE DOSE (UG/KG)
```

```
 %MSTOT       = 0.320        % ORAL EXPOSURE DOSE (UG/KG)
 MSTOT       = 1.024        % ORAL EXPOSURE DOSE (UG/KG)

```

C.2.3.2.21. *Vanden Heuvel et al. (1994).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Vanden Heuvel et al., 1994.
%built and check in August 7 2009
%protocol: single gavage
%Rat_Dioxin_3C June09_2clean.csl
%RAT_NON_GEST_ICF_F083109.CSL  (now 09-11-09)
%dose levels: 0.00005, 0.0001, 0.001, 0.010, 0.1, 1, 10 ug/kg/d + 4 days post treatment
%dose levels equivalent to: 0.05, 0.1, 1, 10, 100, 1000, 10000 ng/kg/d + 4 days post treatment

MAXT            = 0.01
CINT            = 0.01
EXP_TIME_ON     = 0.          %delay before begin exposure (HOUR)
EXP_TIME_OFF    = 120         %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE       = 120
BCK_TIME_ON     = 0.          %DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
BCK_TIME_OFF    = 0.          %TIME OF BACKGROUND EXPOSURE STOP (HOUR)
TIMELIMIT       = 120         %SIMULATION LIMIT TIME (HOUR)
BW_T0           = 250         % Body weight at the beginning of the simulation (g)

%EXPOSURE DOSE SCENARIOS (UG/KG)

 %MSTOT          = 0.00005     % exposure dose ug/kg
 %MSTOT          = 0.0001      % exposure dose ug/kg
 %MSTOT          = 0.001       % exposure dose ug/kg
 %MSTOT          = 0.01        % exposure dose ug/kg
 %MSTOT          = 0.1         % exposure dose ug/kg
 MSTOT          = 1           % exposure dose ug/kg
 %MSTOT          = 10          % exposure dose ug/kg

```

C.2.4. Rat Gestational Model

C.2.4.1. *Model Code*

```
PROGRAM:  'Three Compartment PBPK Model for TCDD in Rat (Gestation)'
! Parameters were change May 16, 2002
! Come from {8MAI_CHR_PRE-EXP_GD}
! Come from {12_Mouse_GD}file
!*****************************************
```

```
!{{IMPORTANT-IMPORTANT-IMPORTANT-IMPORTANT}}
! REDUCTION OF MOTHER AND FETUS COMPARTMENT
! 2M_R_TCDD_JULY2002 ////(JULY 18,2002)////
!TCDD_RED_4Species_2003_4       ////(APR  8 ,2003)////
!TCDD_RED_4Species_2003_9       ////(APR  17 ,2003)////
!TCDD_RED_4Species_2003_12       ////(APR  17 ,2003)////
!*************************************************
!APRIL 18 2003
!TCDD_4C_4SP_2003       ////(APR  18 ,2003)////
! was "Gest 4 species 1.csl"   but update July 2009

!DevTCDD4Species_ICF_afterKKfix_v3_ratgest.csl
!RAT_GESTATIONAL_ICF_F083109.csl
!RAT_GESTATIONAL_ICF_F100609.csl
!*************************************************

 !Legend/Legend/Legend/Legend/Legend/Legend/Legend/Legend/
 !Legend for this PBPK model
 !Mating: control the tenure of exchange between fetus and
   !Mother and also control imitated tissue growth
   !Control: WTFE, WFO, WPLA0, QPLAF,WT0
   !(for rat, mouse, human, and monkey)
 !Control transfer from mother to fetus or fetus to mother by TRANSTIME_ON
   !SWITCH_trans = 0 NO TRANSFER
   !SWITCH_trans = 1 TRANSFER OCCURS
   !Gest_off = 1
   !Gest_on=   0.0
 ! These switches are also controlled by mating parameters

INITIAL  !

    !SIMULATION PARAMETERS ====
CONSTANT PARA_ZERO      = 1E-30
CONSTANT EXP_TIME_ON    = 0.0      ! TIME AT WHICH EXPOSURE BEGINS
(HOURS)
CONSTANT EXP_TIME_OFF   = 530      ! TIME AT WHICH EXPOSURE ENDS (HOURS)
CONSTANT DAY_CYCLE      = 24.0     ! NUMBER OF HOURS BETWEEN DOSES
(HOURS)
CONSTANT BCK_TIME_ON    = 0.0      ! TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOURS)
CONSTANT BCK_TIME_OFF   = 0.0      ! TIME AT WHICH BACKGROUND EXPOSURE
ENDS (HOURS)
CONSTANT TRANSTIME_ON   = 144.0    !CONTROL TRANSFER FROM MOTHER TO
FETUS AT GESTATIONAL DAY 6

 !UNIT CONVERSION
```

```
CONSTANT MW=322 ! MOLECULAR WEIGHT (NG/NMOL)
CONSTANT SERBLO = 0.55
CONSTANT UNITCORR = 1000


   !INTRAVENOUS SEQUENCE
constant IV_LACK        = 0.0
constant IV_PERIOD      = 0.0

   !PREGNANCY PARAMETER ====
CONSTANT MATTING        = 0.0      !BEGINNING OF MATING (HOUR)
CONSTANT N_FETUS        = 10.0     !NUMBER OF FETUS PRESENT

   !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          = 0.0      ! ORAL EXPOSURE DOSE (UG/KG)

   !ORAL ABSORPTION
  MSTOT_NM = MSTOT/MW             ! CONVERTS THE DOSE TO NMOL/G

   !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; ASSUME IDENTICAL
TO KDLI (AhR)

```

```
   !EXCRETION AND ABSORPTION CONSTANT
CONSTANT KST          = 0.36    ! GASTRIC RATE CONSTANT (HR-1), WANG ET AL.
1997
CONSTANT KABS         = 0.48    !INTESTINAL ABSORPTION CONSTANT (HR-1) ),
WANG ET AL. 1997

   ! ELIMINATION CONSTANTS
CONSTANT CLURI        = 0.01     ! URINARY CLEARANCE (ML/HR), EMOND ET AL.
2004

   !INTERSPECIES ELIMINATION VARIABLE
CONSTANT kelv         = 0.15    ! 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           = 100    ! 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 PAS_INDUC    = 1.0      ! INCLUDE INDUCTION? (1 = YES, 0 = NO)
CONSTANT CYP1A2_1OUTZ = 1.6     ! DEGRADATION CONCENTRATION
CONSTANT OF 1A2 (NMOL/ML)
CONSTANT CYP1A2_1A1   = 1.6     ! BASAL CONCENTRATION OF 1A1 (NMOL/ML)
CONSTANT CYP1A2_1EC50 = 0.13     ! DISSOCIATION CONSTANT TCDD-CYP1A2
(NMOL/ML)
CONSTANT CYP1A2_1A2   = 1.6     !BASAL CONCENTRATION OF 1A2 (NMOL/ML)
CONSTANT CYP1A2_1KOUT = 0.1     ! FIRST ORDER RATE OF DEGRADATION (H-1)
CONSTANT CYP1A2_1TAU  = 0.25    !HOLDING TIME (H)
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
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        = 0.3500   !LIVER (UNITLESS), WANG ET AL. 1997
CONSTANT PAPLAF       = 0.3     !TEMPORARY PARAMETER NOT CONFIGURED
```

```
1
2     !FRACTION OF TISSUE WEIGHT =========
3     CONSTANT WLI0          = 0.0360   !LIVER, WANG ET AL. 1997
4
5     !TISSUE BLOOD FLOW EXPRESSED AS A FRACTION OF CARDIAC OUTPUT
6     CONSTANT QFF           = 0.069    ! ADIPOSE TISSUE BLOOD FLOW FRACTION
7     (UNITLESS), WANG ET AL. 1997
8     CONSTANT QLIF          = 0.183    !LIVER (UNITLESS), WANG ET AL. 1997
9
10    !COMPARTMENT TISSUE BLOOD EXPRESSED AS A FRACTION OF THE TOTAL
11    COMPARTMENT VOLUME
12    CONSTANT WFB0          = 0.050    !ADIPOSE TISSUE, WANG ET AL. 1997
13    CONSTANT WREB0         = 0.030    !REST OF THE BODY, WANG ET AL. 1997
14    CONSTANT WLIB0         = 0.266    !LIVER, WANG ET AL. 1997
15    CONSTANT WPLAB0        = 0.500    !TEMPORARY PARAMETER NOT CONFIGURED
16
17    !EXPOSURE SCENARIO FOR UNIQUE OR REPETITIVE WEEKLY OR MONTHLY
18    EXPOSURE
19    !NUMBER OF EXPOSURES PER WEEK
20    CONSTANT WEEK_LACK     = 0.0      !DELAY BEFORE EXPOSURE ENDS (WEEK)
21    CONSTANT WEEK_PERIOD   = 168      ! NUMBER OF HOURS IN THE WEEK (HOURS)
22    CONSTANT WEEK_FINISH   = 168      ! TIME EXPOSURE ENDS (HOURS)
23
24    !NUMBER OF EXPOSURES PER MONTH
25    CONSTANT MONTH_LACK    = 0.0      !DELAY BEFORE EXPOSURE BEGINS
26    (MONTHS)
27
28    !CONSTANT FOR BACKGROUND EXPOSURE==========
29    CONSTANT Day_LACK_BG   = 0.0      !DELAY BEFORE EXPOSURE BEGINS (HOURS)
30    CONSTANT Day_PERIOD_BG = 24       !LENGTH OF EXPOSURE (HOURS)
31
32    !NUMBER OF EXPOSURES PER WEEK
33    CONSTANT WEEK_LACK_BG    = 0.0    !DELAY BEFORE BACKGROUD EXPOSURE
34    BEGINS (WEEKS)
35    CONSTANT WEEK_PERIOD_BG  = 168    !NUMBER OF HOURS IN THE WEEK
36    (HOURS)
37    CONSTANT WEEK_FINISH_BG  = 168    !TIME EXPOSURE ENDS (HOURS)
38
39    !INITIAL BODY WEIGHT
40    CONSTANT BW_T0         = 250      ! WANG ET AL. 1997
41    CONSTANT RATIO_RATF_MOUSEF = 1.0      !RATIO OF FETUS MOUSE/RAT AT
42    GESTATIONAL DAY 22
43
44    ! COMPARTMENT LIPID EXPRESSED AS THE FRACTION OF TOTAL LIPID, POULIN
45    ET AL 2002
46    CONSTANT F_TOTLIP      = 0.855            ! ADIPOSE TISSUE (UNITLESS)
```

```
CONSTANT B_TOTLIP         = 0.0023             ! BLOOD (UNITLESS)
CONSTANT RE_TOTLIP        = 0.019              ! REST OF THE BODY (UNITLESS)
CONSTANT LI_TOTLIP        = 0.060              ! LIVER (UNITLESS)
CONSTANT PLA_TOTLIP       = 0.019
CONSTANT FETUS_TOTLIP     = 0.019

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    =         100      !SIMULATION LIMIT TIME (HOURS)
 CINTXY  = CINT
 PFUNC   = CINT

  !TIME CONVERSION
 DAY        = T/24          ! TIME IN DAYS
 WEEK       = T/168         ! TIME IN WEEKS
 MONTH      = T/730         ! TIME IN MONTHS
 YEAR       = T/8760        ! TIME IN YEARS

DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS

  !CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
  !NUMBER OF EXPOSURES PER DAY
 DAY_LACK        = EXP_TIME_ON    ! DELAY 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_LACK_BG   = BCK_TIME_ON    !DELAY BEFORE BACKGROUD EXPOSURE
BEGINS (MONTHS)
 MONTH_PERIOD_BG  = TIMELIMIT     !BACKGROUND EXPOSURE (MONTHS)
 MONTH_FINISH_BG  = BCK_TIME_OFF   !LENGTH OF BACKGROUND EXPOSURE
(MONTHS)

  !INTRAVENOUS LATE
 IV_FINISH = CINTXY
 B = 1-A ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE
LIVER
```

```
1
2
3   !FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUM
4   E,FETUS,VOLUME
5     ! FROM OFLAHERTY_1992
6
7   RTESTGEST= T-MATTING
8   TESTGEST=DIM(RTESTGEST,0.0)
9
10  WTFER_RODENT= (2.3d-3*EXP(1.49d-2*(TESTGEST))+1.3d-2)*Gest_on
11  WTFER = (WTFER_RODENT*RATIO_RATF_MOUSEF*N_FETUS)
12  WTFE = DIM(WTFER,0.0)
13
14    !
15  FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLU
16  ME,FAT,VOLUME
17    ! FAT GROWTH EXPRESSION LINEAR DURING PREGNANCY
18    ! FROM O'FLAHERTY_1992
19
20  WF0= (((9.66d-5*(TESTGEST))*gest_on)+0.069)
21
22    ! PLACENTA,VOLUME, PLACENTA,VOLUME, PLACENTA,VOLUME,
23  PLACENTA,VOLUME
24    ! WPLA PLACENTA GROWTH  EXPRESSION, SINGLE EXPONENTIAL WITH OFFSET
25    ! FROM O'FLAHERTY_1992  ! FOR EACH PUP
26
27  WPLA0N_RODENT = (0.6/(1+(5d+3*EXP(-0.0225*(TESTGEST)))))*N_FETUS
28  WPLA0R = (WPLA0N_RODENT/WT0)*Gest_on
29  WPLA0 = DIM(WPLA0R,0.0)
30
31    ! PLACENTA,FLOW RATE, PLACENTA,FLOW RATE, PLACENTA,FLOW RATE,
32  PLACENTA,FLOW RATE
33    ! QPLA PLACENTA GROWTH EXPRESSION, DOUBLE EXPONENTIAL WITH OFFSET
34    ! FROM O'FLAHERTY_1992
35
36   QPLARF = (1.67d-7 *exp(9.6d-3*(TESTGEST)) &
37     +1.6d-3*exp(7.9d-3*(TESTGEST))+0.0)*Gest_on*SWITCH_trans
38   QPLAF=DIM(QPLARF,0.0)              !FRACTION OF FLOW RATE IN PLACENTA
39
40    ! GESTATION CONTROL
41  IF (T.LT.MATTING) THEN
42      Gest_off = 1.0
43      Gest_on=   0.0
44  ELSE
45      Gest_off = 0.0
46      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))

  ! 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
2       !************************************
3       ! ABSORPTION SECTION
4       ! ORAL
5       ! INTRAPERITONEAL
6       ! INTRAVENOUS
7       !************************************
8
9       !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIO
10
11    MSTOT_NMBCKGR = MSTOTBCKGR/MW       ! CONVERTS THE BACKGROUND DOSE
12    TO NMOL/G
13    MSTTBCKGR =MSTOT_NMBCKGR *WT0
14
15    DAY_EXPOSURE_BG   = PULSE(DAY_LACK_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
16    WEEK_EXPOSURE_BG  =
17    PULSE(WEEK_LACK_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
18    MONTH_EXPOSURE_BG =
19    PULSE(MONTH_LACK_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)
20
21    MSTTCH_BG =
22    (DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCK
23    GR
24    MSTTFR_BG = MSTTBCKGR/CINT
25
26    CYCLE_BG =DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG
27
28       ! CONDITIONAL ORAL EXPOSURE (BACKGROUND EXPOSURE)
29
30    IF (MSTTCH_BG.EQ.MSTTBCKGR) THEN
31       ABSMSTT_GB= MSTTFR_BG
32    ELSE
33       ABSMSTT_GB = 0.0
34    END IF
35
36    CYCLETOTBG=INTEG(CYCLE_BG,0.0)
37
38      !REPETITIVE ORAL EXPOSURE SCENARIO
39
40    MSTT= MSTOT_NM * WT0                !AMOUNT IN NMOL
41
42    DAY_EXPOSURE   = PULSE(DAY_LACK,DAY_PERIOD,DAY_FINISH)
43    WEEK_EXPOSURE  = PULSE(WEEK_LACK,WEEK_PERIOD,WEEK_FINISH)
44    MONTH_EXPOSURE = PULSE(MONTH_LACK,MONTH_PERIOD,MONTH_FINISH)
45
46    MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
```

```
MSTTFR = MSTT/CINT

CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
SUMEXPEVENT= INTEG (CYCLE,0.0) !NUMBER OF CYCLE GENERATE 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)


! -----IV EXPOSURE ---------

 IV= DOSEIV_NM * WT0 !AMOUNT IN NMOL
 IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
 EXPIV= IVR * (1.0-STEP(PFUNC))
 IVDOSE = integ(EXPIV,0.0)

   !------IV LATE IN THE CYCLE
   ! MODIFICATION ON January 13 2004
 IV_RlateR = DOSEIVNMlate*WT0
 IV_EXPOSURE=PULSE(IV_LACK,IV_PERIOD,IV_FINISH)

 IV_lateT = IV_EXPOSURE *IV_RlateR
 IV_late = IV_lateT/CINT

```

```
SUMEXPEVENTIV= integ (IV_EXPOSURE,0.0) !NUMBER OF CYCLE GENERATE
DURING SIMULATION

   !SYSTEMIC CONCENTRATION OF TCDD

    ! MODIFICATION ON OCTOBER 6, 2009
 CB=
(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late)/(QC+CL
URI) !
  CA = CB ! CONCENTRATION (NMOL/ML)


   !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*(1.0/B_TOTLIP)*(1.0/SERBLO))![NG of TCDD
Serum/Kg OF LIPIP]
   AUCBS_NGKGLIADJ=integ(CBSNGKGLIADJ,0.0)

  PRCT_B = (CB/(MSTT+1E-30))*100.0 !PERCENT OF ORAL DOSE IN BLOOD
  PRCT_BIV = (CB/(IV_RlateR+1E-30))*100.0 ! PERCENT OF IV DOSE IN BLOOD
  CBNGKG= CB*MW*UNITCORR


   !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                     !(NM/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)
  PRCT_F = (CFTOTAL/(MSTT+1E-30))*100.0 ! PERCENT OF ORAL DOSE IN FAT
  PRCT_FIV = (CFTOTAL/(IV_RlateR+1E-30))*100.0 ! PERCENT OF IV DOSE IN FAT
  CFNGKG=CFTOTAL*MW*UNITCORR ! FAT CONCENTRATION NG/KG
    AUCF_NGKGH=integ(CFNGKG,0.0)
```

```
1
2       !REST OF THE BODY COMPARTMENT
3     RAREB= QRE *(CA-CREB)-PARE*(CREB-CRE/PRE)  !(NMOL/H)
4      AREB = INTEG(RAREB,0.0)                  !(NMOL)
5      CREB = AREB/WREB                        !(NMOL/H)
6       !TISSUE COMPARTMENT
7     RARE = PARE*(CREB - CRE/PRE)             !(NMOL/H)
8      ARE = INTEG(RARE,0.0)                   !(NMOL)
9      CRE  = ARE/WRE                         !(NMOL/ML)
10
11      !UNIT CONVERSION POST SIMULATION
12     CRETOTAL= (ARE + AREB)/(WRE + WREB)         ! TOTAL CONCENTRATION IN
13    NMOL/ML
14     PRCT_RE = (CRETOTAL/(MSTT+1E-30))*100.0 ! PERCENT OF ORAL DOSE IN REST
15    OF THE BODY
16     PRCT_REIV = (CRETOTAL/(IV_RlateR+1E-30))*100.0   !PERCENT OF IV DOSE IN
17    REST OF THE BODY
18     CRENGKG=CRETOTAL*MW*UNITCORR ! REST OF THE BODY CONCENTRATION
19    IN NG/KG
20
21
22      !LIVER COMPARTMENT
23      !TISSUE BLOOD COMPARTMENT
24     RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM !
25      ALIB = INTEG(RALIB,0.0)                  !(NMOL)
26       CLIB = ALIB/WLIB                       !(NMOL/ML)
27       !TISSUE COMPARTMENT
28     RALI = PALI*(CLIB - CFLLIR)-REXCLI          !  (NMOL/HR)
29      ALI = INTEG(RALI,0.0)                     !(NMOL)
30       CLI  = ALI/WLI                         !(NMOL/ML)
31
32      !FREE TCDD CONCENTRATION IN LIVER COMPARTMENT
33    PARAMETER (LIVER_1RMN = 1.0E-30)
34     CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
35           +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2 + CFLLIR &
36           +LIVER_1RMN)*PAS_INDUC)))-CFLLI,CFLLI0)
37        CFLLIR=DIM(CFLLI,0.0) ! FREE CONCENTRATION IN LIVER
38
39      CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND
40    CONCENTRATION
41
42      !VARIABLE ELIMINATION BASED ON THE CYP1A2
43     KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv ! INDUCED
44    BILIARY EXCRETION RATE CONSTANT IN LIVER
45      REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT BILIARY EXCRETION
46    RATE
```

```
    EXCLI = INTEG(REXCLI,0.0)

  !UNIT CONVERSION POST SIMULATION
  CLITOTAL= (ALI + ALIB)/(WLI + WLIB) ! TOTAL CONCENTRATION IN NMOL/ML
  PRCT_LI = (CLITOTAL/(MSTT+1E-30))*100
  PRCT_LIIV = (CLITOTAL/(IV_RlateR+1E-30))*100.0
  Rec_occ= CFLLIR/(KDLI+CFLLIR)
  CLINGKG=CLITOTAL*MW*UNITCORR ! LIVER CONCENTRATION NG/KG
    AUCLI_NGKGH=INTEG(CLINGKG,0.0)
  CBNDLINGKG = CBNDLI*MW*UNITCORR
    AUCBNDLI_NGKGH =INTEG(CBNDLINGKG,0.0)


   !CHEMICAL IN CYP450 (1A2) COMPARTMENT
CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ


   ! MODIFICATION ON OCTOBER 6, 2009
CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-
30)**HILL &
    /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
     - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)

! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)

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)

! TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
! FETAL EXPOSURE ONLY DURING EXPOSURE

IF (T.LT.TRANSTIME_ON) THEN
 SWITCH_trans = 0.0
ELSE
 SWITCH_trans = 1.0
END IF

!TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
! MODIFICATION 26 SEPTEMBER 2003

CONSTANT PFETUS= 4.0 !
CONSTANT CLPLA_FET = 0.17 !
```

```
1
2   RAMPF = (CLPLA_FET*CPLA) *SWITCH_trans
3     AMPF=INTEG(RAMPF,0.0)
4
5   !TRANSFER OF DIOXIN FROM FETUS TO PLACENTA
6   RAFPM = (CLPLA_FET*CFETUS_v)*SWITCH_trans !
7     AFPM = INTEG(RAFPM,0.0)
8
9   ! TCDD IN PLACENTA (MOTHER) COMPARTMENT
10  RAPLAB= QPLA*(CA - CPLAB)-PAPLA*(CPLAB -CFLPLAR)   ! NMOL/H)
11   APLAB = INTEG(RAPLAB,0.0)                    ! (NMOL)
12   CPLAB = APLAB/(WPLAB+1E-30)                    ! (NMOL/ML)
13  RAPLA = PAPLA*(CPLAB-CFLPLAR)-RAMPF + RAFPM       ! (NMOL/H)
14   APLA = INTEG(RAPLA,0.0)                      ! (NMOL)
15   CPLA  = APLA/(WPLA+1e-30)                     ! (NMOL/ML)
16
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
25  CONCENTRATION IN NMOL/ML
26    PRCT_PLA = (CPLATOTAL/(MSTT+1E-30))*100
27    PRCT_PLAIV = (CPLATOTAL/(IV_RlateR+1E-30))*100
28
29
30     !FETUS COMPARTMENT
31  RAFETUS= RAMPF-RAFPM
32   AFETUS=INTEG(RAFETUS,0.0)
33  CFETUS=AFETUS/(WTFE+1E-30)
34  CFETOTAL= CFETUS
35  CFETUS_v = CFETUS/PFETUS
36
37    ! UNIT CONVERSION POST SIMULATION
38  CFETUSNGKG = CFETUS*MW*UNITCORR                !(NG/KG)
39  AUC_FENGKGH = INTEG(CFETUSNGKG,0.0)
40  PRCT_FE = (CFETOTAL/(MSTT+1E-30))*100
41  PRCT_FEIV = (CFETOTAL/(IV_RlateR+1E-30))*100
42
43
44  ! ------------CONTROL MASS BALANCE ----------
45  BDOSE= IVDOSE +LYMLUM+LIMLUM
46  BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB+AFETUS
```

```
BDIFF = BDOSE-BMASSE

    !BODY BURDEN (NG)
BODY_BURDEN = AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB !
BBFETUSNG    = AFETUS*MW*UNITCORR    ! UNIT (NG)
    ! BODY BURDEN IN TERMS OF CONCENTRATION (NG/KG)
 BBNGKG
=(((AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB)/WT0)*MW*UNITCORR) !
  AUC_BBNGKGH=INTEG(BBNGKG,0.0)


! ------------COMMAND OF THE 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 THE PROGRAM
```

C.2.4.2. *Input Files*

C.2.4.2.1. *Bell 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

%output @nciout=1 T BBFETUSNG %AJS turned off 9/21/09

%Bell et al.2007 (rat species)
%protocol:  exposure daily dose in diet for 12 weeks followed by a two week mating time and 21
day gestation period
%DevTCDD4Species.csl
%RAT_GESTATIONAL_ICF_F083109.csl (now 09-11-09)
%dose levels: 0.0024, 0.008, 0.046 ug/kg/d with 0.00003 ug/kg/d background
%dose levels: 2.4, 8, 46 ng/kg/d with 0.03 ng/kg/day background

  %EXPOSURES SCENARIOS
 MAXT           =.1
 CINT           = 0.1  %
 EXP_TIME_ON     = 0          % delay before begin exposure (HOUR)
 EXP_TIME_OFF    = 2856       % TIME EXPOSURE STOP (HOUR) 12 weeks exposure + 2
weeks for mating + 21 days gestation with exposure
 DAY_CYCLE       = 24
 BCK_TIME_ON     = 0.         % DELAY BEFORE BACKGROUND EXPOSURE (HOUR)
 BCK_TIME_OFF    = 2856.      % TIME OF BACKGROUND EXPOSURE STOP (HOUR)
 IV_LACK         = 505.
```

```
IV_PERIOD       = 505.
TIMELIMIT       = 2856        % SIMULATION LIMIT TIME (HOUR)
BW_T0           = 85
MATTING         = 2352        % BEGINNING MATTING (HOUR)
TRANSTIME_ON    = 2496        % SHOULD BE MATTING TIME + 6 DAYS(144 HOURS)
N_FETUS         = 10

%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)
```

C.2.4.2.2. *Hojo et al. (2002).*

```
%TO BE USED AFTER THE
%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
%Hojo et al. 2002
%protocol:  Single oral dose at GD8
%dose levels: 0.02 0.06, and 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 = 275g
   %60 ng/kg BW = 262g
   %180 ng/kg BW = 278g

%EXPOSURES SCENARIOS
 MAXT=0.1
 CINT =0.1                    %
 EXP_TIME_ON     = 192         % TIME AT WHICH EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 505         % TIME AT WHICH EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 505
 BCK_TIME_ON     = 0.          % TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
 BCK_TIME_OFF    = 0.          % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
 IV_LACK         = 505
 IV_PERIOD       = 505
 TIMELIMIT       = 504         % SIMULATION TIME LIMIT (HOUR)
% BW_T0          = 190
 MATTING         = 0.          % BEGINNING OF MATING (HOUR)
```

```
TRANSTIME_ON    = 144.          % SHOULD BE MATING TIME + 6 DAYS (144 HOURS)
N_FETUS         = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)

  %MSTOT        = 0.02    % ORAL EXPOSURE DOSE IN UG/KG
  %BW_T0        = 275     % AT 20 NG/KG, BW = 271g

  %MSTOT        = 0.06    % ORAL EXPOSURE DOSE IN UG/KG
  %BW_T0        = 262     % AT 60 NG/KG, BW = 275g

  MSTOT         = 0.18    % ORAL EXPOSURE DOSE IN UG/KG
  BW_T0         = 278     % AT 180 NG/KG, BW = 262g
```

C.2.4.2.3. *Ikeda et al. (2005).*

```
%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

%Ikeda et al. 2005 (rat species)
%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 AT WHICH EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF   = 1008       % TIME AT WHICH EXPOSURE ENDS (HOUR); PRE-
MATING (2 WEEKS) + MATING (1 WEEK) + GESTATION (3 WEEKS)
 DAY_CYCLE      = 168        % WEEKLY CYCLE
 BCK_TIME_ON    = 0.         % TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
 BCK_TIME_OFF   = 167.       % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
 IV_LACK        = 505.
 IV_PERIOD      = 505.
 TIMELIMIT      = 1008       % SIMULATION TIME LIMIT (HOUR)
 BW_T0          = 250
 MATTING        = 504        % BEGINNING OF MATING (HOUR)
 TRANSTIME_ON   = 648        % SHOULD BE MATING TIME + 6 DAYS (144 HOURS)
 N_FETUS        = 10
```

```
%EXPOSURE DOSE SCENARIOS (UG/KG)
  MSTOT          = 0.08       % ORAL EXPOSURE DOSE IN UG/KG
  MSTOTBCKGR     = 0.32   % BACKGROUND EXPOSURE IN UG/KG

```

C.2.4.2.4. ***Kattainen et al. (2001).***

```
%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

%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=0.1
 CINT =0.1

  %EXPOSURES SCENARIOS
 EXP_TIME_ON       = 336          % TIME AT WHICH EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF      = 340          % TIME AT WHICH EXPOSURE ENDS (HOUR)
 DAY_CYCLE         = 505
 BCK_TIME_ON       = 0.           % TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOUR)
 BCK_TIME_OFF      = 0.           % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
 IV_LACK           = 505
 IV_PERIOD         = 505
 TIMELIMIT         = 504          % SIMULATION TIME LIMIT (HOUR)
 BW_T0             = 190
 MATTING           = 0.           % BEGINNING OF MATING (HOUR)
 TRANSTIME_ON      = 144.         % SHOULD BE MATING TIME + 6 DAYS (144
HOURS)
 N_FETUS           = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT          = 0.03          % ORAL EXPOSURE DOSE IN UG/KG
 %MSTOT          = 0.1           % ORAL EXPOSURE DOSE IN UG/KG
 %MSTOT          = 0.3           % ORAL EXPOSURE DOSE IN UG/KG
 MSTOT           = 1             % ORAL EXPOSURE DOSE IN UG/KG

```

C.2.4.2.5. *Markowski et al. (2001).*

```
%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

%Markowski et al.2001
%protocol:  Single gavage at GD18
%dose levels: 0.02 0.06, 0.18, 1 ug/kg  at GD18
%dose levels: 20, 60, 180 ng/kg at GD18


%EXPOSURES SCENARIOS
 MAXT=0.1
 CINT =0.1                    %
 EXP_TIME_ON     = 408          % TIME AT WHICH EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 415          % TIME AT WHICH EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 505
 BCK_TIME_ON     = 0.           % TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
 BCK_TIME_OFF    = 0.           % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
 IV_LACK         = 505
 IV_PERIOD       = 505
 TIMELIMIT       = 504          % SIMULATION TIME LIMIT (HOUR)
 BW_T0           = 190
 MATTING         = 0.           % BEGINNING OF MATING (HOUR)
 TRANSTIME_ON    = 144.         % SHOULD BE MATING TIME + 6 DAYS (144 HOURS)
 N_FETUS         = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT         = 0.02  % ORAL EXPOSURE DOSE IN UG/KG
  %MSTOT         = 0.06   % ORAL EXPOSURE DOSE IN UG/KG
  MSTOT         = 0.18   % ORAL EXPOSURE DOSE IN UG/KG
```

C.2.4.2.6. *Miettinen et al. (2006).*

```
%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

%Miettinnen et al 2006
```

```
%protocol:  Single oral dose 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=0.1
 CINT =0.1                    %

  %EXPOSURES SCENARIOS
 EXP_TIME_ON   = 336         % TIME AT WHICH EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF  = 340         % TIME AT WHICH EXPOSURE ENDS (HOUR)
 DAY_CYCLE     = 505
 BCK_TIME_ON   = 0.          % TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
 BCK_TIME_OFF  = 0.          % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
 IV_LACK       = 505
 IV_PERIOD     = 505
 TIMELIMIT     = 504         % SIMULATION TIME LIMIT (HOUR)
 BW_T0         = 180
 MATTING       = 0.          % BEGINNING OF MATING (HOUR)
 TRANSTIME_ON  = 144.        % SHOULD BE MATING TIME + 6 DAYS (144 HOURS)
 N_FETUS       = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT       = 0.03       % ORAL EXPOSURE DOSE IN UG/KG
  %MSTOT       = 0.1        % ORAL EXPOSURE DOSE IN UG/KG
  %MSTOT       = 0.3        % ORAL EXPOSURE DOSE IN UG/KG
  MSTOT       = 1          % ORAL EXPOSURE DOSE IN UG/KG
```

C.2.4.2.7. ***Murray et al. (1979).***

```
%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

%output @nciout=1 T BBFETUSNG %AJS turned off 9/21/09

%Murray et al.1979 (rat species)
%protocol:  dietary exposure for 90 days followed by gestation (21 days)
%dose levels: 0.001 0.01, 0.1 ug/kg/d
%dose levels: 1, 10, 100  ng/kg/d

  %EXPOSURES SCENARIOS
 MAXT           =.1
```

```
 CINT          = 0.1  %
 EXP_TIME_ON     = 0          % TIME AT WHICH EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF    = 2660       % TIME AT WHICH EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 24
 BCK_TIME_ON     = 0.         % TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
 BCK_TIME_OFF    = 0.         % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
 IV_LACK         = 2664
 IV_PERIOD       = 2664
 TIMELIMIT       = 2664       % SIMULATION TIME LIMIT (HOUR)
 BW_T0           = 85
 MATTING         = 2160       % BEGINNING OF MATING (HOUR)
 TRANSTIME_ON    = 2304       % SHOULD BE MATING TIME + 6 DAYS (144 HOURS)
 N_FETUS         = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
 %MSTOT          = 0.001      % ORAL EXPOSURE DOSE IN UG/KG
 %MSTOT          = 0.01       % ORAL EXPOSURE DOSE N UG/KG
 MSTOT           = 0.1        % ORAL EXPOSURE DOSE N UG/KG
```

C.2.4.2.8. ***Nohara 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

%Nohara et al 2000
%protocol:  exposure daily dose in diet
%dose levels: 0.0125, 0.050, 0.2 or 0.8 ug TCDD:kg body weight by gavage on GD15.
%dose levels: 12.5, 50, 200 or 800 ng TCDD:kg body weight by gavage on GD15.

 MAXT=0.1
 CINT =0.1                %

  %EXPOSURES SCENARIOS
 EXP_TIME_ON   = 336        % TIME AT WHICH EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF  = 340        % TIME AT WHICH EXPOSURE ENDS (HOUR)
 DAY_CYCLE     = 505 TIME AT WHICH BACKGROUND EXPOSURE BEGINS (HOUR)
 BCK_TIME_OFF  = 0.         % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
 IV_LACK       = 505
 IV_PERIOD     = 505
 TIMELIMIT     = 504        % SIMULATION TIME LIMIT (HOUR)
```

```
 BW_T0        = 180
 MATTING      = 0.          % BEGINNING OF MATING (HOUR)
 TRANSTIME_ON  = 144.    % SHOULD BE MATING TIME + 6 DAYS (144 HOURS)
 N_FETUS      = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT       = 0.0125    % ORAL EXPOSURE DOSE IN UG/KG
  %MSTOT       = 0.050   % ORAL EXPOSURE DOSE IN UG/KG
  %MSTOT       = 0.2    % ORAL EXPOSURE DOSE IN UG/KG
  MSTOT       = 0.8    % ORAL EXPOSURE DOSE IN UG/KG

```

C.2.4.2.9. ***Ohsako et al. (2001).***

```
%TO BE USED AFTER THE
%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

%Ohsako et al. 2001
%protocol:  exposure SINGLE DOSE AT GD15
%dose levels: 0.0125, 0.05, and 0.2 and 0.8 ug/kg  AT GD15
%dose levels: 12.5, 50, 200 and 800 ng/kg AT GD15

%EXPOSURES SCENARIOS
 MAXT=0.001
 CINT =0.1                    %
 EXP_TIME_ON    = 360         % TIME AT WHICH EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF   = 505         % TIME AT WHICH EXPOSURE ENDS (HOUR)
 DAY_CYCLE      = 505
 BCK_TIME_ON    = 0.          % TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
 BCK_TIME_OFF   = 0.          % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
 IV_LACK        = 505
 IV_PERIOD      = 505
 TIMELIMIT      = 504         % SIMULATION TIME LIMIT (HOUR)
 BW_T0          = 200
 MATTING        = 0.          % BEGINNING OF MATING (HOUR)
 TRANSTIME_ON   = 144.        % SHOULD BE MATING TIME + 6 DAYS (144 HOURS)
 N_FETUS        = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)

 %MSTOT       = 0.0125    % ORAL EXPOSURE DOSE IN UG/KG
```

```
%MSTOT       = 0.05     % ORAL EXPOSURE DOSE IN UG/KG
%MSTOT       = 0.20     % ORAL EXPOSURE DOSE IN UG/KG
MSTOT        = 0.80     % ORAL EXPOSURE DOSE IN UG/KG

```

C.2.4.2.10. *Schantz et al. (1996) and Amin et al. (2000).*

```
output @clear
prepare @clear T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CFETUSNGKG
AUCLI_NGKGH AUCF_NGKGH AUCBS_NGKGLIADJ AUC_BBNGKGH
AUC_FENGKGH CBNDLINGKG AUCBNDLI_NGKGH

%Amin et al 2000 (rat species) and Schantz et al 1995
%protocol:  Daily doses during gestation day 10 to 16
%DevTCDD4Species.csl
%RAT_GESTATIONAL_ICF_F083109.csl (now 09-11-09)
%dose levels: 25 and 100 ug/kg/day
%dose levels: 0.25 and 0.100 ng/kg/day

  %EXPOSURES SCENARIOS
 MAXT          =.1
 CINT          = 0.1  %
 EXP_TIME_ON     = 240.          % delay before begin exposure (HOUR)
 EXP_TIME_OFF    = 384.        % TIME EXPOSURE STOP (HOUR) 12 weeks exposure + 2
weeks for mating + 21 days gestation with exposure
 DAY_CYCLE       = 24         % weekly cycle
 BCK_TIME_ON     = 1000.          % DELAY BEFORE BACKGROUND EXPOSURE
(HOUR)
 BCK_TIME_OFF    = 1000.        % TIME OF BACKGROUND EXPOSURE STOP (HOUR)
 IV_LACK         = 505.
 IV_PERIOD       = 505.
 TIMELIMIT       = 384.        % SIMULATION LIMIT TIME (HOUR)
 BW_T0          = 250.
 MATTING         = 0        % BEGINNING MATTING (HOUR)
 TRANSTIME_ON    = 144.        % SHOULD BE MATTING TIME + 6 DAYS(144 HOURS)
 N_FETUS         = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT         = .025       % ORAL EXPOSURE DOSE (UG/KG)
  MSTOT         = .100
  MSTOTBCKGR     = 0        % Background Exposure (UG/KG)

```

C.2.4.2.11. *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

%Seo et al. 1995
%protocol:  exposure GD 10-16
%DevTCDD4Species.csl
%RAT_GESTATIONAL_ICF_F083109.csl (now 09-11-09)
%dose levels: 0.025 and 0.1 ug/kg  GD 10-16
%dose levels: 25 and 100 ng/kg GD 10-16

 MAXT=0.1
 CINT =0.1

  %EXPOSURES SCENARIOS
 EXP_TIME_ON        = 240          % delay before begin exposure (HOUR)
 EXP_TIME_OFF       = 385          % TIME EXPOSURE STOP (HOUR)
 DAY_CYCLE          = 24
 BCK_TIME_ON        = 0.           % DELAY BEFORE BACKGROUND EXPOSURE
(HOUR)
 BCK_TIME_OFF       = 0.           % TIME OF BACKGROUND EXPOSURE STOP (HOUR)
 IV_LACK            = 505
 IV_PERIOD          = 505
 TIMELIMIT          = 504          % SIMULATION LIMIT TIME (HOUR)
 BW_T0              = 190
 MATTING            = 0.           % BEGINNING MATING (HOUR)
 TRANSTIME_ON       = 144.         % SHOULD BE MATING TIME + 6 DAYS (144
HOURS)
 N_FETUS            = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
 MSTOT          = 0.025          % ORAL EXPOSURE DOSE (UG/KG)
 %MSTOT          = 0.1           % ORAL EXPOSURE DOSE (UG/KG)
```

C.2.4.2.12. *Shi et al. (2007).*

```
%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
%output @nciout=1 T BBFETUSNG %AJS turned off 9/21/09

%Shi et al 2007
%protocol:  exposure at GD14 and GD21 orl exposure
```

```
%dose levels: 0.001, 0.005, 0.05 and 0.2 ug TCDD:kg body weight by gavage on GD14 and
GD21.
%dose levels: 1, 5, 50 and 200 ng/kg ng TCDD:kg body weight by gavage on GD14 and GD21.
% dose equivalent adjusted 0.143, 0.714, 7.14 and 28.6 ng/kg/d

MAXT=0.001
 CINT =0.1                    %
CFLI0 = 0
CFPLA0 = 0
   %EXPOSURES SCENARIOS
 EXP_TIME_ON      = 312       % TIME AT WHICH EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF     = 485       % TIME AT WHICH EXPOSURE ENDS (HOUR)
 DAY_CYCLE        = 168
 BCK_TIME_ON      = 0.        % TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
 BCK_TIME_OFF     = 0.        % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
 IV_LACK          = 505
 IV_PERIOD        = 505
 TIMELIMIT        = 504       % SIMULATION TIME LIMIT (HOUR)
 BW_T0            = 190       % BODY WEIGHT AT THE BEGINNING OF THE SIMULATION
(G)
 MATTING          = 0.        % BEGINNING OF MATING (HOUR)
 TRANSTIME_ON     = 144.      % SHOULD BE MATING TIME + 6 DAYS (144 HOURS)
 N_FETUS          = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT         = 0.001     % ORAL EXPOSURE DOSE IN UG/KG
   MSTOT          = 0.005     % ORAL EXPOSURE DOSE IN UG/KG
   %MSTOT         = 0.05      % ORAL EXPOSURE DOSE IN UG/KG
   %MSTOT         = 0.2       % ORAL EXPOSURE DOSE IN UG/KG
```

C.2.5. Mouse Standard Model

C.2.5.1. *Model Code*

```
        PROGRAM:  'Three Compartment PBPK Model for TCDD in Mice: Standard Model
(Non-Gestation)'

!Mice_Dioxin_3C_June09_1_icf_afterKKfix_v3_mousenongest.csl
!MICE_NON_GESTAT_ICF_F083109.csl
!MICE_NON_GESTAT_ICF_F093009.csl
!MICE_NON_GESTAT_ICF_F100609.csl
!*************************************************
```

```
INITIAL  ! INITIALIZATION OF PARAMETERS

   !SIMULATION PARAMETERS ====
CONSTANT PARA_ZERO      =   1D-30
CONSTANT EXP_TIME_ON    =    0.0       ! TIME AT WHICH EXPOSURE BEGINS
(HOURS)
CONSTANT EXP_TIME_OFF   =   2832       ! TIME AT WHICH EXPOSURE ENDS
(HOURS)
CONSTANT DAY_CYCLE      =   24         ! NUMBER OF HOURS BETWEEN DOSES
(HOURS)
CONSTANT BCK_TIME_ON    =    0.0       ! TIME AT WHICH BACKGROUND
EXPOSURE BEGINS (HOURS)
CONSTANT BCK_TIME_OFF   =    0.0       ! TIME AT WHICH BACKGROUND
EXPOSURE ENDS (HOURS)

CONSTANT MW=322 ! MOLECULAR WEIGHT (NG/NMOL)
CONSTANT SERBLO = 0.55
CONSTANT UNITCORR = 1000

   !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
```

```
1
2   !===EXCRETION AND ABSORPTION CONSTANT (OPTIMIZED)
3   CONSTANT KST          =   0.3   ! GASTRIC RATE CONSTANT (HR-1),
4   CONSTANT KABS         =   0.48  !INTESTINAL ABSORPTION CONSTANT (HR-1) ),
5   WANG ET AL. 1997
6
7   ! ELIMINATION CONSTANTS
8   CONSTANT CLURI        =     0.09 ! URINARY CLEARANCE (ML/HR)
9
10  ! ==test elimination variable
11  constant kelv         =    0.4       ! INTERSPECIES VARIABLE ELIMINATION CONSTANT
12  (1/HOUR)
13
14  ! CONSTANT TO DIVIDE THE ABSORPTION INTO LYMPHATIC AND PORTAL
15  FRACTIONS
16  CONSTANT A            =     0.7      ! LYMPHATIC FRACTION, WANG ET AL. 1997
17
18  !PARTITION COEFFICIENTS OPTIMIZED
19  CONSTANT PF           =   400        ! ADIPOSE TISSUE/BLOOD
20  CONSTANT PRE          =   3          ! REST OF THE BODY/BLOOD, WANG ET AL. 2000
21  CONSTANT PLI          =   6         ! LIVER/BLOOD, WANG ET AL. 1997
22
23  !===PARAMETER FOR INDUCTION OF CYP 1A2
24  CONSTANT PAS_INDUC=     1.0     ! INCLUDE INDUCTION? (1 = YES, 0 = NO)
25  CONSTANT CYP1A2_1OUTZ = 1.6   ! DEGRADATION CONCENTRATION CONSTANT
26  OF 1A2 (NMOL/ML)
27  CONSTANT CYP1A2_1A1 =   1.5   ! BASAL CONCENTRATION OF 1A1 (NMOL/ML)
28  CONSTANT CYP1A2_1EC50 = 0.13   ! DISSOCIATION CONSTANT TCDD-CYP1A2
29  (NMOL/ML)
30  CONSTANT CYP1A2_1A2 =   1.5   ! BASAL CONCENTRATION OF 1A2 (NMOL/ML)
31  CONSTANT CYP1A2_1KOUT = 0.1   ! FIRST ORDER RATE OF DEGRADATION (H-1)
32  CONSTANT CYP1A2_1TAU  = 1.5  ! HOLDING TIME (H)
33  CONSTANT CYP1A2_1EMAX = 600   ! MAXIMUM INDUCTION OVER BASAL EFFECT
34  (UNITLESS)
35  CONSTANT HILL         = 0.6     !HILL CONSTANT; COOPERATIVELY LIGAND
36  BINDING EFFECT CONSTANT (UNITLESS)
37     !DIFFUSIONAL PERMEABILITY FRACTION
38  CONSTANT PAFF     = 0.12      ! ADIPOSE (UNITLESS), WANG ET AL. 2000
39  CONSTANT PAREF    = 0.03      ! REST OF THE BODY (UNITLESS)
40  CONSTANT PALIF    = 0.35      ! LIVER (UNITLESS)
41
42     !COMPARTMENT TISSUE BLOOD VOLUME  =========
43  CONSTANT WLI0     =  0.0549   ! LIVER, ILSI 1994
44  CONSTANT WF0      =  0.069    ! ADIPOSE
45
46     !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_LACK   = 0.0    ! DELAY BEFORE EXPOSURE ENDS (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_LACK   = 0.0   ! DELAY BEFORE EXPOSURE (MONTH)

   !SET FOR BACKGROUND EXPOSURE==========
   !CONSTANT FOR BACKGROUND EXPOSURE==========
CONSTANT Day_LACK_BG = 0.0    ! DELAY BEFORE EXPOSURE BEGINS (HOURS)
CONSTANT Day_PERIOD_BG = 24   ! LENGTH OF EXPOSURE (HOURS)

   ! NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LACK_BG   = 0.0 ! DELAY BEFORE BACKGROUD 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

   !CONSTANT USED IN CARDIAC OUTPUT EQUATION, KRISHNAN 2001
CONSTANT QCCAR =275         !CONSTANT (ML/MIN/KG)

   ! COMPARTMENT LIPID EXPRESSED AS THE FRACTION OF TOTAL LIPID
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        =       1.0       !COMMUNICATION INTERVAL
MAXTERVAL  MAXT        =      1.0e+10    !MAXIMUM CALCULATION INTERVAL
MINTERVAL  MINT        =     1.0E-10     !MINIMUM CALCULATION INTERVAL
VARIABLE   T           =       0.0       !HOUR
CONSTANT   TIMELIMIT   =       2904.0    !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

    !NMAX =MAX(T,CTFNGKG)
nmax =max(T,CFNGKG)

DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS

    !CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
    !NUMBER OF EXPOSURES PER DAY
 DAY_LACK     = EXP_TIME_ON      ! DELAY 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_LACK_BG   = BCK_TIME_ON    ! DELAY BEFORE BACKGROUD EXPOSURE
BEGINS (MONTHS)
 MONTH_PERIOD_BG = TIMELIMIT     ! BACKGROUND EXPOSURE PERIOD
(MONTHS)
 MONTH_FINISH_BG = BCK_TIME_OFF   ! LENGTH OF BACKGROUND EXPOSURE
(MONTHS)

    ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE LIVER
 B = 1.0-A


    !GROWTH UP EQUATION (G)

PARAMETER (BW_RMN = 1.0E-30)
```

```
WT0= (BW_T0 *(1.0+(0.41*T)/(1402.5+T+BW_RMN)))

   ! VARIABILITY OF REST OF THE BODY DEPENDS ON OTHER ORGANS
   !REST OF THE BODY FRACTION; UPDATED FOR EPA ASSESSMENT
 WRE0 = (0.91 - (WLIB0*WLI0 + WFB0*WF0 + WLI0 + WF0))/(1+WREB0)

   ! REST OF THE BODY BLOOD FLOW FRACTION
 QREF = 1.0-(QFF+QLIF)          !REST OF BODY BLOOD FLOW (ML/HR)
   !SUMMATION OF BLOOD FLOW FRACTION (SHOULD BE EQUAL TO 1)
 QTTQF = QFF+QREF+QLIF         ! SUM MUST EQUAL 1

   !COMPARTMENT VOLUME (G)
 WF  =  WF0  * WT0             ! ADIPOSE
 WRE =  WRE0 * WT0               ! REST OF THE BODY
 WLI =  WLI0 * WT0             ! LIVER

   !COMPARTMENT TISSUE BLOOD (G)
 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*(WT0/1000.0)**0.75

QF  = QFF*QC        ! ADIPOSE TISSUE BLOOD FLOW RATE (ML/HR)
QLI = QLIF*QC       ! LIVER TISSUE BLOOD FLOW RATE (ML/HR)
QRE = QREF*QC       ! REST OF THE BODY BLOOD FLOW RATE (ML/HR)

QTTQ = QF+QRE+QLI   !TOTAL FLOW RATE (ML/HR)

   !PERMEABILITY ORGAN FLOW (ML/HR) =======
PAF  = PAFF*QF      ! ADIPOSE TISSUE
PARE = PAREF*QRE    ! REST OF THE BODY
PALI = PALIF*QLI    ! LIVER TISSUE

   !ABSORPTION SECTION
   !ORAL
   !BACKGROUND EXPOSURE
   !EXPOSURE FOR STEADY STATE CONSIDERATION
   !REPETITIVE EXPOSURE SCENARIO

MSTOT_NMBCKGR = MSTOTBCKGR/322 !AMOUNT IN NMOL/G
MSTTBCKGR =MSTOT_NMBCKGR *WT0

   !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIOS
DAY_EXPOSURE_BG   = PULSE(DAY_LACK_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
```

```
WEEK_EXPOSURE_BG  =
PULSE(WEEK_LACK_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
MONTH_EXPOSURE_BG =
PULSE(MONTH_LACK_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

MSTTCH_BG =
(DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCK
GR
MSTTFR_BG = MSTTBCKGR/CINT

totalBG= integ (MSTTCH_BG,0.0)
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

    !EXPOSURE + !REPETITIVE EXPOSURE SCENARIO
IV= DOSEIV_NM * WT0  !AMOUNT IN NMOL
MSTT= MSTOT_NM * WT0 !AMOUNT IN NMOL

DAY_EXPOSURE   = PULSE(DAY_LACK,DAY_PERIOD,DAY_FINISH)
WEEK_EXPOSURE  = PULSE(WEEK_LACK,WEEK_PERIOD,WEEK_FINISH)
MONTH_EXPOSURE = PULSE(MONTH_LACK,MONTH_PERIOD,MONTH_FINISH)

MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE

SUMEXPEVENT= integ (CYCLE,0.0)*cint !NUMBER OF CYCLE GENERATE DURING
SIMULATION

MSTTFR = MSTT/CINT

   ! CONDITIONAL ORAL EXPOSURE
IF (MSTTCH.EQ.MSTT) THEN
  ABSMSTT= MSTTFR
ELSE
  ABSMSTT = 0.0
END IF

 CYCLETOT=INTEG(CYCLE,0.0)

```

```
1
2       !MASS CHANGE IN THE LUMEN
3     RMSTT= -(KST+KABS)*MST+ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE
4     (NMOL/H)
5      MST = INTEG(RMSTT,0.0)  !AMOUNT OF STAY IN DUODENUM (NMOL)
6
7       !ABSORPTION IN LYMPH CIRCULATION
8     LYRMLUM = KABS*MST*A
9      LYMLUM = INTEG(LYRMLUM,0.0)
10
11      !ABSORPTION IN PORTAL CIRCULATION
12    LIRMLUM = KABS*MST*B
13     LIMLUM = INTEG(LIRMLUM,0.0)
14
15      !PERCENT OF DOSE REMAINING IN THE GI TRACT
16    PRCT_remain_GIT  = (MST/(MSTT+1E-30))*100
17
18    RFECES = KST*MST + REXCLI
19     FECES = INTEG(RFECES,0.0)
20    prctFECES = (FECES/(BDOSE_TOTAL+1E-30))*100
21
22
23      !ABSORPTION OF DIOXIN BY IV ROUTE---------
24     IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
25     EXPIV= IVR * (1.0-STEP(PFUNC))
26     IVDOSE = integ(EXPIV,0.0)
27
28      !SYSTEMIC BLOOD CONCENTRATION (NMOL/ML)
29      ! MODIFICATION ON OCTOBER 6, 2009
30    CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM)/(QC+CLURI) !
31     CA = CB
32
33      !URINARY EXCRETION BY KIDNEY
34      ! MODIFICATION ON OCTOBER 6, 2009
35    RAURI = CLURI *CB
36     AURI = INTEG(RAURI,0.0)
37
38    prctAURI = (AURI/(BDOSE_TOTAL+1E-30))*100
39
40
41      !UNIT CONVERSION POST SIMULATION
42    PRCT_B = (CB/(MSTT+1E-30))*100  ! PERCENT OF DOSE/G TISSUE
43    CBNGKG=CB*MW*UNITCORR
44    CBSNGKGLIADJ= (CB*MW*UNITCORR*(1.0/B_TOTLIP)*(1.0/SERBLO))![NG of TCDD
45    Serum/Kg OF LIPIP]
46    CBPMOL_KG= CB*UNITCORR*UNITCORR       !CONCENTRATION IN PMOL/KG
```

```
CBNGG = CB*MW
   !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)

   !POST SIMULATION UNIT CONVERSION
CFTOTAL    = (AF + AFB)/(WF + WFB) ! TOTAL CONCENTRATION IN FAT(NM/ML)
PRCT_F  = (CFTOTAL/(MSTT+1E-30))*100 ! PERCENT OF DOSE IN FAT
CFNGKG  = CFTOTAL*MW*UNITCORR
CFUGG=(CFTOTAL*MW)/UNITCORR
CFPMOL_KG= CFTOTAL*UNITCORR*UNITCORR      !CONCENTRATION IN
PMOL/KG
CFNGG = CFTOTAL*MW

   !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 SUBCOMPARTMENT
RARE = PARE*(CREB - CRE/PRE)                   !(NMOL/HR)
 ARE = INTEG(RARE,0.0)                         !(NMOL)
 CRE  = ARE/WRE                                !(NMOL/ML)

   !POST SIMULATION UNIT CONVERSION
CRETOTAL= (ARE + AREB)/(WRE + WREB)            ! CONCENTRATION AT STEADY
STATE
PRCT_RE = (CRETOTAL/(MSTT+1E-30))*100


   !LIVER COMPARTMENT
   !TISSUE BLOOD SUBCOMPARTMENT
RALIB = QLI*(CA-CLIB)-PALI*(CLIB-CFLLIR)+LIRMLUM   !(NMOL/HR)
  ALIB = INTeg(RALIB,0.0)                      !(NMOL)
 CLIB = ALIB/WLIB
   !TISSUE SUBCOMPARTMENT
 RALI =  PALI*(CLIB-CFLLIR)-REXCLI             !(NMOL/HR)
  ALI = integ(RALI,0.0)                        !(NMOL)
  CLI  = ALI/WLI                               !(NMOL/ML)

```

```
   !FREE TCCD CONCENTRATION IN LIVER (NMOL/ML)
PARAMETER (LIVER_1RMN = 1.0E-30)
 CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLI &
     +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2+CFLLIR &
     +LIVER_1RMN)*PAS_INDUC)))-CFLLI,CFLLI0)
    CFLLIR=DIM(CFLLI,0.0) ! FREE CONCENTRATION IN LIVER

CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND
CONCENTRATION

  !POST SIMULATION UNIT CONVERSION
CLITOTAL= (ALI + ALIB)/(WLI + WLIB)!
PRCT_LI = (CLITOTAL/(MSTT+1E-30))*100 ! PERCENT OF DOSE IN LIVER
rec_occ_AHR= (CFLLIR/(KDLI+CFLLIR+1E-30))*100.0  ! PERCENT OF AhR
OCCUPANCY
PROT_occ_1A2= (CFLLIR/(KDLI2+CFLLIR))*100.0  ! PERCENT OF 1A2 OCCUPANCY
CLINGKG =(CLITOTAL*MW*UNITCORR)
CBNDLINGKG = CBNDLI*MW*UNITCORR
CLIUGG=(CLITOTAL*MW)/UNITCORR
CLIPMOL_KG= CLITOTAL*UNITCORR*UNITCORR      !CONCENTRATION IN
PMOL/KG
CLINGG = CLITOTAL*MW

  !Fraction increase of induction of CYP1A2
fold_ind=(CYP1A2_1OUT/CYP1A2_1A2)
VARIATIONOfAC =(CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2

  !VARIABLE ELIMINATION BASED ON THE CYP1A2
KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv !INDUCED BILIARY
EXCRETION RATE CONSTANT

REXCLI= (KBILE_LI_T*CFLLIR*WLI) !DOSE-DEPENDENT EXCRETION RATE
 EXCLI = INTEG(REXCLI,0.0)

  !CHEMICAL IN CYP450 (1A2) COMPARTMENT
  !EQUATION FOR INDUCTION OF CYP1A2

CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ

  ! MODIFICATION ON OCTOBER 6, 2009
CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-
30)**HILL &
    /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
     - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)
! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)
```

```
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)

     ! MASS BALANCE CONTROL
 BDOSE= LYMLUM+LIMLUM+IVDOSE
 BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI
 BDIFF = BDOSE-BMASSE
     ! AMOUNT TOTAL PRESENT IN THE GI TRACT
BDOSE_TOTAL =LYMLUM+LIMLUM+FECES

     !BODY BURDEN IN NG
 Body_burden =(AFB+AF+AREB+ARE+ALIB+ALI)*MW

     !BODY BURDEN CONCENTRATION (NG/KG)
 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
```

C.2.5.2. *Input Files*

C.2.5.2.1. *Hassoun et al. (1998) (13 weeks).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Hassoun et al 1998
%built and check in August 7 2009
%protocol:  oral exposure single dose
%dose levels:  0.00045, 0.0015, 0.015, 0.15 ug/kg single dose + 7 days post exposure
%dose levels:  0.45, 1.5, 15, 150 ng/kg single dose + 7 days post exposure
%dose levels equivalent 0.321, 1.07, 10.7, 107 ng/kg/day

MAXT        = 0.01
CINT        = 0.1
EXP_TIME_ON  = 0.       %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF = 2184     %2208 %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE    =  24
```

```
WEEK_PERIOD  = 168
WEEK_FINISH  = 119
BCK_TIME_ON  = 0.       % TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF = 0.       % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT    = 2208     %SIMULATION TIME LIMIT (HOUR)
BW_T0        = 23       % BODY WEIGHT AT THE BEGINNING OF THE SIMULATION (G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
    %MSTOT = 0.00045       % EXPOSURE DOSE IN UG/KG
    %MSTOT = 0.0015    % EXPOSURE DOSE IN UG/KG
    %MSTOT = 0.015     % EXPOSURE DOSE IN UG/KG
    MSTOT = 0.150     % EXPOSURE DOSE IN UG/KG

NTP (1982) (female) (chronic)
%RAT2.m
%clear variable
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG
%output @nciout=168 T SUMEXPEVENT


% NTP subchronic Mice exposure 1982.
%built and check in September 20, 2009
%protocol: repetitive  doses
%MICE_NON_GESTAT_ICF_F092009.csl (now 09-20-09)
%dose levels:  0.02, 0.1, 1 ug/kg/biweekly, ug/kg for 104 weeks + 3 weeks post treatment
%dose levels:  20, 100 and 1000 ng/kg/Biweekly,ng/kg for 104 weeks + 3 weeks post treatment
%dose levels equivalent to: 5.71, 28.57, 285.1 ng/kg/d

MAXT =  0.01
CINT  = 0.1
EXP_TIME_ON      = 0.      %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     = 17472     %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE        = 84
BCK_TIME_ON      = 0.      %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF     = 0.      %TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT        = 17976     %SIMULATION TIME LIMIT (HOUR)
BW_T0            = 23      % 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       = 1.0      % EXPOSURE DOSE IN UG/KG
```

C.2.5.2.2. *NTP (1982) (male) (chronic).*

```
%RAT2.m
%clear variable
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG
%output @nciout=168 T SUMEXPEVENT

% NTP subchronic Mice exposure 1982.
%built and check in September 20, 2009
%protocol: repetitive  doses
%dose levels:  0.005, 0.025, 0.25 ug/kg/biweekly, ug/kg for 104 weeks + 3 weeks post treatment
%dose levels:  5, 25 and 250 ng/kg/Biweekly,ng/kg for 104 weeks + 3 weeks post treatment
%dose levels equivalent to: 1.4, 7.1, 71 ng/kg/d

MAXT =  0.01
CINT  = 0.1
EXP_TIME_ON      = 0.      %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF     = 17472     %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE        = 84
BCK_TIME_ON      = 0.      % TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF     = 0.      %TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
TIMELIMIT        = 17976     %SIMULATION TIME LIMIT (HOUR)
BW_T0          = 25      % BODY WEIGHT AT THE BEGINNING OF THE SIMULATION
(G)


%EXPOSURE DOSE SCENARIOS (UG/KG)
   %MSTOT       = 0.005     % EXPOSURE DOSE IN UG/KG
   %MSTOT       = 0.025     % EXPOSURE DOSE IN UG/KG
   MSTOT        = 0.25      % EXPOSURE DOSE IN UG/KG
```

C.2.5.2.3. *Smialowicz et al. (2008).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG
```

```
% Smialowicz et al, 2008.
%built and check in August 7 2009
%protocol:  oral exposure single dose
%protocol:  5/7 gavage for 13 wk;  Female B6C3F1 mice
%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 TIME LIMIT (HOUR)
EXP_TIME_ON  = 0.           %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF = 2180         %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE    =  24
WEEK_PERIOD  = 168
WEEK_FINISH  = 119
BCK_TIME_ON  = 0.           %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF = 0.           %TIME AT WHICH 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 IN UG/KG
  %MSTOT   = 0.015        % EXPOSURE DOSE IN UG/KG
  %MSTOT   = 0.150        % EXPOSURE DOSE IN UG/KG
  MSTOT   = 0.450        % EXPOSURE DOSE IN UG/KG
```

C.2.5.2.4. ***Toth et al. (1979) (1 year).***

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Toth et al 1979
%built and check in August 7 2009
%protocol:  oral exposure single dose
%dose levels:  7, 700, 7000 ng/kg 1/week for 52 weeks (1 year)
%dose levels:  0.007, 0.7 and 7 ug/kg 1/week for 52 weeks (1 year)
%dose equivalent: 1, 100, 1000 ng/kg/day

MAXT         = 0.01
CINT         = 0.1
TIMELIMIT    = 8736
EXP_TIME_ON  = 0.           %TIME AT WHICH EXPOSURE BEGINS (HOUR)
```

```
EXP_TIME_OFF = 8736       %2208 %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE   = 168
WEEK_PERIOD  = 8760
WEEK_FINISH  = 8760
BCK_TIME_ON  = 0.         %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF = 0.         %TIME AT WHICH 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 IN UG/KG
   %MSTOT = 0.7         % EXPOSURE DOSE IN UG/KG
   MSTOT = 7          % EXPOSURE DOSE IN UG/KG
```

C.2.5.2.5. ***Toth et al. (1979) (2 year).***

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% Toth et al 1979
%built and check in August 7 2009
%protocol:  oral exposure single dose
%dose levels: 7, 700, 7000 ng/kg 1/week for 52 weeks (1 year)
%dose levels:  0.007, 0.7 and 7 ug/kg 1/week for 52 weeks (1 year)
%dose levels equivalent:  1, 100, 1000 ng/kg/day

MAXT        = 0.01
CINT        = 0.1
TIMELIMIT    = 15576       %WEEKLY GAVAGE FOR 1 YEAR; LIFETIME FOLLOW-UP
(AVG 424-649 DAYS); USED MAXIMUM OF 649 DAYS
EXP_TIME_ON  = 0.         %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF = 8736       %2208 %tIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE   = 168
WEEK_PERIOD  = 8760
WEEK_FINISH  = 8760
BCK_TIME_ON  = 0.         %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF = 0.         %TIME AT WHICH 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 IN UG/KG
   %MSTOT = 0.7        % EXPOSURE DOSE IN UG/KG
   MSTOT = 7          % EXPOSURE DOSE IN UG/KG
```

C.2.5.2.6. *White et al. (1986).*

```
output @clear
prepare @clear
prepare T CLINGKG CFNGKG CBSNGKGLIADJ BBNGKG CBNDLINGKG

% White et al 1986
%built and check in August 7 2009

%protocol:  oral exposure single dose
%dose levels:  0.714, 3.57, 7.14, 35.71, 71.43, 142.86 ng /kg/d ug/kg 1/day for 14 consecutive
days
%dose have been modified following Jeff email on Friday August 21 2009
%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
EXP_TIME_ON  = 0.       %TIME AT WHICH EXPOSURE BEGINS (HOUR)
EXP_TIME_OFF = 336      %TIME AT WHICH EXPOSURE ENDS (HOUR)
DAY_CYCLE    =  24
WEEK_PERIOD  = 336
WEEK_FINISH  = 336
BCK_TIME_ON  = 0.       %TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
BCK_TIME_OFF = 0.       %TIME AT WHICH BACKGROUND EXPOSURE ENDS (HOUR)
BW_T0       = 23       % BODY WEIGHT AT THE BEGINNING OF THE SIMULATION (G)

%EXPOSURE DOSE SCENARIOS (UG/KG)
  %MSTOT = 0.010        % EXPOSURE DOSE IN UG/KG
  %MSTOT = 0.050      % EXPOSURE DOSE IN UG/KG
  %MSTOT = 0.100      % EXPOSURE DOSE IN UG/KG
  %MSTOT = 0.500      % EXPOSURE DOSE IN UG/KG
  %MSTOT =  1         % EXPOSURE DOSE IN UG/KG
  MSTOT =  2         % EXPOSURE DOSE IN UG/KG
```

C.2.6. Mouse Gestational Model

C.2.6.1. *Model Code*

```
PROGRAM:  'Three Compartment PBPK Model for TCDD in Mice (Gestation)'
! Parameters were change may 16, 2002
! Come from {8MAI_CHR_PRE-EXP_GD}
! Come from {12_Mouse_GD}file
!*****************************************
!{{IMPORTANT-IMPORTANT-IMPORTANT-IMPORTANT}}
! REDUCTION OF MOTHER AND FETUS COMPARTMENT
! 2M_R_TCDD_JULY2002 ////(JULY 18,2002)////
!TCDD_RED_4Species_2003_4       ////(APR  8 ,2003)////
!TCDD_RED_4Species_2003_9       ////(APR  17 ,2003)////
!TCDD_RED_4Species_2003_12       ////(APR  17 ,2003)////
!*****************************************************
!APRIL 18 2003
!TCDD_4C_4SP_2003       ////(APR  18 ,2003)////
! was "Gest 4 species 1.csl"   but update July 2009

!DevTCDD4Species_ICF_afterKKfix_v3_ratgest.csl
!MICE_GESTATIONAL_ICF_F092309.csl
!MICE_GESTATIONAL_ICF_F100609.csl
!*************************************************

 !Legend/Legend/Legend/Legend/Legend/Legend/Legend/Legend/
 !Legend for this PBPK model
 !Mating: control the tenure of exchange between fetus and
    !Mother and also control imitated tissue growth
    !Ctrl: WTFE, WFO, WPLA0, QPLAF,WT0
    !(for rat, mouse, human, and monkey)
 !Control transfer from mother to fetus and fetus to mother by TRANSTIME_ON
    !SWITCH_trans = 0 NO TRANSFER
    !SWITCH_trans = 1 TRANSFER OCCURS
    !Gest_off = 1
    !Gest_on=   0.
 ! These switches are also controlled by mating parameters

INITIAL  !

     !SIMULATION PARAMETERS ====
CONSTANT PARA_ZERO      = 1E-30
CONSTANT EXP_TIME_ON     = 288.      ! TIME AT WHICH EXPOSURE BEGINS
(HOURS)
CONSTANT EXP_TIME_OFF    = 504      ! TIME AT WHICH EXPOSURE ENDS (HOURS)
CONSTANT DAY_CYCLE      =  504.     ! NUMBER OF HOURS BETWEEN DOSES
(HOURS)
```

```
CONSTANT BCK_TIME_ON    = 0.0      ! TIME AT WHICH BACKGROUND EXPOSURE
BEGINS (HOURS)
CONSTANT BCK_TIME_OFF   = 0.0      ! TIME AT WHICH BACKGROUND EXPOSURE
ENDS (HOURS)
CONSTANT TRANSTIME_ON   = 144      !CONTROL TRANSFER FROM MOTHER TO
FETUS AT GESTATIONAL DAY 6

   !UNIT CONVERSION
CONSTANT MW=322 ! MOLECULAR WEIGHT (NG/NMOL)
CONSTANT SERBLO = 0.55
CONSTANT UNITCORR = 1000

   !INTRAVENOUS SEQUENCY
constant IV_LACK        = 0.0
constant IV_PERIOD      = 0.0

   !PREGNANCY PARAMETER ====
CONSTANT MATTING        = 0.0      !BEGINNING OF MATING (HOUR)
CONSTANT N_FETUS        = 10       !NUMBER OF FETUS PRESENT

   !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          = 0.0      ! ORAL EXPOSURE DOSE (UG/KG)

   !ORAL ABSORPTION
  MSTOT_NM = MSTOT/MW             !CONVERTS THE DOSE TO NMOL/G

   ! 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 PAS_INDUC      = 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)

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```
  !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_LACK     = 0.0      !DELAY BEFORE EXPOSURE ENDS (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_LACK    = 0.0      !DELAY BEFORE EXPOSURE BEGINS
(MONTH)

  !CONSTANT FOR BACKGROUND EXPOSURE==========
CONSTANT Day_LACK_BG   = 0.0      ! DELAY BEFORE EXPOSURE BEGINS (HOUR)
CONSTANT Day_PERIOD_BG = 24       !LENGTH OF EXPOSURE (HOUR)

  !NUMBER OF EXPOSURES PER WEEK
CONSTANT WEEK_LACK_BG    = 0.0     !DELAY BEFORE BACKGROUD 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
```

```
CONSTANT RATIO_RATF_MOUSEF = 0.2       !RATIO OF FETUS MOUSE/RAT AT
GESTATIONAL DAY 22
                          ! FOR RAT (1) AND FOR MOUSE (0.2)

  !COMPARTMENT LIPID EXPRESSED AS THE FRACTION OF TOTAL LIPID, POULIN
ET AL. 2002
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       = 0.060            ! LIVER (UNITLESS)
CONSTANT PLA_TOTLIP      = 0.019             ! PLACENTA (UNITLESS)
CONSTANT FETUS_TOTLIP    = 0.019            ! FETUS (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   =        313      !SIMULATION LIMIT TIME (HOUR)
 CINTXY  = CINT
 PFUNC   = CINT

  !TIME CONVERSION
  DAY       = T/24          ! TIME IN DAYS
  WEEK      = T/168         ! TIME IN WEEKS
  MONTH     = T/730          ! TIME IN MONTHS
  YEAR      = T/8760        ! TIME IN YEARS

DERIVATIVE ! PORTION OF CODE THAT SOLVES DIFFERENTIAL EQUATIONS

  !CHRONIC OR SUBCHRONIC EXPOSURE SCENARIO =======
  !NUMBER OF EXPOSURES PER DAY
 DAY_LACK       = EXP_TIME_ON    ! DELAY 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_LACK_BG   = BCK_TIME_ON    !DELAY BEFORE BACKGROUD EXPOSURE
BEGINS (MONTHS)
```

```
 MONTH_PERIOD_BG  = TIMELIMIT      !BACKGROUND EXPOSURE PERIOD
(MONTHS)
 MONTH_FINISH_BG  = BCK_TIME_OFF   !LENGTH OF BACKGROUND EXPOSURE
(MONTHS)

   !INTRAVENOUS LATE
 IV_FINISH = CINTXY
 B = 1-A ! FRACTION OF DIOXIN ABSORBED IN THE PORTAL FRACTION OF THE
LIVER


!FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUME,FETUS,VOLUM
E,FETUS,VOLUME
  ! FROM OFLAHERTY_1992

RTESTGEST= T-MATTING
TESTGEST=DIM(RTESTGEST,0.0)

WTFER_RODENT= (2.3d-3*EXP(1.49d-2*(TESTGEST))+1.3d-2)*Gest_on
WTFER = (WTFER_RODENT*RATIO_RATF_MOUSEF*N_FETUS)
WTFE = DIM(WTFER,0.0)

  !
FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLUME,FAT,VOLU
ME,FAT,VOLUME
  ! FAT GROWTH EXPRESSION LINEAR DURING PREGNANCY
  ! FROM O'FLAHERTY_1992

WF0= (((9.66d-5*(TESTGEST))*gest_on)+0.069)

  ! PLACENTA,VOLUME, PLACENTA,VOLUME, PLACENTA,VOLUME,
PLACENTA,VOLUME
  ! WPLA PLACENTA GROWTH EXPRESSION, SINGLE EXPONENTIAL WITH OFFSET
  ! FROM O'FLAHERTY_1992  ! FOR EACH PUP

WPLA0N_RODENT = (0.6/(1+(5d+3*EXP(-0.0225*(TESTGEST)))))*N_FETUS
WPLA0R = (WPLA0N_RODENT/WT0)*Gest_on
WPLA0 = DIM(WPLA0R,0.0)

  ! PLACENTA,FLOW RATE, PLACENTA,FLOW RATE, PLACENTA,FLOW RATE,
PLACENTA,FLOW RATE
  ! QPLA PLACENTA GROWTH EXPRESSION, DOUBLE EXPONENTIAL WITH OFFSET
  ! FROM O'FLAHERTY_1992

 QPLARF = (1.67d-7 *exp(9.6d-3*(TESTGEST)) &
  +1.6d-3*exp(7.9d-3*(TESTGEST))+0.0)*Gest_on*SWITCH_trans
```

```
 1    QPLAF=DIM(QPLARF,0.0)            !FRACTION OF FLOW RATE IN PLACENTA
 2
 3     ! GESTATION CONTROL
 4    IF (T.LT.MATTING) THEN
 5       Gest_off = 1
 6       Gest_on=   0.0
 7    ELSE
 8       Gest_off = 0.0
 9       Gest_on  = 1
10    END IF
11
12     ! MOTHER BODY WEIGHT GROWTH EQUATION========
13     ! MODIFICATION TO ADAPT THIS MODEL AT HUMAN MODEL
14     ! BECAUSE LINEAR DESCRIPTION IS NOT GOOD ENOUGH FOR MOTHER GROWTH
15     ! MOTHER BODY WEIGHT GROWTH
16
17     PARAMETER (BW_RMN = 1.0E-30)
18     WT0= BW_T0 *(1.0+(0.41*T)/(1402.5+T+BW_RMN))
19
20     ! VARIABILITY OF REST OF THE BODY DEPENDS ON OTHER ORGANS
21     WRE0 = (0.91 - (WLIB0*WLI0 + WFB0*WF0 +WPLAB0*WPLA0 + WLI0 + WF0 +
22    WPLA0))/(1.0+WREB0)  ! REST OF THE BODY FRACTION; UPDATED FOR EPA
23    ASSESSMENT
24     QREF = 1.0-(QFF+QLIF+QPLAF)          !REST OF BODY BLOOD FLOW RATE (ML/HR)
25     QTTQF = QFF+QREF+QLIF+QPLAF        ! SUM MUST EQUAL 1
26
27     ! COMPARTMENT VOLUME (ML OR G) =========
28     WF  =  WF0  * WT0                ! ADIPOSE TISSUE
29     WRE =  WRE0 * WT0                  ! REST OF THE BODY
30     WLI =  WLI0 * WT0                ! LIVER
31     WPLA=  WPLA0* WT0                   ! PLACENTA
32
33      ! COMPARTMENT TISSUE BLOOD (ML OR G) =========
34     WFB  =  WFB0  * WF                ! ADIPOSE TISSUE
35     WREB =  WREB0 * WRE                  ! REST OF THE BODY
36     WLIB =  WLIB0 * WLI                ! LIVER
37     WPLAB = WPLAB0* WPLA                  ! PLACANTA
38
39      ! CARDIAC OUTPUT FOR THE GIVEN BODY WEIGHT
40      !QC= QCCAR*60*(WT0/1000.0)**0.75
41    CONSTANT QCC=16500                ! EQUIVALENT TO 275 * 60
42    QC= QCC*(WT0/UNITCORR)**0.75
43
44      !COMPARTMENT BLOOD FLOW RATE (ML/HR)
45    QF  = QFF*QC                     !ADIPOSE TISSUE BLOOD FLOW RATE
46    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

   !************************************
   ! ABSORPTION SECTION
   ! ORAL,
   ! INTRAPERITONEAL,
   ! INTRAVENOUS
   !************************************

   !REPETITIVE ORAL BACKGROUND EXPOSURE SCENARIO

MSTOT_NMBCKGR = MSTOTBCKGR/322      !AMOUNT IN NMOL/G
MSTTBCKGR =MSTOT_NMBCKGR *WT0

DAY_EXPOSURE_BG   = PULSE(DAY_LACK_BG,DAY_PERIOD_BG,DAY_FINISH_BG)
WEEK_EXPOSURE_BG  =
PULSE(WEEK_LACK_BG,WEEK_PERIOD_BG,WEEK_FINISH_BG)
MONTH_EXPOSURE_BG =
PULSE(MONTH_LACK_BG,MONTH_PERIOD_BG,MONTH_FINISH_BG)

MSTTCH_BG =
(DAY_EXPOSURE_BG*WEEK_EXPOSURE_BG*MONTH_EXPOSURE_BG)*MSTTBCK
GR
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

CYCLETOTBG=INTEG(CYCLE_BG,0.0)

  !REPETITIVE ORAL EXPOSURE SCENARIO
```

```
1
2   MSTT= MSTOT_NM * WT0                !AMOUNT IN NMOL
3
4   DAY_EXPOSURE   = PULSE(DAY_LACK,DAY_PERIOD,DAY_FINISH)
5   WEEK_EXPOSURE  = PULSE(WEEK_LACK,WEEK_PERIOD,WEEK_FINISH)
6   MONTH_EXPOSURE = PULSE(MONTH_LACK,MONTH_PERIOD,MONTH_FINISH)
7
8   MSTTCH = (DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE)*MSTT
9   MSTTFR = MSTT/CINT
10
11  CYCLE = DAY_EXPOSURE*WEEK_EXPOSURE*MONTH_EXPOSURE
12  SUMEXPEVENT= INTEG (CYCLE,0.0)/cint !NUMBER OF CYCLES GENERATED
13  DURING SIMULATION
14
15    ! CONDITIONAL ORAL EXPOSURE
16  IF (MSTTCH.EQ.MSTT) THEN
17    ABSMSTT= MSTTFR
18  ELSE
19    ABSMSTT = 0.0
20  END IF
21
22
23   CYCLETOT=INTEG(CYCLE,0.0)
24
25    ! MASS CHANGE IN THE LUMEN
26   RMSTT= -(KST+KABS)*MST +ABSMSTT +ABSMSTT_GB ! RATE OF CHANGE
27  (NMOL/H)
28    MST = INTEG(RMSTT,0.0)                !AMOUNT REMAINING IN DUODENUM
29  (NMOL)
30
31    ! ABSORPTION IN LYMPH CIRCULATION
32   LYRMLUM = KABS*MST*A
33    LYMLUM = INTEG(LYRMLUM,0.0)
34
35    ! ABSORPTION IN PORTAL CIRCULATION
36   LIRMLUM = KABS*MST*B
37    LIMLUM = INTEG(LIRMLUM,0.0)
38
39
40  ! -----IV EXPOSURE ---------
41
42   IV= DOSEIV_NM * WT0 !AMOUNT IN NMOL
43   IVR= IV/PFUNC ! RATE FOR IV INFUSION IN BLOOD
44   EXPIV= IVR * (1.0-STEP(PFUNC))
45   IVDOSE = integ(EXPIV,0.0)
46
```

```
    !------IV late in the cycle
    ! MODIFICATION ON January 13 2004
 IV_RlateR = DOSEIVNMlate*WT0
 IV_EXPOSURE=PULSE(IV_LACK,IV_PERIOD,IV_FINISH)

 IV_lateT = IV_EXPOSURE *IV_RlateR
 IV_late = IV_lateT/CINT

SUMEXPEVENTIV= integ (IV_EXPOSURE,0.0) !NUMBER OF CYCLE GENERATE
DURING SIMULATION

    !SYSTEMIC CONCENTRATION OF TCDD
    ! MODIFICATION ON OCTOBER 6, 2009

CB=(QF*CFB+QRE*CREB+QLI*CLIB+EXPIV+LYRMLUM+QPLA*CPLAB+IV_late)/(QC
+CLURI) !
 CA = CB ! CONCENTRATION (NMOL/ML)

    !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 LIPIP]
   AUCBS_NGKGLIADJ=integ(CBSNGKGLIADJ,0.0)

  PRCT_B = (CB/(MSTT+1E-30))*100 ! PERCENT OF ORAL DOSE IN BLOOD
  PRCT_BIV = (CB/(IV_RlateR+1E-30))*100 ! PERCENT OF IV DOSE IN BLOOD
  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)
```

```
  PRCT_F = (CFTOTAL/(MSTT+1E-30))*100 ! PERCENT OF ORAL DOSE IN FAT
  PRCT_FIV = (CFTOTAL/(IV_RlateR+1E-30))*100 ! PERCENT OF IV DOSE IN FAT
  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
  PRCT_RE = (CRETOTAL/(MSTT+1E-30))*100 ! PERCENT OF ORAL DOSE IN REST OF
BODY
  PRCT_REIV = (CRETOTAL/(IV_RlateR+1E-30))*100   ![ PERCENT OF IV DOSE IN REST
OF THE BODY ]
  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)

   !FREE TCDD IN LIVER COMPARTMENT
PARAMETER (LIVER_1RMN = 1.0E-30)
 CFLLI= IMPLC(CLI-(CFLLIR*PLI+(LIBMAX*CFLLIR/(KDLI+CFLLIR &
      +LIVER_1RMN))+((CYP1A2_1O3*CFLLIR/(KDLI2 + CFLLIR &
      +LIVER_1RMN)*PAS_INDUC)))-CFLLI,CFLLI0)
    CFLLIR=DIM(CFLLI,0.0) ! FREE CONCENTRATION IN LIVER

  CBNDLI= LIBMAX*CFLLIR/(KDLI+CFLLIR+LIVER_1RMN) !BOUND
CONCENTRATION

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```
 !VARIABLE ELIMINATION BASED ON THE CYP1A2
 KBILE_LI_T =((CYP1A2_1OUT-CYP1A2_1A2)/CYP1A2_1A2)*Kelv ! INDUCED
BILIARY EXCRETION RATE CONSTANT
 REXCLI = KBILE_LI_T*CFLLIR*WLI ! DOSE-DEPENDENT EXCRETION RATE
  EXCLI = INTEG(REXCLI,0.0)

 !UNIT CONVERSION POST SIMULATION
 CLITOTAL= (ALI + ALIB)/(WLI + WLIB) ! TOTAL CONCENTRATION IN NMOL/ML
 PRCT_LI = (CLITOTAL/(MSTT+1E-30))*100 ! PERCENT ORAL DOSE IN LIVER
 PRCT_LIIV = (CLITOTAL/(IV_RlateR+1E-30))*100 ! PERCENT IV DOSE IN LIVER
 Rec_occ= CFLLIR/(KDLI+CFLLIR)
 CLINGKG=CLITOTAL*MW*UNITCORR ! LIVER CONCENTRATION IN NG/KG
  AUCLI_NGKGH=INTEG(CLINGKG,0.0)
 CBNDLINGKG = CBNDLI*MW*UNITCORR
  AUCBNDLI_NGKGH =INTEG(CBNDLINGKG,0.0)
 CLINGG = CLITOTAL*MW

  !CHEMICAL IN CYP450 (1A2) COMPARTMENT
CYP1A2_1KINP = CYP1A2_1KOUT* CYP1A2_1OUTZ ! BASAL RATE OF CYP1A2
PRODUCTION SET EQUAL TO BASAL RATE OF DEGREDATION

  ! MODIFICATION ON OCTOBER 6, 2009
CYP1A2_1OUT =INTEG(CYP1A2_1KINP * (1.0 + CYP1A2_1EMAX *(CBNDLI+1.0e-
30)**HILL &
    /(CYP1A2_1EC50**HILL + (CBNDLI+1.0e-30)**HILL)) &
     - CYP1A2_1KOUT*CYP1A2_1OUT, CYP1A2_1OUTZ)

! EQUATIONS INCORPORATING DELAY OF CYP1A2 PRODUCTION (NOT USED IN
SIMULATIONS)

        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)

! TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
! FETAL EXPOSURE ONLY DURING EXPOSURE

IF (T.LT.TRANSTIME_ON) THEN
 SWITCH_trans = 0.0
ELSE
 SWITCH_trans = 1
END IF

!TRANSFER OF DIOXIN FROM PLACENTA TO FETUS
```

```
! MODIFICATION 26 SEPTEMBER 2003

CONSTANT PFETUS= 4 !
CONSTANT CLPLA_FET = 0.17 !

RAMPF = (CLPLA_FET*CPLA) *SWITCH_trans
  AMPF=INTEG(RAMPF,0.0)

!TRANSFER OF DIOXIN FROM FETUS TO PLACENTA
RAFPM = (CLPLA_FET*CFETUS_v)*SWITCH_trans !
  AFPM = INTEG(RAFPM,0.0)

! TCDD IN PLACENTA MOTHER COMPARTMENT
RAPLAB= QPLA*(CA - CPLAB)-PAPLA*(CPLAB -CFLPLAR)   ! NMOL/H)
 APLAB = INTEG(RAPLAB,0.0)                    ! (NMOL)
 CPLAB = APLAB/(WPLAB+1E-30)                    ! (NMOL/ML)
RAPLA = PAPLA*(CPLAB-CFLPLAR)-RAMPF + RAFPM       ! (NMOL/H)
 APLA = INTEG(RAPLA,0.0)                      ! (NMOL)
 CPLA  = APLA/(WPLA+1e-30)                     ! (NMOL/ML)

PARAMETER (PARA_ZERO = 1.0E-30)
CFLPLA= IMPLC(CPLA-(CFLPLAR*PPLA +(PLABMAX*CFLPLAR/(KDPLA&
   +CFLPLAR+PARA_ZERO)))-CFLPLA,CFLPLA0)
CFLPLAR=DIM(CFLPLA,0.0)

   !UNIT CONVERSION POST SIMULATION
  CPLATOTAL= (APLA + APLAB)/((WPLA + WPLAB)+1e-30)! TOTAL
CONCENTRATION IN NMOL/ML
  PRCT_PLA = (CPLATOTAL/(MSTT+1E-30))*100
  PRCT_PLAIV = (CPLATOTAL/(IV_RlateR+1E-30))*100
  CPLANGG = CPLATOTAL*MW

   !FETUS COMPARTMENT
RAFETUS= RAMPF-RAFPM
 AFETUS=INTEG(RAFETUS,0.0)
CFETUS=AFETUS/(WTFE+1E-30)
CFETOTAL= CFETUS
CFETUS_v = CFETUS/PFETUS

  ! UNIT CONVERSION POST SIMULATION
CFETUSNGKG = CFETUS*MW*UNITCORR                !(NG/KG)
AUC_FENGKGH = INTEG(CFETUSNGKG,0.0)
PRCT_FE = (CFETOTAL/(MSTT+1E-30))*100
PRCT_FEIV = (CFETOTAL/(IV_RlateR+1E-30))*100
CFETUSNGG = CFETOTAL*MW

```

```
! ------------CONTROL MASS BALANCE ----------
BDOSE= IVDOSE +LYMLUM+LIMLUM
BMASSE = EXCLI+AURI+AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB+AFETUS
BDIFF = BDOSE-BMASSE

    !BODY BURDEN (NG)
BODY_BURDEN = AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB !
BBFETUSNG    = AFETUS*MW*UNITCORR    ! NG
    ! BODY BURDEN IN TERMS OF CONCENTRATION (NG/KG)
 BBNGKG
=(((AFB+AF+AREB+ARE+ALIB+ALI+APLA+APLAB)/WT0)*MW*UNITCORR) !
  AUC_BBNGKGH=INTEG(BBNGKG,0.0)


! ------------COMMAND OF THE 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 THE PROGRAM
```

C.2.6.2. *Input Files*

C.2.6.2.1. *Keller et al. (2007).*

```
%TO BE USED AFTER THE
%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
%output @nciout=10 T SUMEXPEVENT wt0
%kELLER ET AL 2007
%protocol:  SINGLE DOSE from GD13
%dose levels: 0.01, 0.100 1 ug/kg  at GD13
%dose levels:   10, 100 1000 ng/kg  at GD13

%EXPOSURES SCENARIOS
 MAXT=0.01
 CINT =0.1
 EXP_TIME_ON     = 312.         % TIME AT WHICH EXPOSURE BEGINS(HOUR)
 EXP_TIME_OFF    = 330          % TIME AT WHICH EXPOSURE ENDS (HOUR)
 DAY_CYCLE       = 505
 BCK_TIME_ON     = 0.          % TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
 BCK_TIME_OFF    = 0.          % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
```

```
IV_LACK        = 505
IV_PERIOD      = 505
TIMELIMIT      = 504          % SIMULATION TIME LIMIT (HOUR)
BW_T0          = 24
MATTING        = 0.           % BEGINNING OF MATING (HOUR)
TRANSTIME_ON   = 144.         % SHOULD BE MATING TIME + 6 DAYS (144 HOURS)
N_FETUS        = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)

  %MSTOT       = 0.01         % ORAL EXPOSURE DOSE IN UG/KG
  %MSTOT       = 0.1          % ORAL EXPOSURE DOSE IN UG/KG
  MSTOT        = 1            % ORAL EXPOSURE DOSE IN UG/KG
```

C.2.6.2.2. ***Li et al. (2005).***

```
%TO BE USED AFTER THE
%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
%output @nciout=10 T SUMEXPEVENT
%LI ET AL 2006
%protocol:  exposure repetitive DOSE from GD1 to GD3
%dose levels: 0.002, 0.050 AND 0.10 ug/kg/day  at GD1 TO GD8
%dose levels: 2, 50 and 100 ng/kg/day from GD1 to GD8

%EXPOSURES SCENARIOS
 MAXT=0.001
 CINT =0.1
 EXP_TIME_ON    = 0.          % TIME AT WHICH EXPOSURE BEGINS (HOUR)
 EXP_TIME_OFF   = 70          % TIME AT WHICH EXPOSURE ENDS (HOUR); 2 HOURS
LESS THAN GD8; SET EQUAL TO 70 TO BE SURE ONLY 3 DOSES ADMINISTERED
                             % BECAUSE i STARTED TIME 0 FOR GD1
 DAY_CYCLE      = 24
 BCK_TIME_ON    = 0.          % TIME AT WHICH BACKGROUND EXPOSURE BEGINS
(HOUR)
 BCK_TIME_OFF   = 0.          % TIME AT WHICH BACKGROUND EXPOSURE ENDS
(HOUR)
 IV_LACK        = 505
 IV_PERIOD      = 505
 TIMELIMIT      = 216         % SIMULATION TIME LIMIT (HOUR)
 BW_T0          = 27
 MATTING        = 0.          % BEGINNING OF MATING (HOUR)
 TRANSTIME_ON   = 144.        % SHOULD BE MATING TIME + 6 DAYS (144 HOURS)
```

```
N_FETUS       = 10

%EXPOSURE DOSE SCENARIOS (UG/KG)

  MSTOT       = 0.002       % ORAL EXPOSURE DOSE IN UG/KG
  %MSTOT      = 0.05        % ORAL EXPOSURE DOSE IN UG/KG
  %MSTOT      = 0.10        % ORAL EXPOSURE DOSE IN UG/KG
```

C.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.

This conversion accomplishes the following:

1. Allows the human equivalent dose (HED) to be based on equivalent blood concentration (that represents serum plus erythrocyte TCDD), which is proportional to tissue exposure;
2. Avoids criticism that the total blood concentration is normalized to serum lipid alone in an unbalanced way (thus EPA does not contradict Centers for Disease Control and Prevention (CDC) data or methods);
3. Factors out any impact of the lipid content used in the PBPK model; and
4. TCDD concentration in whole blood is encouraged for use in the assessments by the NAS (NAS, 2006, p. 43); see additional information in Section 3.3.

C.3.1. Nongestational Studies

C.3.1.1. *Cantoni et al. (1981)*

Type:	Rat	**Dose:**	10, 100, 1000 ng/kg/week
Strain:	CD-COBS rats	**Route:**	Oral gavage
Body weight:	BW set to 125g	**Regime:**	1 dose/week for 45 weeks
Sex:	Female	**Simulation time:**	7,584 hours (45 weeks + 24 hours before sacrifice)

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.43	Emond	1,018	2,040 (@ 7,392 hours)	982
	CADM	-	-	-
14.29	Emond	4,868	14,649 (@ 7,392 hours)	4,242
	CADM	-	-	-
142.86	Emond	27,559	125,300 (@ 7,392 hours)	21,996
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.43	Emond	247	328 (@ 7,398 hours)	235
	CADM	374	431	431
14.29	Emond	2,175	2,860 (@ 7,399 hours)	1,837
	CADM	3,884	4,330	4,330
142.86	Emond	20,488	26,978 (@ 7,399 hours)	16,255
	CADM	39,067	43,329	43,329
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.43	Emond	175	200 (@ 7,431 hours)	177
	CADM	250	280	244
14.29	Emond	837	938 (@ 7,427 hours)	780
	CADM	1,209	1,352	1,167
142.86	Emond	4,739	5,374 (@ 7,424 hours)	4,145
	CADM	10,050	11,224	9,734
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.43	Emond	26.1	31.7 (@ 7,398 hours)	25.6
	CADM	32.0	35.0	35.0
14.29	Emond	170	210 (@ 7,398 hours)	149
	CADM	225	243	243

142.86	Emond	1,336	1,695 (@ 7,398 hours)	1,088
	CADM	2,106	2,266	2,266
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.43	Emond	6.04	7.76 (@ 7,396 hours)	5.88
	CADM	-	-	-
14.29	Emond	23.7	29.1 (@ 7,396 hours)	21.6
	CADM	-	-	-
142.86	Emond	66.8	80.0 (@ 1 hours)	62.0
	CADM	-	-	-

1 **C.3.1.2.** ***Chu et al. (2007)***

Type:	Rat	**Dose:**	2.5, 25, 250, and 1,000 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	200 g	**Regime:**	1 dose per day for 28 days
Sex:	Female	**Simulation time:**	672 hours

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.5	Emond	696	1,295 (@ 648 hours)	1,036
	CADM	-	-	-
25	Emond	4,222	8,403 (@ 648 hours)	5,727
	CADM	-	-	-
250	Emond	26,889	62,067 (@ 648 hours)	35,103
	CADM	-	-	-
1,000	Emond	93,213	230,320 (@ 648 hours)	122,200
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.5	Emond	148	268 (@ 652 hours)	255
	CADM	-	-	-
25	Emond	1,777	2,953 (@ 653 hours)	2,806
	CADM	-	-	-
250	Emond	19,232	30,262 (@ 653 hours)	28,668
	CADM	-	-	-
1,000	Emond	77,819	120,400 (@ 653 hours)	113,890
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.5	Emond	108	180 (@ 668 hours)	180
	CADM	-	-	-
25	Emond	660	1,020 (@ 659 hours)	1,015
	CADM	-	-	-
250	Emond	4,210	6,433 (@ 655 hours)	6,354
	CADM	-	-	-
1,000	Emond	14,576	22,610 (@ 655 hours)	22,280
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.5	Emond	16.1	27.5 (@ 652 hours)	26.9
	CADM	-	-	-
25	Emond	138	222 (@ 652 hours)	214
	CADM	-	-	-
250	Emond	1,239	1,935 (@ 652 hours)	1,842
	CADM	-	-	-
1,000	Emond	4,801	7,444 (@ 652 hours)	7,067
	CADM	-	-	-

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.5	Emond	4.15	6.51 (@ 652 hours)	6.21
	CADM	-	-	-
25	Emond	20.5	28.5 (@ 652 hours)	27.4
	CADM	-	-	-
250	Emond	63.3	76.0 (@ 652 hours)	74.7
	CADM	-	-	-
1,000	Emond	90.2	99.0 (@ 653 hours)	98.3
	CADM	-	-	-

C.3.1.3. *Crofton et al. (2005)*

Type:	Rats	**Dose:**	0, 0.1, 3, 10, 30, 100, 300, 1000, 3000, and 10,000 ng/kg-day
Strain:	Long Evans	**Route:**	Oral gavage
Body weight:	4 weeks old BW set to 190 g	**Regime:**	One dose per day for four days
Sex:	Female	**Simulation time:**	96 hours

[a]The CADM model was not run because the dosing duration is lower than the resolution of the model (1 week)

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.1	Emond	11.1	22.4 (@ 72 hours)	13.5
	CADM	-	-	-
3	Emond	269	605 (@ 72 hours)	321
	CADM	-	-	-
10	Emond	763	1,873 (@ 72 hours)	892
	CADM	-	-	-
30	Emond	1,905	5,202 (@ 72 hours)	2,169
	CADM	-	-	-

100	Emond	5,104	15,972 (@ 72 hours)	5,605
	CADM	-	-	-
300	Emond	12,706	44,982 (@ 72 hours)	13,509
	CADM	-	-	-
1000	Emond	36,170	143,340 (@ 72 hours)	37,554
	CADM	-	-	-
3000	Emond	99,645	420,850 (@ 72 hours)	102,860
	CADM	-	-	-
10,000	Emond	321,480	1,392,100 (@ 72 hours)	334,220
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.1	Emond	0.919	1.55 (@ 75 hours)	1.18
	CADM	-	-	-
3	Emond	37.4	62.6 (@ 76 hours)	53.3
	CADM	-	-	-
10	Emond	145	242 (@ 77 hours)	214
	CADM	-	-	-
30	Emond	494	818 (@ 78 hours)	742
	CADM	-	-	-
100	Emond	1,839	3,025 (@ 78 hours)	2,793
	CADM	-	-	-
300	Emond	5,925	9,692 (@ 78 hours)	9,028
	CADM	-	-	-
1000	Emond	20,717	33,738 (@ 79 hours)	31,564
	CADM	-	-	-
3000	Emond	63,511	103,140 (@ 79 hours)	96,545
	CADM	-	-	-
10,000	Emond	212,890	344,910 (@ 79 hours)	321,960
	CADM	-	-	-

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.1	Emond	1.00	1.93 (@ 96 hours)	1.93
	CADM	-	-	-
3	Emond	24.6	45.9 (@ 96 hours)	45.9
	CADM	-	-	-
10	Emond	70.3	129 (@ 96 hours)	129
	CADM	-	-	-
30	Emond	177	317 (@ 96 hours)	317
	CADM	-	-	-
100	Emond	480	838 (@ 96 hours)	838
	CADM	-	-	-
300	Emond	1,206	2,065 (@ 96 hours)	2,065
	CADM	-	-	-
1000	Emond	3,452	5,836 (@ 96 hours)	5,836
	CADM	-	-	-
3000	Emond	9,522	16,050 (@ 96 hours)	16,050
	CADM	-	-	-
10,000	Emond	30,657	51,918 (@ 96 hours)	51,918
	CADM	-	-	-

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.1	Emond	0.138	0.224 (@ 79 hours)	0.223
	CADM	-	-	-
3	Emond	4.04	6.56 (@ 78 hours)	6.44
	CADM	-	-	-
10	Emond	13.3	21.5 (@ 78 hours)	21.0
	CADM	-	-	-
30	Emond	39.3	63.5 (@ 78 hours)	61.5
	CADM	-	-	-
100	Emond	129	208 (@ 78 hours)	200
	CADM	-	-	-

300	Emond	384	618 (@ 77 hours)	590
	CADM	-	-	-
1000	Emond	1,270	2,041 (@ 77 hours)	1,942
	CADM	-	-	-
3000	Emond	3,793	6,094 (@ 77 hours)	5,784
	CADM	-	-	-
10,000	Emond	12,595	20,226 (@ 77 hours)	19,154
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.1	Emond	0	0.115 (@ 75 hours)	0
	CADM	-	-	-
3	Emond	2	2.47 (@ 76 hours)	2
	CADM	-	-	-
10	Emond	4	6.42 (@ 76 hours)	5
	CADM	-	-	-
30	Emond	10	14.1 (@ 76 hours)	12
	CADM	-	-	-
100	Emond	22	29.9 (@ 76 hours)	27
	CADM	-	-	-
300	Emond	41	51.9 (@ 77 hours)	49
	CADM	-	-	-
1000	Emond	68	80.2 (@ 1 hours)	77
	CADM	-	-	-
3000	Emond	90	98.6 (@ 1 hours)	96
	CADM	-	-	-
10,000	Emond	104	108 (@ 1 hours)	107
	CADM	-	-	-

C.3.1.4. *Fattore et al. (2000)*

Type:	Rat	**Dose:**	20, 200, 2,000 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Dietary

Body weight:	7 weeks old (BW 150g)	**Regime:**	13 weeks
Sex:	Female and male	**Simulation time:**	2,184 hours

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
20	Emond	5,282	8,259 (@ 2,160 hours)	6,135
	CADM	-	-	-
200	Emond	31,761	56,170 (@ 2,160 hours)	35,183
	CADM	-	-	-
2,000	Emond	262,030	497,250 (@ 2,160 hours)	287,690
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
20	Emond	2,448	3,228 (@ 2,164 hours)	3,078
	CADM	4,471	5,639	5,639
200	Emond	24,136	30,245 (@ 2,164 hours)	28,709
	CADM	45,337	56,499	56,499
2,000	Emond	234,170	288,020 (@ 2,164 hours)	272,590
	CADM	454,031	565,103	565,103
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
20	Emond	890	1,113 (@ 2,166 hours)	1,101
	CADM	1,545	1,796	1,756
200	Emond	5,355	6,542 (@ 2,165 hours)	6,430
	CADM	13,351	15,604	15,292
2,000	Emond	44,176	54,246 (@ 2,165 hours)	53,140
	CADM	131,259	153,534	150,516

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
20	Emond	187	242 (@ 2,164 hours)	233
	CADM	261	324	324
200	Emond	1,556	1,940 (@ 2,164 hours)	1,850
	CADM	2,496	3,084	3,084
2,000	Emond	14,432	17,797 (@ 2,164 hours)	16,891
	CADM	24,836	30,674	30,674
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
20	Emond	24.9	29.8 (@ 2,164 hours)	28.8
	CADM	-	-	-
200	Emond	69.4	76.0 (@ 2,164 hours)	74.7
	CADM	-	-	-
2,000	Emond	104	106 (@ 2,164 hours)	106
	CADM	-	-	-

C.3.1.5. *Hassoun et al. (1998)*

Type:	Mice	**Dose:**	0, 0.45, 1.5, 15, 150 ng/kg-day. Background exposure dose (default) = 0.05 ng/kg-day
Strain:	B6C3F1	**Route:**	Oral gavage
Body weight:	8 to 9 weeks old (BW set to 23g)	**Regime:**	5 days/week for 13 weeks
Sex:	Female	**Simulation time:**	2208 hours* (2,184h + 24h post exposure)

[a]No background has been considered here for this simulation

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.321	Emond	90.5	167 (@ 2,112 hours)	123
	CADM	-	-	-
1.07	Emond	240	441 (@ 2,112 hours)	297
	CADM	-	-	-
10.7	Emond	1,350	2,753 (@ 2,112 hours)	1,396
	CADM	-	-	-
107	Emond	7,328	19,496 (@ 2,112 hours)	6,587
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.321	Emond	19.5	33.0 (@ 2,116 hours)	28.1
	CADM	14.8	24.5	23.2
1.07	Emond	66.7	106 (@ 2,116 hours)	87.4
	CADM	59.4	91.9	84.2
10.7	Emond	680	966 (@ 2,117 hours)	736
	CADM	768	1,000	825
107	Emond	6,768	9,000 (@ 2,117 hours)	6,482
	CADM	8,343	10,306	7,863
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.321	Emond	58.6	91.9 (@ 2,135 hours)	89.4
	CADM	56.5	85.9	82.7
1.07	Emond	156	228 (@ 2,130 hours)	219
	CADM	152	210	199
10.7	Emond	884	1,149 (@ 2,124 hours)	1,075
	CADM	690	815	735
107	Emond	4,818	5,946 (@ 2,120 hours)	5,347
	CADM	2,770	3,224	2,684

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.321	Emond	5.97	9.50 (@ 2,117 hours)	8.93
	CADM	7.43	11.4 (@ 2,121 hours)	10.9
1.07	Emond	16.9	25.3 (@ 2,116 hours)	23.2
	CADM	20.9	29.3	27.7
10.7	Emond	117	158 (@ 2,116 hours)	135
	CADM	119	145	127
107	Emond	849	1,100 (@ 2,116 hours)	865
	CADM	727	875	694
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.321	Emond	0.564	0.885 (@ 2,116 hours)	0.771
	CADM	-	-	-
1.07	Emond	1.47	2.15 (@ 2,116 hours)	1.83
	CADM	-	-	-
10.7	Emond	7.58	9.83 (@ 2,116 hours)	8.07
	CADM	-	-	-
107	Emond	30.3	35.9 (@ 2,117 hours)	29.8
	CADM	-	-	-

C.3.1.6. *Hassoun et al. (2000)*

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:	8 weeks old (BW=215g)	**Regime:**	5 days/week for 13 weeks
Sex:	Female	**Simulation time:**	2184 hours

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	1,068	1,720 (@ 2,112 hours)	1,303
	CADM	-	-	-
7.14	Emond	2,542	4,246 (@ 2,112 hours)	2,901
	CADM	-	-	-
15.7	Emond	4,489	7,835 (@ 2,112 hours)	4,947
	CADM	-	-	-
32.9	Emond	7,718	14,206 (@ 2,112 hours)	8,277
	CADM	-	-	-
71.4	Emond	13,960	27,367 (@ 2,112 hours)	14,637
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	267	399 (@ 2,116 hours)	349
	CADM	-	-	-
7.14	Emond	888	1,259 (@ 2,117 hours)	1,079
	CADM	-	-	-
15.7	Emond	1,948	2,689 (@ 2,117 hours)	2,278
	CADM	-	-	-
32.9	Emond	4,055	5,484 (@ 2,117 hours)	4,607
	CADM	-	-	-
71.4	Emond	8,775	11,692 (@ 2,117 hours)	9,754
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	179	243 (@ 2,126 hours)	235
	CADM	-	-	-
7.14	Emond	427	553 (@ 2,124 hours)	528
	CADM	-	-	-

15.7	Emond	755	958 (@ 2,123 hours)	908
	CADM	-	-	-
32.9	Emond	1,299	1,627 (@ 2,122 hours)	1,529
	CADM	-	-	-
71.4	Emond	2,350	2,928 (@ 2,121 hours)	2,727
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	27.4	38.9 (@ 2,116 hours)	35.7
	CADM	-	-	-
7.14	Emond	76.9	105 (@ 2,116 hours)	93.7
	CADM	-	-	-
15.7	Emond	153	205 (@ 2,116 hours)	180
	CADM	-	-	-
32.9	Emond	295	390 (@ 2,116 hours)	339
	CADM	-	-	-
71.4	Emond	600	785 (@ 2,116 hours)	674
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	6.28	8.48 (@ 2,116 hours)	7.67
	CADM	-	-	-
7.14	Emond	13.7	17.5 (@ 2,116 hours)	15.7
	CADM	-	-	-
15.7	Emond	22.0	27.1 (@ 2,116 hours)	24.4
	CADM	-	-	-
32.9	Emond	32.8	39.2 (@ 2,116 hours)	35.6
	CADM	-	-	-
71.4	Emond	47.5	55.0 (@ 2,116 hours)	50.6
	CADM	-	-	-

C.3.1.7. *Kitchin and Woods (1979)*

Type:	Rats	**Dose:**	0, 0.6, 2, 4, 20, 60, 200, 600, 2000, 5000, 20000 ng/kg-day
Strain:	Sprague-Dawley	**Route:**	Oral gavage
Body weight:	200 to 250 g (BW set to 225 g)	**Regime:**	Single dose
Sex:	Female	**Simulation time:**	24 hours

[a]The CADM model was not run because the dosing duration is lower than the resolution of the model (1 week).

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.6	Emond	46.8	69.5 (@ 0 hours)	18.0
	CADM	-	-	-
2	Emond	122	232 (@ 0 hours)	57.1
	CADM	-	-	-
4	Emond	221	463 (@ 0 hours)	109
	CADM	-	-	-
20	Emond	896	2,318 (@ 0 hours)	462
	CADM	-	-	-
60	Emond	2,291	6,949 (@ 0 hours)	1,165
	CADM	-	-	-
200	Emond	6,393	23,185 (@ 0 hours)	3,073
	CADM	-	-	-
600	Emond	16,676	69,657 (@ 0 hours)	7,345
	CADM	-	-	-
2,000	Emond	50,090	232,550 (@ 0 hours)	19,637
	CADM	-	-	-
5,000	Emond	120,130	581,930 (@ 0 hours)	43,511
	CADM	-	-	-
20,000	Emond	475,600	2,332,100 (@ 0 hours)	158,970
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.6	Emond	3.99	3.81 (@ 4 hours)	1.60
	CADM	-	-	-
2	Emond	11.7	12.9 (@ 4 hours)	6.01
	CADM	-	-	-
4	Emond	23.4	26.3 (@ 4 hours)	13.2
	CADM	-	-	-
20	Emond	129	143 (@ 6 hours)	85.2
	CADM	-	-	-
60	Emond	422	463 (@ 8 hours)	305
	CADM	-	-	-
200	Emond	1,525	1,666 (@ 9 hours)	1,194
	CADM	-	-	-
600	Emond	4,822	5,258 (@ 10 hours)	3,987
	CADM	-	-	-
2,000	Emond	16,606	18,081 (@ 11 hours)	14,296
	CADM	-	-	-
5,000	Emond	41,973	45,674 (@ 11 hours)	36,821
	CADM	-	-	-
20,000	Emond	167,820	182,580 (@ 11 hours)	149,280
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.6	Emond	2.11	3.03 (@ 72 hours)	3.03
	CADM	-	-	-
2	Emond	5.54	9.57 (@ 72 hours)	9.57
	CADM	-	-	-
4	Emond	10.1	18.2 (@ 72 hours)	18.2
	CADM	-	-	-
20	Emond	42.1	76.4 (@ 72 hours)	76.4
	CADM	-	-	-

60	Emond	110	192 (@ 72 hours)	192
	CADM	-	-	-
200	Emond	317	512 (@ 72 hours)	512
	CADM	-	-	-
600	Emond	851	1,250 (@ 72 hours)	1,250
	CADM	-	-	-
2,000	Emond	2,621	3,481 (@ 58 hours)	3,462
	CADM	-	-	-
5,000	Emond	6,361	8,049 (@ 45 hours)	7,887
	CADM	-	-	-
20,000	Emond	25,402	31,187 (@ 35 hours)	29,738
	CADM	-	-	-

BODY BURDEN (ng/kg)

Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.6	Emond	0.429	0.341 (@ 9 hours)	0.331
	CADM	-	-	-
2	Emond	1.18	1.14 (@ 8 hours)	1.09
	CADM	-	-	-
4	Emond	2.24	2.27 (@ 8 hours)	2.15
	CADM	-	-	-
20	Emond	10.7	11.3 (@ 8 hours)	10.4
	CADM	-	-	-
60	Emond	31.8	33.8 (@ 7 hours)	30.3
	CADM	-	-	-
200	Emond	105	112 (@ 7 hours)	98
	CADM	-	-	-
600	Emond	315	337 (@ 7 hours)	288
	CADM	-	-	-
2,000	Emond	1,049	1,123 (@ 7 hours)	945
	CADM	-	-	-
5,000	Emond	2,621	2,806 (@ 7 hours)	2,343
	CADM	-	-	-
20,000	Emond	10,469	11,215 (@ 7 hours)	9,299
	CADM	-	-	-

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.6	Emond	0.284	0.407 (@ 3 hours)	0.238
	CADM	-	-	-
2	Emond	0.728	1.07 (@ 3 hours)	0.476
	CADM	-	-	-
4	Emond	1.30	1.94 (@ 3 hours)	0.798
	CADM	-	-	-
20	Emond	4.90	7.74 (@ 2 hours)	2.95
	CADM	-	-	-
60	Emond	11.2	18.4 (@ 2 hours)	7.03
	CADM	-	-	-
200	Emond	25.1	40.8 (@ 1 hours)	16.7
	CADM	-	-	-
600	Emond	45.8	68.2 (@ 1 hours)	33.0
	CADM	-	-	-
2,000	Emond	73.3	93.1 (@ 1 hours)	59.1
	CADM	-	-	-
5,000	Emond	90.9	104 (@ 1 hours)	79.9
	CADM	-	-	-
20,000	Emond	106	110 (@ 1 hours)	101
	CADM	-	-	-

C.3.1.8. *Kociba et al. (1976)*

Type:	Rats	**Dose:**	1, 10, 100, 1000 ng/kg-day
Strain:	Sprague-Dawley (Spartan)	**Route:**	Oral gavage
Body weight:	170–190 g (bw=180g)	**Regime:**	5 days/week for 13 weeks
Sex:	Female	**Simulation time:**	4,368 hours (13wk exposed + 13 wk post exposures)

BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.714	Emond	398	761 (@ 2,112 hours)	163
	CADM	-	-	-
7.143	Emond	1,817	4,196 (@ 2,112 hours)	372
	CADM	-	-	-
71.43	Emond	9,002	26,872 (@ 2,112 hours)	820
	CADM	-	-	-
714.3	Emond	60,388	226,470 (@ 2,112 hours)	2,072
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.714	Emond	70.9	140 (@ 2,116 hours)	21.4
	CADM	89.0	192	12.1
7.143	Emond	595	1,259 (@ 2,117 hours)	62.4
	CADM	970	2,007	29.0
71.43	Emond	5,391	11,693 (@ 2,117 hours)	183
	CADM	9,841	20,170	88.0
714.3	Emond	51,476	112,580 (@ 2,117 hours)	670
	CADM	98,617	201,814	455
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.714	Emond	68.3	114 (@ 2,129 hours)	28.8
	CADM	120	190	43.0
7.143	Emond	313	553 (@ 2,124 hours)	66.2
	CADM	456	787	67.0
71.43	Emond	1,552	2,925 (@ 2,121 hours)	148
	CADM	3,036	5,748	117
714.3	Emond	10,415	21,127 (@ 2,120 hours)	379
	CADM	28,382	55,013	274

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.714	Emond	9.03	16.1 (@ 2,116 hours)	3.41
	CADM	11.5	20.0	3.75
7.143	Emond	53.7	105 (@ 2,116 hours)	8.44
	CADM	65.3	126	6.22
71.43	Emond	377	785 (@ 2,116 hours)	20.8
	CADM	553	1,113	12.0
714.3	Emond	3,230	6,961 (@ 2,116 hours)	62.4
	CADM	5,401	10,967	37.0
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.714	Emond	2.44	4.17 (@ 2,116 hours)	1.02
	CADM	-	-	-
7.143	Emond	10.1	17.5 (@ 2,116 hours)	2.30
	CADM	-	-	-
71.43	Emond	33.2	55.0 (@ 2,116 hours)	4.95
	CADM	-	-	-
714.3	Emond	69.7	98.2 (@ 2,117 hours)	11.7
	CADM	-	-	-

C.3.1.9. *Kociba et al. (1978) Female*

Type:	Rats	**Dose:**	0, 1, 10, 100 ng/kg-day
Strain:	Sprague-Dawley (Spartan)	**Route:**	Dietary
Body weight:	170–190 g (bw=180)	**Regime:**	104 weeks
Sex:	Female	**Simulation time:**	17,472 hours

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	853	1,058 (@ 17,448 hours)	929
	CADM	-	-	-
10	Emond	3,942	5,098 (@ 17,448 hours)	3,943
	CADM	-	-	-
100	Emond	21,246	31,697 (@ 17,448 hours)	20,441
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	192	226 (@ 17,452 hours)	218
	CADM	292	333	333
10	Emond	1,618	1,742 (@ 17,452 hours)	1,665
	CADM	2,981	3,342	3,342
100	Emond	14,892	15,673 (@ 17,452 hours)	14,907
	CADM	29,917	33,432	33,432
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	147	165 (@ 17,457 hours)	164
	CADM	196	229	181
10	Emond	680	713 (@ 17,454 hours)	706
	CADM	861	1,015	789
100	Emond	3,663	3,788 (@ 17,454 hours)	3,731
	CADM	6,756	7,939	6,203
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	21.2	24.3 (@ 17,452 hours)	23.8
	CADM	26.0	27.0	27.0
10	Emond	131	140 (@ 17,452 hours)	136
	CADM	169	176	176

100	Emond	989	1,039 (@ 17,452 hours)	994
	CADM	1,546	1,601	1,601
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	5.11	5.77 (@ 17,452 hours)	5.59
	CADM	-	-	-
10	Emond	20.0	21.1 (@ 17,452 hours)	20.4
	CADM	-	-	-
100	Emond	59.9	61.5 (@ 17,452 hours)	60.1
	CADM	-	-	-

C.3.1.10. *Kociba et al. (1978) Male*

Type:	Rats	**Dose:**	0, 1, 10, 100 ng/kg-day
Strain:	Sprague-Dawley (Spartan)	**Route:**	Dietary
Body weight:	Body weight approximated to be 250 g	**Regime:**	104 weeks
Sex:	Male	**Simulation time:**	17,472 hours

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	860	1,079 (@ 17,448 hours)	938
	CADM	-	-	-
10	Emond	3,945	5,153 (@ 17,448 hours)	3,916
	CADM	-	-	-
100	Emond	21,334	32,658 (@ 17,448 hours)	20,460
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	194	229 (@ 17,452 hours)	221
	CADM	-	-	-
10	Emond	1,616	1,723 (@ 17,452 hours)	1,649
	CADM	-	-	-
100	Emond	14,898	15,671 (@ 17,452 hours)	14,912
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	148	167 (@ 17,456 hours)	166
	CADM	-	-	-
10	Emond	680	709 (@ 17,454 hours)	703
	CADM	-	-	-
100	Emond	3,677	3,803 (@ 17,453 hours)	3,747
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	21.4	24.6 (@ 17,452 hours)	24.1
	CADM	-	-	-
10	Emond	131	139 (@ 17,452 hours)	134
	CADM	-	-	-
100	Emond	991	1,041 (@ 17,452 hours)	995
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	5.15	5.83 (@ 17,452 hours)	5.64
	CADM	-	-	-
10	Emond	20.0	21.0 (@ 17,452 hours)	20.3
	CADM	-	-	-

100	Emond	60.0	61.5 (@ 17,452 hours)	60.1
	CADM	-	-	-

C.3.1.11. *Latchoumycandane and Mathur (2002)*

Type:	Rat	**Dose:**	0, 1, 10, 100 ng/kg-day
Strain:	Wistar	**Route:**	Mouth pipetting
Body weight:	45 days old (BW set to 200g)	**Regime:**	1/day for 45 days
Sex:	Male	**Simulation time:**	1,104 hours (1,080 daily exposure and 24 hours before sacrifice)

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	437	754 (@ 1,056 hours)	630
	CADM	-	-	-
10	Emond	2,579	4,505 (@ 1,056 hours)	3,274
	CADM	-	-	-
100	Emond	15,092	29,672 (@ 1,056 hours)	17,698
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	79.7	138 (@ 1,060 hours)	128
	CADM	116	217	217
10	Emond	911	1,423 (@ 1,060 hours)	1,282
	CADM	1,669	2,550	2,550
100	Emond	9,650	14,015 (@ 1,061 hours)	12,439
	CADM	17,681	25,915	25,915
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	70.7	113 (@ 1,072 hours)	112
	CADM	150	220	220

10	Emond	420	608 (@ 1,065 hours)	592
	CADM	744	1,009	1,009
100	Emond	2,467	3,425 (@ 1,062 hours)	3,273
	CADM	5,719	7,866	7,866
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	9.68	15.9 (@ 1,060 hours)	15.2
	CADM	14.0	22.2	22.2
10	Emond	77.5	117 (@ 1,060 hours)	108
	CADM	106	157	157
100	Emond	651	933 (@ 1,060 hours)	842
	CADM	988	1,439	1,439
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	2.67	4.12 (@ 1,060 hours)	3.85
	CADM	-	-	-
10	Emond	13.8	18.8 (@ 1,060 hours)	17.5
	CADM	-	-	-
100	Emond	48.8	59.0 (@ 1,060 hours)	56.0
	CADM	-	-	-

C.3.1.12. *Li et al. (1997)*

Type:	Rats	**Dose:**	0, 3, 10, 30, 100, 300, 1000, 3000, 10000, 30000 ng/kg/day
Strain:	Sprague-Dawley	**Route:**	Gastric intubation
Body weight:	22 day old, 55 to 58 g (BW set to 56.5 g)	**Regime:**	One dose for one day
Sex:	Female	**Simulation time:**	24 hours

[a]The CADM model was not run because the dosing duration is lower than the resolution of the model (1 week)

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3	Emond	147	259 (@ 1 hours)	98.9
	CADM	-	-	-
10	Emond	440	862 (@ 1 hours)	295
	CADM	-	-	-
30	Emond	1,156	2,581 (@ 1 hours)	757
	CADM	-	-	-
100	Emond	3,232	8,585 (@ 1 hours)	2,026
	CADM	-	-	-
300	Emond	8,266	25,780 (@ 0 hours)	4,865
	CADM	-	-	-
1,000	Emond	23,875	86,088 (@ 0 hours)	12,873
	CADM	-	-	-
3,000	Emond	66,081	258,670 (@ 0 hours)	33,013
	CADM	-	-	-
10,000	Emond	212,650	864,770 (@ 0 hours)	100,410
	CADM	-	-	-
30,000	Emond	649,740	2,633,500 (@ 0 hours)	294,620
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3	Emond	14.7	18.6 (@ 4 hours)	11.9
	CADM	-	-	-
10	Emond	55.0	65.2 (@ 5 hours)	47.6
	CADM	-	-	-
30	Emond	185	210 (@ 6 hours)	170
	CADM	-	-	-
100	Emond	690	768 (@ 7 hours)	666
	CADM	-	-	-
300	Emond	2,248	2,473 (@ 8 hours)	2,240
	CADM	-	-	-

1,000	Emond	7,938	8,671 (@ 9 hours)	8,094
	CADM	-	-	-
3,000	Emond	24,474	26,639 (@ 9 hours)	25,267
	CADM	-	-	-
10,000	Emond	82,349	89,464 (@ 9 hours)	85,597
	CADM	-	-	-
30,000	Emond	245,610	265,670 (@ 10 hours)	255,390
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3	Emond	8.75	12.7 (@ 24 hours)	12.7
	CADM	-	-	-
10	Emond	26.6	38.0 (@ 24 hours)	38.0
	CADM	-	-	-
30	Emond	70.8	98.9 (@ 24 hours)	98.9
	CADM	-	-	-
100	Emond	202	273 (@ 24 hours)	273
	CADM	-	-	-
300	Emond	530	689 (@ 24 hours)	689
	CADM	-	-	-
1,000	Emond	1,573	1,958 (@ 24 hours)	1,958
	CADM	-	-	-
3,000	Emond	4,433	5,358 (@ 24 hours)	5,358
	CADM	-	-	-
10,000	Emond	14,428	17,119 (@ 24 hours)	17,119
	CADM	-	-	-
30,000	Emond	44,361	51,948 (@ 22 hours)	51,898
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3	Emond	1.60	1.70 (@ 8 hours)	1.68
	CADM	-	-	-

10	Emond	5.33	5.66 (@ 8 hours)	5.56
	CADM	-	-	-
30	Emond	15.9	16.9 (@ 8 hours)	16.5
	CADM	-	-	-
100	Emond	52.8	56.2 (@ 7 hours)	54.5
	CADM	-	-	-
300	Emond	158	169 (@ 7 hours)	163
	CADM	-	-	-
1,000	Emond	525	561 (@ 7 hours)	539
	CADM	-	-	-
3,000	Emond	1,574	1,684 (@ 7 hours)	1,611
	CADM	-	-	-
10,000	Emond	5,240	5,610 (@ 7 hours)	5,360
	CADM	-	-	-
30,000	Emond	15,758	16,815 (@ 7 hours)	16,041
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3	Emond	1	1.37 (@ 3 hours)	1
	CADM	-	-	-
10	Emond	3	4.10 (@ 2 hours)	2
	CADM	-	-	-
30	Emond	6	10.5 (@ 2 hours)	5
	CADM	-	-	-
100	Emond	16	25.9 (@ 2 hours)	12
	CADM	-	-	-
300	Emond	31.25	50.1 (@ 1 hours)	24.58
	CADM	-	-	-
1,000	Emond	56.75	79.8 (@ 1 hours)	47.65
	CADM	-	-	-
3,000	Emond	81.29	98.4 (@ 1 hours)	73.34
	CADM	-	-	-
10,000	Emond	99.77	108 (@ 1 hours)	95.70
	CADM	-	-	-

30,000	Emond	108.04	111 (@ 1 hours)	106.23
	CADM	-	-	-

C.3.1.13. *NTP (1982)—Female Rats, Chronic*

Type:	Rat	**Dose:**	10, 50 and 500 ng/kg/wk, two doses per week
Strain:	Osborne-Mendel	**Route:**	Oral gavage
Body weight	6 weeks old (BW set to 250g)	**Regime:**	Biweekly
Sex:	**Female**	**Simulation time**	17,976 hours (107 weeks)= (104 weeks of exposure + 3 weeks observation post-treatment)

[a]The CADM model simulates for 104 weeks only (17,472 hours). As a result, the terminal values from the CADM model are overestimated compared to the Emond model, which considered an additional 3 weeks post exposure.

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	1,072	1,719 (@ 17,388 hours)	685
	CADM	-	-	-
7.1	Emond	3,111	6,054 (@ 17,388 hours)	1,622
	CADM	-	-	-
71	Emond	16,207	45,310 (@ 17,388 hours)	6,253
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	263	310 (@ 17,394 hours)	143
	CADM	15,318	20,170	7,102
7.1	Emond	1,163	1,338 (@ 17,394 hours)	474
	CADM	30,700	40,353	14,200
71	Emond	10,596	12,182 (@ 17,395 hours)	3,134
	CADM	30,700	40,353	14,200

FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	185	200 (@ 17,412 hours)	124
	CADM	4,655	5,748	2,107
7.1	Emond	537	569 (@ 17,409 hours)	297
	CADM	9,064	11,224	3,964
71	Emond	2,798	2,973 (@ 17,404 hours)	1,173
	CADM	17,879	22,172	7,671
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	27.7	31.2 (@ 17,393 hours)	16.9
	CADM	855	1,113	403
7.1	Emond	98.5	110 (@ 17,393 hours)	46.6
	CADM	1,695	2,208	787
71	Emond	720	814 (@ 17,393 hours)	241
	CADM	3,375	4,395	1,556
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	6.34	7.28 (@ 17,392 hours)	4.17
	CADM	-	-	-
7.1	Emond	16.5	18.5 (@ 17,392 hours)	9.37
	CADM	-	-	-
71	Emond	52.3	56.4 (@ 17,393 hours)	29.1
	CADM	-	-	-

C.3.1.14. *NTP (1982)—Male Rats, Chronic*

Type:	Rat	**Dose:**	10, 50 and 500 ng/kg/wk, two doses per week
Strain:	Osborne-Mendel	**Route:**	Oral gavage
Body weight	6 weeks old (BW set to 350g)	**Regime:**	Biweekly (Simulation has been perform using female BW

Sex:	**Male**	**Simulation time**	17,976 hours (107 weeks)= (104 weeks of exposure + 3 weeks observation post-treatment)

[a]The CADM model simulates for 104 weeks only (17,472 hours). As a result, the terminal values from the CADM model are overestimated compared to the Emond model, which considered an additional 3 weeks post exposure.

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	1,072	1,750 (@ 17,388 hours)	681
	CADM	-	-	-
7.1	Emond	3,116	6,301 (@ 17,388 hours)	1,622
	CADM	-	-	-
71	Emond	16,272	47,951 (@ 17,388 hours)	6,269
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	263	306 (@ 17,394 hours)	141
	CADM	-	-	-
7.1	Emond	1,162	1,334 (@ 17,394 hours)	473
	CADM	-	-	-
71	Emond	10,598	12,170 (@ 17,395 hours)	3,140
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	185	199 (@ 17,412 hours)	123
	CADM	-	-	-
7.1	Emond	538	569 (@ 17,409 hours)	298
	CADM	-	-	-
71	Emond	2,809	2,983 (@ 17,404 hours)	1,185
	CADM	-	-	-

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	27.7	30.9 (@ 17,393 hours)	16.8
	CADM	-	-	-
7.1	Emond	98.6	110 (@ 17,393 hours)	46.6
	CADM	-	-	-
71	Emond	721	816 (@ 17,393 hours)	242
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	6.33	7.22 (@ 17,392 hours)	4.14
	CADM	-	-	-
7.1	Emond	16.4	18.4 (@ 17,392 hours)	9.36
	CADM	-	-	-
71	Emond	52.3	56.3 (@ 17,393 hours)	29.1
	CADM	-	-	-

C.3.1.15. *NTP (1982)—Female Mice, Chronic*

Type:	Mice	**Dose:**	40, 200 and 2000ng/kg/wk, two doses during the week
Strain:	B6C3F1	**Route:**	Oral gavage
Body weight	6 weeks old (BW set to 23g)	**Regime:**	Biweekly
Sex:	Female	**Simulation time**	17,976 hours (107 weeks)= (104 weeks of exposure + 3 weeks observation post-treatment)

[a]The mice chronic exposure could not be simulated with the CADM model because this model simulates for only 123 days.

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
5.7	Emond	1,064	2,684 (@ 17,220 hours)	569
	CADM	-	-	-
28.6	Emond	3,184	10,915 (@ 17,388 hours)	1,334
	CADM	-	-	-
286	Emond	17,406	93,992 (@ 17,220 hours)	4,899
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
5.7	Emond	486	587 (@ 17,227 hours)	209
	CADM	-	-	-
28.6	Emond	2,206	2,629 (@ 17,395 hours)	682
	CADM	-	-	-
286	Emond	20,515	24,353 (@ 17,396 hours)	4,232
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
5.7	Emond	733	789 (@ 17,324 hours)	436
	CADM	-	-	-
28.6	Emond	2,194	2,337 (@ 17,404 hours)	1,059
	CADM	-	-	-
286	Emond	12,003	12,861 (@ 17,400 hours)	4,151
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
5.7	Emond	91.2	103 (@ 17,225 hours)	48.5
	CADM	-	-	-
28.6	Emond	325	370 (@ 17,393 hours)	130
	CADM	-	-	-

286	Emond	2,367	2,740 (@ 17,393 hours)	615
	CADM	-	-	-

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
5.7	Emond	6.13	7.32 (@ 17,225 hours)	3.44
	CADM	-	-	-
28.6	Emond	16.1	18.9 (@ 17,393 hours)	7.68
	CADM	-	-	-
286	Emond	51.8	67.8 (@ 2 hours)	23.6
	CADM	-	-	-

C.3.1.16. *NTP (1982)—Male Mice, Chronic*

Type:	Mice	**Dose:**	10, 50 and 500ng/kg/wk, two doses during the week
Strain:	B6C3F1	**Route:**	Oral gavage
Body weight	6 weeks old (BW set to 25g)	**Regime:**	Biweekly
Sex:	Male	**Simulation time**	17,976 hours (107 weeks)= (104 weeks of exposure + 3 weeks observation post-treatment)

[a]The mice chronic exposure could not be simulated with the CADM model because this model simulates for only 123 days.

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	420	842 (@ 17,136 hours)	270
	CADM	-	-	-
7.1	Emond	1,240	3,302 (@ 17,304 hours)	644
	CADM	-	-	-
71	Emond	6,118	25,730 (@ 17,388 hours)	2,204
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	137	165 (@ 17,142 hours)	76.7
	CADM	-	-	-
7.1	Emond	599	723 (@ 17,311 hours)	247
	CADM	-	-	-
71	Emond	5,331	6,328 (@ 17,395 hours)	1,382
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	289	314 (@ 17,243 hours)	202
	CADM	-	-	-
7.1	Emond	854	918 (@ 17,407 hours)	496
	CADM	-	-	-
71	Emond	4,217	4,490 (@ 17,402 hours)	1,799
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	32.2	36.3 (@ 17,141 hours)	21.1
	CADM	-	-	-
7.1	Emond	109	123 (@ 17,309 hours)	55.8
	CADM	-	-	-
71	Emond	701	802 (@ 17,393 hours)	235
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.4	Emond	2.54	3.04 (@ 17,141 hours)	1.67
	CADM	-	-	-

7.1	Emond	7.06	8.41 (@ 17,309 hours)	3.87
	CADM	-	-	-
71	Emond	26.8	32.4 (@ 2 hours)	12.1
	CADM	-	-	-

C.3.1.17. *NTP (2006) 31 Weeks*

Type:	Rat	**Dose:**	0, 3, 10, 22, 46, 100 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	8 weeks old (BW=215g)	**Regime:**	5 days/weeks for 31 weeks
Sex:	Female and male	**Simulation time:**	5208 hours (31 weeks)

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	1,284	1,792 (@ 3,960 hours)	1,360
	CADM	-	-	-
7.14	Emond	2,932	4,356 (@ 3,960 hours)	2,989
	CADM	-	-	-
15.7	Emond	5,075	7,958 (@ 3,960 hours)	5,039
	CADM	-	-	-
32.9	Emond	8,629	14,416 (@ 3,960 hours)	8,417
	CADM	-	-	-
71.4	Emond	15,503	27,738 (@ 5,136 hours)	14,877
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	341	425 (@ 3,964 hours)	371
	CADM	-	-	-
7.14	Emond	1,077	1,312 (@ 4,133 hours)	1,125
	CADM	-	-	-
15.7	Emond	2,298	2,760 (@ 3,965 hours)	2,336
	CADM	-	-	-

32.9	Emond	4,698	5,599 (@ 3,965 hours)	4,711
	CADM	-	-	-
71.4	Emond	10,036	11,910 (@ 5,141 hours)	9,956
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	220	256 (@ 4,141 hours)	245
	CADM	-	-	-
7.14	Emond	502	571 (@ 4,139 hours)	545
	CADM	-	-	-
15.7	Emond	868	979 (@ 4,138 hours)	926
	CADM	-	-	-
32.9	Emond	1,476	1,657 (@ 4,137 hours)	1,558
	CADM	-	-	-
71.4	Emond	2,653	2,979 (@ 5,144 hours)	2,776
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	34.2	41.2 (@ 3,964 hours)	37.6
	CADM	-	-	-
7.14	Emond	91.7	109 (@ 4,132 hours)	97.2
	CADM	-	-	-
15.7	Emond	178	210 (@ 3,964 hours)	184
	CADM	-	-	-
32.9	Emond	339	398 (@ 4,132 hours)	346
	CADM	-	-	-
71.4	Emond	683	799 (@ 5,140 hours)	687
	CADM	-	-	-

BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	7.48	8.84 (@ 3,964 hours)	7.98
	CADM	-	-	-
7.14	Emond	15.6	17.9 (@ 4,132 hours)	16.1
	CADM	-	-	-
15.7	Emond	24.4	27.5 (@ 3,964 hours)	24.8
	CADM	-	-	-
32.9	Emond	35.7	39.6 (@ 3,964 hours)	36.0
	CADM	-	-	-
71.4	Emond	50.9	55.4 (@ 5,140 hours)	51.1
	CADM	-	-	-

C.3.1.18. *NTP (2006) 53 Weeks*

Type:	Rat	**Dose:**	0, 3, 10, 22, 46, 100 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	8 weeks old (BW=215g)	**Regime:**	5 days/weeks for 105 weeks
Sex:	Female and male	**Simulation time:**	8904 hours (53 weeks)

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	1,354	1,792 (@ 3,960 hours)	1,367
	CADM	-	-	-
7.14	Emond	3,056	4,359 (@ 8,832 hours)	2,993
	CADM	-	-	-
15.7	Emond	5,259	7,958 (@ 3,960 hours)	5,052
	CADM	-	-	-
32.9	Emond	8,918	14,460 (@ 8,832 hours)	8,438
	CADM	-	-	-
71.4	Emond	16,001	27,846 (@ 8,832 hours)	14,916
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	365	425 (@ 3,964 hours)	373
	CADM	-	-	-
7.14	Emond	1,138	1,312 (@ 8,837 hours)	1,127
	CADM	-	-	-
15.7	Emond	2,407	2,760 (@ 3,965 hours)	2,344
	CADM	-	-	-
32.9	Emond	4,902	5,611 (@ 8,837 hours)	4,726
	CADM	-	-	-
71.4	Emond	10,443	11,943 (@ 8,837 hours)	9,989
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	233	256 (@ 8,845 hours)	247
	CADM	-	-	-
7.14	Emond	525	572 (@ 8,843 hours)	546
	CADM	-	-	-
15.7	Emond	904	979 (@ 8,842 hours)	928
	CADM	-	-	-
32.9	Emond	1,533	1,661 (@ 8,841 hours)	1,562
	CADM	-	-	-
71.4	Emond	2,750	2,987 (@ 8,840 hours)	2,785
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	36.4	41.2 (@ 3,964 hours)	37.8
	CADM	-	-	-
7.14	Emond	96.4	109 (@ 8,836 hours)	97.3
	CADM	-	-	-

15.7	Emond	186	210 (@ 8,836 hours)	185
	CADM	-	-	-
32.9	Emond	354	399 (@ 8,836 hours)	347
	CADM	-	-	-
71.4	Emond	709	802 (@ 8,836 hours)	689
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	8.17	9.30 (@ 17,572 hours)	8.43
	CADM	-	-	-
7.14	Emond	16.6	18.0 (@ 17,572 hours)	16.2
	CADM	-	-	-
15.7	Emond	25.6	27.6 (@ 17,572 hours)	24.9
	CADM	-	-	-
32.9	Emond	37.3	39.7 (@ 17,572 hours)	36.2
	CADM	-	-	-
71.4	Emond	52.7	55.5 (@ 17,572 hours)	51.2
	CADM	-	-	-

C.3.1.19. *NTP (2006) 2 Years*

Type:	Rat	**Dose:**	0, 3, 10, 22, 46, 100 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	8 weeks old (BW=215g)	**Regime:**	5 days/weeks for 105 weeks
Sex:	Female and male	**Simulation time:**	17,640 hours* (105 weeks)

[a]The CADM model simulates for 104 weeks only (17,472 hours). As a result, the terminal values from the CADM model may be underestimated compared to the Emond model, which considers the full 105 weeks of exposure.

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	1,408	1,910 (@ 17,568 hours)	1,444
	CADM	-	-	-

7.14	Emond	3,137	4,389 (@ 17,568 hours)	3,007
	CADM	-	-	-
15.7	Emond	5,393	8,039 (@ 17,568 hours)	5,079
	CADM	-	-	-
32.9	Emond	9,129	14,542 (@ 17,568 hours)	8,468
	CADM	-	-	-
71.4	Emond	16,361	27,991 (@ 17,568 hours)	14,951
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	385	460 (@ 17,572 hours)	403
	CADM	632	715	715
7.14	Emond	1,177	1,320 (@ 17,573 hours)	1,135
	CADM	2,127	2,387	2,387
15.7	Emond	2,487	2,779 (@ 17,573 hours)	2,361
	CADM	4,691	5,252	5,252
32.9	Emond	5,051	5,637 (@ 17,573 hours)	4,749
	CADM	9,822	10,984	10,984
71.4	Emond	10,734	11,976 (@ 17,573 hours)	10,018
	CADM	21,366	23,880	23,880
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	243	271 (@ 17,581 hours)	261
	CADM	302	355	277
7.14	Emond	541	575 (@ 17,579 hours)	549
	CADM	667	787	611
15.7	Emond	930	985 (@ 17,578 hours)	934
	CADM	1,242	1,463	1,138
32.9	Emond	1,574	1,667 (@ 17,577 hours)	1,568
	CADM	2,369	2,787	2,173
71.4	Emond	2,821	2,995 (@ 17,576 hours)	2,792
	CADM	4,890	5,748	4,489

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	38.1	44.0 (@ 17,572 hours)	40.4
	CADM	46.0	48.0	48.0
7.14	Emond	99.5	109 (@ 17,572 hours)	97.9
	CADM	125	130	130
15.7	Emond	192	211 (@ 17,572 hours)	186
	CADM	257	267	267
32.9	Emond	364	400 (@ 17,572 hours)	348
	CADM	520	538	538
71.4	Emond	729	804 (@ 17,572 hours)	691
	CADM	1,110	1,149	1,149
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
2.14	Emond	8.17	9.30 (@ 17,572 hours)	8.43
	CADM	-	-	-
7.14	Emond	16.6	18.0 (@ 17,572 hours)	16.2
	CADM	-	-	-
15.7	Emond	25.6	27.6 (@ 17,572 hours)	24.9
	CADM	-	-	-
32.9	Emond	37.3	39.7 (@ 17,572 hours)	36.2
	CADM	-	-	-
71.4	Emond	52.7	55.5 (@ 17,572 hours)	51.2
	CADM	-	-	-

C.3.1.20. *Sewall et al. (1995)*

Type:	Rat	**Dose:**	49, 149.8, 490, and 1750 ng/kg every two weeks or 3.5, 10.7, 35, and 125 ng/kg-day
Strain:	Sprauge-Dawley	**Route:**	Oral gavage
Body weight:	12 wk old (BW set to 250g)	**Regime:**	Once every 2 weeks for 30 weeks
Sex:	Female	**Simulation time:**	5040 hours

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3.5	Emond	1,813	7,535 (@ 4,704 hours)	1,587
	CADM	-	-	-
10.7	Emond	3,916	21,297 (@ 4,704 hours)	3,189
	CADM	-	-	-
35	Emond	9,163	66,137 (@ 4,704 hours)	6,945
	CADM	-	-	-
125	Emond	24,608	228,370 (@ 4,704 hours)	17,298
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3.5	Emond	550	901 (@ 4,711 hours)	459
	CADM	-	-	-
10.7	Emond	1,605	2,632 (@ 4,712 hours)	1,229
	CADM	-	-	-
35	Emond	5,072	8,350 (@ 4,712 hours)	3,618
	CADM	-	-	-
125	Emond	17,683	29,256 (@ 4,713 hours)	12,011
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3.5	Emond	310	383 (@ 4,765 hours)	290
	CADM	-	-	-
10.7	Emond	670	827 (@ 4,763 hours)	590
	CADM	-	-	-
35	Emond	1,569	1,957 (@ 4,760 hours)	1,304
	CADM	-	-	-
125	Emond	4,217	5,376 (@ 4,757 hours)	3,303
	CADM	-	-	-

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3.5	Emond	51.4	72.5 (@ 4,710 hours)	45.3
	CADM	-	-	-
10.7	Emond	130	189 (@ 4,710 hours)	106
	CADM	-	-	-
35	Emond	364	546 (@ 4,710 hours)	274
	CADM	-	-	-
125	Emond	1,164	1,793 (@ 4,710 hours)	824
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
3.5	Emond	10.2	15.8 (@ 2 hours)	9.18
	CADM	-	-	-
10.7	Emond	19.8	34.4 (@ 1 hours)	17.0
	CADM	-	-	-
35	Emond	37.0	63.2 (@ 1 hours)	31.4
	CADM	-	-	-
125	Emond	63.1	90.9 (@ 1 hours)	55.2
	CADM	-	-	-

C.3.1.21. *Smialowicz et al. (2008)*

Type:	Mice	**Dose:**	0, 1.5, 15, 150, 450 ng/kg-day
Strain:	B6C3F1	**Route:**	Oral gavage
Body weight:	13 wk old (BW set to 28g)	**Regime:**	5 days/week for 13 weeks
Sex:	Female	**Simulation time:**	2184

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.07	Emond	241	449 (@ 2,112 hours)	307
	CADM	-	-	-
10.7	Emond	1,358	2,821 (@ 2,112 hours)	1,460
	CADM	-	-	-
107	Emond	7,385	20,036 (@ 2,112 hours)	6,978
	CADM	-	-	-
321	Emond	17,438	54,346 (@ 2,112 hours)	15,650
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.07	Emond	67.1	107 (@ 2,116 hours)	91.5
	CADM	59.0	92.0	88.0
10.7	Emond	683	971 (@ 2,117 hours)	787
	CADM	767	1,000	907
107	Emond	6,784	9,010 (@ 2,117 hours)	7,043
	CADM	8,349	10,306	8,998
321	Emond	20,218	26,379 (@ 2,117 hours)	20,405
	CADM	25,344	31,006	26,967
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.07	Emond	156	229 (@ 2,130 hours)	225
	CADM	151	210	204
10.7	Emond	885	1,155 (@ 2,124 hours)	1,111
	CADM	689	815	774
107	Emond	4,831	5,979 (@ 2,120 hours)	5,591
	CADM	2,771	3,224	2,937
321	Emond	11,420	14,037 (@ 2,119 hours)	12,920
	CADM	6,337	7,509	6,688

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.07	Emond	17.0	25.5 (@ 2,116 hours)	23.9
	CADM	21.0	29.0	29.0
10.7	Emond	117	159 (@ 2,116 hours)	141
	CADM	119	145	135
107	Emond	852	1,103 (@ 2,116 hours)	923
	CADM	727	875	778
321	Emond	2,304	2,958 (@ 2,116 hours)	2,419
	CADM	1,961	2,370	2,080
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1.07	Emond	1.48	2.17 (@ 2,116 hours)	1.90
	CADM	-	-	-
10.7	Emond	7.60	9.86 (@ 2,116 hours)	8.42
	CADM	-	-	-
107	Emond	30.3	36.0 (@ 2,117 hours)	31.1
	CADM	-	-	-
321	Emond	51.1	58.1 (@ 2,117 hours)	51.8
	CADM	-	-	-

C.3.1.22. *Toth et al., 1 Year (1979)*

Type:	Mice	**Dose:**	7, 700, 7000 ng/kg/week
Strain:	Swiss/H/Riop	**Route:**	Gastric intubation
Body weight:	10 weeks old (BW= 27g)	**Regime:**	1/week for 52 weeks
Sex:	Female and male	**Simulation time:**	8,736 hours*

[a]According to the protocol in the paper, the mice were exposed for 52 weeks. However, the post exposure treatment was for an additional 60–285 days. For this simulation, we modeled 52 weeks because we have already reached the maximum when the dosing ends. We did not simulate the scenario using the CADM model because this mice model can only simulate for a maximum of 123 days.

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	315	889 (@ 8,568 hours)	308
	CADM	-	-	-
100	Emond	7,814	63,673 (@ 7,896 hours)	6,014
	CADM	-	-	-
1,000	Emond	50,105	610,490 (@ 8,568 hours)	34,155
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	94.1	131 (@ 8,575 hours)	91.5
	CADM	-	-	-
100	Emond	7,337	10,132 (@ 7,905 hours)	5,669
	CADM	-	-	-
1,000	Emond	70,180	97,655 (@ 8,577 hours)	51,986
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	215	247 (@ 8,613 hours)	230
	CADM	-	-	-
100	Emond	5,337	5,912 (@ 8,594 hours)	4,997
	CADM	-	-	-
1,000	Emond	34,239	38,825 (@ 8,588 hours)	30,516
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	23.4	28.4 (@ 8,574 hours)	24.3
	CADM	-	-	-
100	Emond	929	1,189 (@ 7,902 hours)	781
	CADM	-	-	-

1,000	Emond	7,564	10,044 (@ 8,574 hours)	5,965
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	1.93	2.65 (@ 8,573 hours)	1.90
	CADM	-	-	-
100	Emond	31.8	58.4 (@ 2 hours)	27.7
	CADM	-	-	-
1,000	Emond	78.6	103 (@ 2 hours)	72.7
	CADM	-	-	-

C.3.1.23. *Van Birgelen (1995)*

Type:	Rat	**Dose:**	0, 13.5, 26.4, 46.9, 320, 1024 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	150 g	**Regime:**	Once per day for 13 weeks
Sex:	Female	**Simulation time:**	2184 hours (13 weeks)

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
13.5	Emond	3,969	6,098 (@ 2,160 hours)	4,665
	CADM	-	-	-
26.4	Emond	6,479	10,258 (@ 2,160 hours)	7,457
	CADM	-	-	-
46.9	Emond	9,968	16,284 (@ 2,160 hours)	11,313
	CADM	-	-	-
320	Emond	47,606	86,065 (@ 2,160 hours)	52,581
	CADM	-	-	-
1024	Emond	137,820	258,910 (@ 2,160 hours)	151,680
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
13.5	Emond	1,655	2,208 (@ 2,164 hours)	2,107
	CADM	-	-	-
26.4	Emond	3,228	4,216 (@ 2,164 hours)	4,017
	CADM	-	-	-
46.9	Emond	5,719	7,366 (@ 2,164 hours)	7,008
	CADM	-	-	-
320	Emond	38,484	47,999 (@ 2,164 hours)	45,537
	CADM	-	-	-
1024	Emond	121,640	150,410 (@ 2,164 hours)	142,510
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
13.5	Emond	669	843 (@ 2,167 hours)	835
	CADM	-	-	-
26.4	Emond	1,092	1,357 (@ 2,166 hours)	1,342
	CADM	-	-	-
46.9	Emond	1,680	2,071 (@ 2,166 hours)	2,045
	CADM	-	-	-
320	Emond	8,027	9,816 (@ 2,165 hours)	9,639
	CADM	-	-	-
1024	Emond	23,234	28,519 (@ 2,165 hours)	27,954
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
13.5	Emond	132	173 (@ 2,164 hours)	167
	CADM	-	-	-
26.4	Emond	240	308 (@ 2,164 hours)	296
	CADM	-	-	-

46.9	Emond	404	513 (@ 2,164 hours)	492
	CADM	-	-	-
320	Emond	2,437	3,031 (@ 2,164 hours)	2,887
	CADM	-	-	-
1024	Emond	7,521	9,310 (@ 2,164 hours)	8,846
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
13.5	Emond	19.9	24.2 (@ 2,164 hours)	23.4
	CADM	-	-	-
26.4	Emond	29.0	34.3 (@ 2,164 hours)	33.2
	CADM	-	-	-
46.9	Emond	38.8	45.0 (@ 2,164 hours)	43.7
	CADM	-	-	-
320	Emond	79.1	85.2 (@ 2,164 hours)	84.1
	CADM	-	-	-
1024	Emond	97.5	101 (@ 2,164 hours)	101
	CADM	-	-	-

C.3.1.24. *Vanden Heuvel et al. (1994)*

Type:	Rat	**Dose:**	0.05, 0.1, 1, 10, 100, 1000, 10000 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	10 weeks old (BW 225 to 275g) (BW=250g)	**Regime:**	Single dose
Sex:	Female	**Simulation time:**	24 hours*

[a]1 week is the minimum that can be simulated with the Aylward model

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.05	Emond	3.13	5.90 (@ 0 hours)	1.50
	Aylward	-	-	-

0.1	Emond	6.21	11.9 (@ 0 hours)	2.97
	Aylward	-	-	-
1	Emond	58.0	118 (@ 0 hours)	28.0
	Aylward	-	-	-
10	Emond	484	1,183 (@ 0 hours)	234
	Aylward	-	-	-
100	Emond	3,569	11,963 (@ 0 hours)	1,622
	Aylward	-	-	-
1,000	Emond	26,736	119,860 (@ 0 hours)	9,984
	Aylward	-	-	-
10,000	Emond	240,660	1,200,300 (@ 0 hours)	72,090
	Aylward	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.05	Emond	0.230	0.311 (@ 3 hours)	0.114
	Aylward	-	-	0.0140
0.1	Emond	0.465	0.624 (@ 3 hours)	0.232
	Aylward	-	-	0.0320
1	Emond	5.04	6.34 (@ 4 hours)	2.61
	Aylward	-	-	0.950
10	Emond	59.7	67.9 (@ 5 hours)	34.0
	Aylward	-	-	52.7
100	Emond	733	800 (@ 8 hours)	477
	Aylward	-	-	1,342
1,000	Emond	8,215	8,918 (@ 10 hours)	5,941
	Aylward	-	-	15,967
10,000	Emond	84,520	91,628 (@ 11 hours)	64,335
	Aylward	-	-	162,773
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.05	Emond	0.137	0.261 (@ 83 hours)	0.259
	Aylward	-	-	0.780

0.1	Emond	0.272	0.518 (@ 84 hours)	0.515
	Aylward	-	-	1.57
1	Emond	2.57	4.90 (@ 85 hours)	4.86
	Aylward	-	-	15.3
10	Emond	22.0	41.4 (@ 89 hours)	41.0
	Aylward	-	-	125
100	Emond	170	293 (@ 88 hours)	288
	Aylward	-	-	739
1,000	Emond	1,354	1,905 (@ 69 hours)	1,824
	Aylward	-	-	5,779
10,000	Emond	12,571	15,593 (@ 40 hours)	13,735
	Aylward	-	-	55,825
BODY BURDEN (ng/kg)				
Dose (ng/kg)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.05	Emond	0.0267	0.028 (@ 9 hours)	0.0272
	Aylward	-	-	0.0450
0.1	Emond	0.0534	0.056 (@ 9 hours)	0.0542
	Aylward	-	-	0.0900
1	Emond	0.532	0.561 (@ 9 hours)	0.531
	Aylward	-	-	0.900
10	Emond	5.29	5.59 (@ 8 hours)	5.02
	Aylward	-	-	9.00
100	Emond	53.0	56.3 (@ 7 hours)	46.1
	Aylward	-	-	90.0
1,000	Emond	527	562 (@ 7 hours)	424
	Aylward	-	-	900
10,000	Emond	5,258	5,610 (@ 7 hours)	4,082
	Aylward	-	-	9,000
BOUND LIVER (ng/kg)				
Dose (ng/kg)	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.05	Emond	0.0192	0 (@ 4 hours)	0.00963
	Aylward	-	-	-

0.1	Emond	0.0380	0 (@ 4 hours)	0.0191
	Aylward	-	-	-
1	Emond	0.351	1 (@ 3 hours)	0.180
	Aylward	-	-	-
10	Emond	2.75	4 (@ 3 hours)	1.48
	Aylward	-	-	-
100	Emond	16.1	26 (@ 2 hours)	9.48
	Aylward	-	-	-
1,000	Emond	57.7	77 (@ 2 hours)	40.7
	Aylward	-	-	-
10,000	Emond	100	107 (@ 2 hours)	90.4
	Aylward	-	-	-

C.3.1.25. *White et al. (1986)*

Type:	Mice	**Dose:**	10, 50, 100, 500, 1000, 2000 ng/kg-day
Strain:	B6C3F1	**Route:**	Oral gavage
Body weight:	7 weeks old (BW set to 23g)	**Regime:**	1/day for 14 days
Sex:	Female	**Simulation time:**	336 hours

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	603	1,502 (@ 312 hours)	785
	CADM	-	-	-
50	Emond	2,250	6,387 (@ 312 hours)	2,742
	CADM	-	-	-
100	Emond	3,934	11,970 (@ 312 hours)	4,650
	CADM	-	-	-
500	Emond	14,772	53,188 (@ 312 hours)	16,394
	CADM	-	-	-
1,000	Emond	26,844	102,960 (@ 312 hours)	29,229
	CADM	-	-	-

2,000	Emond	49,896	201,110 (@ 312 hours)	53,697
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	216	375 (@ 317 hours)	343
	CADM	217	468 (336h)	463
50	Emond	1,279	2,164 (@ 317 hours)	1,997
	CADM	1,775	3,261 (336h)	3,261
100	Emond	2,707	4,525 (@ 317 hours)	4,184
	CADM	3,999	6,923 (336h)	6,923
500	Emond	14,802	24,165 (@ 317 hours)	22,383
	CADM	22,705	36,362 (336h)	36,362
1,000	Emond	30,278	49,034 (@ 317 hours)	45,414
	CADM	46,309	73,145 (336h)	73,145
2,000	Emond	61,381	98,703 (@ 317 hours)	91,363
	CADM	93,577	146,695 (336h)	146,695
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	279	507 (@ 336 hours)	507
	CADM	316	537 (336h)	537
50	Emond	1,056	1,846 (@ 336 hours)	1,846
	CADM	1,029	1,564 (336h)	1,564
100	Emond	1,854	3,195 (@ 333 hours)	3,195
	CADM	1,662	2,470 (336h)	2,470
500	Emond	7,008	11,868 (@ 324 hours)	11,816
	CADM	5,711	8,594 (336h)	8,594
1,000	Emond	12,746	21,566 (@ 323 hours)	21,424
	CADM	10,498	15,993 (336h)	15,993
2,000	Emond	23,691	40,177 (@ 322 hours)	39,843
	CADM	19,990	30,726 (336h)	30,726

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	37.7	65.9 (@ 317 hours)	63.8
	CADM	47.9	85.9 (336h)	85.9
50	Emond	175	297 (@ 317 hours)	284
	CADM	207	342 (336h)	342
100	Emond	338	570 (@ 316 hours)	542
	CADM	388	624 (336h)	624
500	Emond	1,597	2,637 (@ 316 hours)	2,480
	CADM	1,761	2,754 (336h)	2,754
1,000	Emond	3,137	5,153 (@ 316 hours)	4,830
	CADM	3,455	5,387 (336h)	5,387
2,000	Emond	6,186	10,118 (@ 316 hours)	9,459
	CADM	6,836	10,643 (336h)	10,643
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
10	Emond	3.49	5.32 (@ 316 hours)	4.82
	CADM	-	-	-
50	Emond	11.4	16.4 (@ 317 hours)	15.1
	CADM	-	-	-
100	Emond	18.1	25.1 (@ 317 hours)	23.4
	CADM	-	-	-
500	Emond	44.2	56.2 (@ 317 hours)	53.8
	CADM	-	-	-
1,000	Emond	59.3	71.9 (@ 317 hours)	69.7
	CADM	-	-	-
2,000	Emond	74.4	86.1 (@ 317 hours)	84.3
	CADM	-	-	-

C.3.2. Gestational Studies

C.3.2.1. *Bell et al. (2007)*

Type:	Rat	**Dose:**	2.4, 8, and 46 ng/kg-day with a 0.03 ng/kg-day background
Strain:	Han/Wistar	**Route:**	Dietary
Body weight:	6 weeks (BW= 85g)	**Regime:**	12 weeks prior to mating, during the two week mating period, and during gestation
Sex:	Female	**Simulation time:**	2,352 hr (98 days) prior to gestation + 504 hr (21 days) during gestation for a total of 2,856 hours

[a]Time averages are computed during the gestation period only.

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2.43	1,998	4,977,500	2,452 (@ 2,352 hours)	1,745
8.03	4,539	11,602,000	5,781 (@ 2,352 hours)	4,023
46.03	15,952	41,518,000	22,096 (@ 2,352 hours)	14,275
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2.43	381	914,700	437 (@ 2,356 hours)	321
8.03	1,201	2,970,500	1,351 (@ 2,356 hours)	1,044
46.03	6,638	16,802,000	7,260 (@ 2,356 hours)	5,980
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2.43	233	585,680	263 (@ 2,336 hours)	211
8.03	528	1,365,300	589 (@ 2,335 hours)	487
46.03	1,851	4,885,900	2,039 (@ 2,334 hours)	1,739

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2.43	43.0	94,428	44.5 (@ 2,836 hours)	43.4
8.03	113	258,160	118 (@ 2,836 hours)	114
46.03	506	1,204,800	529 (@ 2,836 hours)	509
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2.43	17.2	8,674	39.7 (@ 2,530 hours)	6.53
8.03	37.7	19,002	86.7 (@ 2,529 hours)	14.4
46.03	118	59,628	271 (@ 2,527 hours)	45.9
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2.43	8.13	20,295	8.98 (@ 2,356 hours)	7.24
8.03	16.8	43,248	18.2 (@ 2,356 hours)	15.4
46.03	42.7	112,990	44.7 (@ 2,356 hours)	40.5

C.3.2.2. *Hojo et al. (2002)*

Type:	Rat	**Dose:**	20, 60 and 180 ng/kg
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight	20 ng/kg BW = 271g 60 ng/kg BW = 275g 180 ng/kg BW = 262g	**Regime:**	Single dose on GD8
Sex:	Female	**Simulation time**	24 hours

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	1,285	177,790	3,534 (@ 192 hours)	402
60	3,295	452,060	10,477 (@ 192 hours)	1,002

180	8,465	1,114,200	31,887 (@ 192 hours)	2,396
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	128	20,554	144 (@ 198 hours)	43.2
60	420	72,340	465 (@ 200 hours)	147
180	1,364	250,820	1,497 (@ 201 hours)	497
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	32.5	17,253	63.0 (@ 281 hours)	49.4
60	86.4	44,093	161 (@ 284 hours)	124
180	226	108,730	398 (@ 286 hours)	301
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	10.6	3,054	11.3 (@ 200 hours)	8.67
60	31.8	8,702	33.8 (@ 199 hours)	23.6
180	95.0	24,747	101 (@ 199 hours)	63.4
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	15.9	2,334	18.4 (@ 206 hours)	1.64
60	39.8	5,829	45.7 (@ 205 hours)	4.10
180	96.3	13,866	110 (@ 203 hours)	9.72
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	4.88	759	7.74 (@ 194 hours)	1.75
60	11.2	1,848	18.5 (@ 194 hours)	4.26
180	23.6	4,157	38.5 (@ 193 hours)	9.65

C.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:	10 weeks (BW= 250g)	**Regime:**	Initial single loading dose, 2 weekly maintenance doses prior to gestation and 2 weekly maintenance doses during gestation
Sex:	Female	**Simulation time:**	504 hr (21 days) prior to gestation + 504 hr (21 days) during gestation for a total simulation of 1,008 hours

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
16.5	18,103	18,249,000	80,047 (@ 144 hours)	8,009
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
16.5	7,755	7,817,300	17,016 (@ 150 hours)	2,698
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
16.5	2,087	2,103,900	3,663 (@ 184 hours)	1,028
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
16.5	548	552,590	1,085 (@ 149 hours)	262
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
16.5	45.9	46,290	245 (@ 679 hours)	30.2

BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
16.5	44.0	44,361	63.8 (@ 149 hours)	26.8

C.3.2.4. *Kattainen et al. (2001)*

Type:	Rat	**Dose:**	30, 100, 300, and 1,000 ng/kg
Strain:	Han/Wistar (Kuopio) and Long/Evans (Turku/AB) crossing.	**Route:**	Oral gavage
Body weight:	BW not specified (BW set to 190g)*	**Regime:**	Single dose on GD15
Sex:	Female	**Simulation time:**	24 hours

[a]Derelanko and Hollinger (1995).

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	1,763	151,690	4,703 (@ 336 hours)	632
100	4,944	423,680	15,679 (@ 336 hours)	1,761
300	12,712	1,054,600	47,253 (@ 336 hours)	4,327
1,000	37,039	2,878,700	158,470 (@ 336 hours)	11,429
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	193	19,784	219 (@ 342 hours)	78.9
100	713	79,889	793 (@ 344 hours)	324
300	2,298	276,990	2,533 (@ 345 hours)	1,150
1,000	8,054	1,032,300	8,830 (@ 345 hours)	4,412

FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	42.8	12,439	82.8 (@ 426 hours)	77.5
100	123	34,712	230 (@ 431 hours)	217
300	327	86,670	571 (@ 431 hours)	536
1,000	981	238,680	1,551 (@ 425 hours)	1,435
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	15.9	2,562	16.9 (@ 343 hours)	14.1
100	52.7	8,273	56.2 (@ 343 hours)	44.2
300	158	24,176	168 (@ 343 hours)	125
1,000	524	78,767	561 (@ 343 hours)	395
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	4.86	828	6.90 (@ 372 hours)	2.53
100	13.2	2,221	18.2 (@ 372 hours)	6.89
300	31.5	5,200	42.3 (@ 371 hours)	16.2
1,000	82.2	12,907	106 (@ 369 hours)	39.6
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	6.58	634	10.7 (@ 338 hours)	2.73
100	15.8	1,642	26.3 (@ 338 hours)	7.28
300	31.6	3,538	50.6 (@ 337 hours)	16.3
1,000	57.1	7,095	80.1 (@ 337 hours)	34.8

C.3.2.5. *Keller et al. (2007)*

Type:	Mouse	**Dose:**	10, 100, and 1000 ng/kg
Strain:	CBA/J and C3H/HeJ	**Route:**	Oral

Body weight:	Not specified (24 g used in the simulation)	**Regime:**	Single dose on GD13
Sex:	Female	**Simulation time:**	504 hours

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
10	296	18,384	788 (@ 312 hours)	48.4
100	2,365	149,060	7,884 (@ 312 hours)	374
1,000	18,764	1,083,900	78,825 (@ 312 hours)	2,454
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
10	30.6	2,046	39.8 (@ 316 hours)	4.90
100	371	28,867	421 (@ 319 hours)	62.7
1,000	4,214	388,320	4,697 (@ 321 hours)	833
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
10	22.4	7,075	41.1 (@ 386 hours)	35.9
100	188	57,462	333 (@ 396 hours)	291
1,000	1,591	425,300	2,441 (@ 392 hours)	2,064
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
10	5.57	1,024	5.99 (@ 319 hours)	4.99
100	54.3	9,170	59.0 (@ 318 hours)	41.9
1,000	530	79,818	581 (@ 318 hours)	323

FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
10	2.57	386	3.80 (@ 337 hours)	0.795
100	21.8	3,109	30.0 (@ 334 hours)	6.42
1,000	179	22,097	233 (@ 329 hours)	42.6
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
10	1.74	115	3.14 (@ 315 hours)	0.305
100	11.5	857	23.5 (@ 314 hours)	2.30
1,000	46.7	4,430	79.8 (@ 314 hours)	13.3

C.3.2.6. *Li et al. (2006) 3-Day*

Type:	Mouse	**Dose:**	2, 50, and 100 ng/kg-day
Strain:	NIH	**Route:**	Oral gavage
Body weight:	25-28 g (used 27 g in the simulation)	**Regime:**	Daily exposure from GD1 to GD3
Sex:	Female	**Simulation time:**	72 hours

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2	87.5	6,305	216 (@ 48 hours)	75.1
50	1,564	112,720	4,906 (@ 48 hours)	1,312
100	2,823	203,490	9,547 (@ 48 hours)	2,313
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2	8.98	647	15.1 (@ 52 hours)	9.10
50	333	23,971	539 (@ 53 hours)	402
100	718	51,738	1,156 (@ 53 hours)	888

FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2	17.0	1,227	31.1 (@ 72 hours)	31.1
50	315	22,704	548 (@ 72 hours)	548
100	576	41,460	984 (@ 72 hours)	984
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2	2.29	165	3.51 (@ 55 hours)	3.43
50	53.6	3,863	82.2 (@ 54 hours)	77.1
100	105	7,598	162 (@ 53 hours)	150
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2	0.00	0	0.000 (@ 72 hours)	0.00
50	0.0	0	0.000 (@ 72 hours)	0.00
100	0.0	0	0.000 (@ 72 hours)	0.00
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
2	0.538	38.8	0.864 (@ 51 hours)	0.498
50	8.24	594	13.5 (@ 2 hours)	8.16
100	13.6	981	23.7 (@ 2 hours)	13.6

C.3.2.7. *Markowski et al. (2001)*

Type:	Rat	**Dose:**	20, 60 and 180 ng/kg
Strain:	Holtzman rats	**Route:**	Oral gavage
Body weight:	BW not specified (BW set to 190g)*	**Regime:**	Single dose on GD18
Sex:	Female	**Simulation time:**	24 hours

[a]Derelanko and Hollinger (1995).

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	1,234	71,255	3,029 (@ 408 hours)	471
60	3,184	184,690	9,096 (@ 408 hours)	1,317
180	8,152	465,030	27,457 (@ 408 hours)	3,193
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	123	8,315	142 (@ 414 hours)	56.5
60	409	29,656	459 (@ 415 hours)	213
180	1,333	103,210	1,478 (@ 416 hours)	790
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	28.0	4,437	55.6 (@ 498 hours)	55.5
60	74.0	11,462	144 (@ 504 hours)	144
180	195	28,948	363 (@ 504 hours)	363
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	10.6	1,013	11.3 (@ 415 hours)	10.2
60	31.7	2,989	33.7 (@ 415 hours)	29.5
180	94.7	8,834	101 (@ 415 hours)	85.7
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	1.26	157	1.93 (@ 448 hours)	1.43
60	3.21	395	4.79 (@ 449 hours)	3.63
180	7.80	943	11.3 (@ 449 hours)	8.69

BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
20	4.75	299	7.61 (@ 410 hours)	2.12
60	11.0	729	18.2 (@ 410 hours)	5.47
180	23.2	1,621	38.1 (@ 409 hours)	12.9

C.3.2.8. *Mietinnen et al. (2006)*

Type:	Rat	**Dose:**	30, 100, 300 and 1000 ng/kg
Strain:	cross-breeding of Han/Wistar and Long-Evans rats	**Route:**	Oral gavage
Body weight:	BW 11 weeks (BW set to 180g)	**Regime:**	Single dose on GD15
Sex:	Female	**Simulation time:**	24 hours

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	1,756	151,180	4,641 (@ 336 hours)	721
100	4,922	422,480	15,471 (@ 336 hours)	1,758
300	12,657	1,052,000	46,647 (@ 336 hours)	4,994
1,000	36,874	2,872,800	156,480 (@ 336 hours)	11,423
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	193	19,697	219 (@ 342 hours)	78.8
100	711	79,610	791 (@ 344 hours)	323
300	2,293	276,280	2,529 (@ 345 hours)	1,149
1,000	8,044	1,030,600	8,822 (@ 345 hours)	4,409

FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	43.1	12,461	82.9 (@ 425 hours)	77.4
100	124	34,793	231 (@ 430 hours)	217
300	329	86,906	572 (@ 430 hours)	536
1,000	988	239,390	1,555 (@ 424 hours)	1,436
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	15.9	2,560	16.9 (@ 343 hours)	14.1
100	52.7	8,269	56.2 (@ 343 hours)	44.1
300	158	24,169	168 (@ 343 hours)	125
1,000	524	78,769	561 (@ 343 hours)	395
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	4.83	824	6.87 (@ 372 hours)	2.52
100	13.1	2,213	18.1 (@ 372 hours)	6.87
300	31.3	5,182	42.1 (@ 371 hours)	16.2
1,000	81.7	12,867	105 (@ 369 hours)	39.5
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
30	6.56	632	10.7 (@ 338 hours)	2.72
100	15.8	1,639	26.3 (@ 338 hours)	7.27
300	31.6	3,533	50.5 (@ 337 hours)	16.3
1,000	57.0	7,090	80.1 (@ 337 hours)	34.8

C.3.2.9. *Murray et al. (1979) Gestational Portion*

Type:	Rat	**Dose:**	1, 10, and 100 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Diet oral dose

Body weight:	6- to 7 week (Bw= 85g)	**Regime:**	Once per day for 90 days prior to gestation and during gestation
Sex:	Female	**Simulation time:**	2160 hr (90 days) prior gestation + 504 hr (21 days) for a total simulation of 2664 hours

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
1	897	2,389,400	1,291 (@ 2,160 hours)	926
10	4,691	12,497,000	6,780 (@ 2,160 hours)	4,708
100	26,219	69,849,000	42,272 (@ 2,160 hours)	25,849
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
1	129	342,940	186 (@ 2,164 hours)	133
10	1,271	3,385,700	1,657 (@ 2,164 hours)	1,298
100	12,492	33,279,000	15,332 (@ 2,164 hours)	12,876
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
1	105	280,460	142 (@ 2,146 hours)	112
10	551	1,467,700	682 (@ 2,143 hours)	569
100	3,080	8,204,300	3,682 (@ 2,142 hours)	3,162
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
1	15.4	41,059	21.8 (@ 2,644 hours)	21.4
10	108	286,920	141 (@ 2,644 hours)	137
100	847	2,257,100	1,060 (@ 2,644 hours)	1,017

FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
1	1.77	4,720	21.7 (@ 2,339 hours)	3.54
10	8.22	21,889	99.8 (@ 2,337 hours)	16.7
100	37.4	99,722	453 (@ 2,334 hours)	77.0
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
1	3.79	10,101	5.06 (@ 2,163 hours)	3.96
10	17.1	45,522	20.5 (@ 2,164 hours)	17.6
100	55.1	146,790	61.0 (@ 2,164 hours)	56.8

C.3.2.10. *Murray et al. (1979) Adult Portion*

Type:	Rat	**Dose:**	1, 10, and 100 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Dietary
Body weight:	BW set to 4.5 g	**Regime:**	120 days
Sex:	Female	**Simulation time:**	2880 hours

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	619	832 (@ 2,856 hours)	785
	CADM	-	-	-
10	Emond	3,241	4,181 (@ 2,856 hours)	3,717
	CADM	-	-	-
100	Emond	18,038	24,433 (@ 2,856 hours)	19,844
	CADM	-	-	-

LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	128	180 (@ 2,859 hours)	173
	CADM	-	-	-
10	Emond	1,273	1,618 (@ 2,860 hours)	1,540
	CADM	-	-	-
100	Emond	12,601	15,281 (@ 2,860 hours)	14,460
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	106	139 (@ 2,865 hours)	138
	CADM	-	-	-
10	Emond	556	665 (@ 2,864 hours)	657
	CADM	-	-	-
100	Emond	3,095	3,604 (@ 2,862 hours)	3,534
	CADM	-	-	-
BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	14.8	20.0 (@ 2,860 hours)	19.6
	CADM	-	-	-
10	Emond	105	130 (@ 2,860 hours)	126
	CADM	-	-	-
100	Emond	837	1,003 (@ 2,860 hours)	957
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
1	Emond	3.77	4.95 (@ 2,859 hours)	4.77
	CADM	-	-	-
10	Emond	17.1	20.3 (@ 2,859 hours)	19.5
	CADM	-	-	-

100	Emond	55.3	60.9 (@ 2,860 hours)	59.4
	CADM	-	-	-

C.3.2.11. *Nohara et al. (2000)*

Type:	Rat	**Dose:**	12.5, 50, 200 or 800 ng TCDD/kg
Strain:	Holtzman rats	**Route:**	Oral gavage
Body weight:	BW not specified (BW set to 190g)*	**Regime:**	Single dose on GD15
Sex:	Female	**Simulation time:**	24 hours

[a]Derelanko and Hollinger (1995).

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	816	69,459	1,933 (@ 336 hours)	290
50	2,724	235,070	7,736 (@ 336 hours)	981
200	8,912	752,170	31,022 (@ 336 hours)	3,110
800	30,121	2,378,900	125,030 (@ 336 hours)	9,532
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	73.9	7,084	86.2 (@ 341 hours)	28.3
50	336	35,736	378 (@ 343 hours)	143
200	1,492	175,300	1,651 (@ 344 hours)	722
800	6,387	810,340	7,011 (@ 345 hours)	3,449
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	19.7	5,736	38.1 (@ 419 hours)	35.4
50	67.6	19,362	129 (@ 427 hours)	121
200	229	62,032	410 (@ 431 hours)	385

800	803	197,830	1,288 (@ 425 hours)	1,194
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	6.63	1,088	7.05 (@ 343 hours)	6.10
50	26.4	4,212	28.1 (@ 343 hours)	22.9
200	105	16,259	112 (@ 343 hours)	85.1
800	420	63,228	449 (@ 343 hours)	319
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	2.25	385	3.26 (@ 371 hours)	1.17
50	7.43	1,263	10.5 (@ 372 hours)	3.89
200	22.8	3,802	31.0 (@ 372 hours)	11.8
800	68.1	10,862	88.5 (@ 369 hours)	33.6
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	3.24	298	5.12 (@ 338 hours)	1.27
50	9.66	959	16.0 (@ 338 hours)	4.18
200	24.8	2,695	40.7 (@ 337 hours)	12.2
800	51.9	6,315	75.0 (@ 337 hours)	30.6

C.3.2.12. *Ohsako et al. (2001)*

Type:	Rat	**Dose:**	12.5, 50, 200, and 800 ng/kg-day
Strain:	Holtzmann	**Route:**	Oral gavage
Body weight	10 weeks (200g)	**Regime:**	Single dose on GD15
Sex:	Female	**Simulation time**	24 hours

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	845	63,918	2,016 (@ 360 hours)	304
50	2,763	212,870	7,928 (@ 360 hours)	1,020
200	9,022	677,090	31,557 (@ 360 hours)	3,239
800	30,504	2,148,100	127,220 (@ 360 hours)	9,983
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	76.8	6,595	89.0 (@ 365 hours)	30.1
50	340	32,557	383 (@ 367 hours)	152
200	1,504	157,600	1,657 (@ 368 hours)	768
800	6,426	724,530	7,026 (@ 369 hours)	3,689
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	19.6	4,897	38.4 (@ 446 hours)	36.9
50	65.8	16,240	128 (@ 455 hours)	124
200	223	51,709	404 (@ 458 hours)	393
800	780	165,660	1,270 (@ 453 hours)	1,224
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	6.84	966	7.24 (@ 367 hours)	6.38
50	26.6	3,693	28.4 (@ 367 hours)	23.7
200	106	14,210	112 (@ 367 hours)	88.3
800	421	55,466	449 (@ 367 hours)	334
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	1.69	274	2.50 (@ 397 hours)	1.16

50	5.48	881	7.91 (@ 398 hours)	3.79
200	16.8	2,629	23.3 (@ 398 hours)	11.4
800	50.2	7,518	66.4 (@ 396 hours)	32.3
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
12.5	3.34	274	5.25 (@ 362 hours)	1.33
50	9.76	863	16.1 (@ 362 hours)	4.34
200	25.0	2,396	40.7 (@ 361 hours)	12.7
800	52.1	5,566	75.1 (@ 361 hours)	31.7

C.3.2.13. *Schantz et al. (1995) and Amin et al. (2000)*

Type:	Rat	**Dose:**	25 and 100 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	BW not specified (BW set to 250g)	**Regime:**	Daily doses from GD 10 - 16
Sex:	Female	**Simulation time:**	384 hours; time averages are calculated from the beginning of the dosing

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	2,670	384,750	6,800 (@ 360 hours)	3,190
100	8,341	1,201,700	24,522 (@ 360 hours)	9,706
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	512	73,705	871 (@ 365 hours)	778
100	2,371	341,460	4,009 (@ 366 hours)	3,662

FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	169	24,329	307 (@ 384 hours)	307
100	532	76,559	949 (@ 384 hours)	949
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	45	6,492	76.6 (@ 365 hours)	74
100	176	25,401	298 (@ 365 hours)	287
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	25	3,628	30.4 (@ 343 hours)	27
100	74.0	10,655	88.1 (@ 342 hours)	77.8
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	10	1,440	14.4 (@ 364 hours)	13
100	25	3,628	34.2 (@ 364 hours)	32

C.3.2.14. *Seo et al. (1995)*

Type:	Rat	**Dose:**	25 and 100 ng/kg-day
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	BW not specified (BW set to 190g)	**Regime:**	Daily from GD 10 - 16
Sex:	Female	**Simulation time:**	384 hours; time averages are calculated from the beginning of the dosing

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	2,655	766,430	6,796 (@ 384 hours)	2,748
100	8,319	2,372,700	24,284 (@ 384 hours)	8,333
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	506	163,400	972 (@ 389 hours)	606
100	2,358	767,640	4,486 (@ 389 hours)	2,871
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	173	66,734	358 (@ 436 hours)	339
100	545	207,420	1,105 (@ 433 hours)	1,037
BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	45.3	16,124	87.5 (@ 389 hours)	73.6
100	177	61,908	339 (@ 389 hours)	271
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	24.7	5,826	29.8 (@ 343 hours)	10.6
100	72.6	16,930	86.6 (@ 342 hours)	30.2
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
25	9.92	2,937	15.4 (@ 388 hours)	11.0
100	25.1	7,349	36.1 (@ 388 hours)	27.7

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C.3.2.15. *Shi et al. (2007) Gestational Portion*

Type:	Rat	**Dose:**	1, 5, 50 and 200 ng/kg
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	BW not specified (BW set to 190g)*	**Regime:**	Single dose on GD14 and GD21
Sex:	Female	**Simulation time:**	504 hours

[a]Derelanko and Hollinger (1995).

BLOOD CONCENTRATIONS (ng/kg) (Serum lipid adjusted) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
0.143	17.9	9,014	173 (@ 480 hours)	74.7
0.714	81.1	40,871	840 (@ 480 hours)	329
7.14	621	312,880	8,016 (@ 480 hours)	2,310
28.6	1,975	995,020	31,730 (@ 312 hours)	6,960
LIVER CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
0.143	1.16	583	8.44 (@ 484 hours)	5.63
0.714	6.87	3,462	46.8 (@ 485 hours)	35.2
7.14	96.9	48,840	576 (@ 486 hours)	499
28.6	465	234,480	2,581 (@ 487 hours)	2,328
FAT CONCENTRATIONS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
0.143	1.31	662	5.66 (@ 504 hours)	5.66
0.714	6.02	3,032	25.2 (@ 504 hours)	25.2
7.14	46.9	23,608	188 (@ 504 hours)	188
28.6	150	75,504	591 (@ 504 hours)	591

BODY BURDEN (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
0.143	0.229	116	1.08 (@ 487 hours)	1.07
0.714	1.12	565	5.32 (@ 487 hours)	5.23
7.14	10.7	5,389	50.8 (@ 487 hours)	49.4
28.6	41.3	20,788	196 (@ 487 hours)	190
FETUS (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
0.143	0.103	52.0	0.430 (@ 343 hours)	0.151
0.714	0.470	237	1.91 (@ 344 hours)	0.681
7.14	3.53	1,781	13.8 (@ 345 hours)	5.04
28.6	10.6	5,354	41.0 (@ 345 hours)	15.1
BOUND LIVER (ng/kg) and AUC ((ng/kg) • hr)				
Dose (ng/kg-day) Adjusted dose	**Metric**			
	Time-weighted Ave	**Area Under the Curve**	**Max**	**Terminal**
0.143	0.0780	39.3	0.566 (@ 483 hours)	0.341
0.714	0.348	175	2.31 (@ 483 hours)	1.49
7.14	2.44	1,231	16.0 (@ 314 hours)	9.67
28.6	6.67	3,360	40.8 (@ 313 hours)	24.8

C.3.2.16. *Shi et al. (2007) Adult Portion*

Type:	Rat	**Dose:**	1, 5, 50 and 200 ng/kg
Strain:	Sprague Dawley	**Route:**	Oral gavage
Body weight:	BW set to 4.5 g	**Regime:**	Weekly doses for 11 months
Sex:	Female	**Simulation time:**	8040 hours

BLOOD CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.143	Emond	188	262 (@ 7,561 hours)	210
	CADM	-	-	-
0.714	Emond	592	844 (@ 7,560 hours)	603
	CADM	-	-	-
7.14	Emond	2,882	5,023 (@ 7,560 hours)	2,679
	CADM	-	-	-
28.6	Emond	7,665	16,103 (@ 7,560 hours)	6,825
	CADM	-	-	-
LIVER CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.143	Emond	26.1	36.5 (@ 7,564 hours)	29.6
	CADM	-	-	-
0.714	Emond	118	159 (@ 7,564 hours)	120
	CADM	-	-	-
7.14	Emond	1,068	1,415 (@ 7,565 hours)	970
	CADM	-	-	-
28.6	Emond	4,119	5,450 (@ 7,565 hours)	3,574
	CADM	-	-	-
FAT CONCENTRATIONS (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.143	Emond	32.5	40.0 (@ 7,583 hours)	36.7
	CADM	-	-	-
0.714	Emond	102	120 (@ 7,584 hours)	106
	CADM	-	-	-
7.14	Emond	497	571 (@ 7,584 hours)	475
	CADM	-	-	-
28.6	Emond	1,322	1,527 (@ 7,584 hours)	1,217
	CADM	-	-	-

BODY BURDEN (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.143	Emond	3.94	4.99 (@ 7,566 hours)	4.45
	CADM	-	-	-
0.714	Emond	14.0	17.2 (@ 7,566 hours)	14.5
	CADM	-	-	-
7.14	Emond	90.8	112 (@ 7,566 hours)	84.4
	CADM	-	-	-
28.6	Emond	300	374 (@ 7,566 hours)	266
	CADM	-	-	-
BOUND LIVER (ng/kg)				
Dose (ng/kg-day) Adjusted dose	**Model**	**Metric**		
		Time-weighted Ave	**Max**	**Terminal**
0.143	Emond	1.18	1.60 (@ 7,563 hours)	1.31
	CADM	-	-	-
0.714	Emond	3.62	4.75 (@ 7,563 hours)	3.70
	CADM	-	-	-
7.14	Emond	15.6	19.7 (@ 7,564 hours)	14.7
	CADM	-	-	-
28.6	Emond	33.5	40.7 (@ 7,564 hours)	31.2
	CADM	-	-	-

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Table C-1. Model input parameters potentially addressed by selected articles

Articles	Model input parameters potentially addressed										
	Absorption	Desorption	Distribution	Elimination	Kinetics	Induction CYP1A1	Interspecies differences	Age Differences	Aryl hydrocarbon receptor (AhR)	Mode of action	Partition coefficient
Aylward et al., 2004	●	●	●	●	●						
Aylward et al., 2005	●	●	●	●	●						
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	●		●	●							
Millbrath 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., 2009						●					

[a]Partition coefficient estimates and CYP parameter value estimates were derived from Wang et al. (1997, 2000) and Santostefano et al. (1998).

C.4. REFERENCES

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APPENDIX D

Epidemiological Kinetic Modeling

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 D. EPIDEMIOLOGICAL KINETIC MODELING

D.1. BACCARELLI ET AL. (2008) MODELING

D.1.1. Input File for Exposure During Pregnancy

```
CINT = 1   %168 %100              %integration time
  %Exposure scenario
EXP_TIME_ON      = 0         % delay before begin exposure (HOUR)
EXP_TIME_OFF     = 401190    %TIME EXPOSURE STOP (HOUR)
DAY_CYCLE        = 24        %TIME
BCK_TIME_ON      = 401190    %DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF     = 401190    %TIME OF BACKGROUND EXP STOP (HOUR)
IV_LACK          = 401190
IV_PERIOD        = 401190
  %GESTATION CONTROL
MATTING          = 262800    % BEGINNING MATTING (HOUR)at 30 years old
TIMELIMIT        = 269184    %SIMULATION LIMIT TIME (HOUR)
TRANSTIME_ON     = 264312    % EXCHANGE MOTHER FETUS 1512 HOUR POST
MATTING
  %Exposure dose
MSTOT            = 0.021     % ng of TCDD /kg of BW
MSTOTBCKGR       = 0.   %0.1     % ORAL BACKGROUND EXPOSURE DOSE (nG/KG)
DOSEIV           = 0.   %10
DOSEIVLATE       = 0.   %10

   % TRANFER MOTHER TO FETUS CLEARANCE
CLPLA_FET        = 0.001 % MOTHER TO FETUS TRANFERT CLEARANCE(L/HR)
```

D.1.2. Table of Results for Baccarelli et al. (2008)

Table D-1. Estimated continuous intake corresponding to maternal serum concentration in Figure 2A

Variable	Value	Notes
Infant b-TSH	5 uU/mL	BMR
Maternal lipid adjusted serum	270 ng/kg	From Figure 2A
Intake	0.024 ng/kg-day	From Emond model, pregnancy at 30 years

Table D-2. Estimated maximum intake corresponding to maternal serum concentration in Figure 2A

Variable	Value	Notes
Infant b-TSH	--	--
Maternal lipid adjusted serum	309.5 ng/kg	Maximum from Figure 2A
Intake	0.030 ng/kg-day	From Emond model, pregnancy at 30 years

D.2. MOCARELLI ET AL. (2008) MODELING

D.2.1. Input File for Exposure for Pulse to Measurement 0.5 Years After the Seveso Pulse Dose

```
CINT = 1. %
EXP_TIME_ON  = 54312.      % Delay before begin exposure (HOUR) 6.2 years
EXP_TIME_OFF = 54335.    %324120     % HOUR/YEAR !TIME EXPOSURE STOP
(HOUR) 6.2 years + 23 hours
DAY_CYCLE    = 24.       % TIME
BCK_TIME_ON  = 0.        % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200    % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 58692.    % half a year (July 1976 until January 1977) past 6.2 years
MSTOTBCKGR   = 3.7E-4     % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 232.4   % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV       =   0         % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID    = 731       % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1         % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 1.
FEMALE = 0.
Y0 = 0.              % 0 years old at the beginning of the simulation
```

D.2.2. Input File for Exposure from Pulse to the End of the Critical Window 3.8 Years After the Seveso Pulse Dose

```
CINT = 1. %
EXP_TIME_ON  = 54312.      % Delay before begin exposure (HOUR) 6.2 years
EXP_TIME_OFF = 54335.    %324120     % HOUR/YEAR !TIME EXPOSURE STOP
(HOUR) 6.2 years + 23 hours
DAY_CYCLE    = 24.       % TIME
```

```
BCK_TIME_ON  = 0.       % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200.    % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 87600.     % 10 years
MSTOTBCKGR   = 3.7e-4      % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT       = 232.5    % Serveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV      =   0         % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID    = 730       % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1         % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 1.
FEMALE = 0.
Y0 = 0.              % 0 years old at the beginning of the simulation
```

D.2.3. Input File for Continuous Exposure for 10 Years

```
CINT = 1. %
EXP_TIME_ON  = 0.       % Delay before begin exposure (HOUR)
EXP_TIME_OFF = 87600.     % HOUR/YEAR !TIME EXPOSURE STOP (HOUR)
DAY_CYCLE    = 24.        % TIME
BCK_TIME_ON  = 0.       %324120     % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200     %324120     % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 87600.     % 10 years
MSTOTBCKGR   = 0. %3.35E-4      % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT       = 3.903   % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV      =   0         % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID    = 730       % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1         % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 1.
FEMALE = 0.
Y0 = 0.              % 0 years old at the beginning of the simulation
```

D.2.4. Tables of Results for Mocarelli et al. (2008)

Table D-3. Matching critical window average after pulse to critical window average for continuous intake run

Person modeled, beginning at age 0	Lipid adjusted serum (1976) ng/kg from Figure 3E	Pulse dose, 0.5 year lag time (ng/kg)	Average lipid adjusted serum 3.8 years after incident (ng/kg)	Continuous intake for 10 years (ng/kg-day)
Boy, 1st quartile	68	8.135	57.72	0.008024
Boy, 4th quartile	733	232.5	580.5	0.2128

Table D-4. Matching critical window peak after pulse to peak critical window concentration for continuous intake run

Person modeled, beginning at age 0	Lipid adjusted serum (1976) ng/kg from Figure 3E	Pulse dose, 0.5 year lag time (ng/kg)	Peak lipid adjusted serum after incident (ng/kg)	Continuous intake for 10 years (ng/kg-day)
Boy, 1st quartile	68	8.135	248.0	0.03194
Boy, 4th quartile	733	232.5	6674	3.904

D.3. ALALUUSUA ET AL. (2004) MODELING

D.3.1. Input File for Exposure for Pulse to Measurement 0.5 Years After the Seveso Pulse Dose

```
CINT = 1. %
EXP_TIME_ON  = 21900.    % Delay before begin exposure (HOUR) 2.5 years
EXP_TIME_OFF = 21923.    % 21900+23     % HOUR/YEAR !TIME EXPOSURE STOP
(HOUR) 2.5 years and 23 hours
DAY_CYCLE    = 24.       % TIME
BCK_TIME_ON  = 0.        % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200.   % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 26280.    % half a year (July 1976 until January 1977) past 2.5 years
MSTOTBCKGR   = 3.7e-4    % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 24.22    % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV       =  0         % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose
```

```
MEANLIPID    = 730       % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1         % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 1.
FEMALE = 0.
Y0 = 0.              % 0 years old at the beginning of the simulation
```

D.3.2. Input File for Exposure from Pulse to the End of the Critical Window 2.5 Years After the Seveso Pulse Dose

```
CINT = 1. %
EXP_TIME_ON  = 21900.    % Delay before begin exposure (HOUR) 2.5 years
EXP_TIME_OFF = 21923.    % 324120     % HOUR/YEAR !TIME EXPOSURE STOP
(HOUR) 2.5 years and 23 hours
DAY_CYCLE    = 24.       % TIME
BCK_TIME_ON  = 0.        % 324120     % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200.   % 324120     % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 43800.    % 5 years
MSTOTBCKGR   = 3.7e-4    % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 24.22   % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV       =   0         % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID    = 730       % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1         % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 1.
FEMALE = 0.
Y0 = 0.              % 0 years old at the beginning of the simulation
```

D.3.3. Input File for Continuous Exposure for 5 Years

```
CINT = 1. %
EXP_TIME_ON  = 0.       % Delay before begin exposure (HOUR)
EXP_TIME_OFF = 43800.   % 324120     % HOUR/YEAR !TIME EXPOSURE STOP (HOUR)
DAY_CYCLE    = 24.      % TIME
BCK_TIME_ON  = 0.       % 324120     % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200.  % 324120     % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 43800.   % End of critical window (5 years)
MSTOTBCKGR   = 0.       % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 0.03486    % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
```

```
DOSEIV      =  0         % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID   = 730       % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1         % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 1.
FEMALE = 0.
Y0 = 0.              % 0 years old at the beginning of the simulation
```

D.3.4. Tables of Results for Alaluusua et al. (2004)

Table D-5. Matching critical window average after pulse to critical window average for continuous intake run

Person modeled, beginning at age 0	Lipid adjusted serum (1976) ng/kg estimated from tertile bins[a]	Pulse dose, 0.5 year lag time (ng/kg)	Average lipid adjusted serum 2.5 years after incident (ng/kg)	Continuous intake for 5 years (ng/kg-day)
Boy, 1st tertile	130	24.22	110.8	0.03486
Boy, 2nd tertile	383	108.9	322.7	0.1578
Boy, 3rd tertile	1830	1041	1538	1.511
Girl, 1st tertile	130	23.03	110.8	0.03211
Girl, 2nd tertile	383	105.3	324.4	0.1481
Girl, 3rd tertile	1830	1015	1546	1.427
Boy and girl, averaged, 1st tertile	130	-	-	0.03349
Boy and girl, averaged, 2nd tertile	383	-	-	0.1530
Boy and girl, averaged, 3rd tertile	1830	-	-	1.469

[a]Mean of tertile bin assuming a lognormal distribution of serum concentrations.

Table D-6. Matching critical window peak after pulse to peak critical window concentration for continuous intake run

Person modeled, beginning at age 0	Lipid adjusted serum (1976) ng/kg estimated from tertile bins	Pulse dose, 0.5 year lag time (ng/kg)	Peak lipid adjusted serum after incident (ng/kg)	Continuous intake for 5 years (ng/kg-day)
Boy, 1st tertile	130	24.22	618.8	0.2113
Boy, 2nd tertile	383	108.9	2700	1.783
Boy, 3rd tertile	1830	1041	24706	31.35
Girl, 1st tertile	130	23.02	588.0	0.1882
Girl, 2nd tertile	383	105.3	2610	1.642
Girl, 3rd tertile	1830	1015	24113	29.52
Boy and girl, averaged, 1st tertile	130	-	-	0.1998
Boy and girl, averaged, 2nd tertile	383	-	-	1.713
Boy and girl, averaged, 3rd tertile	1830	-	-	30.44

[a]Mean of tertile bin assuming a lognormal distribution of serum concentrations.

D.4. ESKANAZI ET AL. (2002) MODELING

D.4.1. Input File for Exposure for Pulse to Measurement 0.5 Years After the Seveso Pulse Dose

```
CINT = 1. %
EXP_TIME_ON  = 58692.       % Delay before begin exposure (HOUR) 6.7 years
EXP_TIME_OFF = 58715.     % HOUR/YEAR !TIME EXPOSURE STOP (HOUR) 6.7 years +
23 hours
DAY_CYCLE    = 24.        % TIME
BCK_TIME_ON  = 0.         %324120     % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200.    %324120     % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 63072.     % half a year (July 1976 until January 1977) past 6.7 years
MSTOTBCKGR   = 3.7e-4     % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 7193   % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV       =   0        % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID    = 730        % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
```

```
PAS_INDUC= 1        % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 0.
FEMALE = 1.
Y0 = 0.             % 0 years old at the beginning of the simulation
```

D.4.2. Input File for Exposure from Pulse to the End of the Critical Window 6.7 Years After the Seveso Pulse Dose

```
CINT = 1. %
EXP_TIME_ON  = 58692.      % Delay before begin exposure (HOUR) 6.7 years
EXP_TIME_OFF = 58715.    %324120    % HOUR/YEAR !TIME EXPOSURE STOP
(HOUR) 6.7 years + 23 hours
DAY_CYCLE    = 24.       % TIME
BCK_TIME_ON  = 0.        %324120    % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200    %324120    % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 113880.   % 13 years
MSTOTBCKGR   = 3.7e-4    % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 7193    % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
DOSEIV       =   0        % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID    = 730       % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1        % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 0.
FEMALE = 1.
Y0 = 0.             % 0 years old at the beginning of the simulation
```

D.4.3. Input File for Continuous Exposure for 13 Years

```
CINT = 1. %
EXP_TIME_ON  = 0.      % Delay before begin exposure (HOUR)
EXP_TIME_OFF = 113880.    %324120    % HOUR/YEAR !TIME EXPOSURE STOP
(HOUR) 13 years
DAY_CYCLE    = 24.       % TIME
BCK_TIME_ON  = 0.        %324120    % DELAY BEFORE BACKGROUND EXP (HOUR)
BCK_TIME_OFF = 613200.    %324120    % TIME OF BACKGROUND EXP STOP (HOUR)
TIMELIMIT    = 113880.   % 13 years
MSTOTBCKGR   = 0. %3.35E-4      % ORAL BACKGROUND EXPOSURE DOSE (UG/KG)

% oral dose oral dose oral dose
MSTOT        = 166   % Seveso, ORAL DAILY EXPOSURE DOSE (NG/KG)
```

```
DOSEIV      =  0         % 40  %50 %5 %0.5 %0.3 %0.2 %0.1%0.05%0.3 %NG/KG
% oral dose oral dose oral dose

MEANLIPID   = 730       % 711 %664 %778 %468 %671 %730 %662 %592%615%730%
PAS_INDUC= 1         % NON INDUCTION (0) CONTROLE DE L'INDUCTION

%human variable parameter
MALE = 0.
FEMALE = 1.
Y0 = 0.              % 0 years old at the beginning of the simulation
```

D.4.4. Tables of Results for Eskanazi et al. (2002)

Table D-7. Matching critical window average after pulse to critical window average for continuous intake run

Person modeled, beginning at age 0	Lipid adjusted serum (adjusted to 1976-1977 levels) ng/kg from Figure 1A	Pulse dose, 0.5 year lag time (ng/kg)	Average lipid adjusted serum 6.7 years after incident (ng/kg)	Continuous intake for 13 years (ng/kg-day)
Girl, estrous cycle 28.5 days	166	28.40	114.0	0.01660
Girl, estrous cycle 29 days	693	215.5	455.1	0.1224
Girl, estrous cycle 29.5 days	2020	1008	1295	0.5693
Girl, estrous cycle 30 days	8450	7193	5179	4.054

Table D-8. Matching critical window peak after pulse to peak critical window concentration for continuous intake run

Person modeled, beginning at age 0	Lipid adjusted serum (adjusted to 1976-1977 levels) ng/kg from Figure 1A	Pulse dose, 0.5 year lag time (ng/kg)	Peak lipid adjusted serum after incident (ng/kg)	Continuous intake for 13 years (ng/kg-day)
Girl, estrous cycle 28.5 days	166	28.40	838.2	0.1800
Girl, estrous cycle 29 days	693	215.5	6183	3.148
Girl, estrous cycle 29.5 days	2020	1008	28316	20.86
Girl, estrous cycle 30 days	8450	7193	198240	166.6

D.5. REFERENCES

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APPENDIX E

Noncancer Benchmark Dose Modeling

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 E. NONCANCER BENCHMARK DOSE MODELING

E.1. BMDS INPUT TABLES

E.1.1. Amin et al. (2000)

Endpoint	Administered Dose (ng/kg-day)		
	0	25 [a]	100
	Internal Dose (ng/kg blood) [b]		
	0	6,800	24,522
	(n = 10)	(n = 10)	(n = 10)
Saccharin consumed, female (0.25%)	31.67 ± 26.64	24.60 ± 11.98	10.70 ± 5.33
Saccharin consumed, female (0.50%)	22.40 ± 15.98	11.38 ± 7.66	4.54 ± 3.33
Saccharin preference ratio, female (0.25%)	82.14 ± 13.35	58.12 ± 33.88	54.87 ± 19.51
Saccharin preference ratio, female (0.50%)	72.73 ± 24.64	44.48 ± 32.85	33.77 ± 24.64

[a] LOAEL.
[b] From the Emond PRPK model described in 3.3.

E.1.2. Bell et al. (2007a)

Endpoint	Administered Dose (ng/kg-day)			
	0	2.4 [a]	8	46
	Internal Dose (ng/kg blood) [b]			
	0	1,998	4,539	15,952
	(n = 30)	(n = 30)	(n = 30)	(n = 30)
Balano-preputial separation, male pups	1/30 (3%)	5/30 (17%)	6/30 (20%)	15/30 (50%)

[a] LOAEL.
[b] From the Emond PRPK model described in 3.3.

E.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	1,018	4,868	27,559
	(n = 4)	(n = 4)	(n = 3)	(n = 3)
Urinary coporphyrins	0.74 ± 0.35	1.81 ± 0.83 [c]	2.73 ± 1.50 [d]	3.00 ± 2.60 [d]
Urinary porphyrins	2.27 ± 0.49	5.55 ± 0.85 [c]	7.62 ± 1.79 [c]	196.89 ± 63.14 [d]

[a] LOAEL
[b] From the Emond PRPK model described in 3.3.
[c] Statistically significant as compared to control ($p < 0.05$).
[d] Statistically significant as compared to control ($p < 0.01$).

E.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	11.3	273	773	1,922	51,11	12,624	35,697	98,088	316,540
	(n = 14)	(n = 6)	(n = 12)	(n = 6)	(n = 6)	(n = 6)	(n = 6)	(n = 6)	(n = 6)	(n = 4)
Serum T4	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 ± 11.17

[a] NOAEL
[b] LOAEL
[c] From the Emond PRPK model described in 3.3.

E.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]				
	n/a	n/a	n/a	n/a	n/a
	(n = 10)	(n = 10)	(n = 11)	(n = 10)	(n = 4)
Absolute kidney weight, males	5.49 ± 0.54	5.14 ± 0.38	4.71 ± 0.4	4.3±0.47[d]	-
Absolute thymus weight, males	0.56 ± 0.16	0.45 ± 0.07	0.44 ± 0.11	0.35±0.53[e]	-
Body weight, males	713 ± 47.43	682 ± 50.6	651 ± 63.02	603±63.25[d]	433 ± 76 [f]
Relative brain weight, males	0.54 ± 0.05	0.56 ± 0.05	0.6 ± 0.05	0.65±0.05[d]	-
Relative liver weight, males	4.54 ± 0.73	4.1 ± 0.44	5.36 ± 2.02	5.63±0.92[d]	-
Relative thymus weight, males	0.08 ± 0.02	0.07 ± 0.01	0.07 ± 0.01	0.06±0.01[d]	-
Endpoint	**Administered Dose (ng/kg-day)**				
	0	**0.12**	**0.68**	**4.86**	**31**
	Internal Dose (ng/kg blood) [c]				
	0	**n/a**	**n/a**	**n/a**	**n/a**
	(n = 8)	**(n = 10)**	**(n = 9)**	**(n = 10)**	**(n = 4)**
Body weight, females	602 ± 33.94	583 ± 69.57	570 ± 66	531 ± 44.27 [d]	351 ± 98 [f]
Relative liver weight, females	4.3 ± 0.74	4.49 ± 1.11	4.27 ± 0.48	5.54 ± 1.36 [d]	4.3 ± 0.74

[a] NOAEL
[b] LOAEL.
[c] Internal dose not calculated using the Emond PBPK (ginuea pigs).
[d] Statistically significant as compared to control ($p < 0.05$).
[e] Statistically significant as compared to control ($p < 0.01$).
[f] Statistically significant as compared to control ($p < 0.001$).

E.1.6. Hojo et al. (2002)

Endpoint	Administered Dose (ng/kg-day)			
	0	20 [a]	60	180
	Internal Dose (ng/kg blood) [b]			
	0	1,285	3,295	8,465
	(n = 5)	(n = 5)	(n = 6)	(n = 5)
DRL reinforce per min	0.09 ± 0.45	0.54 ± 0.82	1.27 ± 0.54	0.74 ± 0.44
DRL response per min	18.46 ± 7.99	-0.99 ± 10.96	-4.52 ± 7.19	-0.41 ± 15.23

[a] LOAEL.
[b] From the Emond PRPK model described in 3.3.

E.1.7. Kattainen et al. (2001)

Endpoint	Administered Dose (ng/kg-day)				
	0	30 [a]	100	300	1,000
	Internal Dose (ng/kg blood) [b]				
	0	1,763	4,944	12,712	37,039
	(n = 16)	(n = 17)	(n = 15)	(n = 12)	(n = 19)
3rd molar mesio-distal length (molar development)	1.86 ± 0.07	1.58 ± 0.19 [c]	1.6 ± 0.27 [c]	1.5 ± 0.22 [c]	1.35 ± 0.51 [c]
Females 3rd molar eruption	1/16 (10%)	3/17 (20%)	4/15 (30%)	6/12 (50%) [c]	13/19 (70%) [c]

[a] LOAEL.
[b] From the Emond PRPK model described in 3.3.
[c] Statistically significant as compared to control ($p < 0.05$).

E.1.8. Keller et al. (2007, 2008a, b)

Endpoint	Administered Dose (ng/kg-day)			
	0	10 [a]	100	1,000
	Internal Dose (ng/kg blood) [b]			
	0	296	2,365	18,764
Missing mandibular molars in CBA J mice	0/29 (0%)	2/23 (10%)	6/29 (20%)	30/30 (100%)

[a] LOAEL.
[b] From the Emond PRPK model described in 3.3.

E.1.9. Kociba et al. (1978)

Endpoint	Administered Dose (ng/kg-day)			
	0	1 [a]	10 [b]	100
	Internal Dose (ng/kg blood) [c]			
	0	853	3,942	21,246
	(n = 5)	(n = 5)	(n = 5)	(n = 5)
Urinary coproporphyrin, females	9.8 ± 1.3	8.6 ± 2	16.4 ± 4.7 [d]	17.4 ± 4 [d]
Uroporphyrin per creatinine, females	0.157 ± 0.05	0.143 ± 0.04	0.181 ± 0.05	0.296 ± 0.07[d]

[a] NOAEL
[b] LOAEL.
[c] From the Emond PRPK model described in 3.3.
[d] Statistically significant as compared to control ($p < 0.05$).

E.1.10. Latchoumycandane and Mathur (2002)

Endpoint	Administered Dose (ng/kg-day)			
	0	1 [a]	10	100
	Internal Dose (ng/kg blood) [b]			
	0	437	2,579	15,092
	(n = 6)	(n = 6)	(n = 6)	(n = 6)
Daily sperm production	22.19 ± 2.67	15.67 ± 2.65 [c]	13.65 ± 2.19 [c]	13.1 ± 3.16 [c]

[a] LOAEL.
[b] From the Emond PRPK model described in 3.3.
[c] Statistically significant as compared to control ($p < 0.05$).

E.1.11. 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	147	440	1,156	3,232	8,266	23,875	66,081	212,650	649,740
	(n = 10)	(n =10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)
FSH	23.86 ± 29.65	22.16 ± 48.51	85.23 ± 94.33	73.30 ± 48.51	126.14 ± 159.01	132.10 ± 115.89	116.76 ± 51.21	304.26 ± 153.62	346.88 ± 150.93	455.11 ± 285.68

[a] NOAEL
[b] LOAEL.
[c] From the Emond PRPK model described in 3.3.

E.1.12. Li et al. (2006)

Endpoint	Administered Dose (ng/kg-day)			
	0	2 [a]	50	100
	Internal Dose (ng/kg blood) [b]			
	0	87.5	1,564	2,823
	(n = 10)	(n = 10)	(n = 10)	(n = 10)
Serum estradiol	10. ± 12.48	20 ± 19.97	24.74 ± 15.00	17.90 ± 18.31

Serum progesterone	65.25 ± 11.10	43.36 ± 40.48 [c]	27.46 ± 33.30	25.19 ± 43.756

[a] LOAEL.
[b] From the Emond PRPK model described in 3.3.
[c] Statistically significant as compared to control ($p < 0.01$).

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3 **E.1.13. Markowski et al. (2001)**

	Administered Dose (ng/kg-day)			
	0	**20 [a]**	**60**	**180**
	Internal Dose (ng/kg blood) [b]			
	0	**1,234**	**3,184**	**8,152**
Endpoint	**(n = 7)**	**(n = 4)**	**(n = 6)**	**(n = 7)**
FR10 run opp	13.29 ± 8.65	11.25 ± 5.56	5.75 ± 3.53	7 ± 6.01
FR2 revolutions	119.29 ± 69.9	108.5 ± 61	56.5 ± 31.21	68.14 ± 33.23
FR5 run opp	26.14 ± 12.28	23.5 ± 7.04	12.8 ± 6.17	13.14 ± 7.14

[a] LOAEL.
[b] From the Emond PRPK model described in 3.3.

4 **E.1.14. Mietinnin et al. (2006)**

	Administered Dose (ng/kg-day)				
	0	**30 [a]**	**100**	**300**	**1,000**
	Internal Dose (ng/kg blood) [b]				
	0	**1,756**	**4,922**	**12,657**	**36,874**
Endpoint	**(n = 42)**	**(n = 29)**	**(n = 15)**	**(n = 24)**	**(n = 32)**
Cariogenic lesions in pups	25/42 (60%)	23/29 (79%) [b]	19/25 (76%)	20/24 (83%) [c]	29/32 (91%) [c]

[a] LOAEL.
[b] From the Emond PRPK model described in 3.3.
[c] Statistically significant as compared to control ($p < 0.05$).

5

E.1.15. 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	420	1,240	6,118
	(n = 73)	(n = 49)	(n = 49)	(n = 50)
Toxic hepatitis, male mice	1/73 (1.4%)	5/49 (10%)	5/49 (6.1%)	44/50 (88%)

[a] LOAEL.
[b] From the Emond PRPK model described in 3.3.

E.1.16. National Toxicology Program (2006)

Endpoint	Administered Dose (ng/kg-day)					
	0	2.14 [a]	7.14	15.7	32.9	71.4
	Internal Dose (ng/kg blood) [b]					
	0	1,408	3,137	5,393	9,128	16,361
	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)
Alveolar metaplasia	2/53 (0%)	19/54 (40%)[c,]	33/53 (60%)[c]	35/52 (70%)[c]	45/53 (80%)[c]	46/52 (90%)[c]
Gingival hyperplasia squamous, 2 years	1/53 (2%)	7/54 (13%)[d]	14/53 (26%)[c]	13/53 (25%)[c]	15/53 (28%)[c]	16/53 (30%)[c]
Liver, hepatocyte hypertrophy, 2 years	0/53 (0%)	19/54 (40%)[c,]	19/53 (40%)[c]	42/53 (80%)[c]	41/53 (80%)[c]	52/53 (100%)[c]
Heart, cardiomyopathy	10/53 (19%)	12/54 (22%)	22/53[c] (42%)	25/52[c] (48%)	32/53[c] (60%)	36/52[c] (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[c] (23%)	17/53[c] (32%)	30/53[c] (57%)	48/53[c] (91%)
Liver, necrosis	1/53 (2%)	4/54 (7%)	4/53 (8%)	8/53[d] (15%)	10/53[c] (19%)	17/53[c] (32%)
Liver, pigmentation	4/53	9/54	34/53[c]	48/53[c]	52/53[c]	53/53[c]

Endpoint	Administered Dose (ng/kg-day)					
	0	2.14 [a]	7.14	15.7	32.9	71.4
	Internal Dose (ng/kg blood) [b]					
	0	1,408	3,137	5,393	9,128	16,361
	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)	(n = 10)
	(8%)	(17%)	(64%)	(91%)	(98%)	(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, 2 years	0/53 (0%)	4/54 (10%)[d]	3/53 (10%)	20/53 (40%)[c]	38/53 (70%)[d]	53/53 (100%)[c]
Lung, alveolar to bronchiolar epithelial metaplasia (Alveolar epithelium, metaplasia, bronchiolar)	2/53 (4%)	19/54 [c] (35%)	33/53[c] (62%)	35/52[c] (67%)	45/53[c] (85%)	46/52[c] (89%)

[a] LOAEL.
[b] From the Emond PRPK model described in 3.3.
[c] Statistically significant as compared to control ($p < 0.01$).
[d] Statistically significant as compared to control ($p < 0.05$).

E.1.17. Ohsako et al. (2001)

Endpoint	Administered Dose (ng/kg-day)				
	0	12.5 [a]	50 [b]	200	800
	Internal Dose (ng/kg blood) [c]				
	0	845	2,763	9,022	30,504
	(n = 12)	(n = 10)	(n = 10)	(n = 10)	(n = 12)
Anogenital PND120	28.91 ± 3.54	28.08 ± 2.52	25.31 ± 3.59 [d]	26.07 ± 3.59 [e]	23.87 ± 2.36 [d]

[a] NOAEL for selected endpoint.
[b] LOAEL for selected endpoint.
[c] From the Emond PRPK model described in 3.3.
[d] Statistically significant as compared to control ($p < 0.01$).
[e] Statistically significant as compared to control ($p < 0.05$).

E.1.18. Schantz et al. (1996)

Endpoint	Administered Dose (ng/kg-day)		
	0	25	100
	Internal Dose (ng/kg blood) [a]		
	0	6,800	24,522
	(n = 10)	(n = 10)	(n = 10)
Maze errors per block	3.55 ± 0.64	2.76 ± 0.81 [b]	2.34 ± 0.81 [c]

[a] From the Emond PRPK model described in 3.3.
[b] Statistically significant as compared to control ($p < 0.05$).
[c] Statistically significant as compared to control ($p < 0.001$).

E.1.19. 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	**188**	**592**	**2,882**	**7,665**
	(n = 10)	**(n = 10)**	**(n = 10)**	**(n = 10)**	**(n = 10)**
Serum estradiol	102.86 ± 41.41	86.19 ± 19.58	63.33 ± 29.36 [d]	48.1 ± 18.82 [d]	38.57 ± 22.59 [d]

[a] NOAEL.
[b] LOAEL.
[c] From the Emond PRPK model described in 3.3.
[d] Statistically significant as compared to control ($p < 0.05$).

E.1.20. 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	**241**	**1,358**	**7,385**	**17,438**
	(n = 15)	**(n = 14)**	**(n = 15)**	**(n = 15)**	**(n = 8)**
PFC per 10^6 Cells	1491 ± 716	1129±171 [c]	945 ± 516 [c]	677 ± 465 [c]	161 ± 117 [c]
PFC per spleen	27.8 ± 13.4	21 ± 13.6 [c]	17.6 ± 9.4 [c]	12.6 ± 8.7 [c]	3 ± 3.1 [c]

[a] LOAEL.
[b] From the Emond PRPK model described in 3.3.
[c] Statistically significant as compared to control ($p < 0.05$).

E.1.21. Toth et al. (1979)

Endpoint	Administered Dose (ng/kg-day)			
	0	1 [a]	100	1,000
	Internal Dose (ng/kg blood) [b]			
	0	316	7,814	50,105
	(n =38)	(n = 44)	(n = 44)	(n = 43)
Amyloidosis	0/38 (0%)	5/44 (11%)	10/44 (23%)	17/43 (40%)
Skin Lesions	0/38 (0%)	5/44 (11%)	13/44 (30%)	25/43 (58%)

[a] LOAEL.
[b] From the Emond PRPK model described in 3.3.

E.1.22. 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	3,969	6,479	9,968	47,606	137,820
	n = 8	n = 8	n = 8	n = 8	n = 8	n = 8
Hepatic retinol	14.9 ± 8.77	8.4 ± 3.39 [c]	8.2 ± 2.26 [c]	5.1 ± 0.85 [c]	2.2 ± 0.85 [c]	0.6 ± 0.57 [c]
Hepatic retinol palmitate	472 ± 271.53	94 ± 67.88 [c]	107 ± 76.37 [c]	74 ± 39.6 [c]	22 ± 22.63 [c]	3 ± 2.83 [c]
Plasma FT4	23.4 ± 3.11	24.5 ± 5.66	22.4 ± 2.83	19.3 ± 9.33	16.3 ± 4.24 [c]	10.3 ± 4.81 [c]
Plasma TT4	40.9 ± 6.79	41.4 ± 5.37	41.4 ± 6.51	32.3 ± 7.35 [c]	33.6 ± 6.22 [c]	25.5 ± 7.64 [c]

[a] LOAEL.
[b] From the Emond PRPK model described in 3.3.
[c] Statistically significant as compared to control ($p < 0.05$).

E.1.23. 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	602	2,250	3,934	14,772	26,844	49,896
	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)
CH50	91 ± 14.14	54 ± 8.5 [c]	63 ± 11[c]	56 ± 26 [c]	41 ± 17 [c]	32 ± 17 [c]	17 ± 17 [c]

[a] LOAEL.
[b] From the Emond PRPK model described in 3.3.
[c] Statistically significant as compared to control ($p < 0.05$).

E.2. ALTERNATE DOSE: BLOOD SERUM BMDS RESULTS

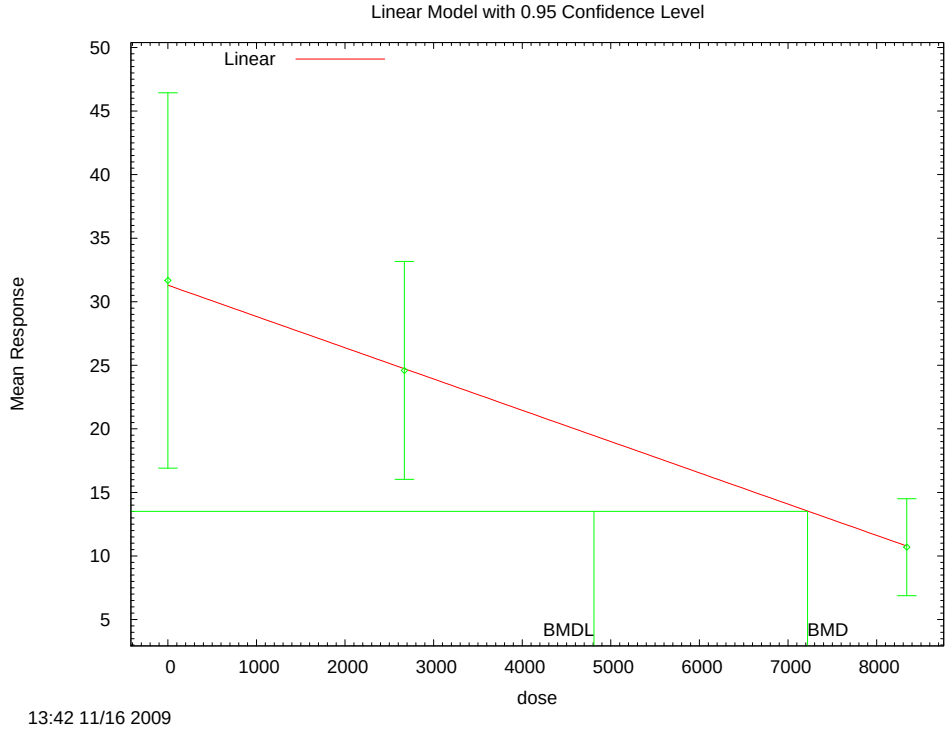
E.2.1. Amin et al. (2000): Saccharin Consumed, Female (0.25%)

E.2.1.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of freedom	Variance *p*-value [a]	χ^2 Test statistic	χ^2 *p*-value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
Linear [c]	**1**	**0.00**	**0.35**	**0.55**	**179.21**	**7.2E+03**	**4.8E+03**	**nonconstant variance**
Polynomial	1	0.00	0.35	0.55	179.21	7.2E+03	4.8E+03	nonconstant variance
Power	1	0.00	0.35	0.55	179.21	7.2E+03	4.8E+03	nonconstant variance, power restricted ≥1, bound hit
Power [d]	0	0.00	0.00	NA	180.86	6.6E+03	2.7E+03	nonconstant variance, power unrestricted
Linear	1	0.00	0.00	0.95	191.69	5.3E+03	3.5E+03	constant variance
Polynomial	1	0.00	0.00	0.95	191.69	5.3E+03	3.5E+03	constant variance
Power	1	0.00	0.00	0.95	191.69	5.3E+03	3.5E+03	constant variance, power restricted ≥1, bound hit
Power	0	0.00	0.00	NA	193.68	5.2E+03	1.3E+03	constant variance, power unrestricted

[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected.
[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix.
[d]Alternate model also presented in this appendix.

E.2.1.2. *Figure for Selected Model: Linear, Nonconstant Variance*



13:42 11/16 2009

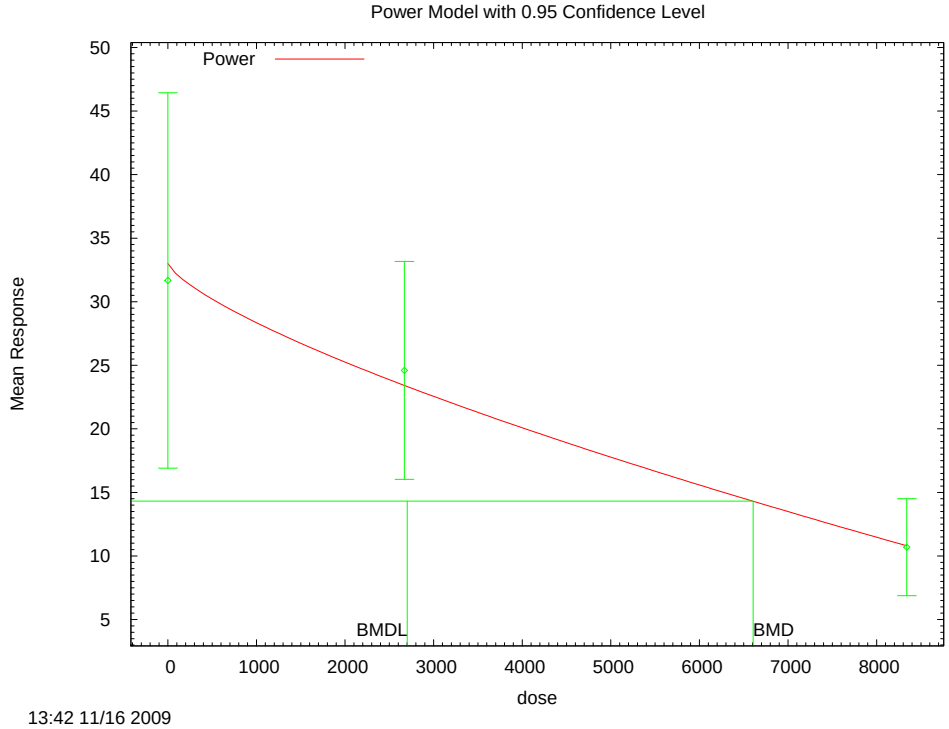
E.2.1.3. *Output File for Selected Model: Linear, Nonconstant Variance*

```
 ******************************************************************
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Linear_BMR1_25_s_c.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Linear_BMR1_25_s_c.plt
                                                Mon Nov 16 13:42:20 2009
 ******************************************************************

 Rel Male Thymus wt, Tbl 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
   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 =     31.5152
                      beta_1 =  -0.0025051


          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           -2.542          1.65042           -5.77677            0.692762
          rho          2.40977         0.541752            1.34795             3.47158
       beta_0          31.2702          4.19399            23.0501             39.4903
       beta_1      -0.00246009      0.000552567         -0.0035431        -0.00137708


    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         0.0717
 2670    10       24.6         24.7           12         13.4        -0.0253
 8341    10       10.7         10.8         5.33         4.91        -0.0363


 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         -85.605740           4     179.211479
                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             0.353184          1          0.5523

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 =        7219.69


             BMDL =        4809.97
```

E.2.1.4. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



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E.2.1.5. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Pwr_Unrest_BMR1_25_s_c.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Pwr_Unrest_BMR1_25_s_c.plt
                                                 Mon Nov 16 13:42:20 2009
 ========================================================================

 Rel Male Thymus wt, Tbl 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =      5.29482
                           rho =            0
                        control =      31.6727
                          slope =  -0.00381519
                          power =     0.953851


            Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho      control        slope        power

    lalpha             1        -0.99         0.34       -0.095       -0.061

       rho         -0.99            1        -0.42         0.11        0.068

   control          0.34        -0.42            1        -0.61        -0.56

     slope        -0.095         0.11        -0.61            1            1

     power        -0.061        0.068        -0.56            1            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             1.60692
            rho          2.38455         0.692047             1.02817             3.74094
        control            32.99          5.40753             22.3915             43.5886
          slope       -0.0286289        0.0946744            -0.214187            0.156929
          power         0.736753         0.351085           0.0486403             1.42487


     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
 2670    10       24.6         23.4           12         12.4          0.302
 8341    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 = 6606.37


            BMDL = 2702.55
```

E.2.2. Amin et al. (2000): Saccharin Consumed, Female (0.50%)

E.2.2.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
linear [c]	**1**	**<.0001**	**3.52**	**0.06**	**158.58**	**8.0E+03**	**5.2E+03**	**nonconstant variance**
polynomial	1	<.0001	3.52	0.06	158.58	8.0E+03	5.2E+03	nonconstant variance
power	1	<.0001	3.52	0.06	158.58	8.0E+03	5.2E+03	nonconstant variance, power restricted ≥1, bound hit
power [d]	0	<.0001	0.00	NA	157.06	5.2E+03	9.1E+02	nonconstant variance, power unrestricted

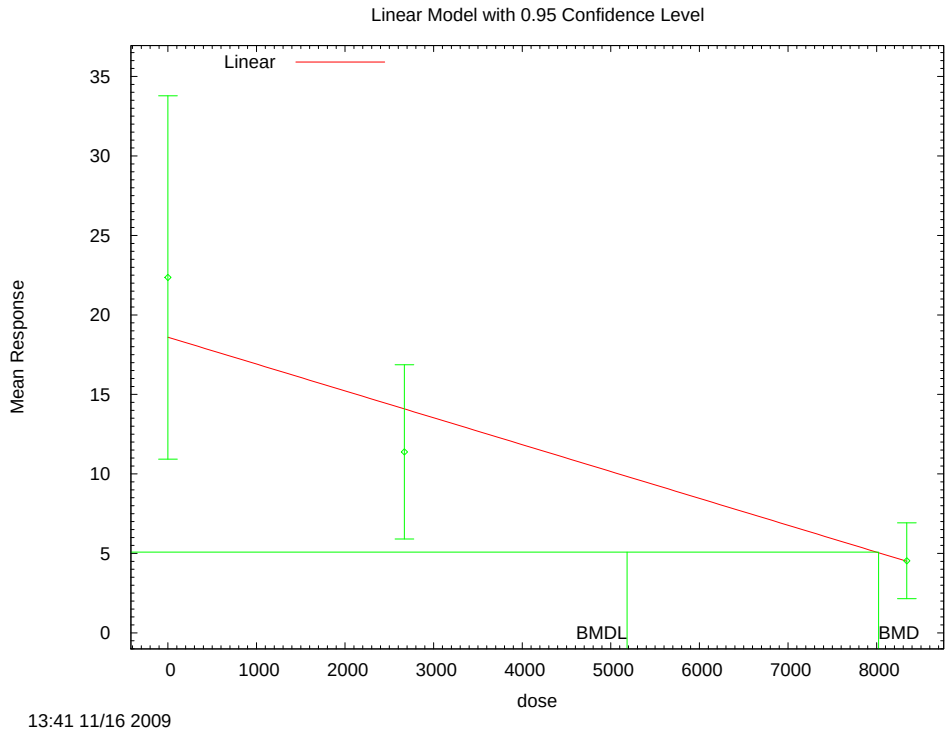
[a]Values <0.1 means nonconstant variance model should be selected; values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

E.2.2.2. *Figure for Selected Model: Linear, Nonconstant Variance*



13:41 11/16 2009

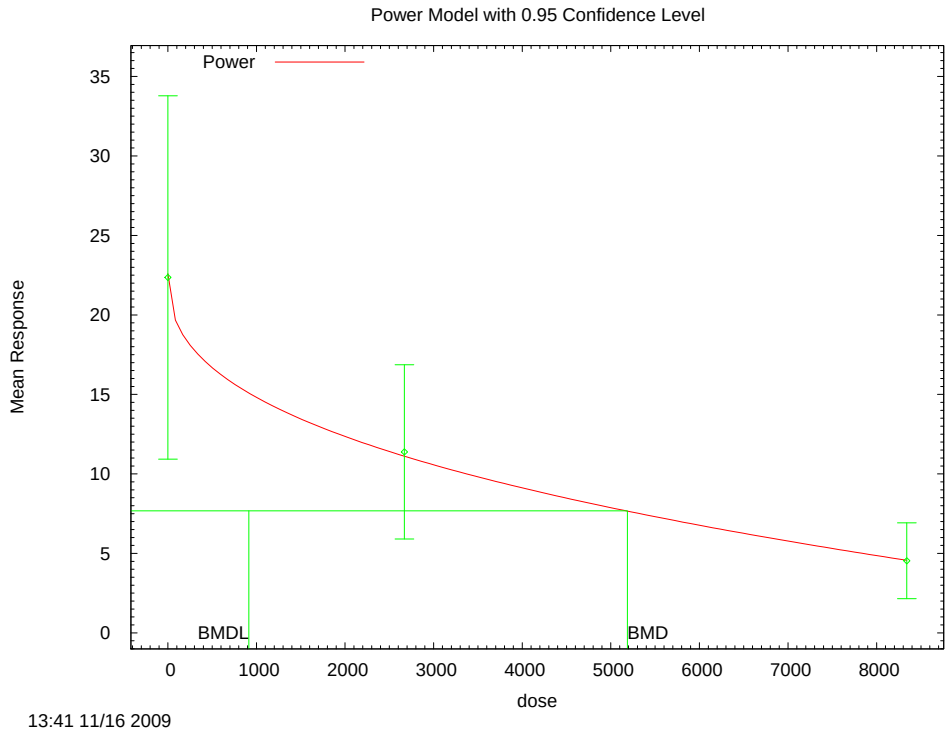
E.2.2.3. *Output File for Selected Model: Linear, Nonconstant Variance*

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Linear_BMR1_50_s_c.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Linear_BMR1_50_s_c.plt
                                                Mon Nov 16 13:41:55 2009
 ================================================================

 Rel Male Thymus wt, Tbl 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
   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 =     20.0674
                       beta_1 =  -0.00199124


            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        -0.981979         0.982197           -2.90705            0.943092
            rho          2.11795         0.401142            1.33173             2.90417
         beta_0          18.6205          3.17872            12.3903             24.8507
         beta_1      -0.00168815      0.000408035         -0.00248788        -0.000888416


     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          0.872
 2670    10       11.4         14.1         7.66         10.1         -0.855
 8341    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         -75.291848           4     158.583695
                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              3.52323          1         0.06051

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 =        8021.29


             BMDL =        5183.12
```

E.2.2.4. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



E.2.2.5. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Pwr_Unrest_BMR1_50_s_c.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Pwr_Unrest_BMR1_50_s_c.plt
                                                  Mon Nov 16 13:41:56 2009
 ========================================================================

 Rel Male Thymus wt, Tbl 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =    -0.381559
                         power =      0.42572


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho      control        slope        power

    lalpha            1        -0.96         0.34         -0.2        -0.15

       rho        -0.96            1        -0.47         0.23         0.15

   control         0.34        -0.47            1        -0.63        -0.52

     slope         -0.2         0.23        -0.63            1         0.99

     power        -0.15         0.15        -0.52         0.99            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          4.48415             13.8405            31.4181
          slope         -0.50513         0.841243            -2.15394            1.14368
          power         0.396043         0.168878           0.0650481           0.727037


     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
 2670    10       11.4         11.1         7.66         7.46          0.105
 8341    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 = 5186.92


            BMDL = 913.947
```

E.2.3. Amin et al. (2000): Saccharin Preference Ratio, Female (0.25%)

E.2.3.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
linear [c]	**1**	**0.01**	**9.51**	**0.00**	**227.81**	**9.2E+03**	**4.4E+03**	**nonconstant variance**
polynomial	1	0.01	9.51	0.00	227.81	9.2E+03	4.4E+03	nonconstant variance
power	1	0.01	9.51	0.00	227.81	9.2E+03	4.4E+03	nonconstant variance, power restricted ≥1, bound hit
power [d]	1	0.01	1.22	0.27	219.52	8.3E+05	error	nonconstant variance, power unrestricted

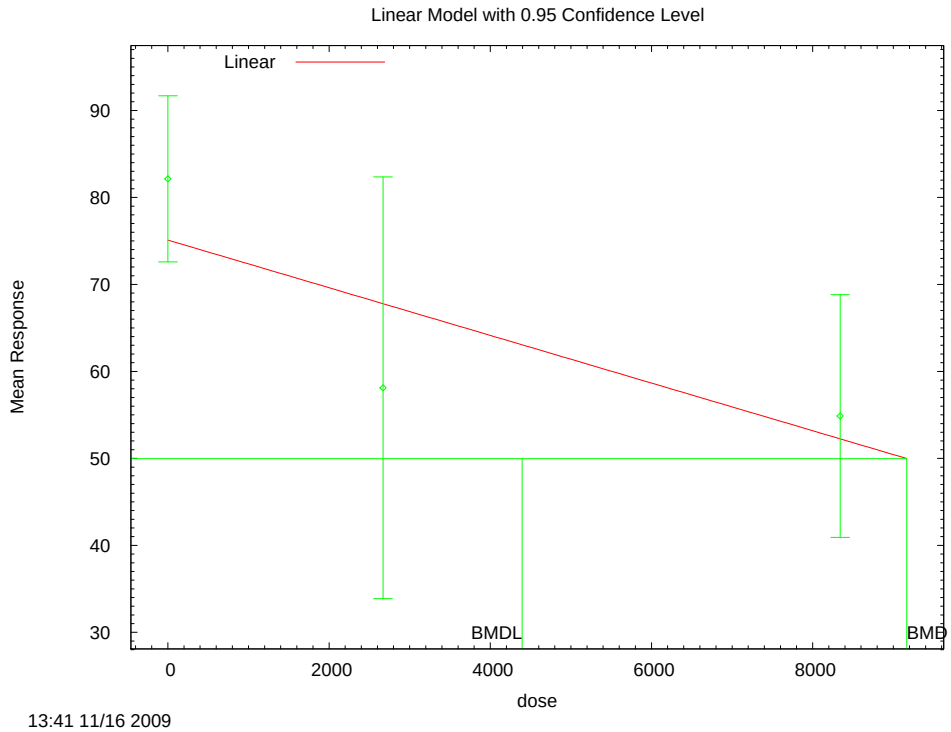
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.3.2. *Figure for Selected Model: Linear, Nonconstant Variance*



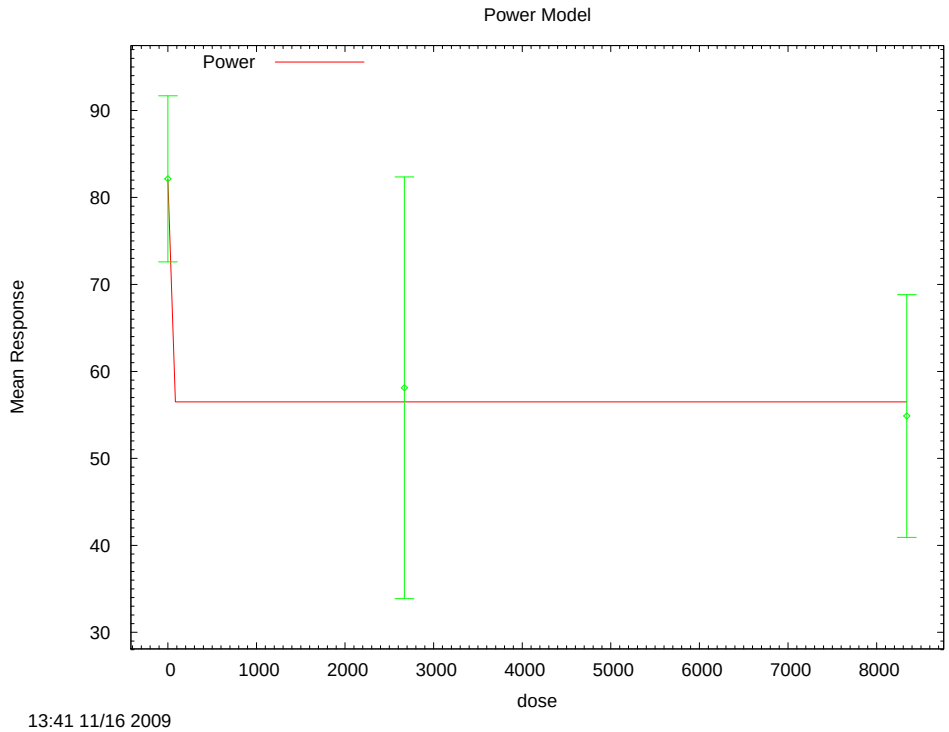
E.2.3.3. *Output File for Selected Model: Linear, Nonconstant Variance*

```
 ========================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Linear_BMR1_25_s_p_f.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Linear_BMR1_25_s_p_f.plt
                                                 Mon Nov 16 13:41:29 2009
 ========================================================================

 Rel Male Thymus wt Tbl 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
   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 =     75.4969
                       beta_1 =  -0.00284822


            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

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha          3.02282          9.21151           -15.0314             21.077
            rho         0.793523          2.21122           -3.54039            5.12744
         beta_0          75.1183          6.74307            61.9021            88.3345
         beta_1      -0.00274398       0.00127757         -0.00524797        -0.000239995


     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          0.883
 2670    10       58.1         67.8         33.9         24.2          -1.27
 8341    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        -109.902600           4     227.805201
               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               9.5093          1        0.002044

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 =        9167.26


             BMDL =        4394.21
```

E.2.3.4. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



E.2.3.5. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Pwr_Unrest_BMR1_25_s_p_f.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Pwr_Unrest_BMR1_25_s_p_f.plt
                                                 Mon Nov 16 13:41:30 2009
 ================================================================

 Rel Male Thymus wt Tbl 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =      6.34368
                           rho =            0
                       control =      82.1429
                         slope =     -9.98589
                         power =     0.111278


           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           -1        -0.26         0.64

       rho           -1            1         0.27        -0.63

   control        -0.26         0.27            1        -0.56

     slope         0.64        -0.63        -0.56            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha           22.273          8.00764            6.57832             37.9677
            rho         -3.90063          1.89036           -7.60567            -0.195596
        control          82.1429          4.00411             74.295             89.9908
          slope         -25.6494          7.11029           -39.5853            -11.7135
          power                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    10       82.1         56.5         13.3         26.3           3.09
 2670    10       58.1         56.5         33.9         26.3          0.195
 8341    10       54.9         56.5         19.5         26.3         -0.195


 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         -105.759821           4     219.519641
                 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              1.22374          1          0.2686

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

 Since the power was estimated to be 0, the BMD is infinite.
 Setting BMD = 100*(maximum dose).

                Benchmark Dose Computation

Specified effect =            1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD = 834064

Warning:  optimum may not have been found.  Bad completion code in Optimization routine.

BMDL computation failed.
```

E.2.4. Amin et al. (2000): Saccharin Preference Ratio, Female (0.50%)

E.2.4.1. *Summary Table of BMDS Modeling Results*

Saccharin preference ratio, female (0.50%) (Amin et al., 2000)								
Model	**Degrees of Freedom**	**Variance *p*-Value [a]**	**χ^2 Test Statistic**	**χ^2 *p*-Value [b]**	**AIC**	**BMD (ng/kg-d)**	**BMDL (ng/kg-d)**	**Model Notes**
linear [c]	**1**	**0.56**	**2.23**	**0.14**	**234.25**	**6.4E+03**	**4.0E+03**	**constant variance**
polynomial	1	0.56	2.23	0.14	234.25	6.4E+03	4.0E+03	constant variance
power	1	0.56	2.23	0.14	234.25	6.4E+03	4.0E+03	constant variance, power restricted ≥1, bound hit
power [d]	0	0.56	0.00	NA	234.02	2.1E+03	1.3E-05	constant variance, power unrestricted

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.4.2. *Figure for Selected Model: Linear, Constant Variance*

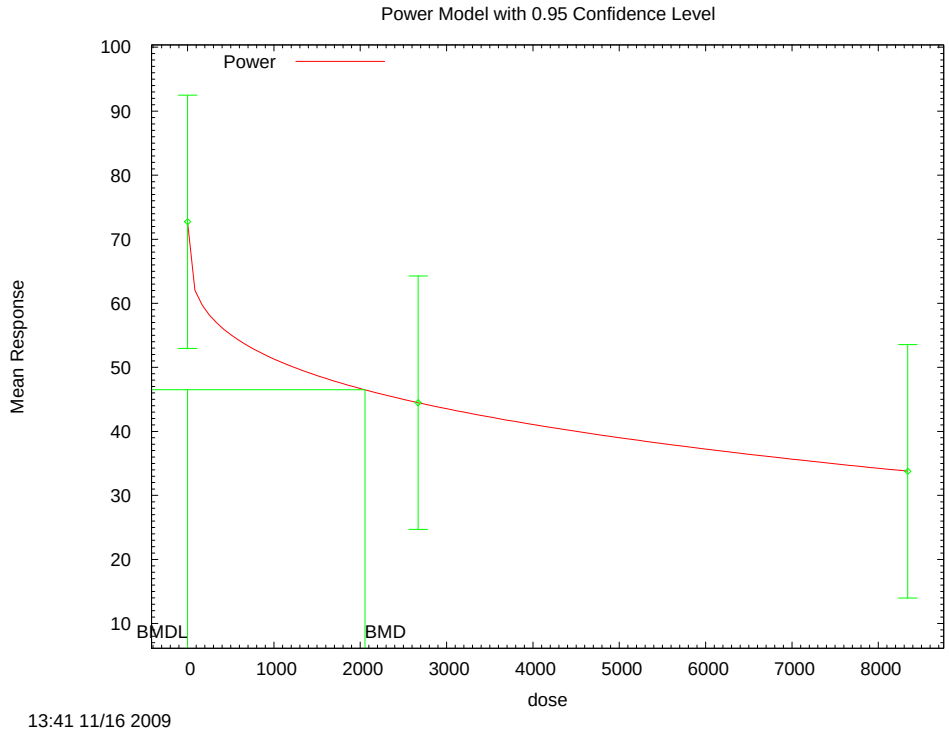
E.2.4.3. *Output File for Selected Model: Linear, Constant Variance*

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\LinearCV_BMR1_50_s_p_f.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\LinearCV_BMR1_50_s_p_f.plt
                                                Mon Nov 16 13:41:03 2009
 ================================================================

 Rel Male Thymus wt, Tbl 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 = 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 =      65.8731
                        beta_1 =  -0.00423638


           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    -4.3e-009    -3.4e-010

    beta_0    -4.3e-009            1        -0.73

    beta_1    -3.4e-010        -0.73            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha          741.152          191.365            366.084             1116.22
         beta_0          65.8731          7.22637            51.7096             80.0365
         beta_1      -0.00423638       0.00142921         -0.00703759         -0.00143517


     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          0.796
2670    10       44.5         54.6         32.9         27.2          -1.17
8341    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         -114.123097            3     234.246193
              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              2.22635          1          0.1357

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 =        6426.26


            BMDL =        4028.71
```

E.2.4.4. *Figure for Unrestricted Model: Power, Constant Variance, Power Unrestricted*



13:41 11/16 2009

E.2.4.5. *Output File for Unrestricted Model: Power, Constant Variance, Power Unrestricted*

```
 ========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\PwrCV_Unrest_BMR1_50_s_p_f.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\PwrCV_Unrest_BMR1_50_s_p_f.plt
                                                  Mon Nov 16 13:41:04 2009
 ========================================================================

 Rel Male Thymus wt, Tbl 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =     -3.04504
                        power =     0.282321


          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    -2.2e-008     3.9e-009     1.5e-009

   control    -2.2e-008            1         -0.3        -0.22

     slope     3.9e-009         -0.3            1         0.99

     power     1.5e-009        -0.22         0.99            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         -3.04504          8.78405            -20.2615             14.1714
          power         0.282321         0.326249           -0.357114            0.921757


     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      8.48e-008
 2670    10       44.5         44.5         32.9         26.2     -1.25e-008
 8341    10       33.8         33.8         24.6         26.2     -3.93e-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 = 2054.47


            BMDL = 1.26421e-005
```

E.2.5. Bell et al. (2007): Balano-Preputial Separation in Male Pups (10% extra risk)

E.2.5.1. *Summary Table of BMDS Modeling Results*

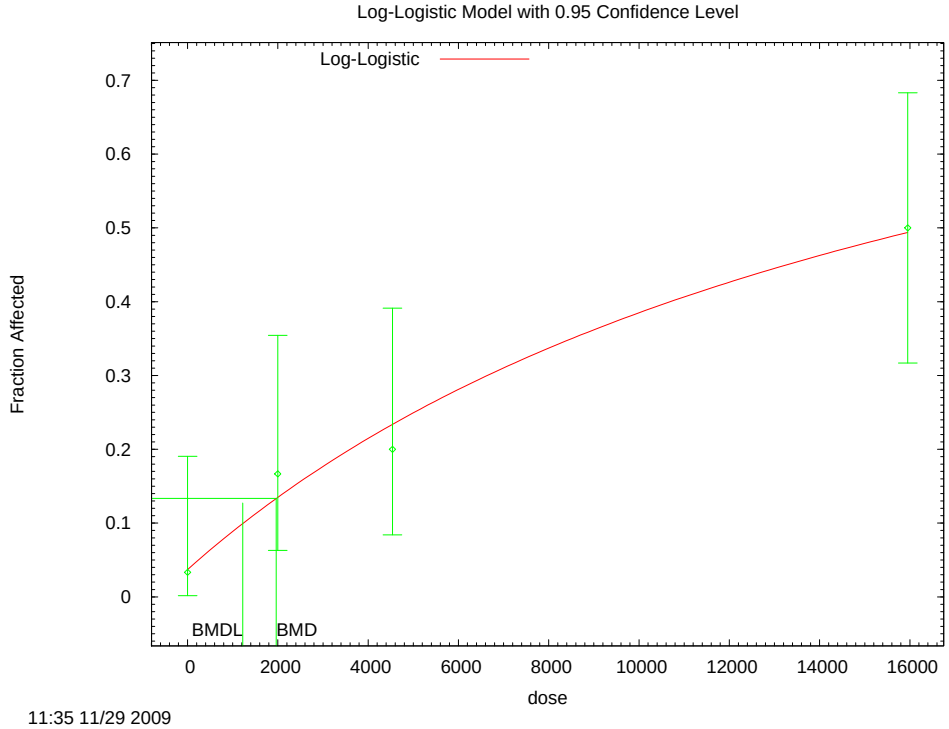
Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	2	0.69	0.71	112.07	2.5E+03	1.7E+03	power restricted ≥1, bound hit
logistic	2	2.10	0.35	113.86	5.3E+03	4.1E+03	
log-logistic [b]	**2**	**0.47**	**0.79**	**111.88**	**2.0E+03**	**1.2E+03**	**slope restricted ≥1, bound hit**
log-logistic [c]	1	0.44	0.51	113.86	1806	264.4	slope unrestricted
log-probit	1	0.54	0.46	113.96	1.8E+03	3.1E+02	slope restricted ≥1
multistage, 1-degree	2	0.69	0.71	112.07	2.5E+03	1.7E+03	betas restricted ≥0, bound hit
probit	2	1.96	0.38	113.65	5.0E+03	3.8E+03	
Weibull	2	0.69	0.71	112.07	2.5E+03	1.7E+03	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

[c] Alternate model also presented in this appendix

E.2.5.2. *Figure for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*

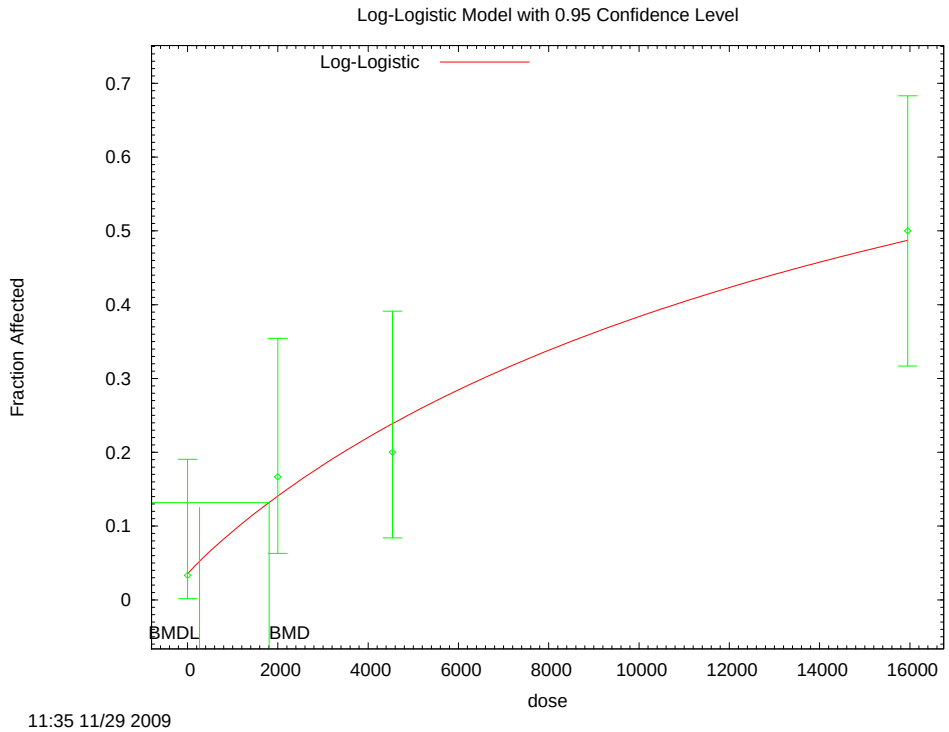


E.2.5.3. *Output File for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*

```
 ========================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov29\Blood\LogLogistic_BMR2_BPS_d49.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov29\Blood\LogLogistic_BMR2_BPS_d49.plt
                                                 Sun Nov 29 11:35:46 2009
 ========================================================================

 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 =     -9.77382
                          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        -0.48

 intercept        -0.48            1



                                  Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0371259            *                *                   *
      intercept         -9.77952            *                *                   *
          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         -53.9377         2      0.460052      2          0.7945
  Reduced model         -63.9797         1        20.544      3       0.0001309

            AIC:         111.875


                                  Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
      0.0000     0.0371         1.114     1.000          30       -0.110
   1997.8780     0.1349         4.048     5.000          30        0.509
   4539.2839     0.2339         7.018     6.000          30       -0.439
  15952.0000     0.4940        14.820    15.000          30        0.066

 Chi^2 = 0.47      d.f. = 2        P-value = 0.7914


    Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

              BMD =        1963.13

             BMDL =        1223.41
```

E.2.5.4. *Figure for Unrestricted Model: Log-Logistic, Slope Unrestricted*



E.2.5.5. *Output File for Unrestricted Model: Log-Logistic, Slope Unrestricted*

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov29\Blood\LogLogistic_Unrest_BMR2_BPS_d49.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov29\Blood\LogLogistic_Unrest_BMR2_BPS_d49.plt
                                                 Sun Nov 29 11:35:48 2009
 ================================================================

 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 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 =     -8.67441
                          slope =     0.877628


            Asymptotic Correlation Matrix of Parameter Estimates

              background    intercept        slope

background            1        -0.38         0.34

 intercept        -0.38            1           -1

     slope         0.34           -1            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
      background        0.0352883            *                 *                   *
       intercept         -9.31114            *                 *                   *
           slope         0.948644            *                 *                   *

* - 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          -53.928         3      0.440703      1          0.5068
   Reduced model         -63.9797         1        20.544      3       0.0001309

            AIC:          113.856


                                  Goodness  of  Fit
                                                                      Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0353         1.059     1.000          30       -0.058
  1997.8780     0.1404         4.212     5.000          30        0.414
  4539.2839     0.2382         7.145     6.000          30       -0.491
 15952.0000     0.4861        14.584    15.000          30        0.152

 Chi^2 = 0.44      d.f. = 1        P-value = 0.5076


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        1806.29

             BMDL =         264.35
```

E.2.6. Bell et al. (2007): Balano-Preputial Separation in Male Pups (5% extra risk)

E.2.6.1. *Summary Table of BMDS Modeling Results*

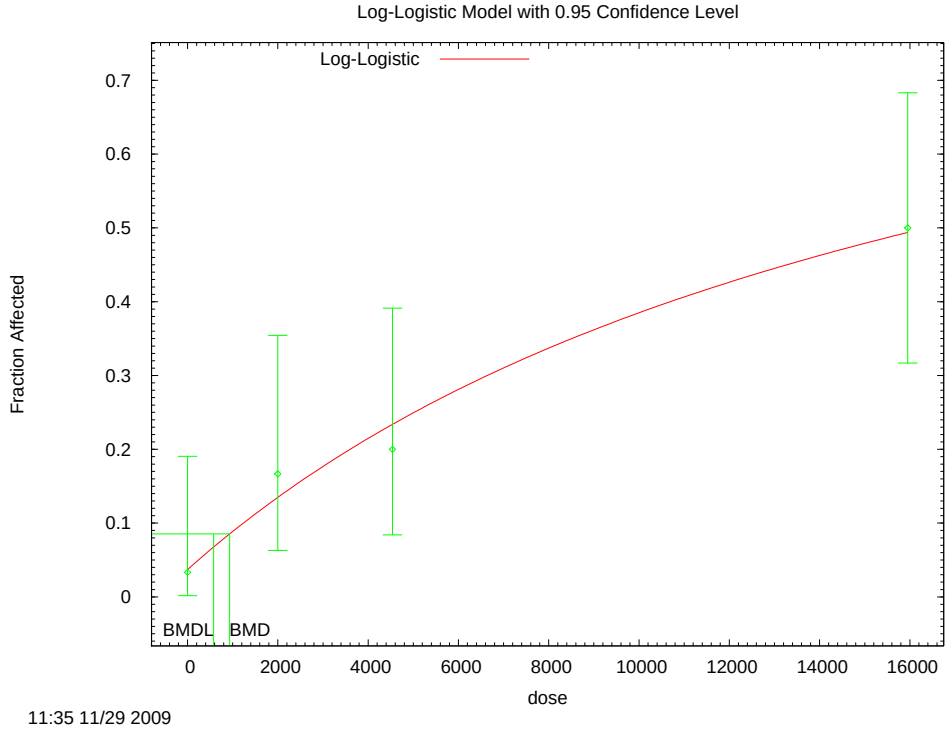
Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	2	0.69	0.71	112.07	1.2E+03	8.2E+02	power restricted ≥1, bound hit
logistic	2	2.10	0.35	113.86	3.0E+03	2.3E+03	
log-logistic [b]	**2**	**0.47**	**0.79**	**111.88**	**9.3E+02**	**5.8E+02**	**slope restricted ≥1, bound hit**
log-logistic [c]	1	0.44	0.51	113.86	8.2E+02	4.5E+01	slope unrestricted
log-probit	1	0.54	0.46	113.96	9.5E+02	7.2E+01	slope restricted ≥1
multistage, 1-degree	2	0.69	0.71	112.07	1.2E+03	8.2E+02	betas restricted ≥0, bound hit
probit	2	1.96	0.38	113.65	2.8E+03	2.1E+03	
Weibull	2	0.69	0.71	112.07	1.2E+03	8.2E+02	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

[c] Alternate model also presented in this appendix

E.2.6.2. *Figure for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*

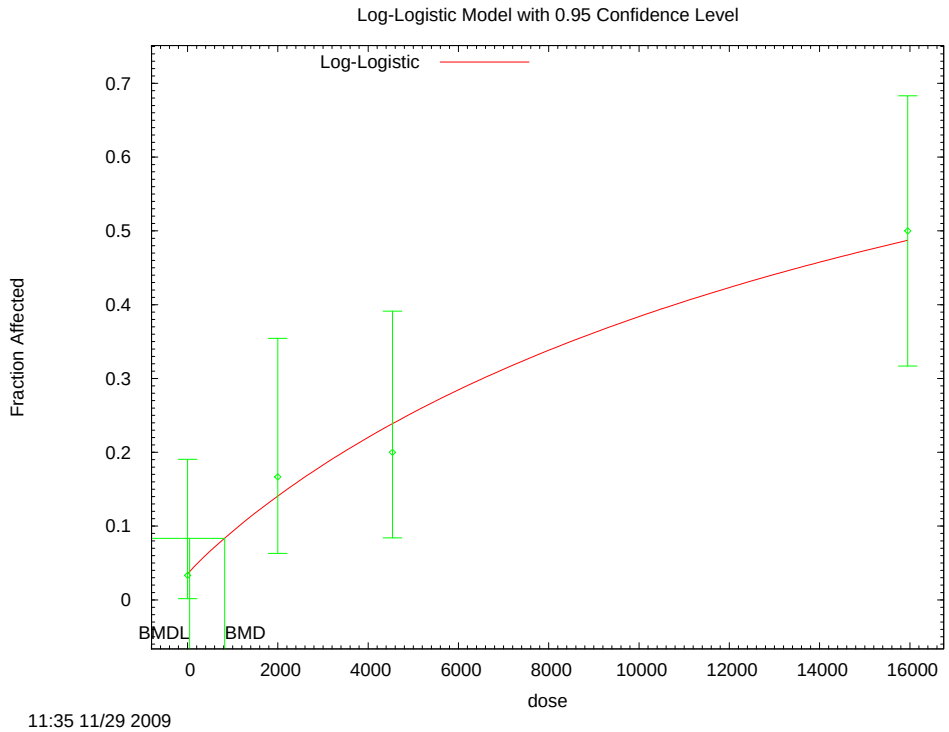


E.2.6.3. *Output File for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov29\Blood\LogLogistic_BMR1_BPS_d49.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov29\Blood\LogLogistic_BMR1_BPS_d49.plt
                                                 Sun Nov 29 11:35:45 2009
 ================================================================

 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 =     -9.77382
                          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        -0.48

 intercept        -0.48            1



                                 Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0371259            *                *                   *
      intercept         -9.77952            *                *                   *
          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         -53.9377         2      0.460052      2          0.7945
  Reduced model         -63.9797         1        20.544      3       0.0001309

            AIC:         111.875


                                  Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
      0.0000     0.0371         1.114     1.000          30       -0.110
   1997.8780     0.1349         4.048     5.000          30        0.509
   4539.2839     0.2339         7.018     6.000          30       -0.439
  15952.0000     0.4940        14.820    15.000          30        0.066

 Chi^2 = 0.47      d.f. = 2        P-value = 0.7914


    Benchmark Dose Computation

Specified effect =          0.05

Risk Type        =      Extra risk

Confidence level =          0.95

              BMD =       929.901

             BMDL =       579.512
```

E.2.6.4. *Figure for Unrestricted Model: Log-Logistic, Slope Unrestricted*



E.2.6.5. *Output File for Unrestricted Model: Log-Logistic, Slope Unrestricted*

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov29\Blood\LogLogistic_Unrest_BMR1_BPS_d49.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov29\Blood\LogLogistic_Unrest_BMR1_BPS_d49.plt
                                                 Sun Nov 29 11:35:47 2009
 ================================================================

 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 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 = -8.67441
slope = 0.877628

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.38	0.34
intercept	-0.38	1	-1
slope	0.34	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0352883	*	*	*
intercept	-9.31114	*	*	*
slope	0.948644	*	*	*

* - 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	-53.928	3	0.440703	1	0.5068
Reduced model	-63.9797	1	20.544	3	0.0001309

AIC: 113.856

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0353	1.059	1.000	30	-0.058
1997.8780	0.1404	4.212	5.000	30	0.414
4539.2839	0.2382	7.145	6.000	30	-0.491
15952.0000	0.4861	14.584	15.000	30	0.152

Chi^2 = 0.44 d.f. = 1 P-value = 0.5076

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 821.69

BMDL = 45.4953

E.2.7. Cantoni et al. (1981): Urinary Copro-Porhyrins

E.2.7.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.00	11.91	0.00	32.88	1.8E+04	8.6E+03	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.00	11.91	0.00	32.88	1.8E+04	8.6E+03	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**1**	**0.00**	**0.48**	**0.49**	**23.46**	**2.9E+02**	**9.9E+01**	**nonconstant variance, power restricted ≥1**
exponential (M5)	1	0.00	0.48	0.49	23.46	2.9E+02	9.9E+01	nonconstant variance, power restricted ≥1
exponential (M5) [d]	1	0.00	0.48	0.49	23.46	2.9E+02	9.9E+01	nonconstant variance, power unrestricted
Hill	1	0.00	0.07	0.79	23.05	2.4E+02	error	nonconstant variance, n restricted >1, bound hit
Hill [d]	0	0.00	0.00	NA	24.97	1.4E+02	error	nonconstant variance, n unrestricted
linear	2	0.00	10.62	0.00	31.59	8.1E+03	1.5E+03	nonconstant variance
polynomial	2	0.00	10.62	0.00	31.59	8.1E+03	1.5E+03	nonconstant variance
power	2	0.00	10.62	0.00	31.59	8.1E+03	1.5E+03	nonconstant variance, power restricted ≥1, bound hit
power [d]	1	0.00	0.26	0.61	23.23	1.5E+01	2.3E-06	nonconstant variance, power unrestricted

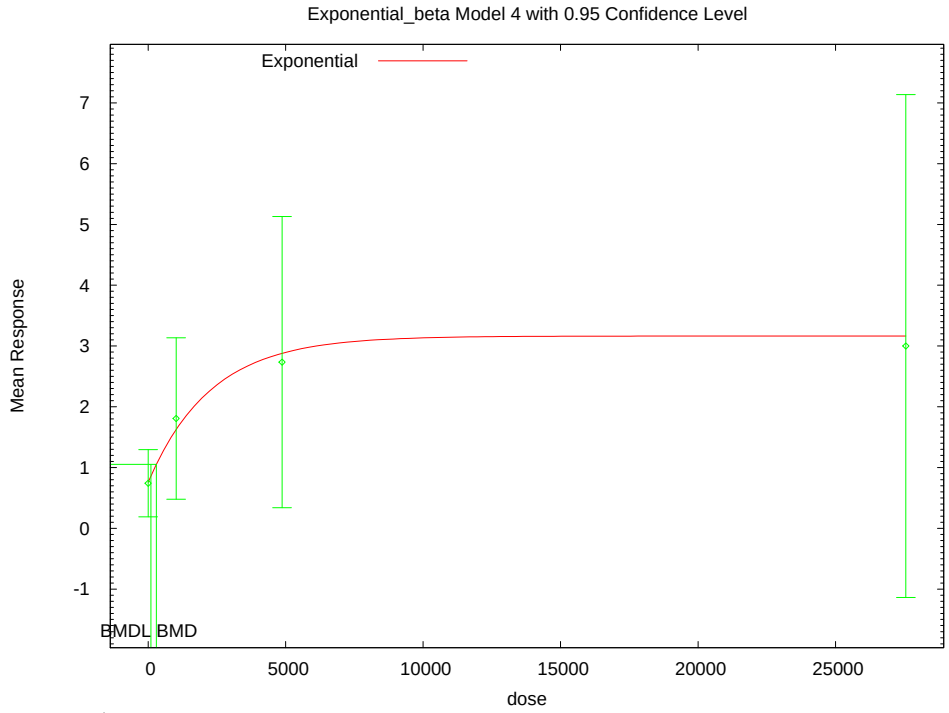
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.7.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



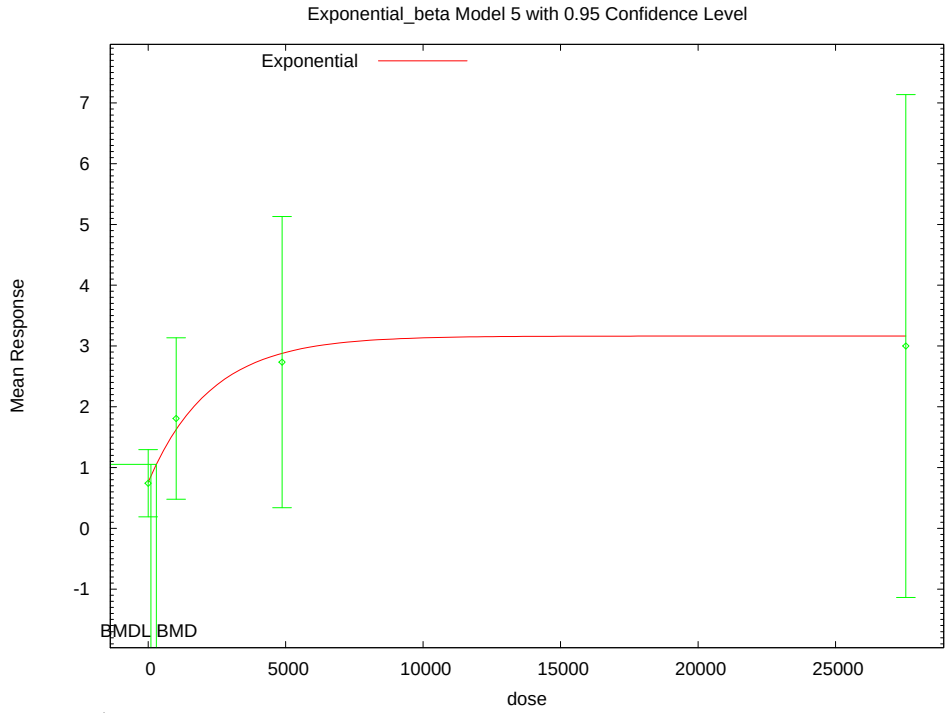
E.2.7.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Exp_BMR1_urin_copropor.(d)
         Gnuplot Plotting File:
                                                  Mon Nov 16 13:43:37 2009
 ================================================================

 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         0.000109864
                        c             4.47268
                        d                    1



                  Parameter Estimates

                 Variable          Model 4
                 --------          -------
                  lnalpha          -1.75303
                      rho           2.63218
                        a           0.76122
                        b       0.000438426
                        c           4.15614
                        d                  1


          Table of Stats From Input Data

    Dose      N         Obs Mean     Obs Std Dev
    -----    ---       ----------   -------------
        0      4       0.7414       0.3475
     1018      4        1.807       0.8341
     4868      4        2.734        1.506
    2.756e+004      4            3          2.6


                Estimated Values of Interest

     Dose      Est Mean      Est Std     Scaled Residual
    ------    ----------    ---------    ----------------
        0        0.7612       0.2907          -0.1366
     1018         1.626       0.7892           0.4589
     4868         2.879        1.674          -0.1742
2.756e+004         3.164        1.895          -0.1727


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       -6.729565           5      23.45913


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                       0.4847           1              0.4863


  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 =      294.122

              BMDL =      99.3366
```

E.2.7.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



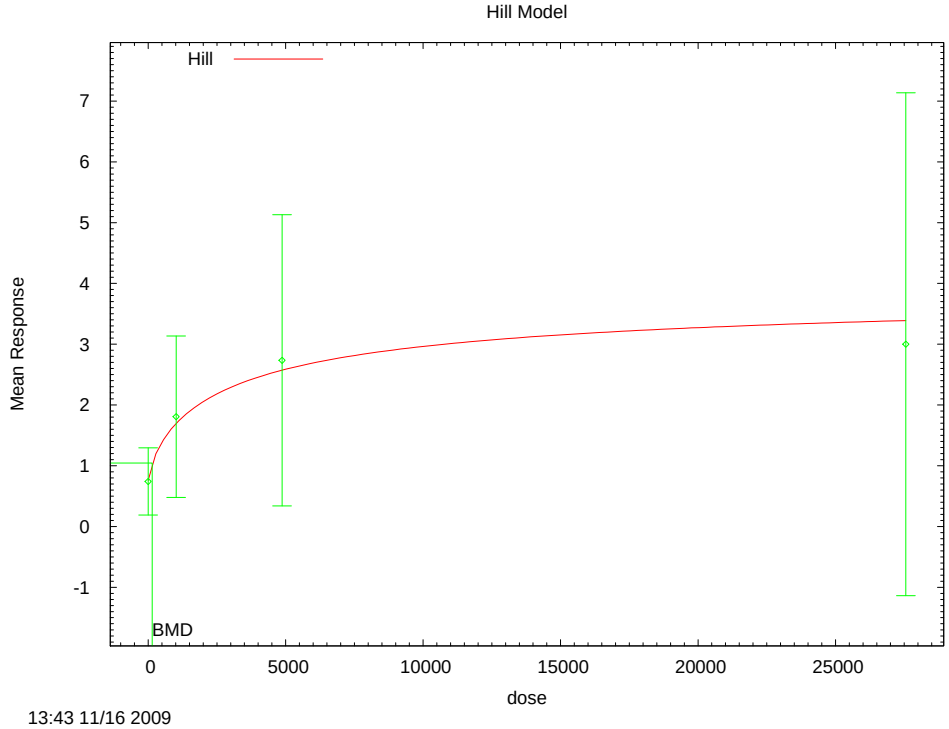
E.2.7.5. *Output file for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Exp_Unrest_BMR1_urin_copropor.(d)
         Gnuplot Plotting File:
                                                  Mon Nov 16 13:43:39 2009
 ================================================================

 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 5
                --------          --------
                  lnalpha             -1.50063
                      rho              2.60979
                        a             0.704303
                        b          0.000109864
                        c              4.47268
                        d                    1



                  Parameter Estimates

                 Variable          Model 5
                 --------          -------
                  lnalpha          -1.75303
                      rho           2.63218
                        a           0.76122
                        b       0.000438426
                        c           4.15614
                        d                 1


          Table of Stats From Input Data

    Dose      N         Obs Mean     Obs Std Dev
    -----    ---       ----------   -------------
        0      4       0.7414       0.3475
     1018      4        1.807       0.8341
     4868      4        2.734        1.506
    2.756e+004      4            3          2.6


                Estimated Values of Interest

     Dose      Est Mean      Est Std     Scaled Residual
    ------    ----------    ---------    ----------------
        0       0.7612       0.2907          -0.1366
     1018        1.626       0.7892           0.4589
     4868        2.879        1.674          -0.1742
2.756e+004        3.164        1.895          -0.1727


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
                       5       -6.729565           5      23.45913


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 7a: Does Model 5 fit the data? (A3 vs 5)


                          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 7a                       0.4847           1              0.4863


  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 7a is greater than .1.  Model 5 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 =      294.122

              BMDL =      99.3366
```

E.2.7.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



13:43 11/16 2009

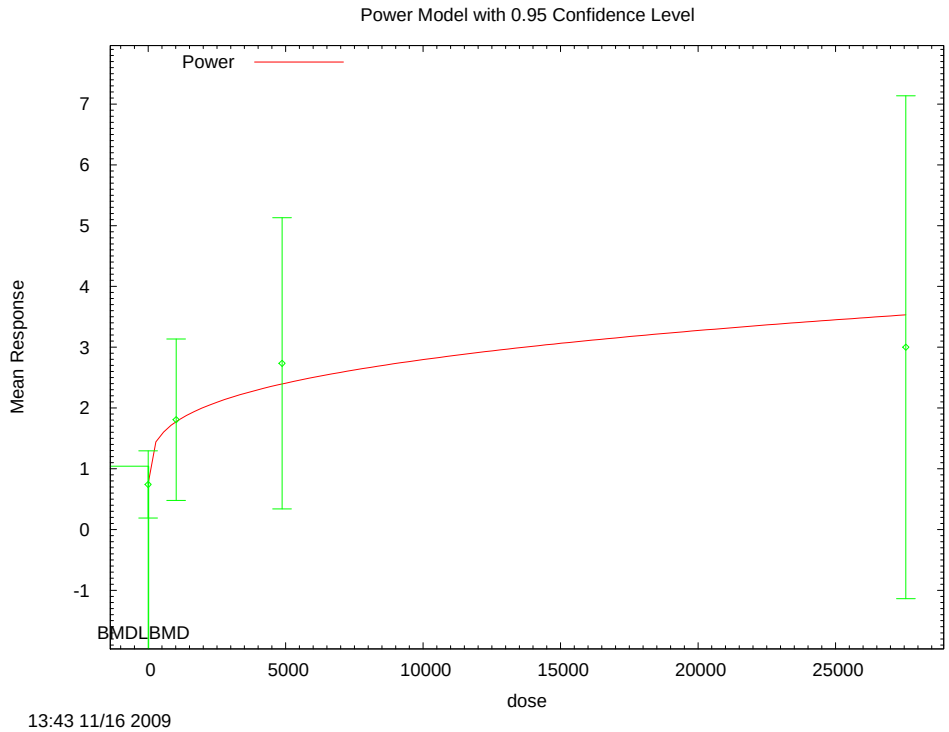
E.2.7.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_urin_copropor.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_urin_copropor.plt
                                                 Mon Nov 16 13:43:40 2009
 ================================================================

 Figure1-UrinaryCoproporphyrin_3months
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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
                    intercept =    0.741372
                            v =     2.25875
                            n =   0.0266478
                            k =     8454.34


          Asymptotic Correlation Matrix of Parameter Estimates

                lalpha          rho    intercept            v            n            k

    lalpha            1        -0.62        -0.53       -0.013        0.027      -0.0092

       rho        -0.62            1         0.43         -0.2       -0.017       -0.051

 intercept        -0.53         0.43            1       -0.081        0.032        0.011

         v       -0.013         -0.2       -0.081            1        -0.88         0.96

         n        0.027       -0.017        0.032        -0.88            1        -0.92

         k      -0.0092       -0.051        0.011         0.96        -0.92            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -1.78758         0.616312            -2.99553           -0.579633
            rho          2.64296         0.750855             1.17131             4.11461
      intercept         0.759014          0.14058            0.483483             1.03455
              v          3.18202          2.82949            -2.36368             8.72772
              n         0.739248         0.896737            -1.01832             2.49682
              k          3317.45          9482.63            -15268.2             21903.1



     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        0.759        0.348        0.284         -0.124
 1018     4       1.81          1.7        0.834        0.822           0.27
 4868     4       2.73         2.57         1.51         1.43          0.224
2.756e+004     4          3         3.39          2.6         2.05          -0.38

 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          -12.901663            5      35.803325
              A2           -6.203643            8      28.407287
              A3           -6.487204            6      24.974409
          fitted           -6.487204            6      24.974409
               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         -1.9007e-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 =        143.414


BMDL computation failed.
```

E.2.7.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



E.2.7.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Pwr_Unrest_BMR1_urin_copropor.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Pwr_Unrest_BMR1_urin_copropor.plt
                                                 Mon Nov 16 13:43:39 2009
 ================================================================

 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 =	0.226515
power =	0.224935

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.62	-0.53	-0.03	0.024
rho	-0.62	1	0.43	0.052	-0.16
control	-0.53	0.43	1	-0.15	0.086
slope	-0.03	0.052	-0.15	1	-0.98
power	0.024	-0.16	0.086	-0.98	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-1.78125	0.617808	-2.99213	-0.570369
rho	2.64332	0.744947	1.18325	4.10339
control	0.75678	0.139979	0.482426	1.03113
slope	0.123953	0.145639	-0.161493	0.4094
power	0.304254	0.135074	0.0395142	0.568993

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
1018	4	1.81	1.78	0.834	0.877	0.0705
4868	4	2.73	2.4	1.51	1.3	0.515
2.756e+004	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           -6.617381            5      23.234762
               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             0.260353          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 = 15.247


             BMDL = 2.31222e-006
```

E.2.8. Cantoni et al. (1981): Urinary Porphyrins

E.2.8.1. *Summary Table of BMDS Modeling Results*

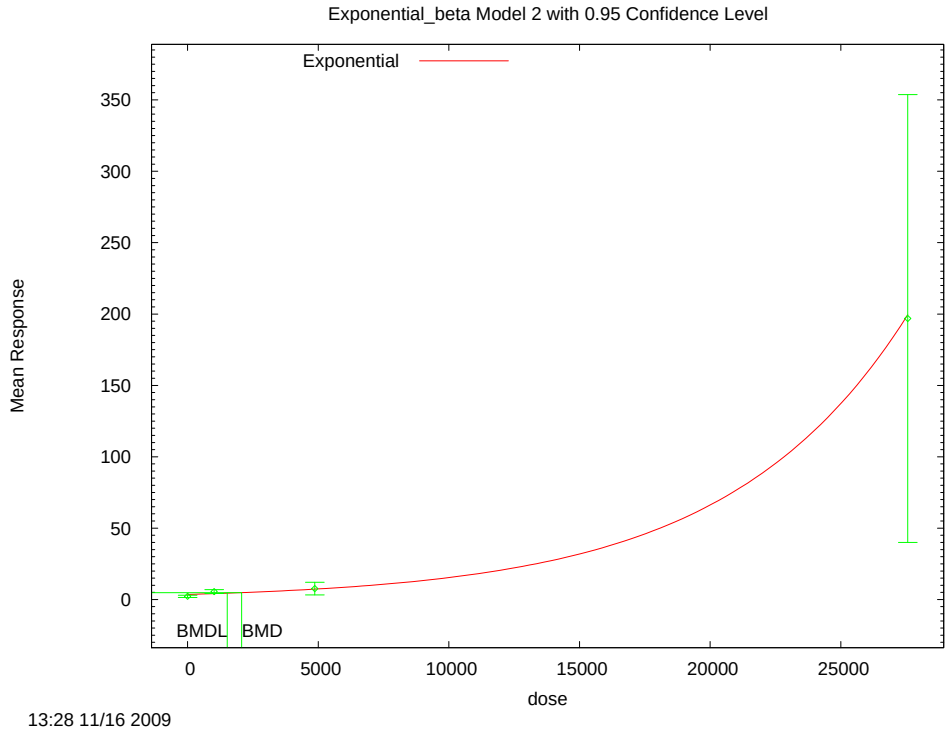
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2) [c]	**2**	**<0.0001**	**16.12**	**0.00**	**55.46**	**2.1E+03**	**1.5E+03**	**nonconstant variance, power restricted ≥1**
exponential (M3)	2	<0.0001	16.12	0.00	55.46	2.1E+03	1.5E+03	nonconstant variance, power restricted ≥1
exponential (M4)	1	<0.0001	17.85	<0.0001	59.19	1.4E+02	8.0E+01	nonconstant variance, power restricted ≥1
exponential (M5)	0	<0.0001	17.74	N/A	61.08	1.6E+02	8.0E+01	nonconstant variance, power restricted ≥1
Hill	0	<.0001	18.86	NA	62.20	3.4E+03	1.8E+03	nonconstant variance, n restricted >1
linear	2	<.0001	17.85	0.00	57.19	1.4E+02	8.0E+01	nonconstant variance
polynomial	1	<.0001	16.63	<.0001	57.97	1.9E+02	8.9E+01	nonconstant variance
power	1	<.0001	17.74	<.0001	59.08	1.6E+02	8.0E+01	nonconstant variance, power restricted ≥1

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.2.8.2. *Figure for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*



E.2.8.3. *Output File for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Exp_BMR1_Urinary_porphyrins.(d)
         Gnuplot Plotting File:
                                                  Mon Nov 16 13:28:56 2009
 ================================================================

 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              2.1565
                        b         3.49686e-008
                        c              91300.7
                        d                    1



                  Parameter Estimates

                 Variable          Model 2
                 --------          -------
                  lnalpha          -4.64559
                      rho           3.18357
                        a           2.32146
                        b      2.51372e-009
                        c            838302
                        d           1.04944


          Table of Stats From Input Data

    Dose      N         Obs Mean     Obs Std Dev
    -----    ---       ----------   -------------
        0      4         2.27         0.49
     1018      4         5.55         0.85
     4868      3         7.62         1.79
    2.756e+004      3        196.9        63.14


                Estimated Values of Interest

     Dose      Est Mean      Est Std     Scaled Residual
    ------    ----------    ---------    ----------------
        0         3.579        1.262           -2.074
     1018         4.152        1.445            1.936
     4868         7.281        2.411           0.2437
2.756e+004         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       -23.73172           4      55.46344


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                      16.12             2           0.0003153


  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 =      2070.13

             BMDL =      1521.05
```

E.2.9. Crofton et al. (2005): Serum T4

E.2.9.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	8	0.76	44.20	<0.0001	516.36	6.3E+04	3.4E+04	constant variance, power restricted ≥1
exponential (M3)	8	0.76	44.20	<0.0001	516.36	6.3E+04	3.4E+04	constant variance, power restricted ≥1
exponential (M4) [c]	**7**	**0.76**	**2.29**	**0.94**	**476.45**	**2.9E+03**	**1.7E+03**	**constant variance, power restricted ≥1**
exponential (M5)	6	0.76	2.08	0.91	478.23	3.2E+03	1.7E+03	constant variance, power restricted ≥1
exponential (M5) [d]	6	0.76	2.08	0.91	478.23	3.2E+03	1.7E+03	constant variance, power unrestricted
Hill	6	0.76	1.29	0.97	477.45	3.2E+03	1.7E+03	constant variance, n restricted >1
Hill [d]	6	0.76	1.29	0.97	477.45	3.2E+03	1.7E+03	constant variance, n unrestricted
linear	8	0.76	50.31	<.0001	522.46	1.3E+05	9.7E+04	constant variance
polynomial	8	0.76	50.31	<.0001	522.46	1.3E+05	9.7E+04	constant variance
power	8	0.76	50.31	<.0001	522.46	1.3E+05	9.7E+04	constant variance, power restricted ≥1, bound hit
power [d]	7	0.76	16.95	0.02	491.10	1.4E+03	1.8E+02	constant variance, power unrestricted

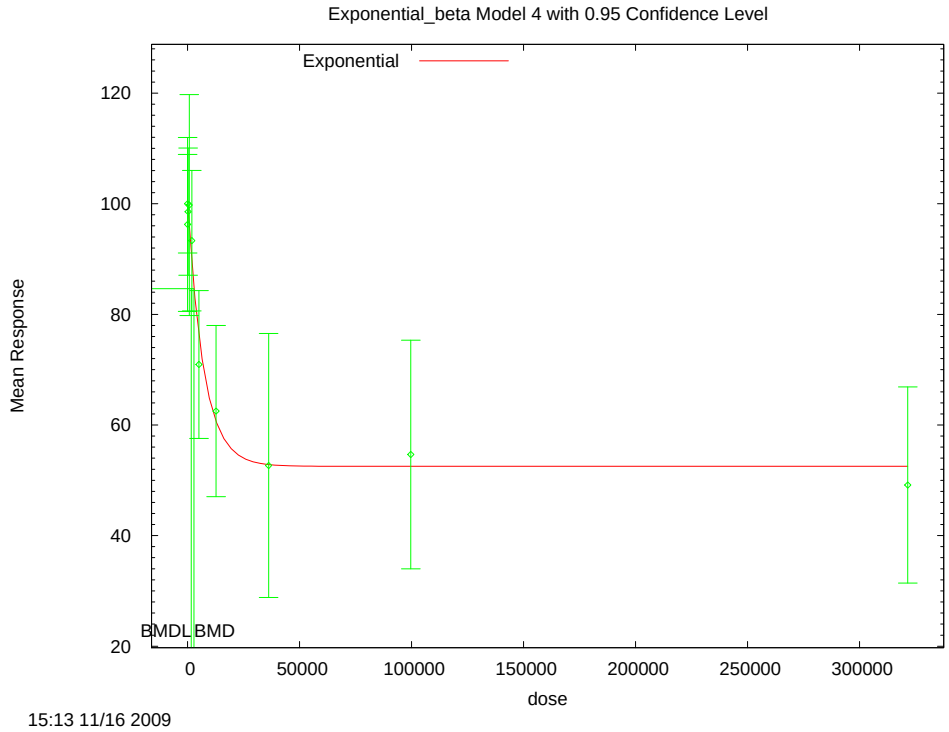
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.9.2. *Figure for Selected Model: Exponential (M4), Constant Variance, Power Restricted ≥1*



E.2.9.3. *Output File for Selected Model: Exponential (M4), Constant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\ExpConstVar_BMR1_SerumT4.(d)
         Gnuplot Plotting File:
                                                  Mon Nov 16 15:13:33 2009
 ================================================================

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~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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	1.16502e-005
c	0.445764
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	5.50322
rho	0
a	99.7846
b	0.000149614
c	0.533127
d	1.19797

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	14	100	15.44
11.15	6	96.27	14.98
269.2	12	98.57	18.11
763	6	99.76	19.04
1905	6	93.32	12.11
5104	6	70.94	12.74
1.271e+004	6	62.52	14.75
3.617e+004	6	52.68	22.73
9.965e+004	6	54.66	19.71
3.215e+005	4	49.15	11.15

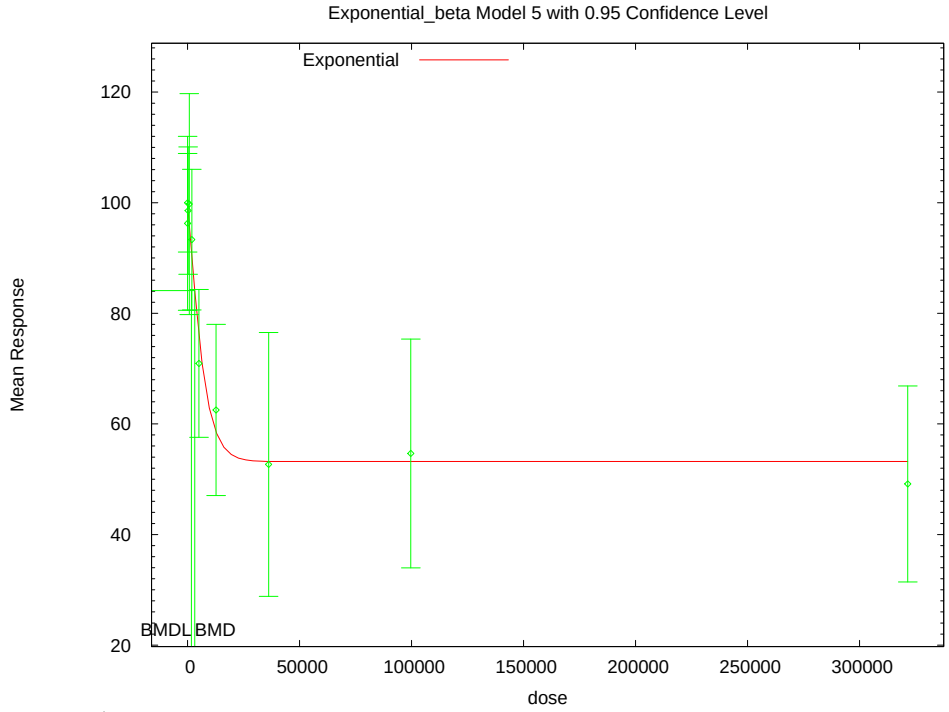
Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	100.3	15.69	-0.07977
11.15	100.3	15.69	-0.6232
269.2	98.58	15.69	-0.0008246
763	95.52	15.69	0.6615
1905	89.21	15.69	0.6428
5104	76.04	15.69	-0.7955
1.271e+004	60.7	15.69	0.2839
3.617e+004	52.85	15.69	-0.02601
9.965e+004	52.53	15.69	0.3323

```
3.215e+005         52.53        15.69           -0.432


   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       -234.2238            4      476.4476


   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                        2.293           7              0.9419


     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 =      2860.82

                  BMDL =      1670.13
```

E.2.9.4. *Figure for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*



E.2.9.5. *Output File for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\ExpConstVar_Unrest_BMR1_SerumT4.(d)
         Gnuplot Plotting File:
                                                  Mon Nov 16 15:13:40 2009
 ================================================================

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~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 5
                 --------          --------
                   lnalpha             5.47437
                       rho(S)                0
                         a             104.999
                         b         1.16502e-005
                         c             0.445764
                         d                    1

     (S) = Specified


                    Parameter Estimates

                  Variable          Model 5
                  --------          -------
                   lnalpha           5.50322
                       rho                 0
                         a           99.7846
                         b       0.000149614
```
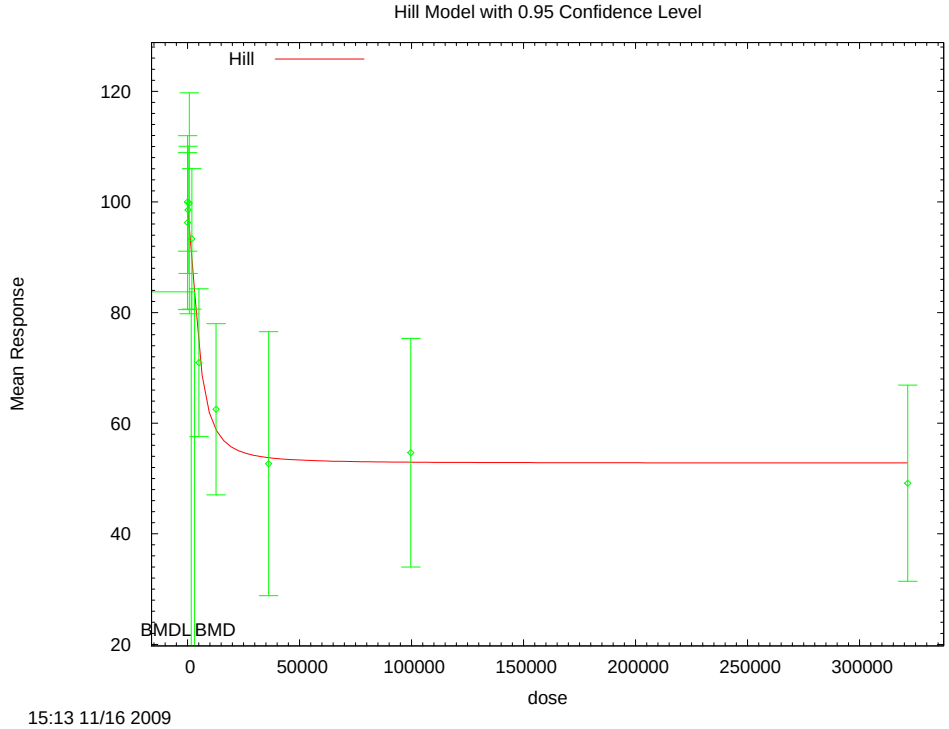

```
                          c          0.533127
                          d           1.19797


              Table of Stats From Input Data

       Dose      N         Obs Mean     Obs Std Dev
       -----    ---       ----------   -------------
           0     14          100        15.44
       11.15      6         96.27        14.98
       269.2     12         98.57        18.11
         763      6         99.76        19.04
        1905      6         93.32        12.11
        5104      6         70.94        12.74
       1.271e+004      6        62.52        14.75
       3.617e+004      6        52.68        22.73
       9.965e+004      6        54.66        19.71
       3.215e+005      4        49.15        11.15


                    Estimated Values of Interest

        Dose      Est Mean      Est Std     Scaled Residual
      ------    ----------    ---------    ----------------
           0         99.78        15.67           0.0512
       11.15         99.76        15.67          -0.5465
       269.2          98.8        15.67         -0.05054
         763         96.45        15.67           0.5173
        1905          90.5        15.67           0.4419
        5104         75.78        15.67          -0.7573
   1.271e+004         58.58        15.67            0.616
   3.617e+004         53.22        15.67         -0.08476
   9.965e+004          53.2        15.67           0.2291
   3.215e+005          53.2        15.67          -0.5174


   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
                        5       -234.1158            5      478.2316


   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 7a: Does Model 5 fit the data? (A3 vs 5)


                         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 7a                        2.077           6              0.9125


  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 7a is greater than .1.  Model 5 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 =      3175.08

              BMDL =      1706.36
```

E.2.9.6. *Figure for Unrestricted Model: Hill, Constant Variance, n Unrestricted*



E.2.9.7. *Output File for Unrestricted Model: Hill, Constant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\HillConstVar_Unrest_BMR1_SerumT4.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\HillConstVar_Unrest_BMR1_SerumT4.plt
                                                 Mon Nov 16 15:13:42 2009
 ================================================================

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   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 = 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
```
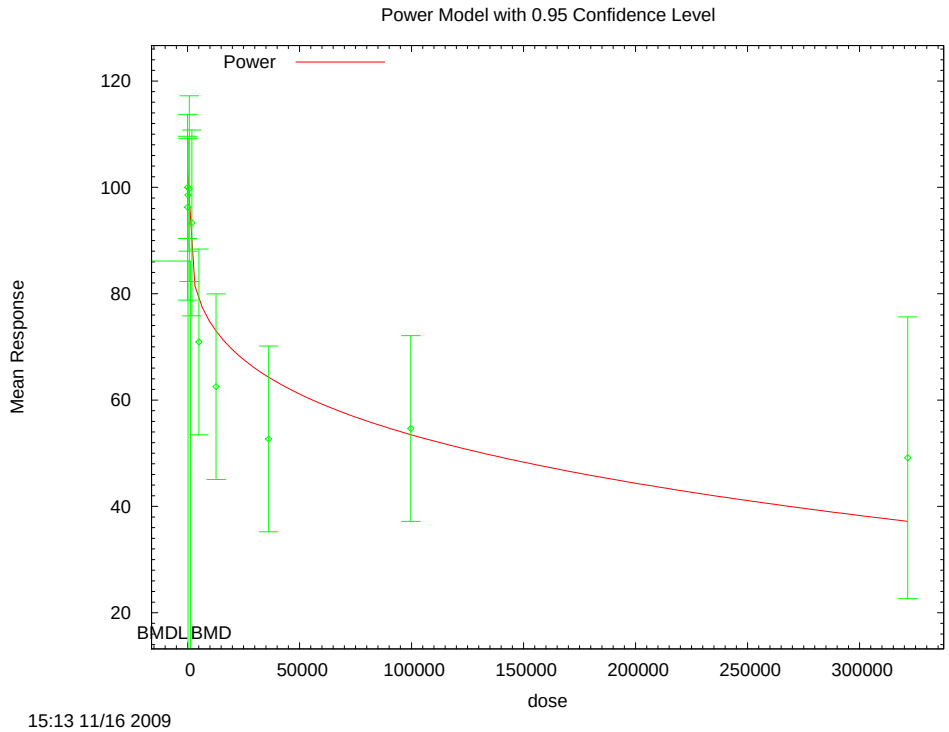

```
                          alpha =      276.969
                            rho =            0   Specified
                      intercept =       99.999
                              v =      -50.854
                              n =       1.5549
                              k =      4585.23


           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     1.9e-009      -2e-008    -1.1e-008     1.1e-008

    intercept     1.9e-009            1        -0.58         -0.3         -0.2

            v      -2e-008        -0.58            1          0.6        -0.36

            n    -1.1e-008         -0.3          0.6            1        -0.34

            k     1.1e-008         -0.2        -0.36        -0.34            1


                                  Parameter Estimates

                                                                95.0% Wald Confidence Interval
          Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
             alpha          242.825          40.4708             163.504             322.146
         intercept          99.3375          2.66145             94.1212             104.554
                 v         -46.4797          5.51009            -57.2793            -35.6801
                 n          1.85655         0.927361           0.0389606             3.67415
                 k          4564.01          1406.15                1808             7320.02


           Table of Data and Estimated Values of Interest

    Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
   ------     ---   --------     --------   -----------  -----------   ----------

       0    14        100         99.3         15.4         15.6          0.159
   11.15     6       96.3         99.3           15         15.6         -0.483
   269.2    12       98.6         99.1         18.1         15.6         -0.116
     763     6       99.8         97.7           19         15.6          0.321
    1905     6       93.3         91.7         12.1         15.6           0.26
    5104     6       70.9         73.7         12.7         15.6         -0.433
   1.271e+004     6       62.5         58.9         14.8         15.6          0.568
   3.617e+004     6       52.7         53.8         22.7         15.6         -0.181
   9.965e+004     6       54.7           53         19.7         15.6           0.26
   3.215e+005     4       49.1         52.9         11.1         15.6         -0.479


    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         -233.077445          11     488.154889
            A2         -230.202783          20     500.405566
            A3         -233.077445          11     488.154889
         fitted        -233.724271           5     477.448543
             R         -268.403817           2     540.807634


                   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              76.4021         18          <.0001
   Test 2              5.74932          9          0.7647
   Test 3              5.74932          9          0.7647
   Test 4              1.29365          6           0.972

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 =        3156.67

            BMDL =       1668.07
```

E.2.9.8. *Figure for Unrestricted Model: Power, Constant Variance, Power Unrestricted*



E.2.9.9. *Output File for Unrestricted Model: Power, Constant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\PowerConstVar_Unrest_BMR1_SerumT4.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\PowerConstVar_Unrest_BMR1_SerumT4.plt
                                                 Mon Nov 16 15:13:43 2009
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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
```

```
                          alpha =      276.969
                            rho =            0   Specified
                        control =       99.999
                          slope =     -0.28302
                          power =      0.42875


            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    -1.9e-010    -1.9e-010

    control       3e-010            1        -0.73        -0.62

      slope    -1.9e-010        -0.73            1         0.98

      power    -1.9e-010        -0.62         0.98            1



                                 Parameter Estimates

                                                          95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha          301.804          50.3007             203.217             400.392
         control          103.499          3.94867               95.76             111.239
           slope         -3.01678          1.68354            -6.31645            0.282886
           power         0.242881        0.0442912            0.156071             0.32969



      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    14        100          103         15.4         17.4         -0.754
11.15     6       96.3         98.1           15         17.4         -0.256
269.2    12       98.6         91.8         18.1         17.4           1.36
  763     6       99.8         88.4           19         17.4            1.6
 1905     6       93.3         84.6         12.1         17.4           1.23
 5104     6       70.9         79.5         12.7         17.4          -1.21
1.271e+004     6       62.5         73.6         14.8         17.4          -1.56
3.617e+004     6       52.7         64.9         22.7         17.4          -1.72
9.965e+004     6       54.7         54.1         19.7         17.4          0.077
3.215e+005     4       49.1         37.9         11.1         17.4            1.3



 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	-233.077445	11	488.154889
A2	-230.202783	20	500.405566
A3	-233.077445	11	488.154889
fitted	-241.552045	4	491.104090
R	-268.403817	2	540.807634

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	76.4021	18	<.0001
Test 2	5.74932	9	0.7647
Test 3	5.74932	9	0.7647
Test 4	16.9492	7	0.01773

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 = 1350.28

BMDL = 182.329

E.2.10. Hojo et al. (2002): DRL Reinforce Per Min

E.2.10.1. *Summary Table of BMDS Modeling Results*

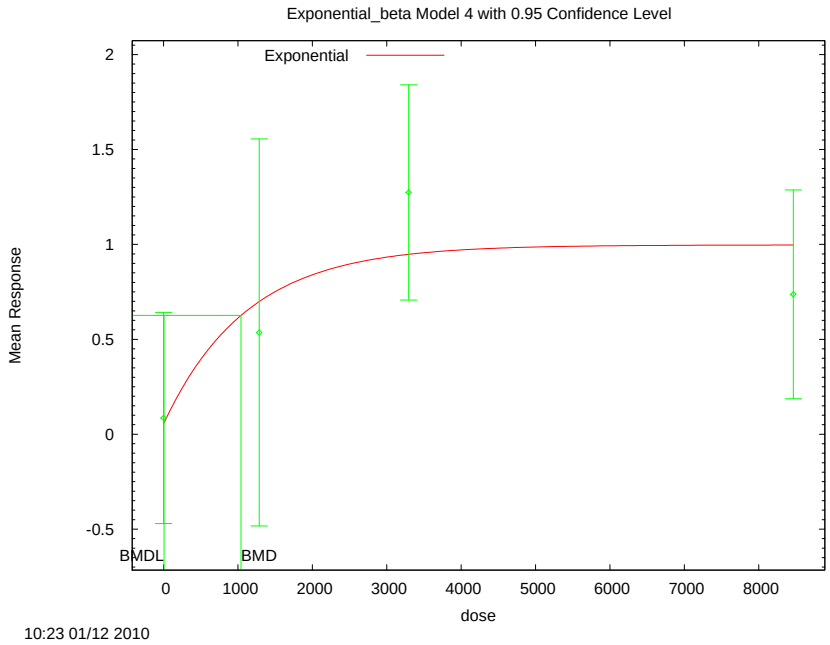
Model [a]	Degrees of Freedom	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
Hill	0	NA	6.465	1.320E+03	4.017E-04	
linear	2	0.009	9.126	1.070E+04	4.762E+03	
polynomial	2	0.009	9.126	1.070E+04	4.762E+03	
power	2	0.009	9.126	1.070E+04	4.762E+03	power bound hit
exponential (M2)	2	0.007	9.614	1.284E+04	6.859E+03	
exponential (M3)	1	0.001	12.870	2.720E+08	1.522E+05	
exponential (M4) [c]	1	0.054	5.490	1.041E+03	4.944E+00	
exponential (M5)	0	N/A	6.465	1.367E+03	1.245E+01	

[a] Constant variance model selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model, BMDS output presented in this appendix

E.2.10.2. *Figure for Selected Model: Exponental (M4)*



Hojo et al., 2002: DRL reinforce per min

E.2.10.3. *Output File for Selected Model: Exponential (M4)*

Hojo et al., 2002: DRL reinforce per min

```
=====================================================================
          Exponential Model. (Version: 1.61;  Date: 7/24/2009)
          Input Data File: C:\1\Blood\21_Hojo_2002_DRL_rein_min_exp_ExpCV_1.(d)
          Gnuplot Plotting File:
                                                  Tue Jan 12 10:23:58 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	0.000197777
c	16.3733
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	-1.11954
rho	0
a	0.054752
b	0.000895762
c	18.2107
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	5	0.086	0.448
1285	5	0.536	0.821
3295	6	1.274	0.54
8465	5	0.737	0.443

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.05475	0.5713	0.1223
1285	0.6991	0.5713	-0.6381
3295	0.9478	0.5713	1.398
8465	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         1.255168           4       5.489665


   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                      3.721             1             0.05374


     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 =      1040.67

                 BMDL =      4.94408
```

E.2.11. Hojo et al. (2002): DRL Response Per Min

E.2.11.1. *Summary Table of BMDS Modeling Results*

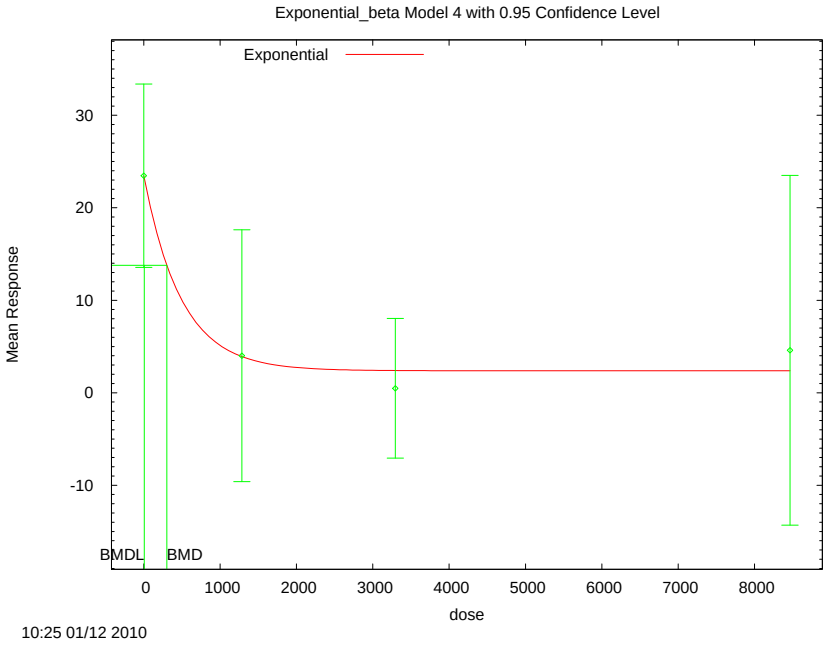
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.30	1.13	0.57	122.98	1.1E+03	error	constant variance, power restricted ≥1
exponential (M3)	2	0.30	1.13	0.57	122.98	1.1E+03	error	constant variance, power restricted ≥1
exponential (M4) [c]	**1**	**0.30**	**0.50**	**0.48**	**124.36**	**8.4E+02**	**5.6E+01**	**constant variance, power restricted ≥1**
exponential (M5)	0	0.30	0.50	N/A	126.35	2.0E+03	4.9E+01	constant variance, power restricted ≥1
Hill	0	0.30	0.50	NA	126.35	2.9E+03	3.2E-11	constant variance, n restricted >1
linear	2	0.30	11.00	0.00	132.86	3.7E+04	1.7E+04	constant variance
polynomial	2	0.30	11.00	0.00	132.86	3.7E+04	1.7E+04	constant variance
power	2	0.30	11.00	0.00	132.86	3.7E+04	1.7E+04	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.2.11.2. *Figure for Selected Model: Exponential (M4)*



Hojo et al., 2002: DRL response per min

E.2.11.3. *Output File for Selected Model: Exponential (M4)*

Hojo et al., 2002: DRL response per min

```
 ================================================================
         Exponential Model. (Version: 1.61;  Date: 7/24/2009)
         Input Data File: C:\1\Blood\23_Hojo_2002_DRL_resp_min_exp_ExpCV_1.(d)
         Gnuplot Plotting File:
                                                 Tue Jan 12 10:25:21 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	4.51689
rho(S)	0
a	24.6362
b	0.00047963
c	0.0184785
d	1

(S) = Specified

Parameter Estimates

Variable	Model 4
lnalpha	4.54096
rho	0
a	23.4674
b	0.00203802
c	0.101322
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	5	23.46	7.986
1285	5	4.013	10.96
3295	6	0.478	7.194
8465	5	4.594	15.23

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	23.47	9.684	-0.001011
1285	3.914	9.684	0.02275
3295	2.403	9.684	-0.487
8465	2.378	9.684	0.5117

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       -58.18012           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 =      301.607

              BMDL =      7.54952
```

E.2.12. Kattainen et al. (2001): 3rd Molar Mesio-Distal Length (Molar Development)

E.2.12.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	3	<0.0001	38.96	<0.0001	-122.90	6.4E+04	3.8E+04	nonconstant variance, power restricted ≥1
exponential (M3)	3	<0.0001	38.96	<0.0001	-122.90	6.4E+04	3.8E+04	nonconstant variance, power restricted ≥1
exponential (M4)	2	<0.0001	79.12	<0.0001	-80.75	error	error	nonconstant variance, power restricted ≥1
exponential (M5)	2	<0.0001	13.81	0.00	-146.06	8.5E+02	5.1E+02	nonconstant variance, power restricted ≥1
Hill [c]	**2**	**<.0001**	**8.72**	**0.01**	**-151.15**	**6.3E+02**	**3.4E+02**	**nonconstant variance, n restricted >1, bound hit**
Hill [d]	1	<.0001	2.92	0.09	-154.95	3.0E+00	2.9E-02	nonconstant variance, n unrestricted
linear	3	<.0001	39.59	<.0001	-122.28	7.4E+04	4.7E+04	nonconstant variance
polynomial	2	<.0001	36.61	<.0001	-123.26	3.0E+04	1.4E+04	nonconstant variance
power	3	<.0001	39.59	<.0001	-122.28	7.4E+04	4.7E+04	nonconstant variance, power restricted ≥1, bound hit

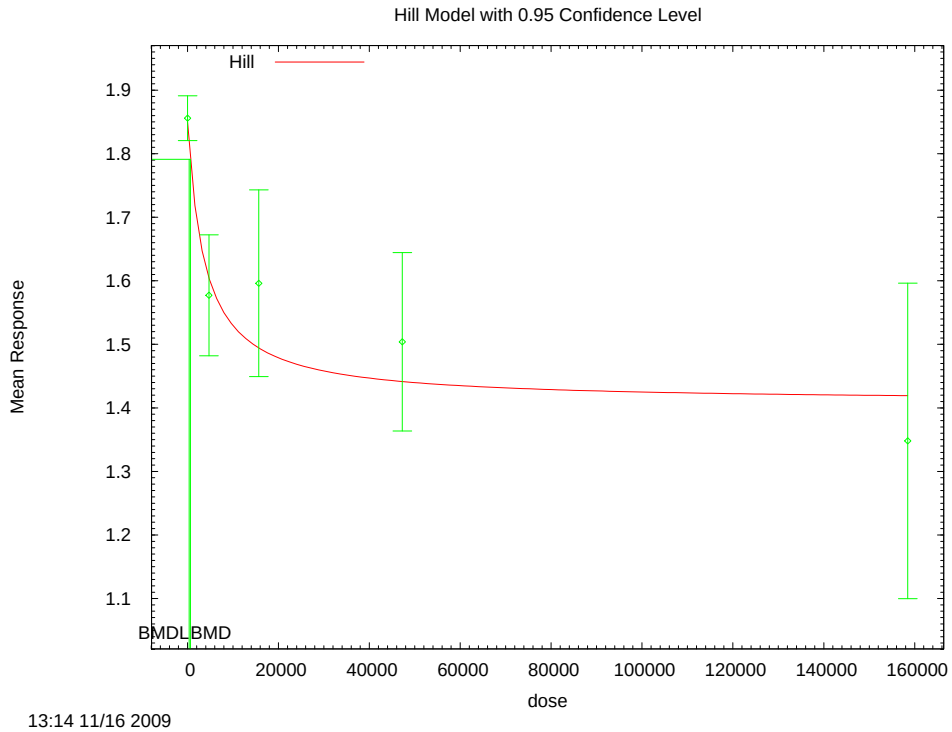
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.12.2. *Figure for Selected Model: Hill, Nonconstant Variance, n Restricted >1, Bound Hit*



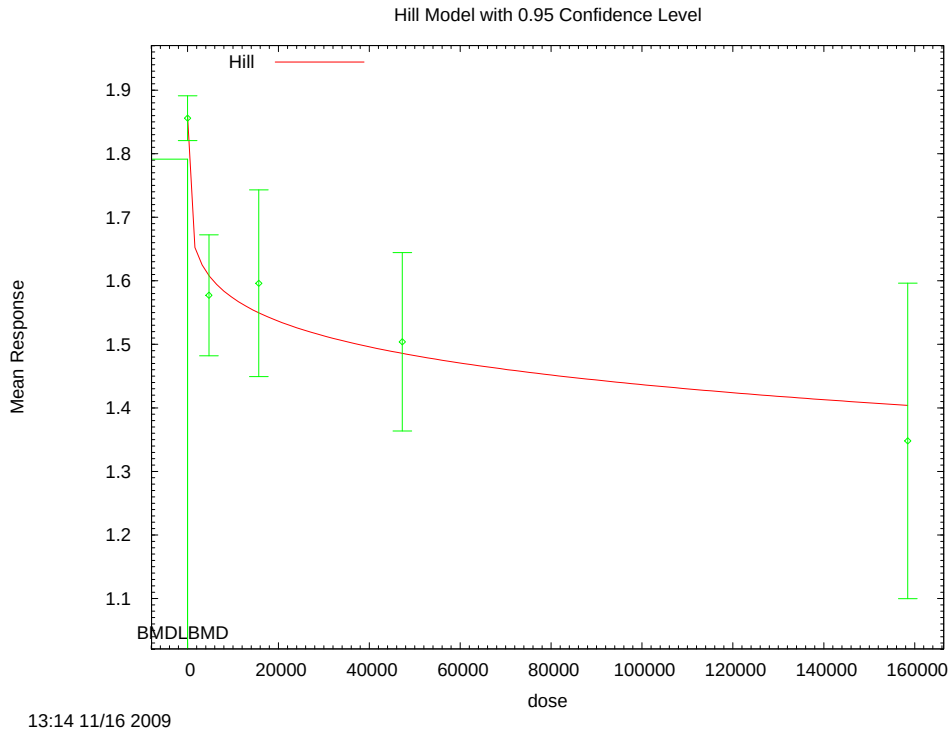
E.2.12.3. *Output File for Selected Model: Hill, Nonconstant Variance, n Restricted >1, Bound Hit*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Hill_BMR1_3rd_molar.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Hill_BMR1_3rd_molar.plt
                                                  Mon Nov 16 13:14:09 2009
 ================================================================

 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 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 = 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 =     0.825979
                              k =      4284.51


           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          3.34591          1.40451            0.593124              6.0987
            rho         -14.3329          2.62142            -19.4708            -9.19505
      intercept           1.8548        0.0159016             1.82364             1.88597
              v        -0.441028        0.0588146           -0.556302           -0.325753
              n                1                NA
              k          3764.75          1228.49             1356.95             6172.54

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
 4703    17       1.58         1.61        0.185        0.176         -0.767
1.568e+004    15        1.6          1.5        0.265        0.293           1.28
4.725e+004    12        1.5         1.45        0.221        0.378          0.527
1.585e+005    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          80.574735            5    -151.149469
              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              8.71916          2         0.01278

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 =        634.985

            BMDL =       335.879
```

E.2.12.4. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



E.2.12.5. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_3rd_molar.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_3rd_molar.plt
                                                Mon Nov 16 13:14:09 2009
 ================================================================

 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 =    0.825979
                            k =     4284.51


          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        0.012

 intercept        -0.18         0.22            1       -0.026       -0.058       0.0019

         v         0.18        -0.18       -0.026            1         0.52        -0.96

         n        -0.28         0.29       -0.058         0.52            1        -0.71

         k       -0.011        0.012       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          3.21867          1.42224           0.431136            6.00621
           rho         -14.0858          2.68326           -19.3449           -8.82671
     intercept          1.85564         0.016023            1.82424            1.88705
             v         -2.44363          2.81206           -7.95516            3.06791
             n         0.196843        0.0500689          0.0987096           0.294976
             k     2.75627e+008     2.27948e+009       -4.19207e+009       4.74332e+009


     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         0.0163
 4703    17       1.58          1.6        0.185         0.18         -0.597
1.568e+004    15        1.6         1.54        0.265        0.234          0.856
4.725e+004    12        1.5         1.48        0.221        0.316          0.259
1.585e+005    19       1.35          1.4        0.515        0.471         -0.465


 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	83.472636	6	-154.945271
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	2.92336	1	0.08731

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 = 2.96451

BMDL = 0.0287389

E.2.13. Kattainen et al. (2001): Females 3rd Molar Eruption

E.2.13.1. *Summary Table of BMDS Modeling Results*

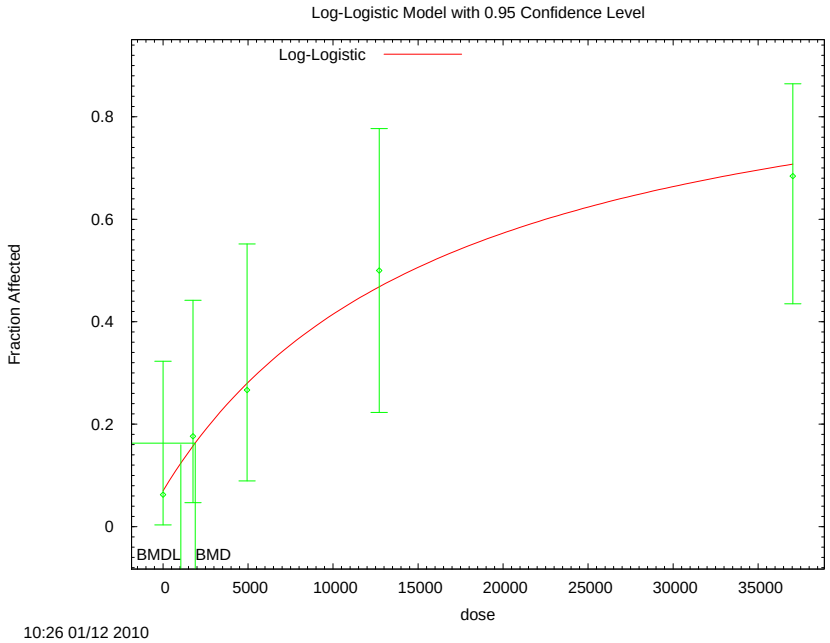
Model	Degrees of Freedom	χ^2 p-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
logistic	3	0.360	88.508	7.290E+03	5.273E+03	
log-logistic [b]	3	0.982	85.227	1.896E+03	1.050E+03	slope bound hit
log-probit, unrestricted	2	0.941	87.181	1.641E+03	1.895E+02	slope unrestricted
probit	3	0.379	88.352	6.958E+03	5.177E+03	
multistage, 4-degree	3	0.781	86.155	3.195E+03	2.076E+03	final ß=0
log-logistic, unrestricted [c]	2	0.949	87.162	1.527E+03	1.456E+02	slope unrestricted

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.13.2. *Figure for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*



Kattainen et al., 2001: 3rd molar eruption in pups

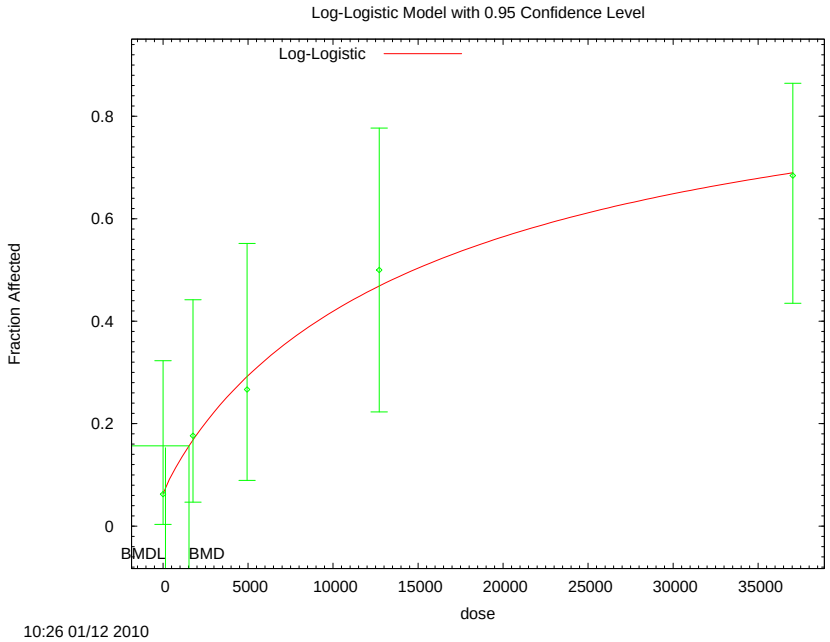
E.2.13.3. *Output File for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*

Kattainen et al., 2001: 3rd molar eruption in pups

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\24_Katt_2001_3molar_erup_LogLogistic_BMR1.(d)
         Gnuplot Plotting File:  C:\1\Blood\24_Katt_2001_3molar_erup_LogLogistic_BMR1.plt
                                                Tue Jan 12 10:26:06 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 =       -9.748
                         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        0.0699182            *               *                   *
      intercept         -9.74484            *               *                   *
          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        -40.6136         2      0.170098      3          0.9823
    Reduced model        -50.7341         1        20.411      4       0.0004142

              AIC:         85.2273


                                   Goodness  of  Fit
                                                                          Scaled
       Dose     Est._Prob.    Expected    Observed     Size       Residual
    ---------------------------------------------------------------------------
     0.0000     0.0699         1.119     1.000          16       -0.116
  1763.4151     0.1570         2.669     3.000          17        0.220
  4943.6112     0.2788         4.182     4.000          15       -0.105
 12712.0000     0.4670         5.604     6.000          12        0.229
 37039.0000     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 =        1896.22

            BMDL =        1049.96
```

E.2.13.4. *Figure for Unrestricted Model: Log-Logistic, Unrestricted*



Kattainen et al., 2001: 3rd molar eruption in pups

E.2.13.5. *Output File for Unrestricted Model: Log-Logistic, Slope Unrestricted*

Kattainen et al., 2001: 3rd molar eruption in pups

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\24_Katt_2001_3molar_erup_LogLogistic_Unrest_BMR1.(d)
         Gnuplot Plotting File:  C:\1\Blood\24_Katt_2001_3molar_erup_LogLogistic_Unrest_BMR1.plt
                                                 Tue Jan 12 10:26:07 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 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 =      -8.7855
                          slope =     0.902051


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.43         0.38

 intercept        -0.43            1        -0.99

     slope         0.38        -0.99            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0630017            *               *                   *
      intercept         -8.87185            *               *                   *
          slope         0.910471            *               *                   *

* - 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        -40.5812         3      0.105153      2          0.9488
   Reduced model        -50.7341         1        20.411      4       0.0004142
```

```
            AIC:         87.1623

                                  Goodness  of  Fit
                                                                          Scaled
      Dose      Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------------
     0.0000      0.0630         1.008     1.000          16       -0.008
  1763.4151      0.1684         2.862     3.000          17        0.089
  4943.6112      0.2922         4.383     4.000          15       -0.218
 12712.0000      0.4692         5.630     6.000          12        0.214
 37039.0000      0.6903        13.117    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 =        1526.84
            BMDL =        145.591
```

E.2.14. Kattainen et al., 2001: 3rd molar length in pups

E.2.14.1. *Summary Table of BMDS modeling results*

Model [a]	Degrees of Freedom	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	3	<0.0001	-124.869	1.319E+04	7.850E+03	
exponential (M3)	3	<0.0001	-124.869	1.319E+04	7.850E+03	power bound hit
exponential (M4)	2	0.002	-147.122	3.351E+02	2.001E+02	
exponential (M5)	2	0.002	-147.122	3.351E+02	2.001E+02	power bound hit
Hill [c]	2	0.022	-152.241	2.477E+02	1.328E+02	n lower bound hit
linear	3	<.0001	-124.026	1.567E+04	1.009E+04	
polynomial	4	<.0001	-84.747	error	error	
power	3	<.0001	-124.026	1.567E+04	1.009E+04	power bound hit
Hill, unrestricted [d]	1	<.0001	-78.747	2.007E+05	error	n unrestricted

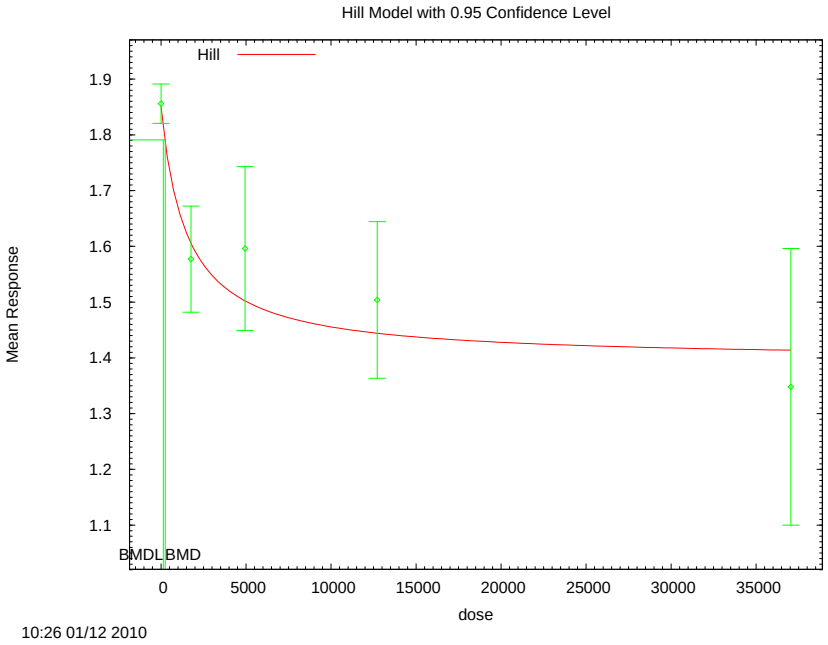
[a] Non-constant variance model selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model, BMDS output presented in this appendix

[d] Alternate model, BMDS output also presented in this appendix

E.2.14.2. *Figure for selected model: Hill*



Kattainen et al., 2001: 3rd molar length in pups

E.2.14.3. *Output for selected model: Hill*

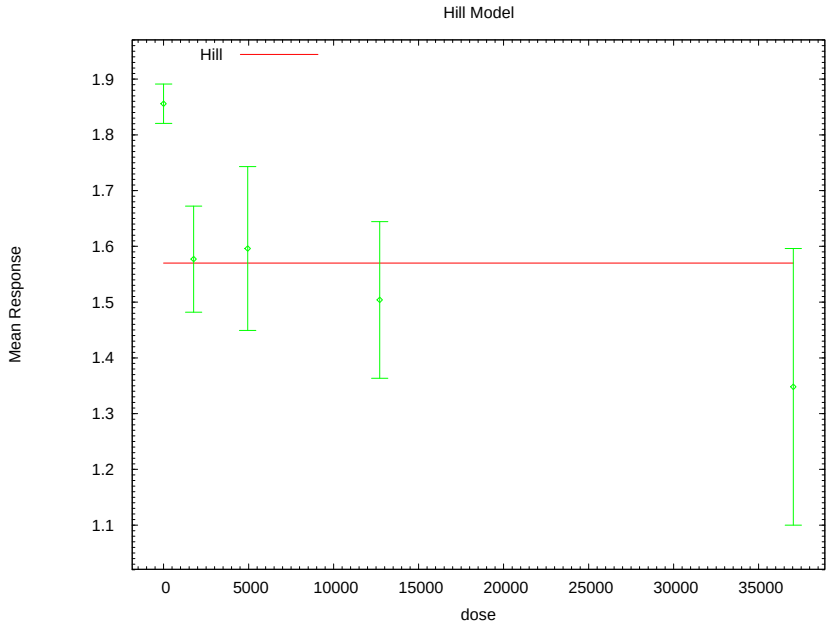
Kattainen et al., 2001: 3rd molar length in pups

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\Blood\25_Katt_2001_3molar_length_Hill_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\25_Katt_2001_3molar_length_Hill_1.plt
                                                 Tue Jan 12 10:26:49 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 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 = 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 =     0.845971
                              k =       1606.5


            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          3.31075          1.40399            0.558982             6.06253
              rho         -14.2656           2.6274            -19.4152            -9.11596
        intercept          1.85483        0.0159478             1.82357             1.88609
                v         -0.45369        0.0620284            -0.575263           -0.332116
                n                1               NA
                k          1512.49          494.187              543.903             2481.08

 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
  1763    17       1.58         1.61        0.185        0.175         -0.789
  4944    15        1.6         1.51        0.265         0.28           1.22
1.271e+004    12        1.5         1.45        0.221        0.371           0.51
3.704e+004    19       1.35         1.42        0.515        0.432         -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          81.120729           5    -152.241459
              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              7.62717          2         0.02207

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 =        247.728

            BMDL =       132.818
```

E.2.14.4. *Figure for additional model presented: Hill, unrestricted*



Kattainen et al., 2001: 3rd molar length in pups

E.2.14.5. *Output for additional model presented: Hill, unrestricted*

Kattainen et al., 2001: 3rd molar length in pups

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\Blood\25_Katt_2001_3molar_length_Hill_Unrest_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\25_Katt_2001_3molar_length_Hill_Unrest_1.plt
                                                Tue Jan 12 10:26:49 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 =     0.845971
                              k =       1606.5


            Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho    intercept            v            n            k

    lalpha      NA             NA             NA             NA             NA             NA

       rho      NA             NA             NA             NA             NA             NA

 intercept      NA             NA                  1      NA            0.00038      0.00013

         v      NA             NA             NA             NA             NA             NA

         n      NA             NA             0.00038      NA                  1         -1.1

         k      NA             NA             0.00013      NA               -1.1            1



                                  Parameter Estimates

                                                                95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha          7.01946              NA                  NA                  NA
            rho         -20.2971              NA                  NA                  NA
      intercept          1.57098              NA                  NA                  NA
              v          4.02956              NA                  NA                  NA
              n          13.2039              NA                  NA                  NA
              k           240356              NA                  NA                  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    16       1.86         1.57       0.0661        0.342           3.34
 1763    17       1.58         1.57        0.185        0.342         0.0747
 4944    15        1.6         1.57        0.265        0.342          0.284
1.271e+004    12        1.5         1.57        0.221        0.342          -0.68
3.704e+004    19       1.35         1.57        0.515        0.342          -2.85



 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	56.758717	6	-101.517434
A2	85.856450	10	-151.712901
A3	84.934314	7	-155.868628
fitted	45.373551	6	-78.747101
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	79.1215	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 = 200720

BMDL computation failed.

E.2.15. Keller et al. (2006): Missing Mandibular Molars in CBA J Mice

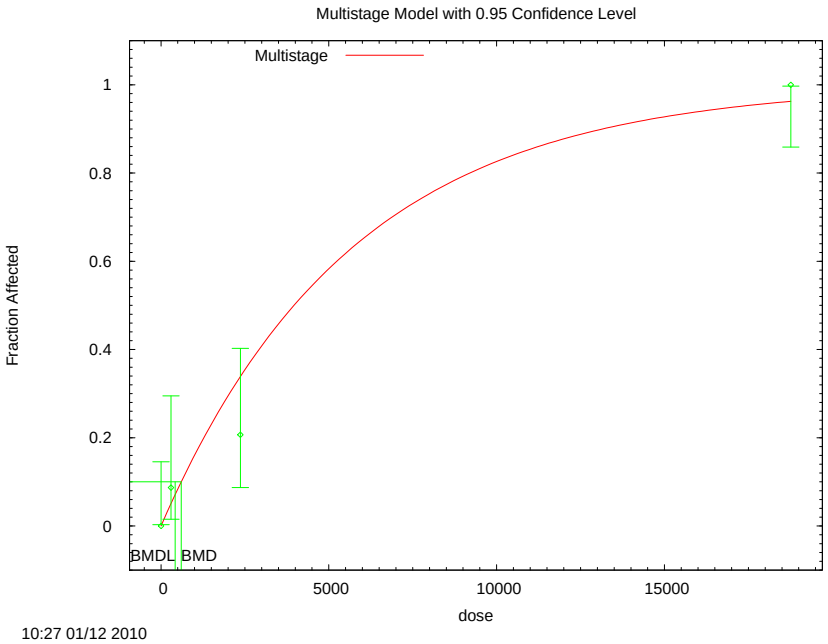
E.2.15.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 p-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	1	0.105	52.510	1.844E+03	4.959E+02	
logistic	2	0.334	49.984	1.692E+03	1.220E+03	
log-logistic	1	0.105	52.524	2.210E+03	1.330E+03	
log-probit, unrestricted	1	0.105	52.524	2.119E+03	1.336E+03	slope unrestricted
multistage, 1-degree [b]	3	0.255	50.434	6.014E+02	4.203E+02	
multistage, 2-degree	1	0.122	51.394	1.057E+03	5.324E+02	
multistage, 3-degree	1	0.150	50.855	9.452E+02	5.285E+02	
probit	2	0.342	49.905	1.614E+03	1.132E+03	
Weibull	1	0.108	52.221	1.514E+03	5.160E+02	

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model, BMDS output presented in this appendix

E.2.15.2. *Figure for Selected Model: Multistage, 1-Degree*



Keller et al., 2007: Missing molars

E.2.15.3. *Output File for Selected Model: Multistage, 1-Degree*

Keller et al., 2007: Missing molars

```
 ================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\1\Blood\26_Keller_2007_mand_molars_Multi1_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\26_Keller_2007_mand_molars_Multi1_1.plt
                                                 Tue Jan 12 10:27:33 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) = 5.51735e+015


           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)      0.000175192            *               *                   *

* - 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        -24.2169         1       5.27424      3          0.1528
   Reduced model         -71.326         1       99.4926      3         <.0001

           AIC:         50.4338


                                  Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          29        0.000
   296.0903     0.0506         1.163     2.000          23        0.797
  2364.8010     0.3392         9.837     6.000          29       -1.505
 18764.0000     0.9626        28.879    30.000          30        1.079

 Chi^2 = 4.06      d.f. = 3        P-value = 0.2547


    Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

              BMD =       601.401

             BMDL =       420.296

             BMDU =       862.599

Taken together, (420.296, 862.599) is a 90     % two-sided confidence
interval for the BMD
```

E.2.16. Kociba et al. (1978): Urinary Coproporphyrins, Females (Table 2)

E.2.16.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.03	18.65	<0.0001	82.98	1.3E+04	7.4E+03	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.03	18.65	<0.0001	82.98	1.3E+04	7.4E+03	nonconstant variance, power restricted ≥1
exponential (M4)	**1**	**0.03**	**7.49**	**0.01**	**73.82**	**8.6E+02**	**4.0E+02**	**nonconstant variance, power restricted ≥1**
exponential (M5)	0	0.03	0.72	N/A	69.05	3.4E+03	8.7E+02	nonconstant variance, power restricted ≥1
exponential (M5)	0	0.03	0.72	N/A	69.05	3.4E+03	8.7E+02	nonconstant variance, power unrestricted
Hill	0	0.03	0.72	NA	69.05	3.0E+03	error	nonconstant variance, n restricted >1
Hill	0	0.03	0.72	NA	69.05	3.0E+03	error	nonconstant variance, n unrestricted
linear	2	0.03	17.90	0.00	82.23	9.9E+03	2.1E+03	nonconstant variance
polynomial	2	0.03	17.90	0.00	82.23	9.9E+03	2.1E+03	nonconstant variance
power	2	0.03	17.90	0.00	82.23	9.9E+03	2.1E+03	nonconstant variance, power restricted ≥1, bound hit
power	1	0.03	12.36	0.00	78.69	6.3E+02	5.6E-06	nonconstant variance, power unrestricted
exponential (M2)	2	0.03	11.60	0.00	81.00	1.4E+04	9.5E+03	constant variance, power restricted ≥1
exponential (M3)	2	0.03	11.60	0.00	81.00	1.4E+04	9.5E+03	constant variance, power restricted ≥1
exponential (M4) [c]	1	0.03	4.05	0.04	75.44	1.4E+03	6.5E+02	constant variance, power restricted ≥1
exponential (M5)	0	0.03	0.41	N/A	73.80	3.5E+03	8.8E+02	constant variance, power restricted ≥1
exponential (M5) [d]	0	0.03	0.41	N/A	73.80	3.5E+03	8.8E+02	constant variance, power unrestricted
Hill	0	0.03	0.41	NA	73.80	3.3E+03	error	constant variance, n restricted >1
Hill [d]	0	0.03	0.41	NA	73.80	3.3E+03	error	constant variance, n unrestricted
linear	2	0.03	11.02	0.00	80.41	1.1E+04	7.3E+03	constant variance
polynomial	2	0.03	11.02	0.00	80.41	1.1E+04	7.3E+03	constant variance

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
power	2	0.03	11.02	0.00	80.41	1.1E+04	7.3E+03	constant variance, power restricted ≥1, bound hit
power [d]	1	0.03	7.99	0.00	79.38	2.5E+03	1.9E+02	constant variance, power unrestricted

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.17. Kociba et al. (1978): Uroporphyrin per Creatinine, Females

E.2.17.1. *Summary Table of BMDS Modeling Results*

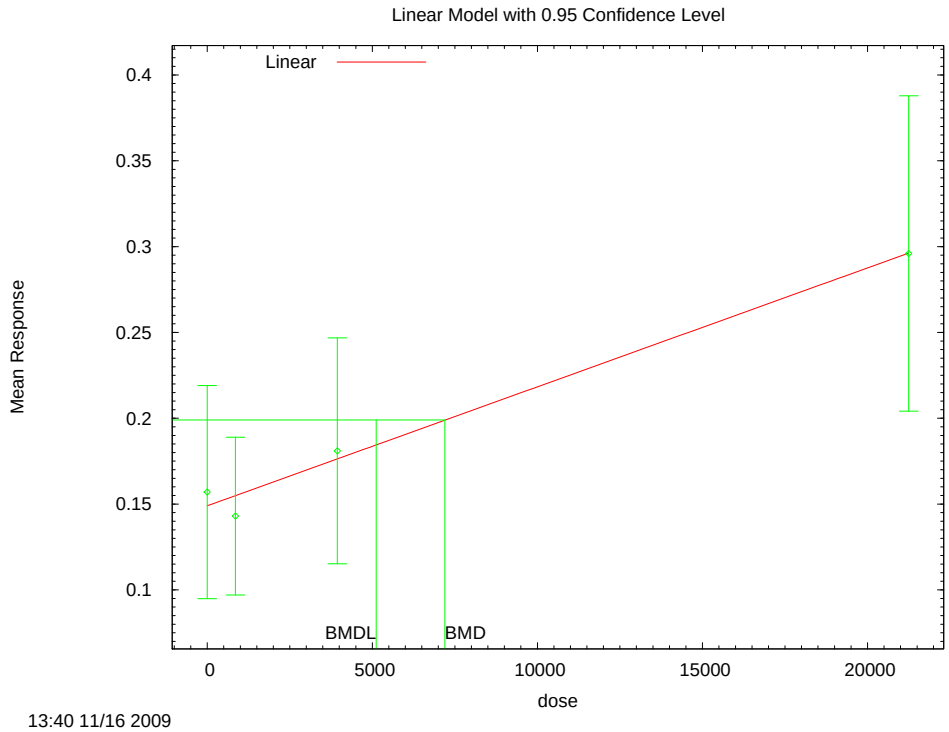
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.49	1.09	0.58	-93.46	7.6E+03	5.3E+03	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.49	1.09	0.58	-93.46	7.6E+03	5.3E+03	nonconstant variance, power restricted ≥1
exponential (M4)	1	0.49	0.97	0.32	-91.57	5.7E+03	1.9E+03	nonconstant variance, power restricted ≥1
exponential (M5)	0	0.49	0.51	N/A	-90.03	4.0E+03	2.0E+03	nonconstant variance, power restricted ≥1
Hill	0	0.49	0.51	NA	-90.03	4.1E+03	2.0E+03	nonconstant variance, n restricted >1
linear	2	0.49	0.98	0.61	-93.57	5.9E+03	3.7E+03	nonconstant variance
polynomial	2	0.49	0.98	0.61	-93.57	5.9E+03	3.7E+03	nonconstant variance
power	1	0.49	0.97	0.33	-91.58	6.3E+03	3.7E+03	nonconstant variance, power restricted ≥1
exponential (M2)	2	0.49	0.56	0.75	-93.83	9.0E+03	6.9E+03	constant variance, power restricted ≥1
exponential (M3)	2	0.49	0.56	0.75	-93.83	9.0E+03	6.9E+03	constant variance, power restricted ≥1
exponential (M4)	1	0.49	0.46	0.50	-91.93	6.7E+03	2.2E+03	constant variance, power restricted ≥1
exponential (M5)	0	0.49	0.20	N/A	-90.19	4.2E+03	2.3E+03	constant variance, power restricted ≥1
linear [c]	**2**	**0.49**	**0.46**	**0.79**	**-93.93**	**7.2E+03**	**5.1E+03**	**constant variance**
polynomial	2	0.49	0.46	0.79	-93.93	7.2E+03	5.1E+03	constant variance

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.2.17.2. *Figure for Selected Model: Linear, Constant Variance*



13:40 11/16 2009

E.2.17.3. *Output File for Selected Model: Linear, Constant Variance*

```
 ========================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File:
C:\USEPA\BMDS21\AD\Blood\LinearConstVar_BMR1_Females_uroporphyrin_per_creatinine.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\LinearConstVar_BMR1_Females_uroporphyrin_per_creatinine.plt
                                                    Mon Nov 16 13:40:10 2009
 ========================================================================

 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 = 6.92935e-006


             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    -5.8e-012     2.2e-011

       beta_0    -5.8e-012            1         -0.6

       beta_1     2.2e-011         -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            0.121762            0.176517
            beta_1     6.92935e-006     1.29185e-006        4.39737e-006        9.46132e-006


         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
 852.5     5      0.143        0.155        0.037       0.0499          -0.54
  3942     5      0.181        0.176        0.053       0.0499          0.204
2.125e+004     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           49.963861            3     -93.927722
                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             0.462975          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 =        7197.95


             BMDL =        5116.98
```

E.2.18. Latchoumycandane and Mathur (2002): Daily Sperm Production

E.2.18.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.85	19.80	<0.0001	94.90	1.2E+04	5.7E+03	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.85	19.80	<0.0001	94.90	1.2E+04	5.7E+03	nonconstant variance, power restricted ≥1
exponential (M4)	1	0.85	0.16	0.69	77.26	1.0E+02	3.9E+01	nonconstant variance, power restricted ≥1
exponential (M5)	1	0.85	0.16	0.69	77.26	1.0E+02	3.9E+01	nonconstant variance, power restricted ≥1
Hill	1	0.85	0.00	0.95	77.10	6.3E+01	6.2E+00	nonconstant variance, n restricted >1, bound hit
Hill	0	0.85	0.00	NA	79.10	5.1E+01	1.7E-05	nonconstant variance, n unrestricted
linear	2	0.85	20.13	<.0001	95.23	1.3E+04	7.3E+03	nonconstant variance
polynomial	1	0.85	9.62	0.00	86.72	1.4E+03	7.9E+02	nonconstant variance
power	2	0.85	20.13	<.0001	95.23	1.3E+04	7.3E+03	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	2	0.85	20.71	<0.0001	93.82	9.6E+03	5.2E+03	constant variance, power restricted ≥1
exponential (M3)	2	0.85	20.71	<0.0001	93.82	9.6E+03	5.2E+03	constant variance, power restricted ≥1
exponential (M4) [d]	1	0.85	0.15	0.70	75.26	1.1E+02	4.4E+01	constant variance, power restricted ≥1
exponential (M5)	0	0.85	0.15	N/A	77.26	1.6E+02	4.4E+01	constant variance, power restricted ≥1
Hill, rextricted [c]	**1**	**0.85**	**0.00**	**0.98**	**118.11**	**3.40E+02**	**1.51E-02**	**constant variance, n restricted >1, bound hit**
Hill, unrestricted [d]	0	0.85	0.00	NA	120.11	**3.32E+02**	**8.77E-03**	constant variance, n unrestricted
linear	2	0.85	21.13	<.0001	94.24	1.1E+04	6.7E+03	constant variance
polynomial	1	0.85	11.01	0.00	86.13	1.1E+03	7.1E+02	constant variance
power	2	0.85	21.13	<.0001	94.24	1.1E+04	6.7E+03	constant variance, power restricted ≥1, bound hit

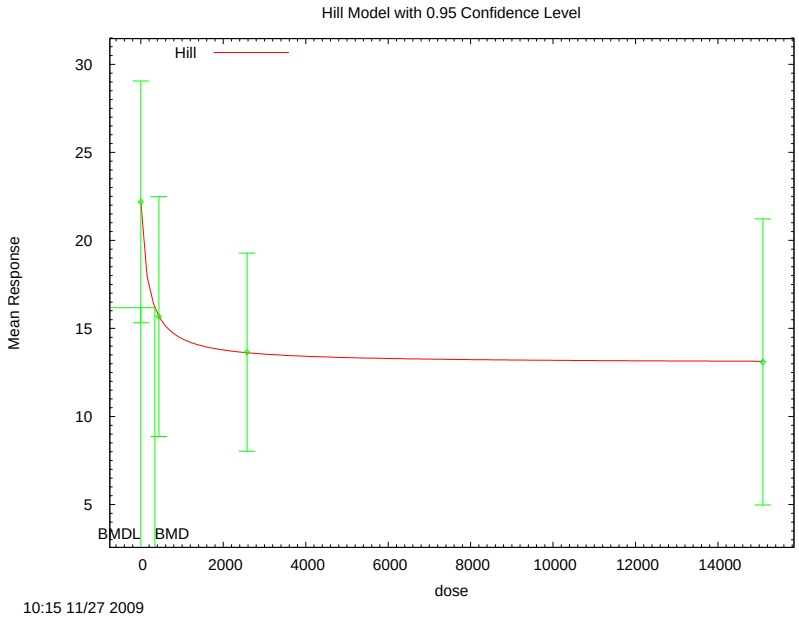
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.18.2. *Figure for Selected Model: Hill, Constant Variance, n Restricted >1, Bound Hit*



E.2.18.3. *Output File for Selected Model: Hill, Constant Variance, n Restricted >1, Bound Hit*

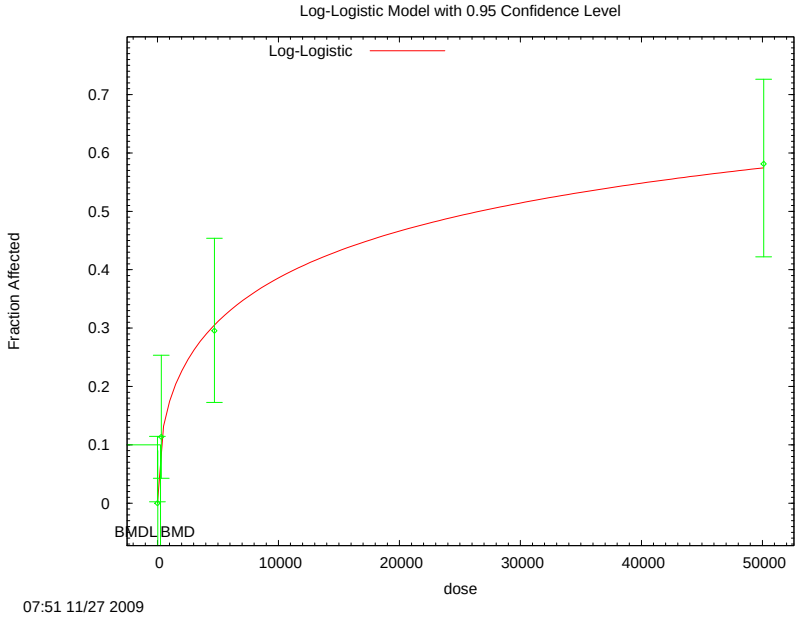
```
================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\Usepa\Bmds2\Data\HilTCDSet.(d)
        Gnuplot Plotting File:  C:\Usepa\Bmds2\Data\HilTCDSet.plt
                                              Fri Nov 27 10:15:04 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = m_sperm
   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 =      43.3822
                               rho =            0   Specified
                         intercept =        22.19
                                 v =        -9.09
                                 n =      1.93174
                                 k =      304.417


             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     6.6e-010    -7.3e-008     6.3e-008

 intercept     6.6e-010             1        -0.75        -0.23

           v    -7.3e-008        -0.75            1        -0.24

           k     6.3e-008        -0.23        -0.24            1


                                  Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
          alpha          36.1524          10.4363             15.6976
56.6072
      intercept          22.1894          2.45468             17.3783
27.0005
              v         -9.16864           3.2083            -15.4568            -
2.88049
              n                1               NA
              k           178.32          300.643            -410.929
767.569

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         6.54         6.01       0.000252
436.7     6       15.7         15.7         6.49         6.01       -0.00371
 2579     6       13.7         13.6         5.36         6.01         0.0148
1.509e+004     6       13.1         13.1         7.74         6.01        -0.0113
```

```
 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          -55.052739            5     120.105478
              A2          -54.653533            8     125.307067
              A3          -55.052739            5     120.105478
          fitted          -55.052919            4     118.105839
               R          -58.755106            2     121.510213


                    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              8.20315          6          0.2236
   Test 2             0.798411          3          0.8498
   Test 3             0.798411          3          0.8498
   Test 4          0.000361116          1          0.9848

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 =       339.732

            BMDL =      0.015111
```

E.2.18.4. *Figure for Unrestricted Model: Hill, Constant Variance, n Unrestricted*



E.2.18.5. *Output File for Unrestricted Model: Hill, Constant Variance, n Unrestricted*

```
=================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\Usepa\Bmds2\Data\LogTcdSet.(d)
        Gnuplot Plotting File:  C:\Usepa\Bmds2\Data\LogTcdSet.plt
                                          Fri Nov 27 07:51:12 2009
 =================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = r_skin
   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 =     -4.78342
                          slope =     0.469549


           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        -0.98

     slope        -0.98            1



                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0            *                *                  *
      intercept         -4.84059            *                *                  *
          slope         0.475472            *                *                  *

* - 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        -71.5376         2     0.0398444      2          0.9803
  Reduced model        -95.8498         1       48.6642      3         <.0001

           AIC:         147.075


                                 Goodness  of  Fit
                                                                  Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
```

```
     0.0000     0.0000         0.000     0.000          38        0.000
   316.0000     0.1087         4.784     5.000          44        0.105
  4714.0000     0.3060        13.464    13.000          44       -0.152
 50105.0000     0.5756        24.753    25.000          43        0.076

  Chi^2 = 0.04      d.f. = 2        P-value = 0.9803


    Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =        259.682

            BMDL =         31.788
```

E.2.19. Li et al. (1997): Follicle-Stimulating Hormone

E.2.19.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	8	<0.0001	1095.433	2.898E+05	2.286E+05	
exponential (M3)	8	<0.0001	1095.433	2.898E+05	2.286E+05	power bound hit
exponential (M4)	7	<0.0001	1059.480	1.891E+04	5.471E+03	
exponential (M5)	6	<0.0001	1066.195	6.118E+04	4.729E+02	
Hill	7	<.0001	1056.455	2.993E+03	1.081E+03	n lower bound hit
linear	8	<.0001	1077.819	1.109E+05	7.503E+04	
polynomial	9	<.0001	1155.670	error	error	
power [c]	8	<.0001	1077.819	1.109E+05	7.503E+04	power bound hit
Hill, unrestricted	6	0.001	1039.476	1.206E+02	error	n unrestricted
power, unrestricted [d]	7	0.002	1037.471	1.078E+02	1.353E+01	power unrestricted

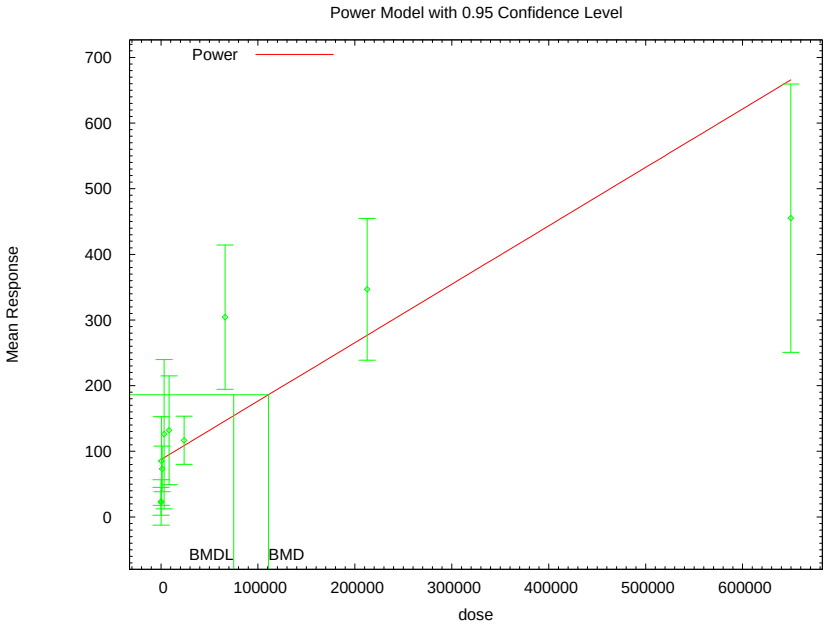
[a] Non-constant variance model selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model, BMDS output presented in this appendix

[d] Alternate model, BMDS output also presented in this appendix

E.2.19.2. *Figure for Selected Model: Power*



Li et al., 1997: FSH

E.2.19.3. *Output for Selected Model: Power*

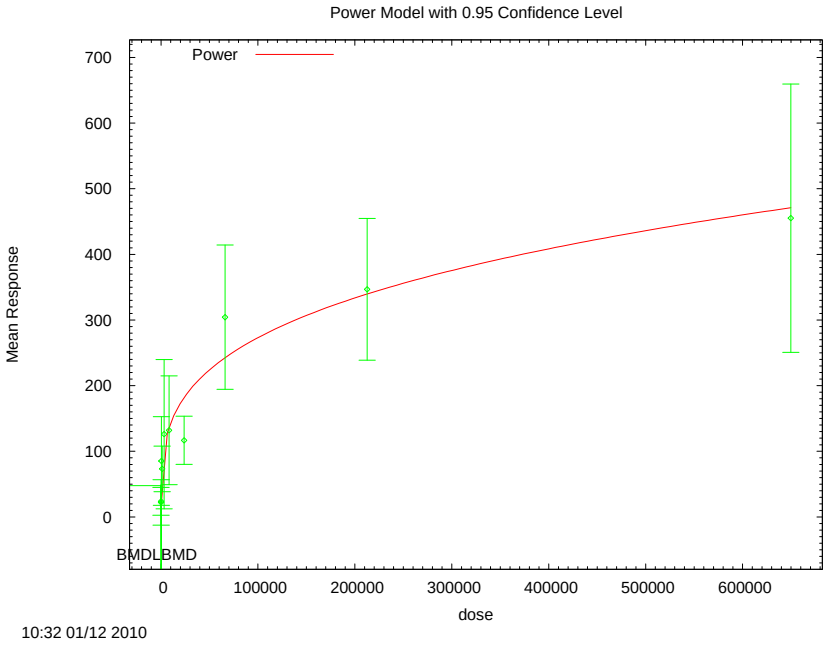
Li et al., 1997: FSH

```
 ===============================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\Blood\72_Li_1997_FSH_Power_BMR1.(d)
         Gnuplot Plotting File:  C:\1\Blood\72_Li_1997_FSH_Power_BMR1.plt
                                                Tue Jan 12 10:32:04 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 =      8.17907
                            power =     0.293959


             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       -0.035

          rho        -0.99            1          0.2        0.035

      control        -0.29          0.2            1        -0.36

        slope       -0.035        0.035        -0.36            1


                                  Parameter Estimates

                                                          95.0% Wald Confidence Interval
          Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
            lalpha          3.49167          1.22596             1.08884             5.89451
               rho          1.27289         0.242042            0.798492             1.74728
           control          87.5089          12.9454             62.1364             112.881
             slope      0.000889717      0.000166742        0.000562908         0.00121653
             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         87.5         29.6         98.7          -2.04
146.5    10       22.2         87.6         48.5         98.8           -2.1
440.1    10       85.2         87.9         94.3           99        -0.0854
 1156    10       73.3         88.5         48.5         99.4         -0.485
 3232    10        126         90.4          159          101           1.12
 8266    10        132         94.9          116          104           1.13
2.388e+004    10        117          109          51.2          113          0.224
6.608e+004    10        304          146           154          137           3.65
2.127e+005    10        347          277           151          205           1.08
6.497e+005    10        455          666           286          359          -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        -534.909723           4    1077.819445
             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              64.4002          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 = 110907


             BMDL = 75025.9
```

E.2.19.4. *Figure for Unrestricted Model: Power, Unrestricted*



Li et al., 1997: FSH

E.2.19.5. *Output for Unrestricted Model: 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_Power_Unrest_BMR1.(d)
         Gnuplot Plotting File:  C:\1\Blood\72_Li_1997_FSH_Power_Unrest_BMR1.plt
                                                Tue Jan 12 10:32:11 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 =      8.17907
                          power =     0.293959


            Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho      control        slope        power

     lalpha            1        -0.99        -0.69        -0.17         0.26

        rho        -0.99            1         0.65         0.13        -0.23

    control        -0.69         0.65            1        -0.12        0.029

      slope        -0.17         0.13        -0.12            1        -0.97

      power         0.26        -0.23        0.029        -0.97            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha           3.6735          1.12114              1.4761              5.8709
            rho          1.17908         0.221492            0.744961             1.61319
        control          15.8235           6.8753             2.34812             29.2988
          slope          7.68345          2.90499             1.98976             13.3771
          power          0.30464        0.0336473            0.238692            0.370587


      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
146.5    10       22.2         50.9         48.5         63.7          -1.43
440.1    10       85.2         64.9         94.3         73.5          0.875
 1156    10       73.3         81.7         48.5         84.1         -0.315
 3232    10        126          106          159         98.1          0.652
 8266    10        132          136          116          114         -0.102
2.388e+004    10        117          181         51.2          135          -1.52
6.608e+004    10        304          242          154          160           1.24
2.127e+005    10        347          338          151          194          0.139
6.497e+005    10        455          469          286          236         -0.187


 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	-513.735602	5	1037.471204
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	22.052	7	0.002489

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 = 107.761

BMDL = 13.5336

E.2.20. Li et al. (2006): Hormone Levels (Estradiol)

E.2.20.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.44	4.95	0.08	271.02	7.7E+03	2.8E+03	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.44	4.95	0.08	271.02	7.7E+03	2.8E+03	nonconstant variance, power restricted ≥1
exponential (M4)	1	0.44	0.34	0.56	268.41	error	error	nonconstant variance, power restricted ≥1
exponential (M5)	0	0.44	0.34	N/A	270.41	error	error	nonconstant variance, power restricted ≥1
exponential (M5)	0	0.44	0.34	N/A	270.41	error	error	nonconstant variance, power unrestricted
Hill	1	0.44	0.34	0.56	268.41	error	error	nonconstant variance, n restricted >1
linear	2	0.44	4.87	0.09	270.95	8.7E+03	2.7E+03	nonconstant variance
polynomial	2	0.44	4.87	0.09	270.95	8.7E+03	2.7E+03	nonconstant variance
power	2	0.44	4.87	0.09	270.95	8.7E+03	2.7E+03	nonconstant variance, power restricted ≥1, bound hit
power	2	0.44	0.34	0.84	266.41	2.8E+05	error	nonconstant variance, power unrestricted
exponential (M2)	2	0.44	3.72	0.16	269.03	7.8E+03	3.1E+03	constant variance, power restricted ≥1
exponential (M3)	2	0.44	3.72	0.16	269.03	7.8E+03	3.1E+03	constant variance, power restricted ≥1
exponential (M4)	1	0.44	0.91	0.34	268.21	error	error	constant variance, power restricted ≥1
exponential (M5)	0	0.44	0.91	N/A	270.21	error	error	constant variance, power restricted ≥1
exponential (M5) [d]	0	0.44	0.91	N/A	270.21	error	error	constant variance, power unrestricted
Hill	0	0.44	0.91	NA	270.21	error	error	constant variance, n restricted >1
Hill [d]	0	0.44	0.96	NA	270.26	5.1E+15	5.1E+15	constant variance, n unrestricted
linear [c]	**2**	**0.44**	**3.65**	**0.16**	**268.95**	**8.8E+03**	**3.0E+03**	**constant variance**
polynomial	2	0.44	3.65	0.16	268.95	8.8E+03	3.0E+03	constant variance
power	2	0.44	3.65	0.16	268.95	8.8E+03	3.0E+03	constant variance, power restricted ≥1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
power [d]	1	0.44	0.96	0.33	268.27	5.2E+13	error	constant variance, power unrestricted

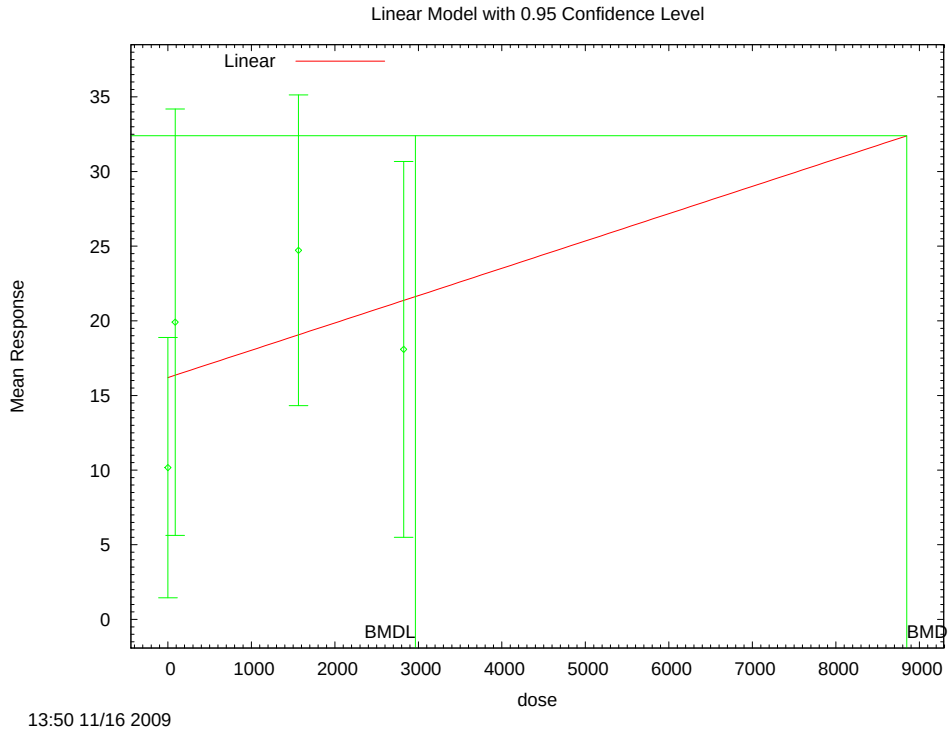
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.20.2. *Figure for Selected Model: Linear, Constant Variance*



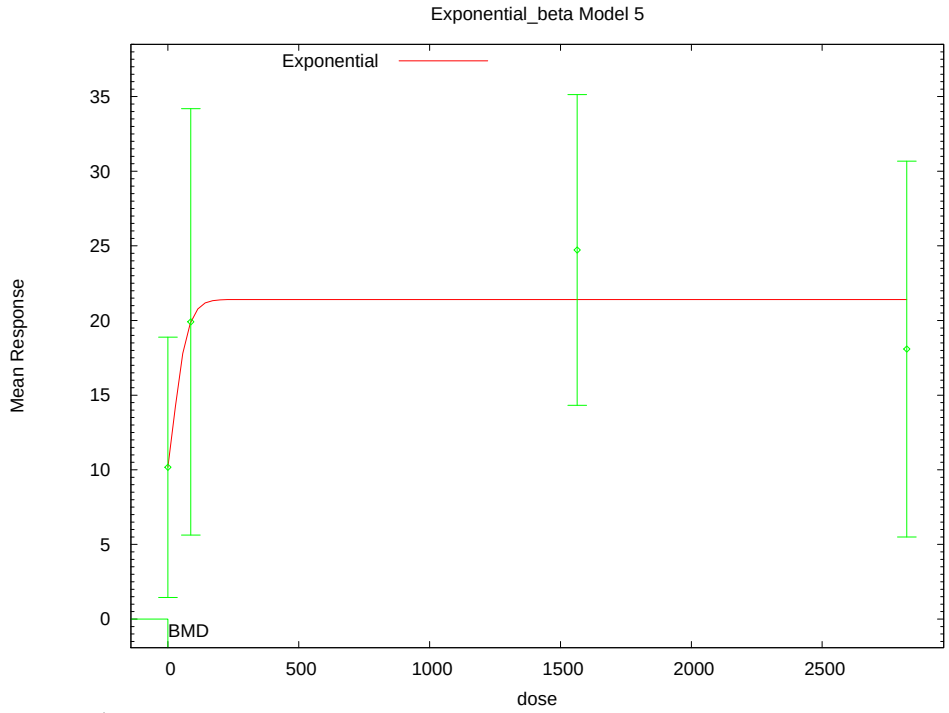
E.2.20.3. *Output File for Unrestricted Model: Linear, Constant Variance*

```
 ========================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\LinearConst_BMR1_Li_Estradiol_3d.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\LinearConst_BMR1_Li_Estradiol_3d.plt
                                                 Mon Nov 16 13:50:03 2009
 ========================================================================

 Figure 3, 3-day estradiol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =      267.211
                            rho =            0   Specified
                         beta_0 =      16.1706
                         beta_1 =   0.00183421


           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     2.7e-011     6.4e-013

     beta_0     2.7e-011            1        -0.69

     beta_1     6.4e-013        -0.69            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha          263.435          58.9058            147.981             378.888
         beta_0           16.1706          3.55948            9.19411              23.147
         beta_1       0.00183421       0.00220486        -0.00248724          0.00615566


      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
87.49    10       19.9         16.3           20         16.2          0.697
 1564    10       24.7           19         14.6         16.2           1.11
 2823    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        -131.476105            3     268.952210
              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              3.64516          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 =        8848.86


             BMDL =       2963.62
```

E.2.20.4. *Figure for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*



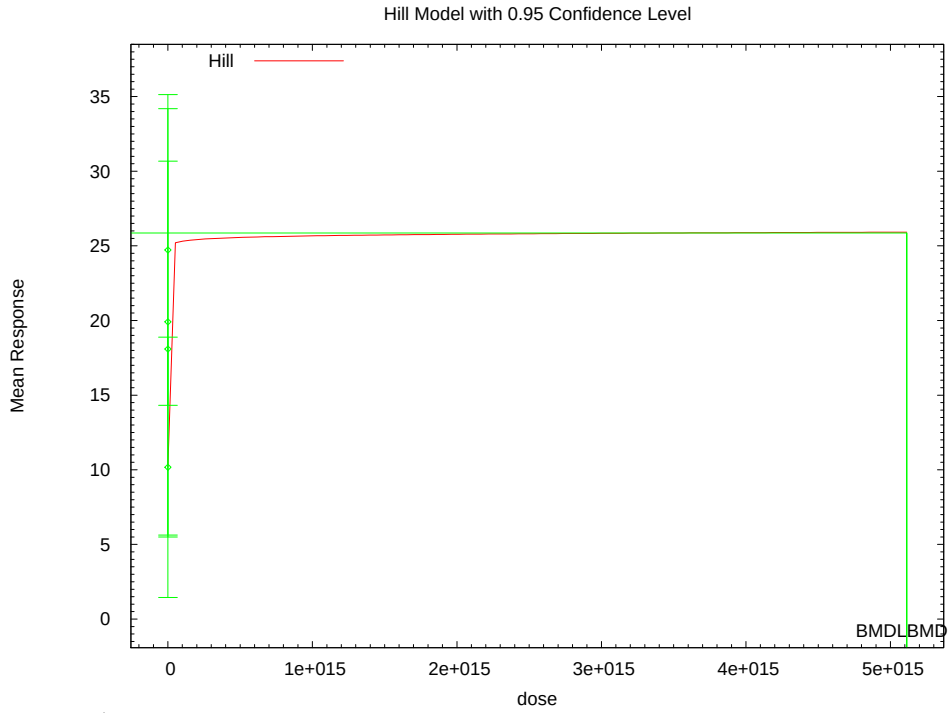
E.2.20.5. *Output File for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\ExpConst_Unrest_BMR1_Li_Estradiol_3d.(d)
         Gnuplot Plotting File:
                                                  Mon Nov 16 13:50:07 2009
 ================================================================

 Figure 3, 3-day estradiol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 5
                --------          --------
                  lnalpha             5.48268
                      rho(S)                0
                        a             9.65979
                        b          0.000592388
                        c             2.68754
                        d                    1

  (S) = Specified


                   Parameter Estimates

                 Variable          Model 5
                 --------          -------
                  lnalpha           5.50531
                      rho                 0
                        a           10.1682
                        b         0.0192802
                        c           2.10526
                        d            1.3399

  NC = No Convergence


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0     10        10.17        12.18
  87.49     10        19.91        19.97
   1564     10        24.72        14.55
   2823     10        18.09         17.6


              Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         10.17        15.68       2.254e-007
  87.49         19.91        15.68      -2.355e-007
   1564         21.41        15.68            0.669
   2823         21.41        15.68           -0.669


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       -129.6535           5      269.3071
                        A2       -128.2947           8      272.5893
                        A3       -129.6535           5      269.3071
                         R       -131.8192           2      267.6383
                         5       -130.1062           5      270.2123


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 7a: Does Model 5 fit the data? (A3 vs 5)


                            Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                       7.049            6             0.3163
  Test 2                       2.718            3             0.4372
  Test 3                       2.718            3             0.4372
 Test 7a                      0.9053            0                N/A


  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.

  Degrees of freedom for Test 7a are less than or equal to 0.
  The Chi-Square test for fit is not valid.


Benchmark Dose Computations:

  Specified Effect = 1.000000

         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD = Not_Computed

              BMDL =            0
```

E.2.20.6. *Figure for Unrestricted Model: Hill, Constant Variance, n Unrestricted*



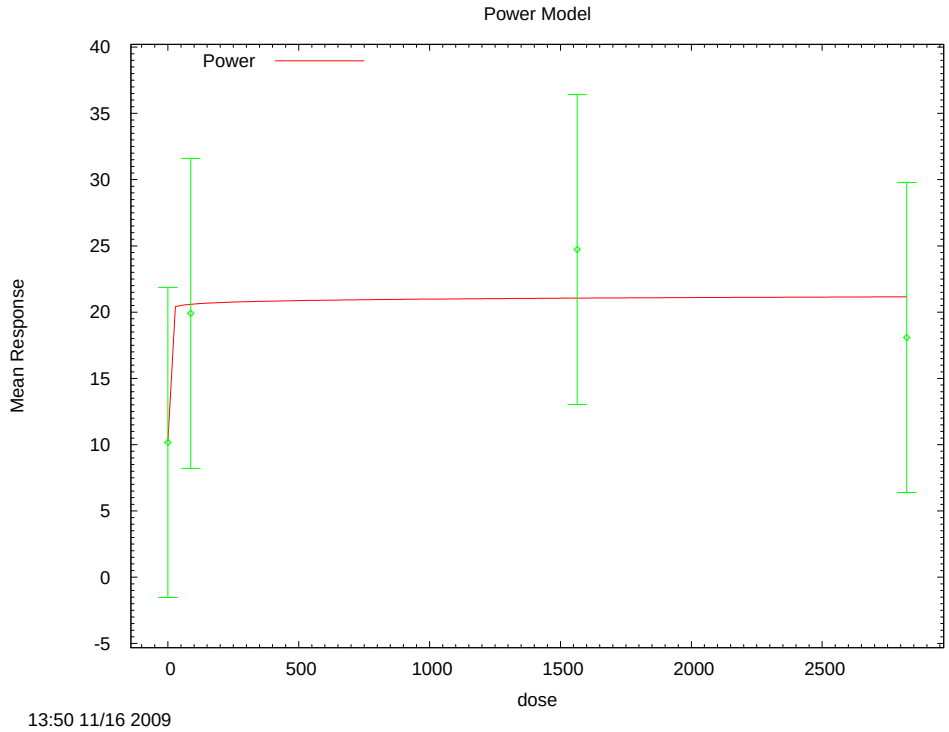
E.2.20.7. *Output File for Unrestricted Model: Hill, Constant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\HillConst_Unrest_BMR1_Li_Estradiol_3d.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\HillConst_Unrest_BMR1_Li_Estradiol_3d.plt
                                                  Mon Nov 16 13:50:08 2009
 ================================================================

 Figure 3, 3-day estradiol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 =      267.211
                              rho =            0   Specified
                        intercept =      10.1682
                                v =      14.5566
                                n =    0.0272301
                                k =      109.605


            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     9.3e-007      NA             0.00038      NA

    intercept     9.3e-007            1      NA               0.047      NA

            v       NA             NA             NA             NA             NA

            n       0.00038        0.047      NA                1      NA

            k       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
             alpha          246.316              NA                NA                  NA
         intercept           10.168              NA                NA                  NA
                 v          23.0562              NA                NA                  NA
                 n         0.030228              NA                NA                  NA
                 k          68005.7              NA                NA                  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       10.2         10.2         12.2         15.7      4.22e-005
   87.49    10       19.9         20.5           20         15.7         -0.127
    1564    10       24.7           21         14.6         15.7          0.743
    2823    10       18.1         21.1         17.6         15.7         -0.615

   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         -129.653527            5     269.307054
              A2         -128.294657            8     272.589314
              A3         -129.653527            5     269.307054
           fitted        -130.132269            5     270.264537
                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             0.957483          0              NA

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

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 =   5.11313e+015

            BMDL =  5.11313e+015
```

E.2.20.8. *Figure for Unrestricted Model: Power, Constant Variance, Power Unrestricted*



E.2.20.9. *Output File for Unrestricted Model: Power, Constant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\PowerConst_Unrest_BMR1_Li_Estradiol_3d.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\PowerConst_Unrest_BMR1_Li_Estradiol_3d.plt
                                                  Mon Nov 16 13:50:08 2009
 ================================================================

 Figure 3, 3-day estradiol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 = 267.211
rho = 0 Specified
control = 10.1682
slope = 10.1311
power = 0.00388985

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	3.9e-009	-6.4e-009	1.1e-008
control	3.9e-009	1	-0.4	0.038
slope	-6.4e-009	-0.4	1	-0.91
power	1.1e-008	0.038	-0.91	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	246.319	55.0786	138.367	354.271
control	10.1675	4.96274	0.440676	19.8943
slope	9.71449	12.3808	-14.5514	33.9803
power	0.0151875	0.171197	-0.320352	0.350727

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	10.2	12.2	15.7	0.000148
87.49	10	19.9	20.6	20	15.7	-0.132
1564	10	24.7	21	14.6	15.7	0.744
2823	10	18.1	21.1	17.6	15.7	-0.612

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	-130.132565	4	268.265130
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	0.958076	1	0.3277

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 = 5.21395e+013

BMDL computation failed.

E.2.21. Li et al. (2006): Hormone Levels (Progesterone)

E.2.21.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance p-Value [a]	χ^2 Test Statistic	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2) [c]	**2**	**0.00**	**14.72**	**0.00**	**327.86**	**2.0E+03**	**7.1E+02**	**nonconstant variance, power restricted ≥1**
exponential (M3)	2	0.00	14.72	0.00	327.86	2.0E+03	7.1E+02	nonconstant variance, power restricted ≥1
exponential (M4)	1	0.00	0.60	0.44	315.74	8.3E+00	1.4E-02	nonconstant variance, power restricted ≥1
exponential (M5)	0	0.00	0.60	N/A	317.74	2.0E+01	3.5E-02	nonconstant variance, power restricted ≥1
exponential (M5) [d]	0	0.00	0.60	N/A	317.74	2.0E+01	3.5E-02	nonconstant variance, power unrestricted
Hill	1	0.00	0.60	0.44	315.73	9.0E-01	6.3E-03	nonconstant variance, n restricted >1, bound hit
Hill [d]	0	0.00	0.62	NA	317.75	1.9E-01	error	nonconstant variance, n unrestricted
linear	2	0.00	15.21	0.00	328.35	2.4E+03	1.3E+03	nonconstant variance
polynomial	2	0.00	15.21	0.00	328.35	2.4E+03	1.3E+03	nonconstant variance
power	2	0.00	15.21	0.00	328.35	2.4E+03	1.4E+03	nonconstant variance, power restricted ≥1, bound hit
power [d]	1	0.00	0.55	0.46	315.69	1.4E-39	1.4E-39	nonconstant variance, power unrestricted
exponential (M2)	2	0.00	2.22	0.33	327.49	2.8E+03	1.1E+03	constant variance, power restricted ≥1
exponential (M3)	2	0.00	2.22	0.33	327.49	2.8E+03	1.1E+03	constant variance, power restricted ≥1
exponential (M4)	1	0.00	0.02	0.88	327.29	2.0E+02	8.3E-01	constant variance, power restricted ≥1
exponential (M5)	1	0.00	0.02	0.88	327.29	2.0E+02	7.8E-01	constant variance, power restricted ≥1
exponential (M5)	1	0.00	0.02	0.88	327.29	2.0E+02	7.8E-01	constant variance, power unrestricted
Hill	0	0.00	0.02	NA	329.29	1.3E+02	1.6E-09	constant variance, n restricted >1
Hill	0	0.00	0.00	NA	329.27	5.5E+02	1.0E-03	constant variance, n unrestricted
linear	2	0.00	2.72	0.26	327.99	2.9E+03	1.7E+03	constant variance
polynomial	2	0.00	2.72	0.26	327.99	2.9E+03	1.7E+03	constant variance

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
power	2	0.00	2.72	0.26	327.99	2.9E+03	1.7E+03	constant variance, power restricted ≥1, bound hit
power	1	0.00	0.02	0.90	327.28	8.1E+02	2.8E-12	constant variance, power unrestricted

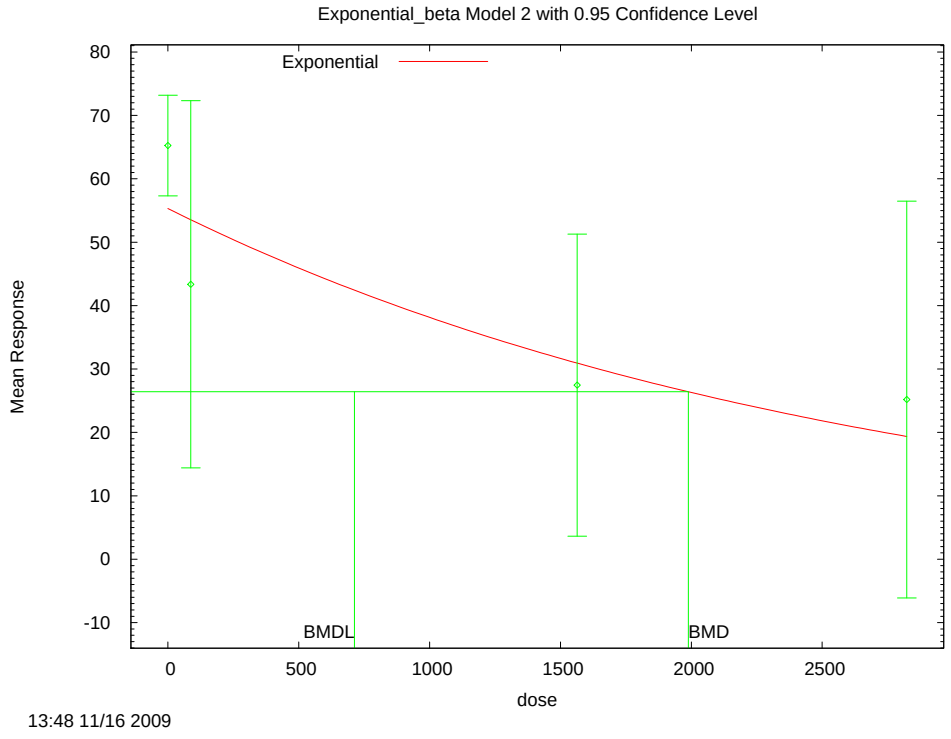
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.21.2. *Figure for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*



E.2.21.3. *Output File for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*

```
================================================================
        Exponential Model. (Version: 1.5;  Date: 4/23/2009)
        Input Data File: C:\USEPA\BMDS21\AD\Blood\Exp_BMR1_Li_Progesterone_3d.(d)
        Gnuplot Plotting File:
                                              Mon Nov 16 13:48:35 2009
```

```
 ========================================================================

 Figure 4, 3-day progesterone
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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             15.2703
                       rho            -2.36741
                         a             68.5132
                         b           0.00136853
                         c             0.350182
                         d                    1



                    Parameter Estimates

                  Variable          Model 2
                  --------          -------
                   lnalpha           19.9572
                       rho          -3.64854
                         a           65.2616
                         b         0.0274418
                         c          0.490738
                         d           1.59344


          Table of Stats From Input Data

     Dose      N         Obs Mean     Obs Std Dev
     -----    ---       ----------   -------------
         0     10        65.25         11.1
     87.49     10        43.36        40.48
      1564     10        27.46         33.3
      2823     10        25.19        43.75
```

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	55.31	28.9	1.088
87.49	53.54	29.21	-1.102
1564	30.93	34.87	-0.314
2823	19.36	40.57	0.4542

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	-152.5679	6	317.1358
R	-163.9025	2	331.805
2	-159.928	4	327.856

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 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	24.18	6	0.000484
Test 2	15.64	3	0.001344
Test 3	1.51	2	0.4699
Test 4	14.72	2	0.0006361

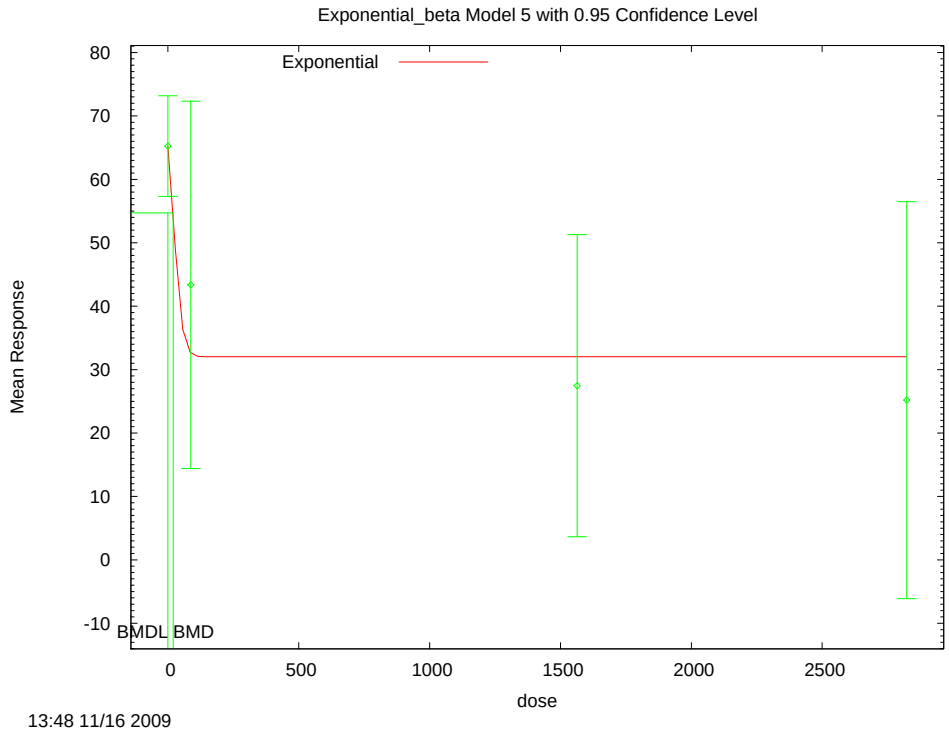
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

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 =      1988.62

               BMDL =      712.505
```

E.2.21.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



E.2.21.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Exp_Unrest_BMR1_Li_Progesterone_3d.(d)
         Gnuplot Plotting File:
                                                  Mon Nov 16 13:48:36 2009
 ================================================================

 Figure 4, 3-day progesterone
```

```
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 5
                  --------          --------
                    lnalpha             15.2703
                        rho             -2.36741
                          a              68.5132
                          b           0.00136853
                          c             0.350182
                          d                    1



                    Parameter Estimates

                   Variable          Model 5
                   --------          -------
                    lnalpha           19.9572
                        rho          -3.64854
                          a           65.2616
                          b         0.0274418
                          c          0.490738
                          d           1.59344


           Table of Stats From Input Data

     Dose      N         Obs Mean     Obs Std Dev
     -----    ---       ----------   -------------
         0     10        65.25         11.1
     87.49     10        43.36        40.48
      1564     10        27.46         33.3
      2823     10        25.19        43.75


                  Estimated Values of Interest

     Dose      Est Mean      Est Std     Scaled Residual
```

0	65.26	10.55	-0.003266
87.49	32.61	37.4	0.909
1564	32.03	38.65	-0.3733
2823	32.03	38.65	-0.5591

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	-152.5679	6	317.1358
R	-163.9025	2	331.805
5	-152.8697	6	317.7393

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 7a: Does Model 5 fit the data? (A3 vs 5)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	24.18	6	0.000484
Test 2	15.64	3	0.001344
Test 3	1.51	2	0.4699
Test 7a	0.6035	0	N/A

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.

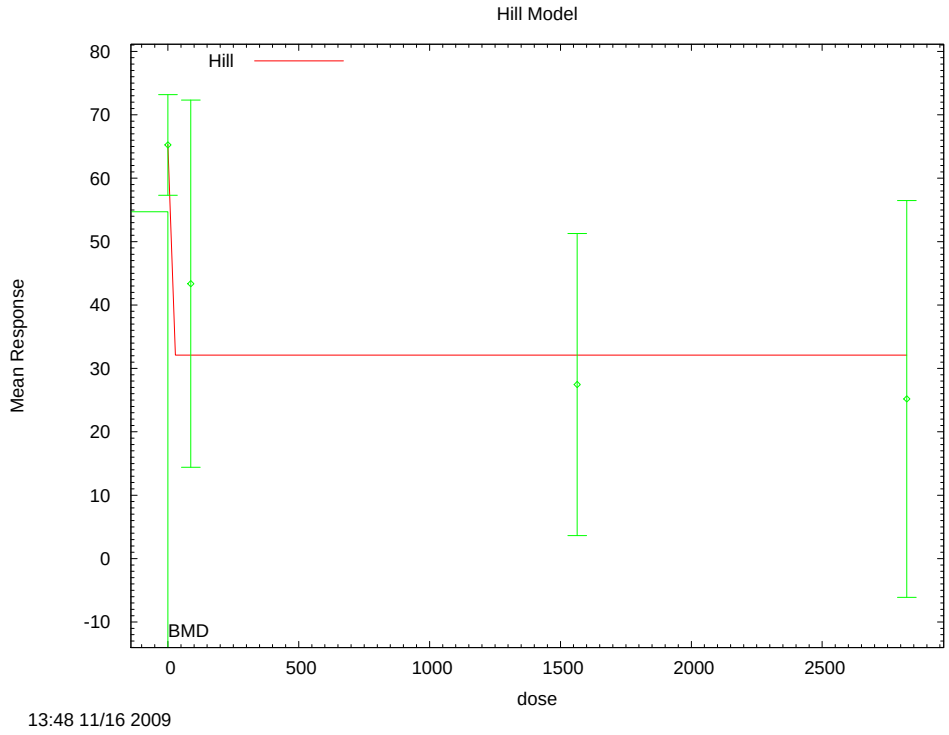
The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

Degrees of freedom for Test 7a are less than or equal to 0.
The Chi-Square test for fit is not valid.

```
   Benchmark Dose Computations:

     Specified Effect = 1.000000

            Risk Type = Estimated standard deviations from control

     Confidence Level = 0.950000

                  BMD =      19.9163

                 BMDL =      0.03489
```

E.2.21.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



E.2.21.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ========================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_Li_Progesterone_3d.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_Li_Progesterone_3d.plt
                                                  Mon Nov 16 13:48:37 2009
 ========================================================================

 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 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 =	7.08699
rho =	0
intercept =	65.2507
v =	-40.059
n =	4.4725
k =	80.0627

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	intercept	v	n	k
lalpha	1	-1	-0.17	0.84	6e-008	1.1e-008
rho	-1	1	0.19	-0.82	-5.6e-008	-1e-008
intercept	-0.17	0.19	1	-0.43	1e-008	1.9e-009
v	0.84	-0.82	-0.43	1	1.4e-009	2.6e-010
n	6e-008	-5.6e-008	1e-008	1.4e-009	1	1.1
k	1.1e-008	-1e-008	1.9e-009	2.6e-010	1.1	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	19.8437	5.41703	9.22649	30.4609
rho	-3.62235	1.35086	-6.27	-0.974711
intercept	65.2507	3.33016	58.7237	71.7777
v	-33.2448	7.73875	-48.4125	-18.0772
n	5.43075	5.32553e+006	-1.04378e+007	1.04378e+007
k	0.22398	1.45115e+006	-2.84421e+006	2.84421e+006

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	65.3	65.3	11.1	10.5	-7.47e-007
87.49	10	43.4	32	40.5	38.3	0.939
1564	10	27.5	32	33.3	38.3	-0.375
2823	10	25.2	32	43.7	38.3	-0.563

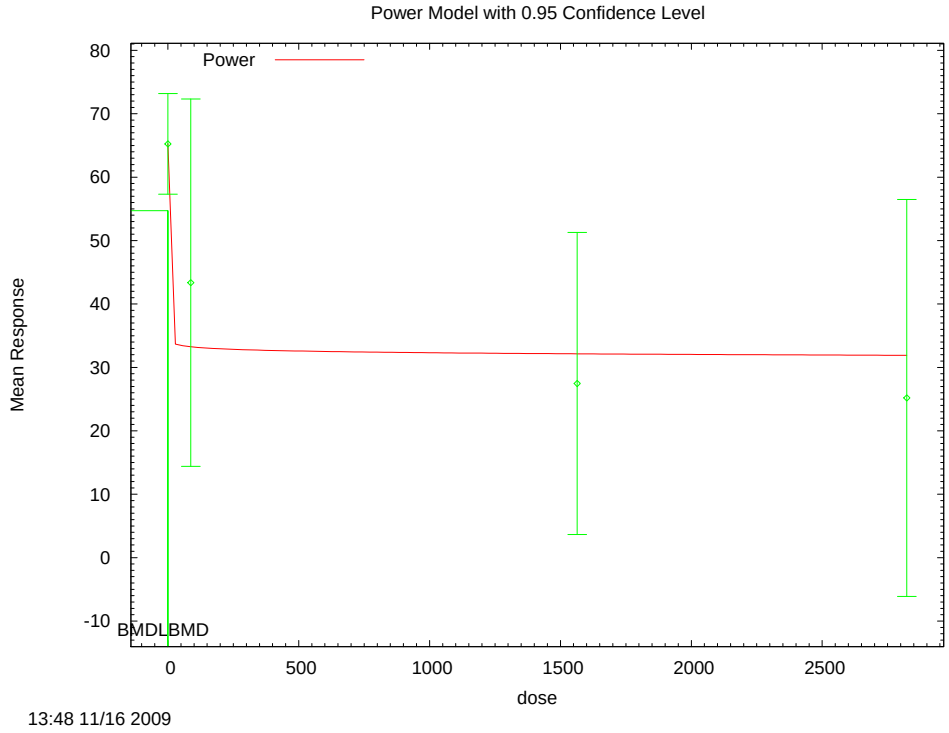
Degrees of freedom for Test A3 vs fitted <= 0

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         -159.632675            5     329.265349
             A2         -151.812765            8     319.625529
             A3         -152.567898            6     317.135795
         fitted         -152.876553            6     317.753105
              R         -163.902499            2     331.804998


                   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              24.1795          6        0.000484
  Test 2              15.6398          3        0.001344
  Test 3              1.51027          2          0.4699
  Test 4              0.61731          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 =       0.19442
```

```
BMDL computation failed.
```

E.2.21.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



E.2.21.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Power_Unrest_BMR1_Li_Progesterone_3d.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\Power_Unrest_BMR1_Li_Progesterone_3d.plt
                                                  Mon Nov 16 13:48:37 2009
 ================================================================

 Figure 4, 3-day progesterone
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =      7.08699
                            rho =            0
                        control =      65.2507
                          slope =     -9.66956
                          power =     0.178886


            Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho      control        slope        power

     lalpha            1           -1        -0.17         0.57         0.15

        rho           -1            1         0.19        -0.55        -0.13

    control        -0.17         0.19            1        -0.22         0.02

      slope         0.57        -0.55        -0.22            1         0.84

      power         0.15        -0.13         0.02         0.84            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          lalpha          20.0647           5.5864             9.11557             31.0139
             rho         -3.67315          1.39112            -6.39969           -0.946614
         control          65.2739          3.34327             58.7212             71.8266
           slope         -30.3669          13.1525            -56.1453            -4.58852
           power        0.0117985        0.0472043          -0.0807202            0.104317


       Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    10       65.3         65.3         11.1         10.6       -0.00695
87.49    10       43.4         33.3         40.5         36.5          0.876
 1564    10       27.5         32.2         33.3         38.8         -0.382
 2823    10       25.2         31.9         43.7         39.3         -0.541


 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	-152.567898	6	317.135795
fitted	-152.844599	5	315.689197
R	-163.902499	2	331.804998

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	24.1795	6	0.000484
Test 2	15.6398	3	0.001344
Test 3	1.51027	2	0.4699
Test 4	0.553402	1	0.4569

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 = 1.42955e-039

BMDL = 1.42955e-039

E.2.22. Markowski et al. (2001): FR10 Run Opportunities

E.2.22.1. *Summary Table of BMDS Modeling Results*

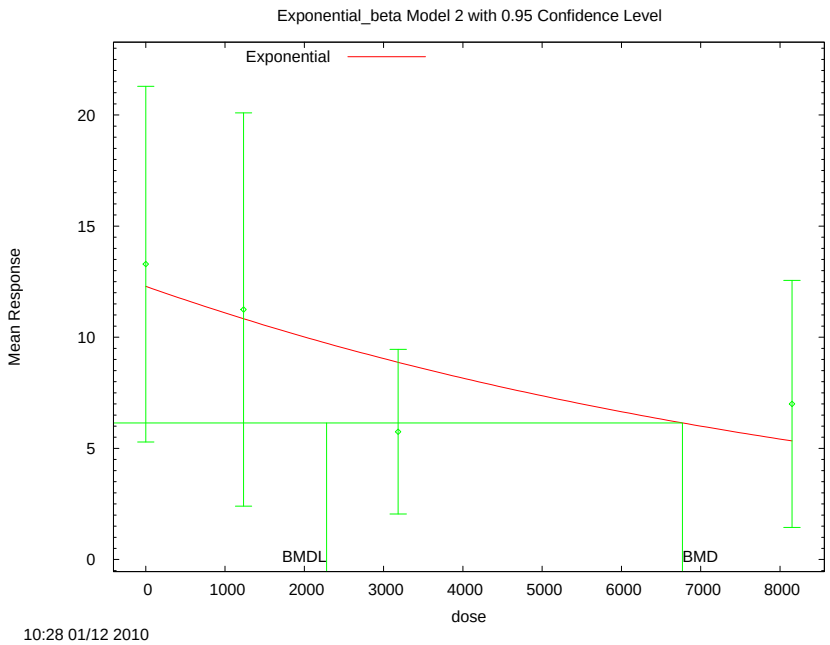
Model [a]	Degrees of Freedom	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2) [c]	2	0.304	117.151	6.769E+03	2.281E+03	
exponential (M3)	2	0.304	117.151	6.769E+03	2.281E+03	power bound hit
exponential (M4)	1	0.370	117.574	2.732E+03	1.151E+01	
exponential (M5)	0	N/A	118.918	1.834E+03	9.541E-03	
Hill	0	NA	118.918	1.428E+03	1.932E-04	
linear	2	0.226	117.744	8.734E+03	4.535E+03	
polynomial	2	0.226	117.744	8.734E+03	4.535E+03	
power	2	0.226	117.744	8.734E+03	4.535E+03	power bound hit

[a] Non-constant variance model selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model, BMDS output presented in this appendix

E.2.22.2. *Figure for Selected Model: Exponential (M2)*



Markowski et al., 2001: FR10 run opportunities

E.2.22.3. *Output File 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_Markowski_2001_FR10_run_opp_ExpCV_BMR1.(d)
         Gnuplot Plotting File:
                                                  Tue Jan 12 10:28:14 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              6.7793
                          b         7.36629e-005
                          c                    0
                          d                    1

     (S) = Specified


                     Parameter Estimates

                   Variable          Model 2
                   --------          -------
                    lnalpha           3.63129
                        rho                 0
                          a           12.2912
                          b        0.00010238
                          c                 0
                          d                 1
```

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	7	13.29	8.65
1234	4	11.25	5.56
3184	6	5.75	3.53
8152	7	7	6.01

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	12.29	6.145	0.43
1234	10.83	6.145	0.1359
3184	8.872	6.145	-1.245
8152	5.335	6.145	0.7168

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	-55.57543	3	117.1509

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 =      6769.45

              BMDL =      2280.85
```

E.2.23. Markowski et al. (2001): FR2 Revolutions

E.2.23.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
power, unrestricted	1	0.053	216.124	1.570E+04	3.350E+02	power unrestricted
exponential (M2)	2	0.236	217.220	6.704E+03	2.553E+03	
exponential (M3)	2	0.236	217.220	6.704E+03	2.553E+03	power bound hit
exponential (M4)	1	0.262	217.588	2.702E+03	1.655E+01	
exponential (M5) [c]	0	N/A	218.532	1.922E+03	7.384E+02	
Hill	1	0.654	216.532	1.458E+03	4.757E+02	n lower bound hit
linear	2	0.180	217.765	8.361E+03	4.426E+03	
polynomial	2	0.180	217.765	8.361E+03	4.426E+03	
Hill, unrestricted	1	0.654	216.532	1.458E+03	error	n unrestricted
power, unrestricted [d]	1	0.161	218.297	4.538E+03	8.152E-12	power unrestricted

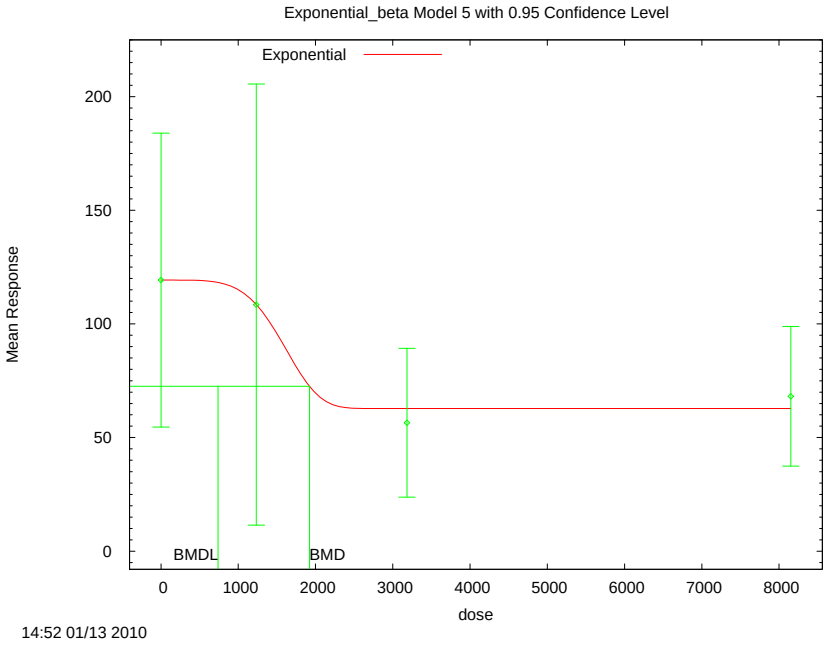
[a] Constant variance model selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model, BMDS output presented in this appendix

[d] Alternate model, BMDS output also presented in this appendix

E.2.23.2. *Figure for Selected Model: Exponential (M5)*



Markowski et al., 2001: FR2 revolutions

E.2.23.3. *Output File for Selected Model: Exponential (M5)*

Markowski et al., 2001: FR2 revolutions

```
 ================================================================
          Exponential Model. (Version: 1.61;  Date: 7/24/2009)
          Input Data File: C:\1\Blood\34_Markowski_2001_FR2_rev_ExpCV_1.(d)
          Gnuplot Plotting File:
                                                 Wed Jan 13 14:52:52 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 5
lnalpha	7.68046
rho(S)	0
a	125.255
b	0.000305547
c	0.429602
d	1

(S) = Specified

Parameter Estimates

Variable	Model 5
lnalpha	7.68885
rho	0
a	119.29
b	0.000585299
c	0.526177
d	4.76993

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	7	119.3	69.9
1234	4	108.5	61
3184	6	56.5	31.21
8152	7	68.14	33.23

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	119.3	46.73	-1.267e-006
1234	108.5	46.73	2.704e-006
3184	62.77	46.73	-0.3285
8152	62.77	46.73	0.3042

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

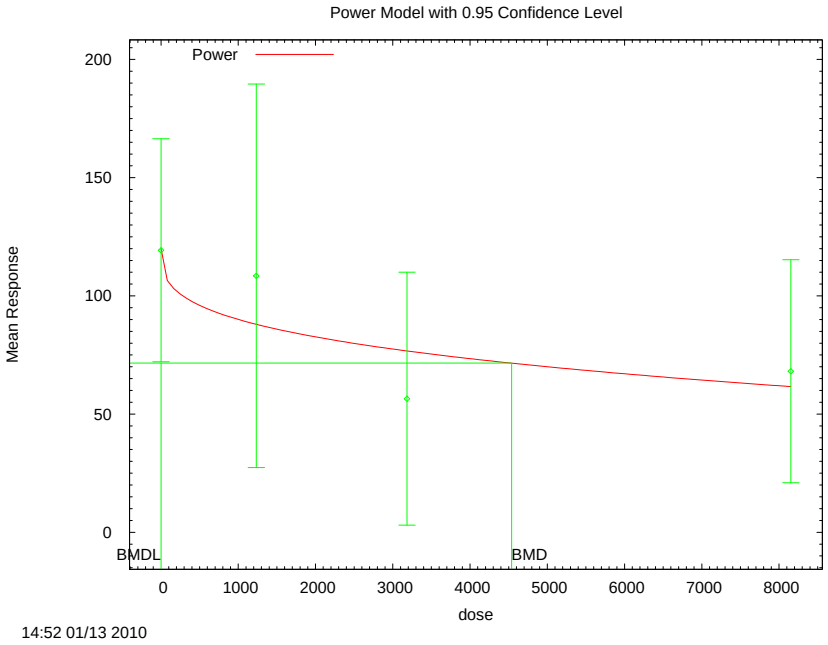
Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

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       -104.1655           5       218.331
                         A2       -101.1402           8      218.2803
                         A3       -104.1655           5       218.331
                          R       -107.5993           2      219.1985
                          5       -104.2662           5      218.5323


    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 7a: Does Model 5 fit the data? (A3 vs 5)


                              Tests of Interest

      Test          -2*log(Likelihood Ratio)       D. F.         p-value
    --------        ------------------------      ------     --------------
      Test 1                      12.92             6            0.04435
      Test 2                      6.051             3             0.1092
      Test 3                      6.051             3             0.1092
     Test 7a                     0.2013             0                N/A


      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.

      Degrees of freedom for Test 7a are less than or equal to 0.
      The Chi-Square test for fit is not valid.


    Benchmark Dose Computations:

      Specified Effect = 1.000000

             Risk Type = Estimated standard deviations from control

      Confidence Level = 0.950000

                   BMD =      1921.95

                  BMDL =      738.412
```

E.2.23.4. *Figure for Unrestricted Model: Power, Unrestricted*



Markowski et al., 2001: FR2 revolutions

E.2.23.5. *Output for Unrestricted Model: Power, Unrestricted*

Markowski et al., 2001: FR2 revolutions

```
 ======================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\1\Blood\34_Markowski_2001_FR2_rev_PowerCV_Unrest_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\34_Markowski_2001_FR2_rev_PowerCV_Unrest_1.plt
                                                Wed Jan 13 14:52:55 2010
 ======================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 =   -0.0418736
                        power =     0.825655


          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     3.2e-009    -4.2e-009    -2.8e-009

    control     3.2e-009            1        -0.39        -0.28

      slope    -4.2e-009        -0.39            1         0.99

      power    -2.8e-009        -0.28         0.99            1



                                Parameter Estimates

                                                                  95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha          2350.46          678.52             1020.59             3680.33
         control          120.079          18.0799             84.6433             155.515
           slope         -3.33162          10.4368            -23.7875             17.1242
           power         0.318007         0.351246           -0.370423             1.00644


      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        -0.0431
 1234     4        109           88           61         48.5          0.844
 3184     6       56.5         76.8         31.2         48.5          -1.02
 8152     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         -105.148400            4     218.296799
                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              1.96576          1          0.1609

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 = 4538.4


             BMDL = 8.15173e-012
```

E.2.24. Markowski et al. (2001): FR5 Run Opp

E.2.24.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.205	133.194	4.012E+03	1.927E+03	
exponential (M3)	2	0.205	133.194	4.012E+03	1.927E+03	power bound hit
exponential (M4)	1	0.253	133.335	1.710E+03	5.425E+02	
exponential (M5)	1	0.212	133.587	1.757E+03	5.030E+02	power bound hit
Hill [c]	1	0.939	132.032	1.366E+03	7.212E+02	n lower bound hit
linear	2	0.122	134.230	5.715E+03	3.500E+03	
polynomial	2	0.122	134.230	5.715E+03	3.500E+03	
power	2	0.122	134.230	5.715E+03	3.500E+03	power bound hit
Hill, unrestricted	1	0.939	132.032	1.366E+03	6.598E+02	n unrestricted
power, unrestricted [d]	1	0.134	134.272	2.109E+03	8.152E-12	power unrestricted

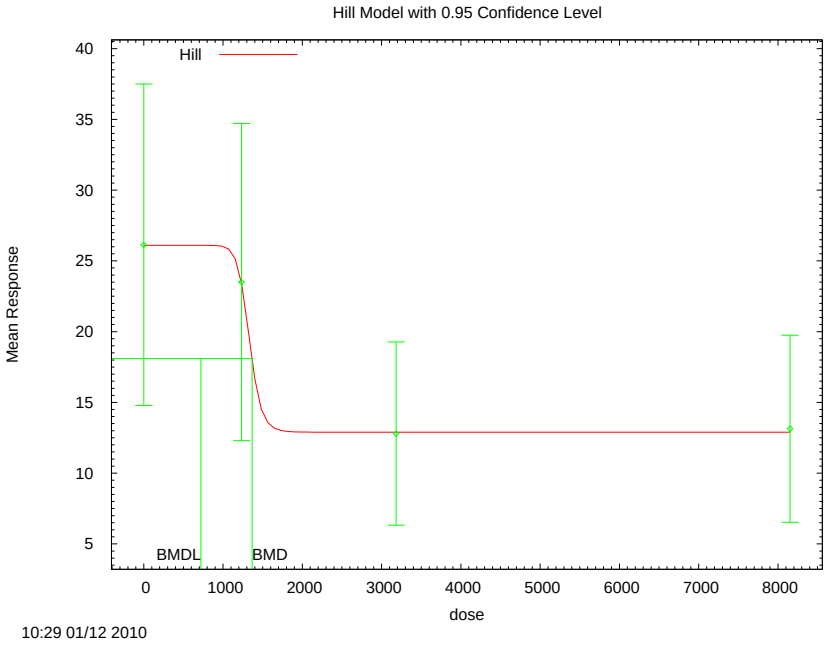
[a] Constant variance model selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model, BMDS output presented in this appendix

[d] Alternate model, BMDS output also presented in this appendix

E.2.24.2. *Figure for Selected Model: Hill*



Markowski et al., 2001: FR5 run opportunities

E.2.24.3. *Output File 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\Blood\35_Markowski_2001_FR5_run_opp_HillCV_BMR1.(d)
         Gnuplot Plotting File:  C:\1\Blood\35_Markowski_2001_FR5_run_opp_HillCV_BMR1.plt
                                                Tue Jan 12 10:29:45 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 =      2.78062
                              k =      1968.39


           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    -1.9e-010     1.7e-008     1.8e-008

  intercept    -1.9e-010             1        -0.81        -0.51

          v     1.7e-008         -0.81            1         0.36

          k     1.8e-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           1332.5          165.441              1008.24             1656.76

  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     -3.13e-008
  1234     4       23.5         23.5         7.04         8.04     -1.71e-008
  3184     6       12.8           13         6.17         8.04        -0.0558
  8152     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

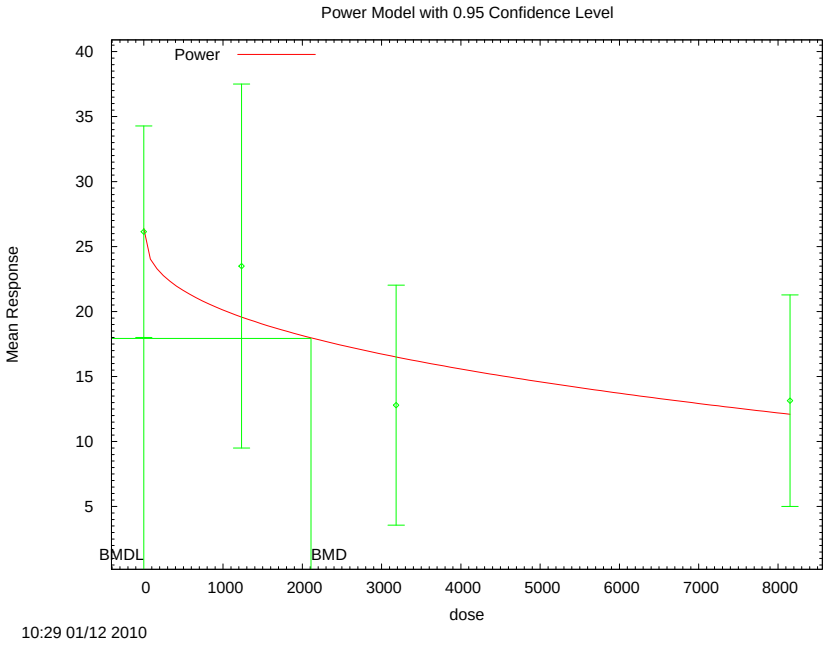
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 1366.29

BMDL = 721.238

E.2.24.4. *Figure for Unrestricted Model: Power, Unrestricted*



Markowski et al., 2001: FR5 run opportunities

E.2.24.5. *Output File for Unrestricted Model: Power, Unrestricted*

Markowski et al., 2001: FR5 run opportunities

```
 ================================================================
          Power Model. (Version: 2.15;  Date: 04/07/2008)
          Input Data File: C:\1\Blood\35_Markowski_2001_FR5_run_opp_PowerCV_Unrest_BMR1.(d)
          Gnuplot Plotting File:
C:\1\Blood\35_Markowski_2001_FR5_run_opp_PowerCV_Unrest_BMR1.plt
                                                  Tue Jan 12 10:29:46 2010
 ================================================================

 Table 3
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 =  -0.00843066
                          power =     0.845567


            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      -2e-008      -1e-008    -1.3e-008

     control      -2e-008            1        -0.43        -0.34

       slope      -1e-008        -0.43            1         0.99

       power    -1.3e-008        -0.34         0.99            1



                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
         Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
            alpha          70.905          20.4685             30.7875             111.023
          control          26.3577         3.12942             20.2242             32.4913
            slope         -0.41863         1.06088            -2.49792             1.66066
            power         0.392134        0.282163           -0.160895            0.945164


       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        -0.0684
 1234     4       23.5         19.5         7.04         8.42          0.942
 3184     6       12.8         16.5         6.17         8.42          -1.07
 8152     7       13.1         12.1         7.14         8.42          0.342


 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          -63.136095           4     134.272189
                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              2.24592          1           0.134

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 = 2109.29


             BMDL = 8.15175e-012
```

E.2.25. Mietinnin et al. (2006): Cariogenic Lesions in Pups

E.2.25.1. *Summary Table of BMDS Modeling Results*

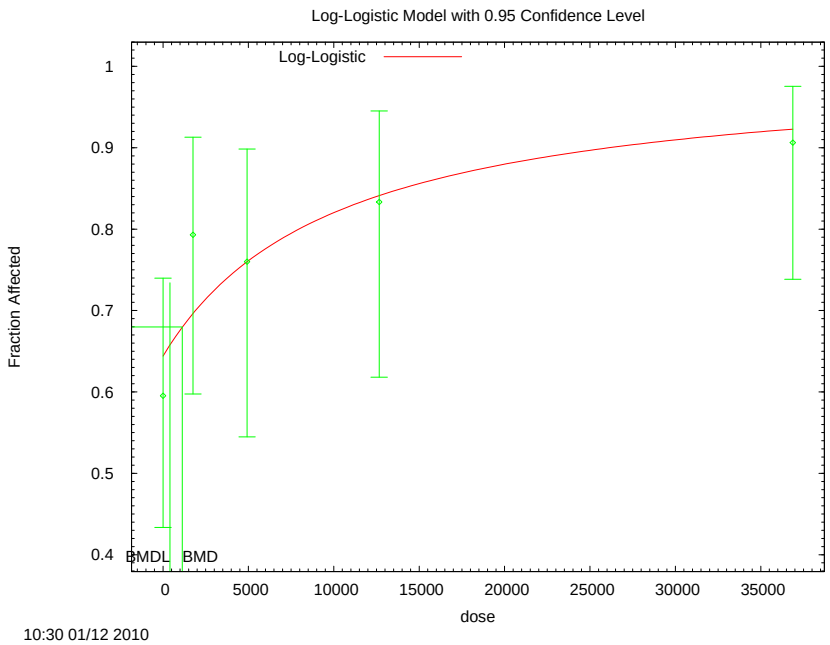
Model	Degrees of Freedom	χ^2 p-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	3	0.410	162.281	2.689E+03	1.494E+03	power bound hit
logistic	3	0.371	162.518	3.248E+03	1.937E+03	
log-logistic [b]	3	0.603	161.291	1.129E+03	4.091E+02	slope bound hit
log-probit, unrestricted	2	0.732	161.972	5.141E+01	error	slope unrestricted
multistage, 4-degree	3	0.410	162.281	2.689E+03	1.494E+03	final ß=0
probit	3	0.350	162.656	3.596E+03	2.284E+03	
Weibull	3	0.410	162.281	2.689E+03	1.494E+03	power bound hit
log-logistic, unrestricted [c]	2	0.728	161.983	3.912E+01	error	slope unrestricted

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model, BMDS output presented in this appendix

[c] Alternate model, BMDS output also presented in this appendix

E.2.25.2. *Figure for Selected Model: Log-Logistic*



Mietinnen et al., 2006: Cariogenic lesions in pups

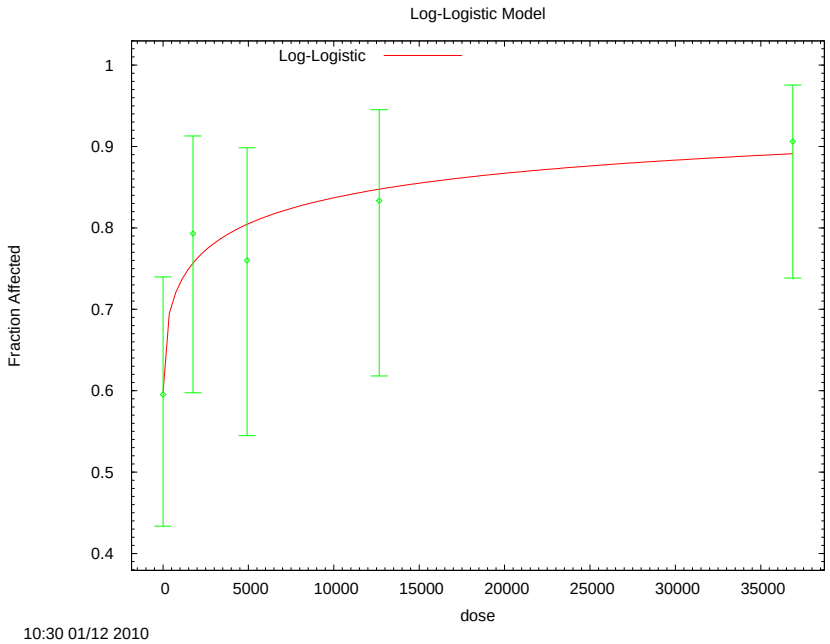
E.2.25.3. *Output File for Selected Model: Log-Logistic*

Mietinnen et al., 2006: Cariogenic lesions in pups

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\36_Miet_06_carc_lesions_LogLogistic_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\36_Miet_06_carc_lesions_LogLogistic_1.plt
                                                  Tue Jan 12 10:30:32 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 =      -9.1668
                          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         0.644146            *               *                   *
      intercept         -9.22611            *               *                   *
          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        -78.6457         2       1.93773      3          0.5854
   Reduced model        -83.2067         1       11.0597      4          0.0259

            AIC:         161.291


                                  Goodness  of  Fit
                                                                        Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------------
     0.0000     0.6441        27.054    25.000          42       -0.662
  1755.6399     0.6966        20.201    23.000          29        1.131
  4922.4989     0.7603        19.007    19.000          25       -0.003
 12657.0000     0.8416        20.197    20.000          24       -0.110
 36874.0000     0.9231        29.540    29.000          32       -0.359

  Chi^2 = 1.86      d.f. = 3        P-value = 0.6025


    Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =        1128.77

            BMDL =        409.065
```

E.2.25.4. *Figure for Unrestricted Model: Log-Logistic, Slope Unrestricted*



Mietinnen et al., 2006: Cariogenic lesions in pups

E.2.25.5. *Output File for Unrestricted Model: Log-Logistic, Slope Unrestricted*

Mietinnen et al., 2006: Cariogenic lesions in pups

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\1\Blood\36_Miet_06_carc_lesions_LogLogistic_Unrest_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\36_Miet_06_carc_lesions_LogLogistic_Unrest_1.plt
                                                Tue Jan 12 10:30:33 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 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 =     -3.69546
                         slope =     0.442957


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.34         0.24

 intercept        -0.34            1        -0.99

     slope         0.24        -0.99            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background         0.597745            *                *                   *
      intercept         -3.90353            *                *                   *
          slope         0.465358            *                *                   *

* - 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        -77.9913         3       0.62887      2          0.7302
   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
  1755.6399     0.7566        21.941    23.000          29        0.458
  4922.4989     0.8042        20.104    19.000          25       -0.557
 12657.0000     0.8474        20.338    20.000          24       -0.192
 36874.0000     0.8910        28.512    29.000          32        0.277

 Chi^2 = 0.63      d.f. = 2        P-value = 0.7282


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        39.1207

           Benchmark dose computation failed.  Lower limit includes zero.
```

E.2.26. National Toxicology Program (1982): Male Mice, Toxic Hepatitis

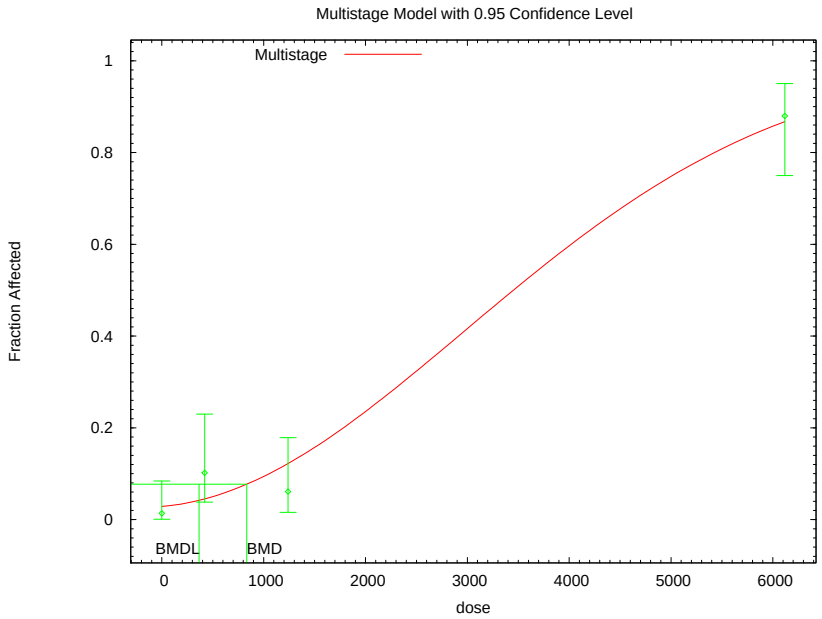
E.2.26.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	1	4.92	0.03	113.10	2.1E+03	1.1E+03	power restricted ≥1
logistic [b]	**2**	**4.77**	**0.09**	**110.35**	**1.7E+03**	**1.3E+03**	
log-logistic	1	4.93	0.03	113.09	2.1E+03	1.2E+03	slope restricted ≥1
log-probit	1	4.89	0.03	113.11	1.9E+03	1.3E+03	slope restricted ≥1
multistage 2-degree	1	6.04	0.01	113.71	1.3E+03	7.0E+02	betas restricted ≥0
probit	2	4.99	0.08	110.51	1.5E+03	1.2E+03	
Weibull	1	5.00	0.03	113.04	2.2E+03	9.3E+02	power restricted ≥1

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

E.2.26.2. *Figure for Selected Model: Multistage, 2nd Degree*



E.2.26.3. *Output File for Selected Model: Multistage, 2nd Degree*

```
 ========================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov29\Blood\Multistage_BMR2_Toxic_hepatitis.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov29\Blood\Multistage_BMR2_Toxic_hepatitis.plt
                                                 Sun Nov 29 13:16:19 2009
 ========================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 4
 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 =    0.0298369
                        Beta(1) =            0
                        Beta(2) = 5.57954e-008


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)      Beta(2)

Background            1         -0.8         0.74

   Beta(1)         -0.8            1        -0.97

   Beta(2)         0.74        -0.97            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0286224            *                *                   *
        Beta(1)     1.97711e-005            *                *                   *
        Beta(2)     5.00241e-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        -51.0633         4
   Fitted model        -53.8523         3       5.57784      1         0.01819
  Reduced model        -121.743         1       141.358      3         <.0001

            AIC:         113.705


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0286         2.089     1.000          73       -0.765
   420.0366     0.0451         2.211     5.000          49        1.920
  1239.6134     0.1223         5.991     3.000          49       -1.304
  6117.5662     0.8676        43.381    44.000          50        0.258

 Chi^2 = 6.04      d.f. = 1        P-value = 0.0140


    Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

              BMD =        1267.05

             BMDL =        698.659

             BMDU =        1628.68

Taken together, (698.659, 1628.68) is a 90     % two-sided confidence
interval for the BMD
```

E.2.27. National Toxicology Program (2006): Alveolar Metaplasia

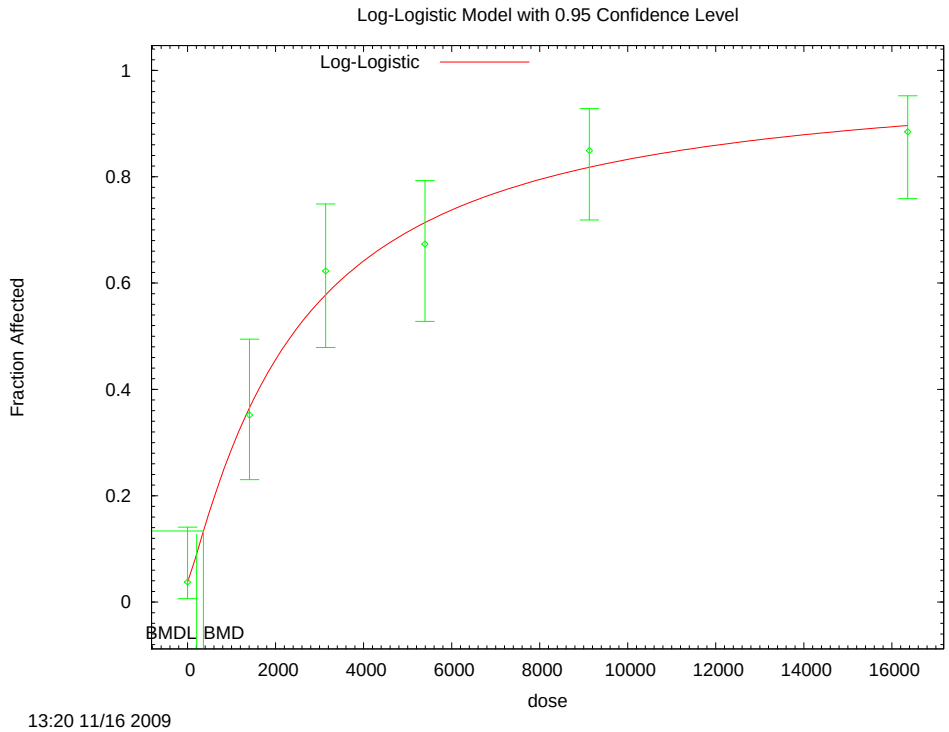
E.2.27.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	13.37	0.01	320.09	2.7E+02	2.3E+02	power restricted ≥1, bound hit
gamma	4	13.37	0.01	320.09	5.4E+02	4.6E+02	power restricted ≥1, bound hit
logistic	4	33.08	0.00	343.28	6.8E+02	5.8E+02	
logistic	4	33.08	0.00	343.28	1.3E+03	1.1E+03	
log-logistic	3	1.32	0.72	312.56	1.8E+02	9.8E+01	slope restricted ≥1
log-logistic [b]	**3**	**1.32**	**0.72**	**312.56**	**3.6E+02**	**2.1E+02**	**slope restricted ≥1**
log-probit	3	1.44	0.70	312.68	2.2E+02	7.4E+01	slope restricted ≥1
log-probit	3	1.44	0.70	312.68	3.8E+02	1.5E+02	slope restricted ≥1
multistage, 2-degree	4	13.37	0.01	320.09	2.7E+02	2.3E+02	betas restricted ≥0, bound hit
multistage, 2-degree	4	13.37	0.01	320.09	5.4E+02	4.6E+02	betas restricted ≥0, bound hit
probit	4	35.22	0.00	347.07	7.2E+02	6.2E+02	
probit	4	35.22	0.00	347.07	1.4E+03	1.2E+03	
Weibull	4	13.37	0.01	320.09	2.7E+02	2.3E+02	power restricted ≥1, bound hit
Weibull	4	13.37	0.01	320.09	5.4E+02	4.6E+02	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

E.2.27.2. *Figure for Selected Model: Log-Logistic, Slope Restricted ≥1*



E.2.27.3. *Output File for Selected Model: Log-Logistic, Slope Restricted ≥1*

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\LogLogistic_BMR2_Alveolar_metaplasia.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\LogLogistic_BMR2_Alveolar_metaplasia.plt
                                                  Mon Nov 16 13:20:58 2009
 ================================================================

 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 = 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 = -8.78161
slope = 1.1228

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.13	0.1
intercept	-0.13	1	-1
slope	0.1	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0373474	*	*	*
intercept	-8.85134	*	*	*
slope	1.13159	*	*	*

* - 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	1.32714	3	0.7227
Reduced model	-216.802	1	128.374	5	<.0001

AIC: 312.558

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0373	1.979	2.000	53	0.015
1408.4504	0.3682	19.881	19.000	54	-0.249
3137.0446	0.5807	30.777	33.000	53	0.619
5392.9593	0.7162	37.244	35.000	52	-0.690
9128.8027	0.8197	43.445	45.000	53	0.556
16361.0000	0.8976	46.674	46.000	52	-0.308

Chi^2 = 1.32 d.f. = 3 P-value = 0.7232

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 357.926

BMDL = 206.635

E.2.28. National Toxicology Program (2006): Gingival Hyperplasia Squamous, 2 Years

E.2.28.1. *Summary Table of BMDS Modeling Results*

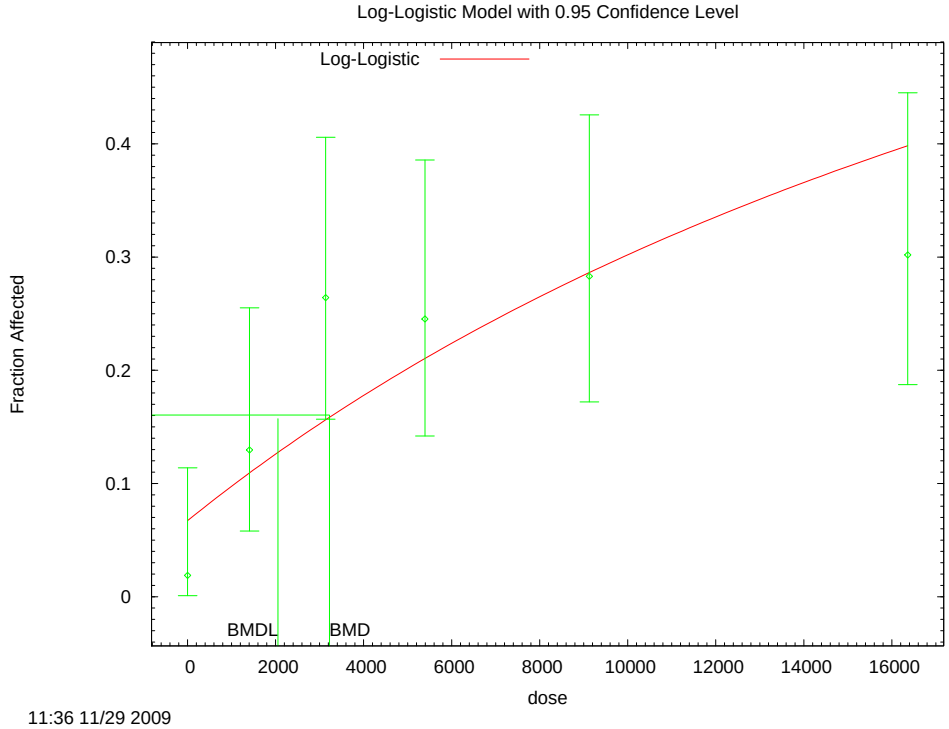
Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	10.30	0.04	314.99	4.3E+03	2.8E+03	power restricted ≥1, bound hit
logistic	4	12.16	0.02	318.60	7.7E+03	5.8E+03	
log-logistic [b]	**4**	**9.26**	**0.06**	**313.35**	**3.2E+03**	**2.1E+03**	**slope restricted ≥1, bound hit**
log-logistic [c]	3	1.62	0.66	307.51	3.9E+02	6.9E-03	slope unrestricted
log-probit	3	1.56	0.67	307.44	4.6E+02	2.6E-02	slope restricted ≥1
multistage, 1-degree	4	10.30	0.04	314.99	4.3E+03	2.8E+03	betas restricted ≥0, bound hit
probit	4	11.97	0.02	318.24	7.3E+03	5.5E+03	
Weibull	4	10.30	0.04	314.99	4.3E+03	2.8E+03	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

[c] Alternate model also presented in this appendix

E.2.28.2. *Figure for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*

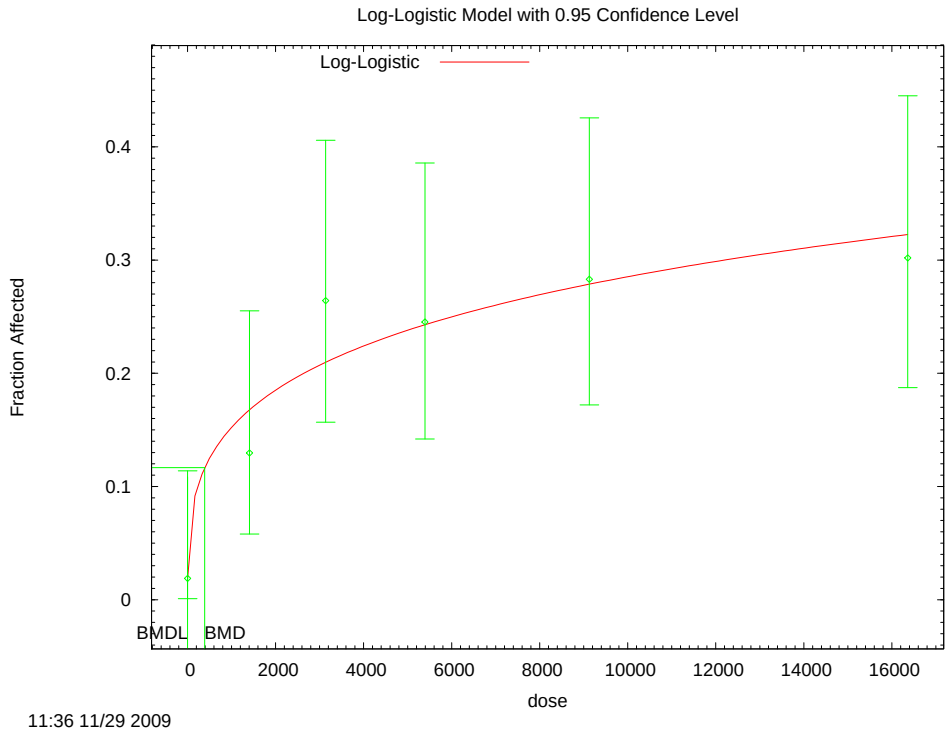


E.2.28.3. *Output File for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov29\Blood\LogLogistic_BMR2_Ging_Hyp_2yr.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov29\Blood\LogLogistic_BMR2_Ging_Hyp_2yr.plt
                                                  Sun Nov 29 11:36:25 2009
 ================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =    0.0188679
                      intercept =     -10.0647
                          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        0.0671889            *                *                   *
      intercept         -10.2754            *                *                   *
          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       9.45083      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
   1408.4504     0.1104         5.961     7.000          54        0.451
   3137.0446     0.1582         8.386    14.000          53        2.113
   5392.9593     0.2134        11.311    13.000          53        0.566
   9128.8027     0.2905        15.395    15.000          53       -0.119
  16361.0000     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 =        3223.25

             BMDL =        2054.88
```

E.2.28.4. *Figure for Unrestricted Model: Log-Logistic, Slope Unrestricted*



E.2.28.5. *Output File for Unrestricted Model: Log-Logistic, Slope Unrestricted*

```
 ===============================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov29\Blood\LogLogistic_Unrest_BMR2_Ging_Hyp_2yr.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\Nov29\Blood\LogLogistic_Unrest_BMR2_Ging_Hyp_2yr.plt
                                                Sun Nov 29 11:36:27 2009
 ===============================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 = -4.87817
slope = 0.424322

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.16	0.11
intercept	-0.16	1	-0.99
slope	0.11	-0.99	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0185138	*	*	*
intercept	-4.42531	*	*	*
slope	0.373718	*	*	*

* - 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	1.60686	3	0.6578
Reduced model	-162.631	1	25.3627	5	0.0001186

AIC: 307.507

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0185	0.981	1.000	53	0.019
1408.4504	0.1681	9.078	7.000	54	-0.756
3137.0446	0.2101	11.136	14.000	53	0.966
5392.9593	0.2433	12.893	13.000	53	0.034
9128.8027	0.2792	14.795	15.000	53	0.063
16361.0000	0.3230	17.117	16.000	53	-0.328

Chi^2 = 1.62 d.f. = 3 P-value = 0.6555

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 388.363

BMDL = 0.00694785

E.2.29. National Toxicology Program (2006): Heart, Cardiomyopathy

E.2.29.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	2.65	0.62	394.49	1.5E+03	1.2E+03	power restricted ≥1, bound hit
logistic	4	6.73	0.15	398.64	2.7E+03	2.2E+03	
log-logistic	3	1.32	0.72	395.20	1.2E+03	7.3E+02	slope restricted ≥1
log-probit	3	1.11	0.78	394.98	1.3E+03	4.9E+02	slope restricted ≥1
multistage, 2-degree [b]	**4**	**2.65**	**0.62**	**394.49**	**1.5E+03**	**1.2E+03**	**betas restricted ≥0, bound hit**
probit	4	6.71	0.15	398.61	2.6E+03	2.2E+03	
Weibull	4	2.65	0.62	394.49	1.5E+03	1.2E+03	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

E.2.29.2. *Figure for Selected Model: Multistage, 2-Degree, Betas Restricted ≥0, Bound Hit*

E.2.29.3. *Output File for Selected Model: Multistage, 2-Degree, Betas Restricted ≥0, Bound Hit*

```
 ================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Multistage_BMR2_Cardiomyopathy.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Multistage_BMR2_Cardiomyopathy.plt
                                                 Mon Nov 16 13:37:37 2009
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 6
 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 =     0.234028
                        Beta(1) = 6.08803e-005
                        Beta(2) =            0


           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)

Background            1        -0.69

   Beta(1)        -0.69            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background         0.196221            *                *                   *
        Beta(1)     6.98634e-005            *                *                   *
        Beta(2)                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         -193.93         6
    Fitted model        -195.247        2       2.63378      4          0.6209
   Reduced model        -216.802        1       45.7449      5         <.0001

            AIC:         394.493


                                  Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------------
      0.0000     0.1962        10.400    10.000          53       -0.138
   1408.4504     0.2715        14.663    12.000          54       -0.815
   3137.0446     0.3544        18.784    22.000          53        0.924
   5392.9593     0.4485        23.325    25.000          52        0.467
   9128.8027     0.5752        30.487    32.000          53        0.420
  16361.0000     0.7437        38.673    36.000          52       -0.849

  Chi^2 = 2.65      d.f. = 4        P-value = 0.6176


    Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        1508.09

             BMDL =        1170.08

             BMDU =        2325.84

Taken together, (1170.08, 2325.84) is a 90     % two-sided confidence
interval for the BMD
```

E.2.30. National Toxicology Program (2006): Hepatocyte Hypertrophy, 2 Years

E.2.30.1. *Summary Table of BMDS Modeling Results*

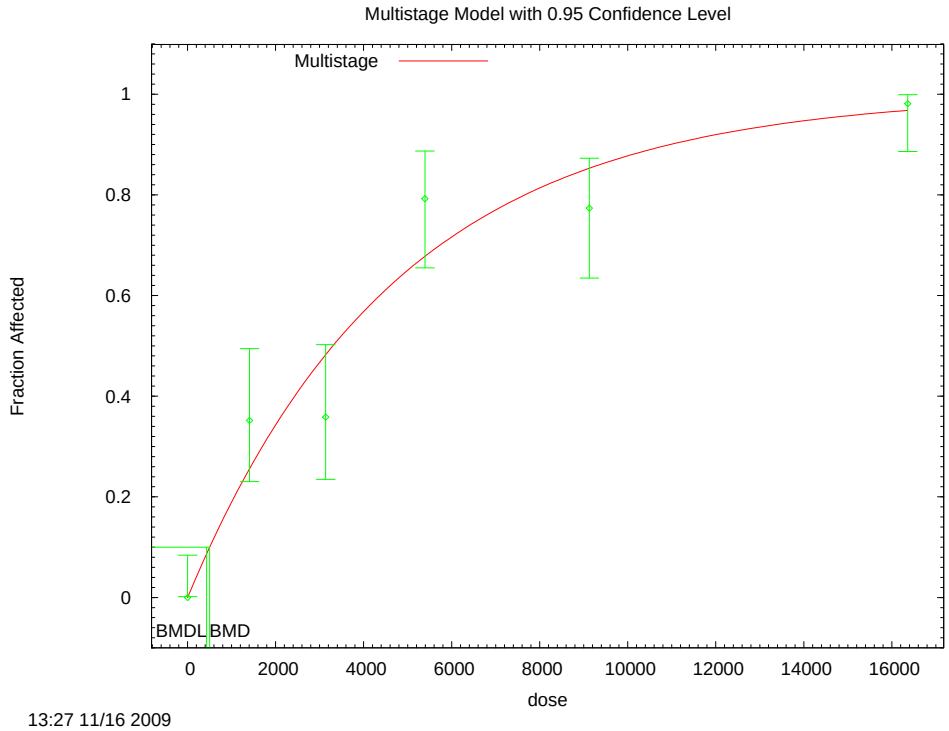
Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	5	12.03	0.03	273.88	2.4E+02	2.1E+02	power restricted ≥1, bound hit
gamma	5	12.03	0.03	273.88	5.0E+02	4.3E+02	power restricted ≥1, bound hit
logistic	4	26.14	0.00	297.90	7.4E+02	6.2E+02	
logistic	4	26.14	0.00	297.90	1.4E+03	1.2E+03	
log-logistic	4	14.32	0.01	279.21	3.7E+02	1.8E+02	slope restricted ≥1

log-logistic	4	14.32	0.01	279.21	6.3E+02	3.6E+02	slope restricted ≥1
log-probit	4	13.74	0.01	278.36	4.3E+02	2.3E+02	slope restricted ≥1
log-probit	4	13.74	0.01	278.36	6.6E+02	3.9E+02	slope restricted ≥1
multistage, 2-degree	5	12.03	0.03	273.88	2.4E+02	2.1E+02	betas restricted ≥0, bound hit
multistage, 2-degree [b]	**5**	**12.03**	**0.03**	**273.88**	**5.0E+02**	**4.3E+02**	**betas restricted ≥0, bound hit**
probit	4	28.00	0.00	299.73	7.2E+02	6.2E+02	
probit	4	28.00	0.00	299.73	1.4E+03	1.2E+03	
Weibull	5	12.03	0.03	273.88	2.4E+02	2.1E+02	power restricted ≥1, bound hit
Weibull	5	12.03	0.03	273.88	5.0E+02	4.3E+02	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

E.2.30.2. *Figure for Selected Model: Multistage, 2-Degree, Betas Restricted ≥0, Bound Hit*



E.2.30.3. *Output File for Selected Model: Multistage, 2-Degree, Betas Restricted ≥0, Bound Hit*

```
 ================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File:
C:\USEPA\BMDS21\AD\Blood\Multistage_BMR2_Hepatocyte_hypertrophy_2years.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\Multistage_BMR2_Hepatocyte_hypertrophy_2years.plt
                                                  Mon Nov 16 13:27:47 2009
 ================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 6
 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 =     0.117028
                       Beta(1) =  0.000142077
                       Beta(2) = 5.42278e-009


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)
                 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)       0.00021035           *               *                   *
        Beta(2)                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        -135.938         1       11.9043      5         0.03612
    Reduced model         -219.97         1       179.968      5         <.0001

             AIC:         273.876


                                  Goodness  of  Fit
                                                                        Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          53        0.000
  1408.4504     0.2564        13.846    19.000          54        1.606
  3137.0446     0.4831        25.604    19.000          53       -1.815
  5392.9593     0.6784        35.955    42.000          53        1.778
  9128.8027     0.8534        45.232    41.000          53       -1.643
 16361.0000     0.9680        51.303    52.000          53        0.544

 Chi^2 = 12.03     d.f. = 5        P-value = 0.0344


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        500.882

            BMDL =        433.488

            BMDU =        637.074

Taken together, (433.488, 637.074) is a 90     % two-sided confidence
interval for the BMD
```

E.2.31. National Toxicology Program (2006): Liver, Eosinophilic Focus, Multiple

E.2.31.1. *Summary Table of BMDS Modeling Results*

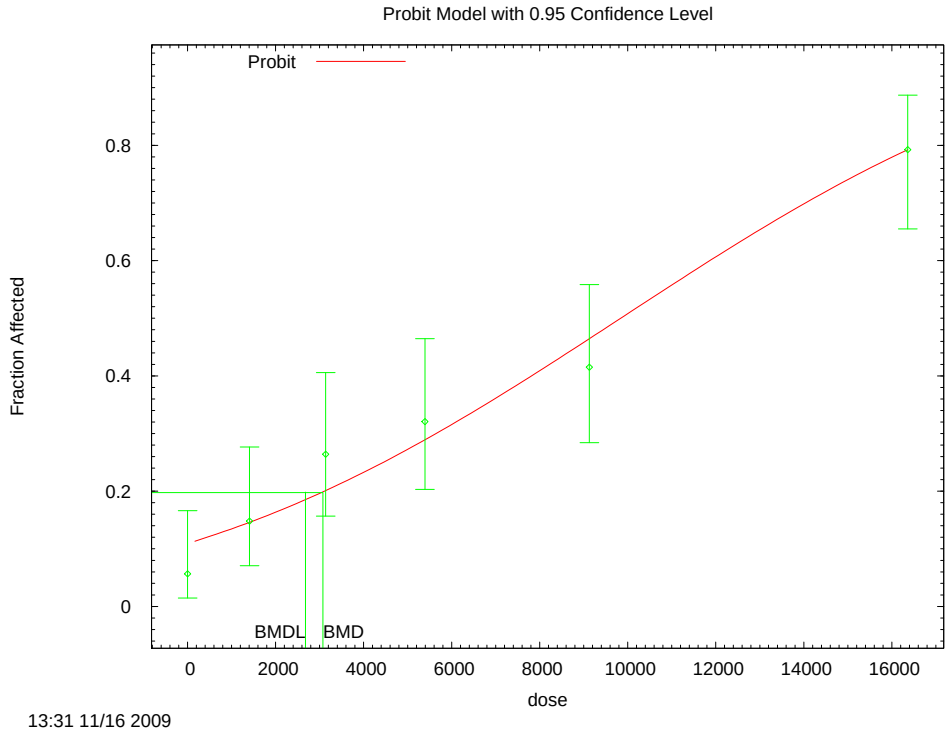
Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	3	3.72	0.29	331.90	2.0E+03	1.2E+03	power restricted ≥1
logistic	4	4.01	0.40	330.40	3.3E+03	2.8E+03	
log-logistic	3	5.29	0.15	333.52	2.3E+03	1.1E+03	slope restricted ≥1
log-probit	3	5.90	0.12	334.15	2.3E+03	1.2E+03	slope restricted ≥1
multistage, 2-degree	3	2.69	0.44	330.82	2.0E+03	1.3E+03	betas restricted ≥0

probit [b]	**4**	**3.62**	**0.46**	**329.94**	**3.1E+03**	**2.7E+03**	
Weibull	3	3.47	0.32	331.63	2.1E+03	1.2E+03	power restricted ≥1

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

E.2.31.2. *Figure for Selected Model: Probit*



E.2.31.3. *Output File for Selected Model: Probit*

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Probit_BMR2_liver_eosin_focus.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Probit_BMR2_liver_eosin_focus.plt
                                                 Mon Nov 16 13:31:29 2009
 ================================================================

 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 =    -1.28017
                         slope =  0.000129308


          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         0.125131           -1.47978           -0.98928
          slope      0.000124995     1.49436e-005        9.57063e-005         0.000154284


                          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       3.80457      4          0.4331
  Reduced model        -202.816         1       83.4925      5         <.0001

          AIC:         329.944


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
     0.0000     0.1085         5.751     3.000          53       -1.215
  1408.4504     0.1449         7.826     8.000          54        0.067
  3137.0446     0.1998        10.588    14.000          53        1.172
  5392.9593     0.2876        15.242    17.000          53        0.533
  9128.8027     0.4628        24.526    22.000          53       -0.696
 16361.0000     0.7912        41.932    42.000          53        0.023

  Chi^2 = 3.62      d.f. = 4        P-value = 0.4593


    Benchmark Dose Computation

 Specified effect =           0.1

 Risk Type        =      Extra risk
```

```
Confidence level =           0.95

              BMD =        3076.08

             BMDL =        2679.85
```

E.2.32. National Toxicology Program (2006): Liver, Fatty Change, Diffuse

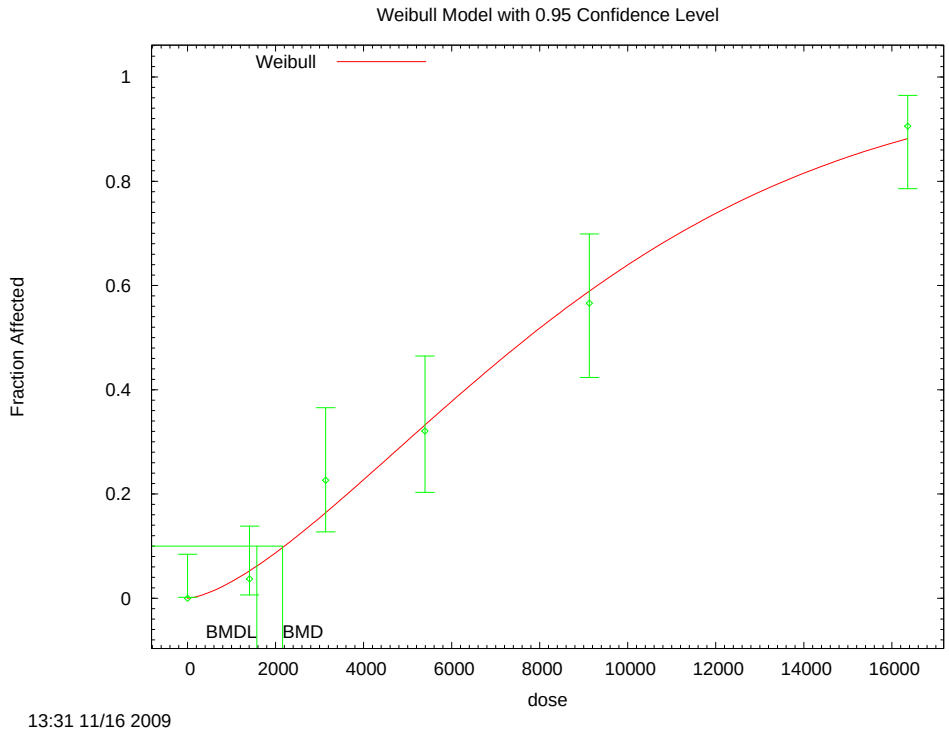
E.2.32.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	2.42	0.66	252.35	2.2E+03	1.6E+03	power restricted ≥1
logistic	4	9.22	0.06	262.13	3.2E+03	2.8E+03	
log-logistic	4	4.36	0.36	254.41	2.3E+03	1.8E+03	slope restricted ≥1
log-probit	4	4.30	0.37	254.43	2.3E+03	1.8E+03	slope restricted ≥1
multistage, 2-degree	4	2.03	0.73	252.07	2.0E+03	1.4E+03	betas restricted ≥0
probit	4	8.50	0.07	260.92	3.1E+03	2.6E+03	
Weibull [b]	**4**	**2.06**	**0.72**	**251.99**	**2.2E+03**	**1.6E+03**	**power restricted ≥1**

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

E.2.32.2. *Figure for Selected Model: Weibull, Power Restricted ≥1*



E.2.32.3. *Output File for Selected Model: Weibull, Power Restricted ≥1*

```
 ================================================================
         Weibull Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Weibull_BMR2_liver_fatty_change_diff.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\Weibull_BMR2_liver_fatty_change_diff.plt
                                                  Mon Nov 16 13:31:55 2009
 ================================================================

 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
```

```
                  Default Initial (and Specified) Parameter Values
                     Background =   0.00925926
                          Slope = 1.61086e-007
                          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           -1

      Power           -1            1



                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
      Background                0               NA
           Slope     1.01566e-006     1.55672e-006       -2.03545e-006        4.06678e-006
           Power          1.50443         0.168998              1.1732             1.83566

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       -123.994         2       2.00421      4           0.735
    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
   1408.4504     0.0539         2.912     2.000          54       -0.550
   3137.0446     0.1688         8.949    12.000          53        1.119
   5392.9593     0.3415        18.102    17.000          53       -0.319
   9128.8027     0.6024        31.929    30.000          53       -0.542
  16361.0000     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 =        2158.24

              BMDL =       1573.34
```

E.2.33. National Toxicology Program (2006): Liver Necrosis

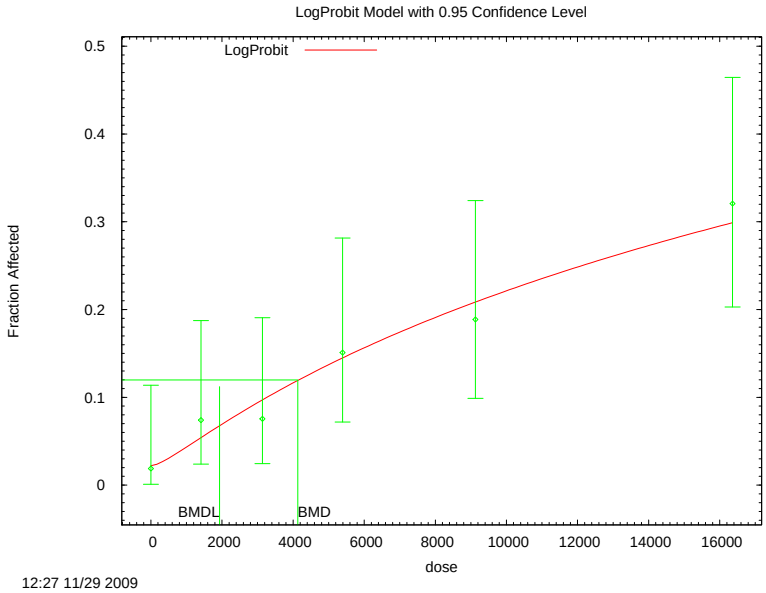
E.2.33.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	0.80	0.94	234.40	4.8E+03	3.5E+03	power restricted ≥1, bound hit
logistic	4	2.75	0.60	236.74	8.2E+03	6.8E+03	
log-logistic	4	0.77	0.94	234.38	4.4E+03	3.1E+03	slope restricted ≥1, bound hit
log-logistic	3	0.75	0.86	236.38	4.3E+03	1.9E+03	slope unrestricted
log-probit [b]	**3**	**0.99**	**0.80**	**236.60**	**4.1E+03**	**1.9E+03**	**slope unrestricted**
multistage, 2-degree	4	0.80	0.94	234.40	4.8E+03	3.5E+03	betas restricted ≥0, bound hit
probit	4	2.38	0.67	236.29	7.7E+03	6.4E+03	
Weibull	4	0.80	0.94	234.40	4.8E+03	3.5E+03	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

E.2.33.2. *Figure for Selected Model: Log-Probit*



E.2.33.3. *Output File for Selected Model: Log-Probit*

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov29\Blood\LogProbit_BMR2_liver_necrosis.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov29\Blood\LogProbit_BMR2_liver_necrosis.plt
                                                Sun Nov 29 12:27:13 2009
 ================================================================

 NTP_liver_necrosis
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 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 (and Specified) Parameter Values
                    background =    0.0188679
                     intercept =     -5.04893
                         slope =     0.457364


           Asymptotic Correlation Matrix of Parameter Estimates

             background    intercept        slope

background            1        -0.59         0.55

 intercept        -0.59            1           -1

     slope         0.55           -1            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background        0.0221159        0.0221444          -0.0212863           0.0655182
      intercept         -5.58721          1.71363            -8.94586            -2.22855
          slope         0.517092         0.185108            0.154287            0.879898


                         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      0.972296      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
   1408.4504     0.0544         2.938     4.000          54        0.637
   3137.0446     0.0976         5.174     4.000          53       -0.543
   5392.9593     0.1457         7.720     8.000          53        0.109
   9128.8027     0.2096        11.106    10.000          53       -0.373
  16361.0000     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 =         4132.6

             BMDL =        1930.47
```

E.2.34. National Toxicology Program (2006): Liver, Pigmentation

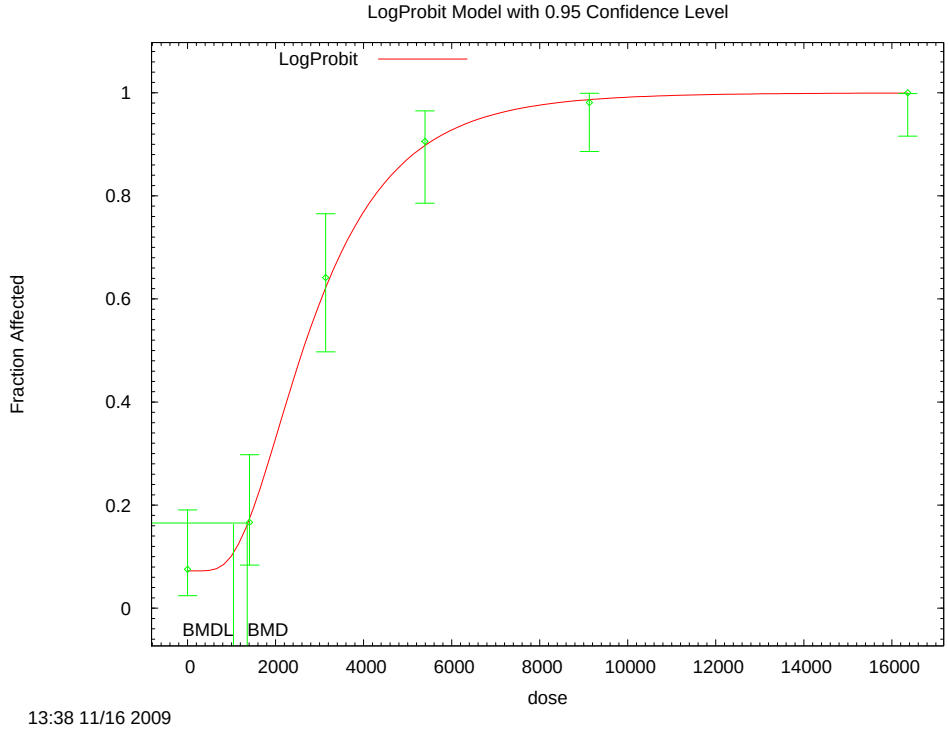
E.2.34.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	3	2.10	0.55	196.97	1.2E+03	8.2E+02	power restricted ≥1
logistic	4	5.42	0.25	197.07	1.0E+03	8.4E+02	
log-logistic	3	0.16	0.98	195.53	1.4E+03	1.1E+03	slope restricted ≥1
log-probit [b]	**3**	**0.29**	**0.96**	**195.53**	**1.4E+03**	**1.0E+03**	**slope restricted ≥1**
multistage, 2-degree	3	7.47	0.06	199.96	1.0E+03	5.5E+02	betas restricted ≥0
probit	4	15.44	0.00	200.50	9.4E+02	7.9E+02	
Weibull	3	4.42	0.22	199.01	9.7E+02	6.6E+02	power restricted ≥1

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

E.2.34.2. *Figure for Selected Model: Log-Probit, Slope Restricted ≥1*



E.2.34.3. *Output File for Selected Model: Log-Probit, Slope Restricted ≥1*

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\LogProbit_BMR2_Pigmentation.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\LogProbit_BMR2_Pigmentation.plt
                                                Mon Nov 16 13:38:02 2009
 ================================================================

 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 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 (and Specified) Parameter Values
background = 0.0754717
intercept = -12.1574
slope = 1.53218

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.35	0.33
intercept	-0.35	1	-1
slope	0.33	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0725493	0.0338874	0.00613127	0.138967
intercept	-14.4941	2.03052	-18.4738	-10.5144
slope	1.83177	0.246866	1.34792	2.31562

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	0.290885	3	0.9617
Reduced model	-210.717	1	232.198	5	<.0001

AIC: 195.526

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0725	3.845	4.000	53	0.082
1408.4504	0.1769	9.552	9.000	54	-0.197
3137.0446	0.6291	33.342	34.000	53	0.187
5392.9593	0.9013	47.771	48.000	53	0.105
9128.8027	0.9874	52.334	52.000	53	-0.412
16361.0000	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 = 1356.93

BMDL = 1041.17

E.2.35. National Toxicology Program (2006): Liver, Toxic Hepatopathy

E.2.35.1. *Summary Table of BMDS Modeling Results*

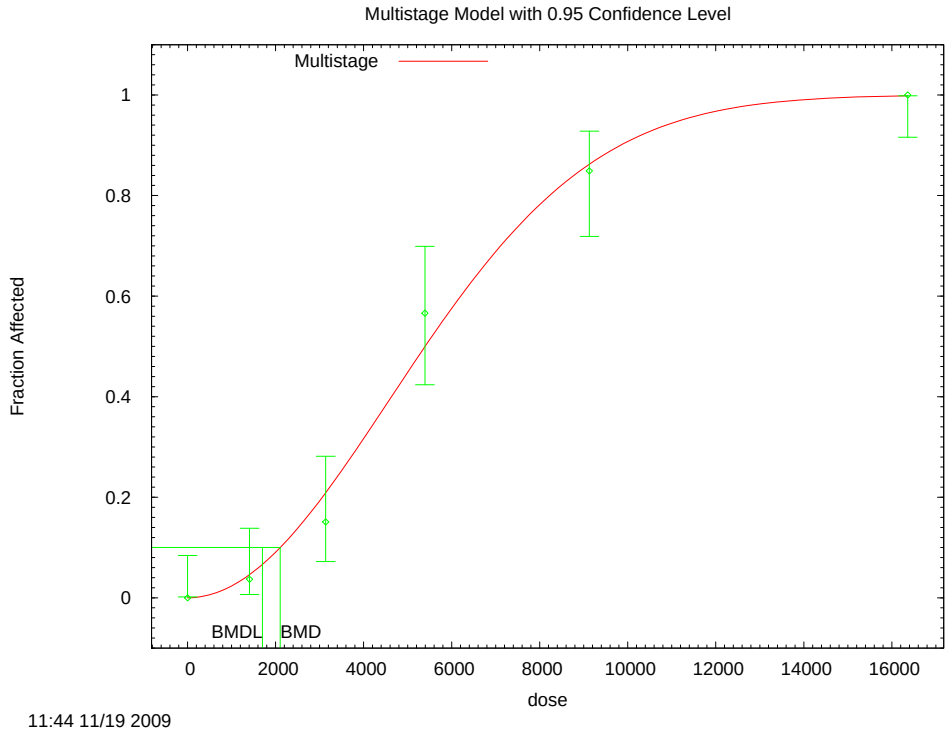
Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	1.90	0.75	185.76	2.4E+03	1.9E+03	power restricted ≥1
logistic	4	6.59	0.16	191.14	2.7E+03	2.2E+03	
log-logistic	3	3.01	0.39	189.58	2.6E+03	2.1E+03	slope restricted ≥1
log-probit	3	2.99	0.39	189.58	2.7E+03	2.1E+03	slope restricted ≥1
multistage, 2-degree [b]	**5**	**2.28**	**0.81**	**184.08**	**2.1E+03**	**1.7E+03**	**betas restricted ≥0, bound hit**
probit	4	5.60	0.23	189.82	2.5E+03	2.1E+03	
Weibull	4	2.11	0.72	185.79	2.3E+03	1.8E+03	power restricted ≥1

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

[c] Alternate model also presented in this appendix

E.2.35.2. *Figure for Selected Model: Multistage, 2-Degree, Betas Restricted ≥0, Bound Hit*



E.2.35.3. *Output File for Selected Model: Multistage, 2-Degree, Betas Restricted ≥0, Bound Hit*

```
 ================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Multistage_BMR2_Toxic_hepatopathy.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Multistage_BMR2_Toxic_hepatopathy.plt
                                                Thu Nov 19 11:44:22 2009
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 6
 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
                        Beta(1) =           0
                        Beta(2) = 3.75131e+011


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)
                 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(2)           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)      2.3767e-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	-89.8076	6			
Fitted model	-91.0417	1	2.46809	5	0.7813
Reduced model	-218.207	1	256.799	5	<.0001

AIC: 184.083

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	53	0.000
1408.4504	0.0461	2.487	2.000	54	-0.316
3137.0446	0.2086	11.053	8.000	53	-1.032
5392.9593	0.4990	26.449	30.000	53	0.975
9128.8027	0.8620	45.687	45.000	53	-0.274
16361.0000	0.9983	52.909	53.000	53	0.303

Chi^2 = 2.28 d.f. = 5 P-value = 0.8087

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

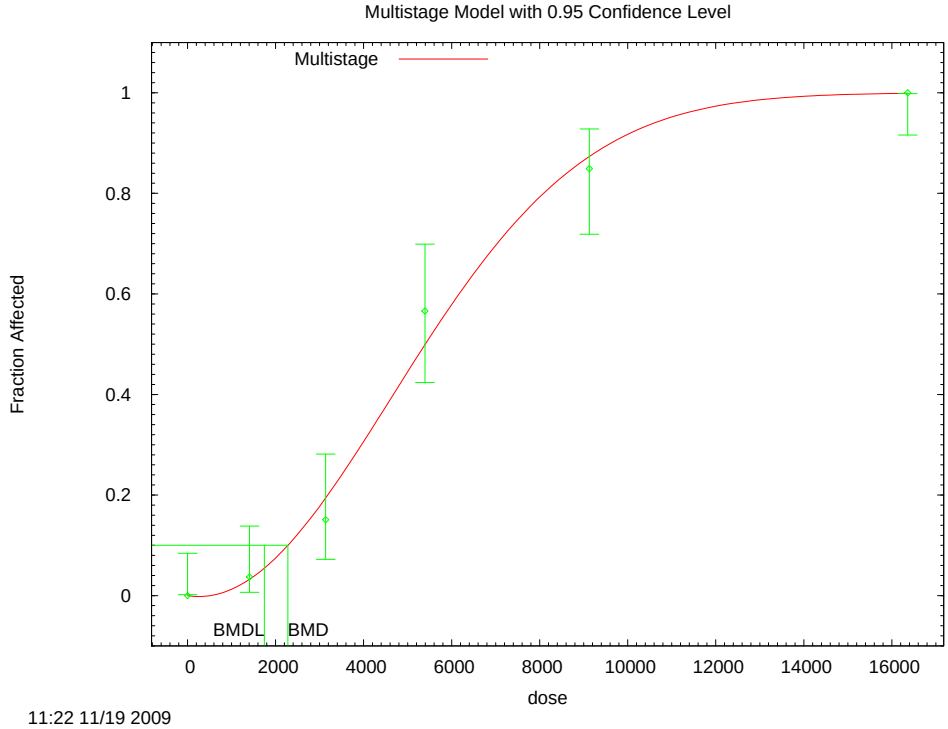
BMD = 2105.48

BMDL = 1698.91

BMDU = 2318.05

Taken together, (1698.91, 2318.05) is a 90 % two-sided confidence interval for the BMD

E.2.35.4. *Figure for Unrestricted Model: Multistage, 2-Degree, Betas Unrestricted*



E.2.35.5. *Output File for Unrestricted Model: Multistage, 2-Degree, Betas Unrestricted*

```
 ===============================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Multistage_Unrest_BMR2_Toxic_hepatopathy.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\Multistage_Unrest_BMR2_Toxic_hepatopathy.plt
                                                Thu Nov 19 11:22:30 2009
 ===============================================================

 0
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2)]

   The parameter betas are not restricted


   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 = 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 =           1
                        Beta(1) = -6.1241e+015
                        Beta(2) = 7.17596e+011


           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(2)

   Beta(1)            1        -0.92

   Beta(2)        -0.92            1



                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
      Background                0           *               *                   *
         Beta(1)    -1.36642e-005           *               *                   *
         Beta(2)     2.62877e-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         -89.8076         6
   Fitted model         -90.8336         2       2.05202      4          0.7262
  Reduced model         -218.207         1       256.799      5         <.0001

           AIC:          185.667


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          53        0.000
 1408.4504     0.0324         1.748     2.000          54        0.194
 3137.0446     0.1941        10.289     8.000          53       -0.795
 5392.9593     0.4989        26.439    30.000          53        0.978
 9128.8027     0.8733        46.285    45.000          53       -0.531
16361.0000     0.9989        52.942    53.000          53        0.241

 Chi^2 = 1.97      d.f. = 4        P-value = 0.7420


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =       2278.69
```

```
              BMDL =        1743.86

              BMDU =        2713.68

Taken together, (1743.86, 2713.68) is a 90     % two-sided confidence
interval for the BMD
```

E.2.36. National Toxicology Program (2006): Lung, Alveolar to Bronchiolar Epithelial Metaplasia (Alveolar Epithelium, Metaplasia, Bronchiolar)

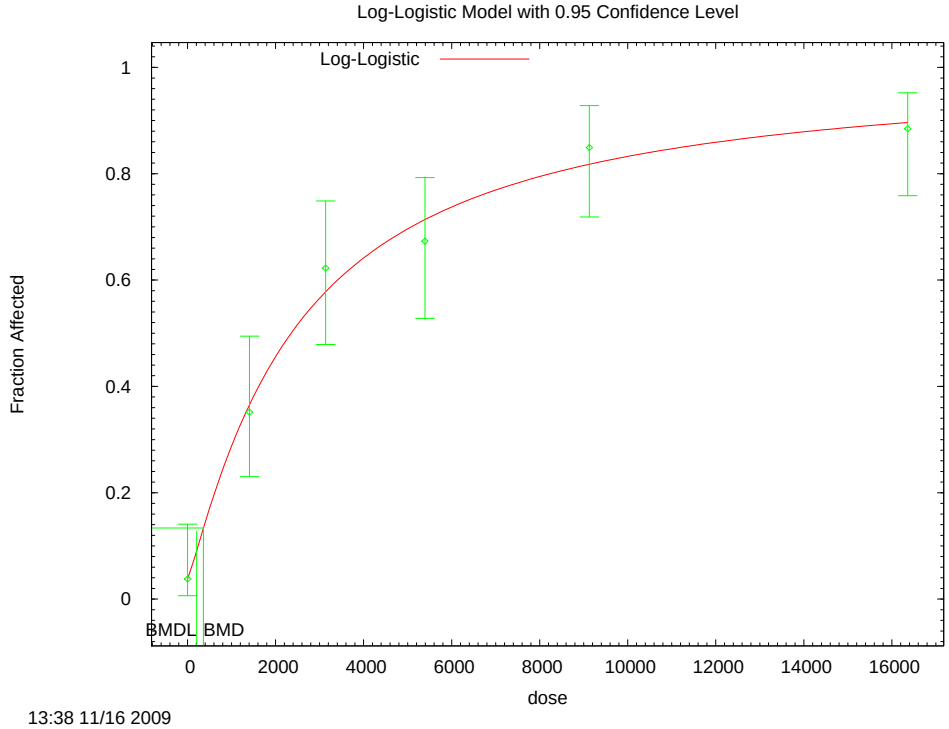
E.2.36.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	13.37	0.01	320.09	5.4E+02	4.6E+02	power restricted ≥1, bound hit
logistic	4	33.08	0.00	343.28	1.3E+03	1.1E+03	
log-logistic [b]	**3**	**1.32**	**0.72**	**312.56**	**3.6E+02**	**2.1E+02**	**slope restricted ≥1**
log-probit	3	1.44	0.70	312.68	3.8E+02	1.5E+02	slope restricted ≥1
multistage, 2-degree	4	13.37	0.01	320.09	5.4E+02	4.6E+02	betas restricted ≥0, bound hit
probit	4	35.22	0.00	347.07	1.4E+03	1.2E+03	
Weibull	4	13.37	0.01	320.09	5.4E+02	4.6E+02	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

E.2.36.2. *Figure for Selected Model: Log-Logistic, Slope Restricted ≥1*



E.2.36.3. *Output File for Selected Model: Log-Logistic, Slope Restricted ≥1*

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\LogLogistic_BMR2_Alv_bronch_epith_metapl.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\LogLogistic_BMR2_Alv_bronch_epith_metapl.plt
                                                  Mon Nov 16 13:38:53 2009
 ================================================================

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   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 = 0.0377358
intercept = -8.78161
slope = 1.1228

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.13	0.1
intercept	-0.13	1	-1
slope	0.1	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0373474	*	*	*
intercept	-8.85134	*	*	*
slope	1.13159	*	*	*

* - 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	1.32714	3	0.7227
Reduced model	-216.802	1	128.374	5	<.0001

AIC: 312.558

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0373	1.979	2.000	53	0.015
1408.4504	0.3682	19.881	19.000	54	-0.249
3137.0446	0.5807	30.777	33.000	53	0.619
5392.9593	0.7162	37.244	35.000	52	-0.690
9128.8027	0.8197	43.445	45.000	53	0.556
16361.0000	0.8976	46.674	46.000	52	-0.308

Chi^2 = 1.32 d.f. = 3 P-value = 0.7232

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 357.926

BMDL = 206.635

E.2.37. National Toxicology Program (2006): Oval Cell Hyperplasia, 2 Years

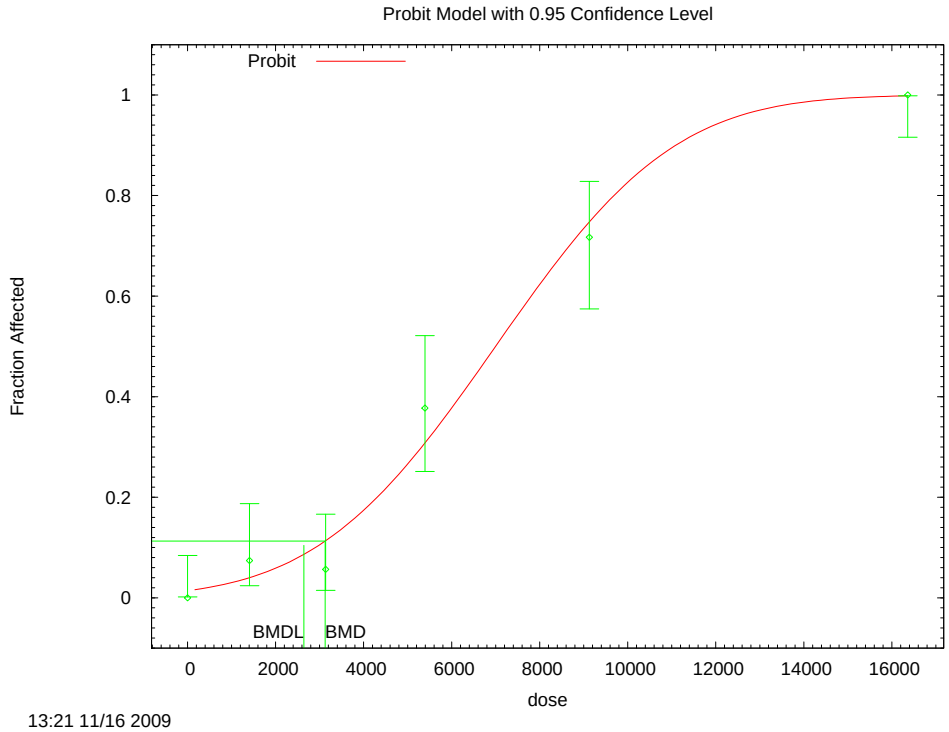
E.2.37.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	3	6.94	0.07	199.47	3.7E+03	2.8E+03	power restricted ≥1
logistic	4	6.40	0.17	196.80	3.3E+03	2.8E+03	
log-logistic	3	8.21	0.04	201.66	3.8E+03	3.1E+03	slope restricted ≥1
log-probit	3	7.00	0.07	200.12	3.9E+03	3.3E+03	slope restricted ≥1
multistage, 2-degree	4	7.05	0.13	197.13	2.5E+03	2.0E+03	betas restricted ≥0
probit [b]	4	5.64	0.23	195.45	3.1E+03	2.6E+03	
Weibull	**3**	**6.85**	**0.08**	**198.38**	**3.2E+03**	**2.3E+03**	**power restricted ≥1**

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

E.2.37.2. *Figure for Selected Model: Probit*



E.2.37.3. *Output File for Selected Model: Probit*

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Probit_BMR2_Oval_cell_hyperplasia.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Probit_BMR2_Oval_cell_hyperplasia.plt
                                                 Mon Nov 16 13:21:57 2009
 ================================================================

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   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 =     -2.29925
                          slope =  0.000307725


           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         0.208022           -2.59759           -1.78216
          slope      0.000313001      3.3114e-005         0.000248098         0.000377903


                         Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -92.4898         6
     Fitted model       -95.7243         2       6.46898      4          0.1668
    Reduced model       -210.191         1       235.402      5         <.0001
```

```
            AIC:         195.449


                                  Goodness  of  Fit
                                                                          Scaled
      Dose      Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------------
     0.0000     0.0143         0.756     0.000          53       -0.876
  1408.4504     0.0401         2.168     4.000          54        1.270
  3137.0446     0.1135         6.017     3.000          53       -1.306
  5392.9593     0.3079        16.317    20.000          53        1.096
  9128.8027     0.7478        39.631    38.000          53       -0.516
 16361.0000     0.9983        52.911    53.000          53        0.299

 Chi^2 = 5.64      d.f. = 4        P-value = 0.2274


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         3125.6

            BMDL =        2640.99
```

E.2.38. National Toxicology Program (2006): Toxic Hepatopathy

E.2.38.1. *Summary Table of BMDS Modeling Results*

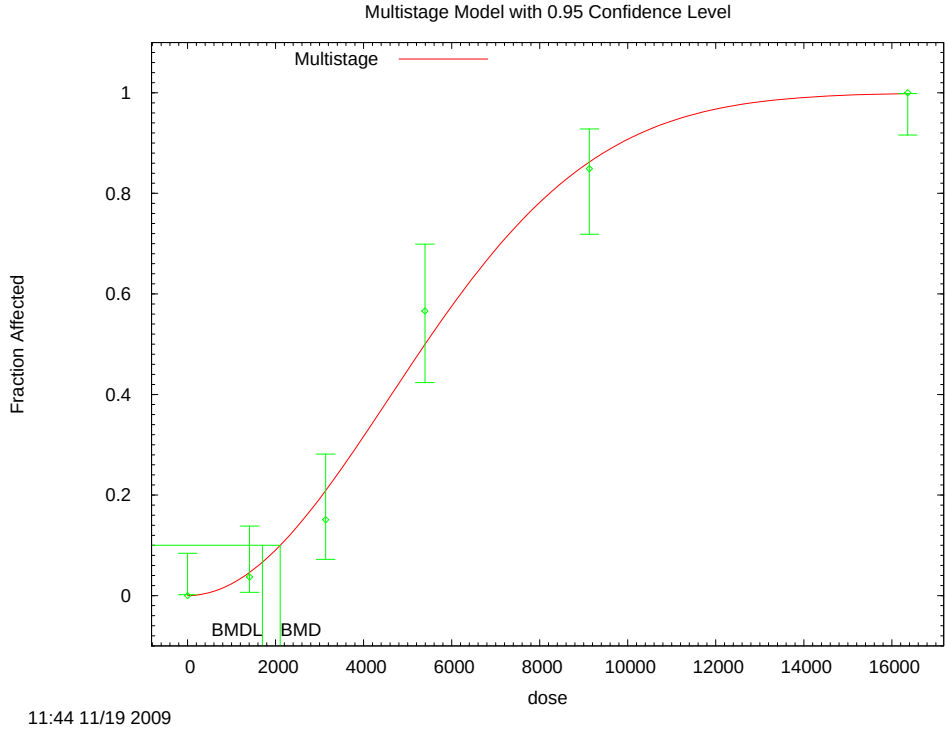
Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	1.90	0.75	185.76	2.4E+03	1.9E+03	power restricted ≥1
logistic	4	6.59	0.16	191.14	2.7E+03	2.2E+03	
log-logistic	3	3.01	0.39	189.58	2.6E+03	2.1E+03	slope restricted ≥1
log-probit	3	2.99	0.39	189.58	2.7E+03	2.1E+03	slope restricted ≥1
multistage, 2-degree [b]	**5**	**2.28**	**0.81**	**184.08**	**2.1E+03**	**1.7E+03**	**betas restricted ≥0, bound hit**
probit	4	5.60	0.23	189.82	2.5E+03	2.1E+03	
Weibull	4	2.11	0.72	185.79	2.3E+03	1.8E+03	power restricted ≥1

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

[c] Alternate model also presented in this appendix

E.2.38.2. *Figure for Selected Model: Multistage, 2-Degree, Betas Restricted ≥0, Bound Hit*



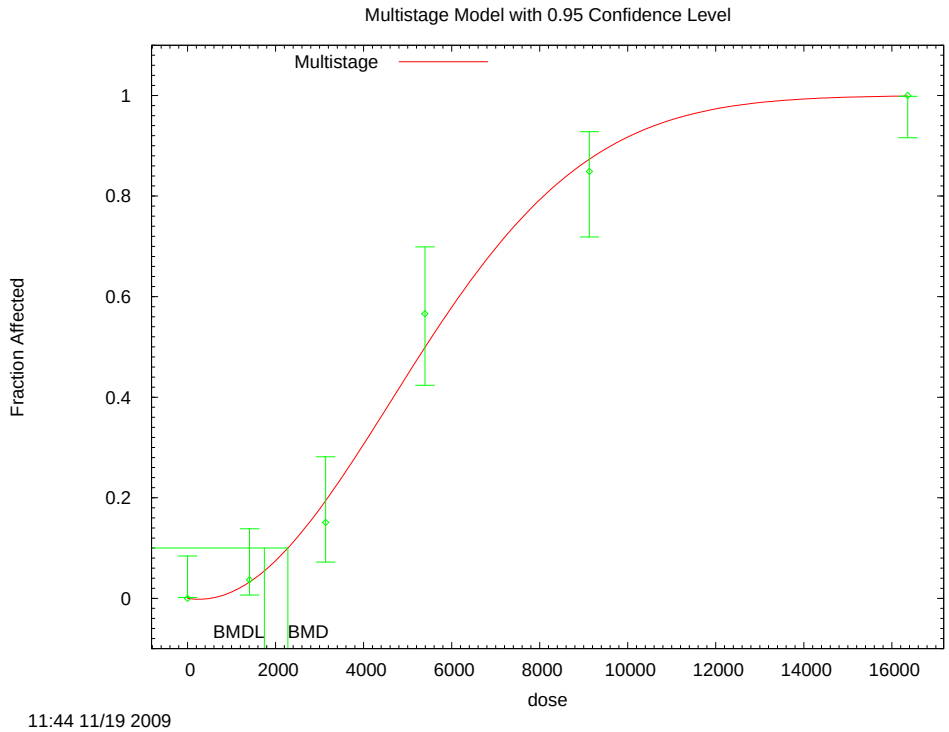
E.2.38.3. *Output File for Selected Model: Multistage, 2-Degree, Betas Restricted ≥0, Bound Hit*

```
 ========================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Multistage_BMR2_Toxic_hepatopathy.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Multistage_BMR2_Toxic_hepatopathy.plt
                                                    Thu Nov 19 11:44:22 2009
 ========================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 6
 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
                       Beta(1) =            0
                       Beta(2) = 3.75131e+011


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -Background    -Beta(1)
                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(2)            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)      2.3767e-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        -89.8076         6
  Fitted model        -91.0417         1       2.46809      5          0.7813
 Reduced model        -218.207         1       256.799      5         <.0001

          AIC:         184.083


                                 Goodness  of  Fit
                                                                  Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          53        0.000
 1408.4504     0.0461         2.487     2.000          54       -0.316
 3137.0446     0.2086        11.053     8.000          53       -1.032
 5392.9593     0.4990        26.449    30.000          53        0.975
 9128.8027     0.8620        45.687    45.000          53       -0.274
16361.0000     0.9983        52.909    53.000          53        0.303

 Chi^2 = 2.28      d.f. = 5        P-value = 0.8087


  Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        2105.48
```

```
            BMDL =        1698.91

            BMDU =        2318.05

Taken together, (1698.91, 2318.05) is a 90     % two-sided confidence
interval for the BMD
```

E.2.38.4. *Figure for Unrestricted Model: Multistage, 2-Degree, Betas Unrestricted*



E.2.38.5. *Output File for Unrestricted Model: Multistage, 2-Degree, Betas Unrestricted*

```
 ========================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File:
C:\USEPA\BMDS21\AD\Blood\Multistage_Unrest_BMR2_2nd_Toxic_hepatopathy.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\Multistage_Unrest_BMR2_2nd_Toxic_hepatopathy.plt
                                                  Thu Nov 19 11:44:23 2009
 ========================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2)]

   The parameter betas are not restricted
```

```
  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 = 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 =           1
                       Beta(1) = -6.1241e+015
                       Beta(2) = 7.17596e+011


          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(2)

  Beta(1)            1        -0.92

  Beta(2)        -0.92            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background                0            *               *                   *
        Beta(1)    -1.36642e-005            *               *                   *
        Beta(2)     2.62877e-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        -89.8076         6
   Fitted model        -90.8336         2       2.05202      4          0.7262
  Reduced model        -218.207         1       256.799      5         <.0001

          AIC:         185.667


                               Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          53        0.000
  1408.4504     0.0324         1.748     2.000          54        0.194
  3137.0446     0.1941        10.289     8.000          53       -0.795
  5392.9593     0.4989        26.439    30.000          53        0.978
  9128.8027     0.8733        46.285    45.000          53       -0.531
 16361.0000     0.9989        52.942    53.000          53        0.241

 Chi^2 = 1.97      d.f. = 4        P-value = 0.7420
```

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        2278.69

             BMDL =        1743.86

             BMDU =        2713.68

Taken together, (1743.86, 2713.68) is a 90     % two-sided confidence
interval for the BMD
```

E.2.39. Ohsako et al. (2001): Anogenital Distance in Male Pups

E.2.39.1. *Summary Table of BMDS Modeling Results*

Model [a]	Degrees of Freedom	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	3	0.092	185.349	2.358E+04	1.529E+04	
exponential (M3)	3	0.092	185.349	2.358E+04	1.529E+04	power bound hit
exponential (M4)	2	0.190	184.217	2.617E+03	8.029E+02	
exponential (M5)	1	0.092	185.741	2.204E+03	8.487E+02	
Hill [c]	2	0.261	183.587	3.628E+03	8.053E+02	n lower bound hit
linear	3	0.086	185.490	2.436E+04	1.638E+04	
polynomial	3	0.086	185.490	2.436E+04	1.638E+04	
power	3	0.086	185.490	2.436E+04	1.638E+04	power bound hit
Hill, unrestricted [d]	1	0.106	185.515	4.741E+03	4.517E+02	n unrestricted

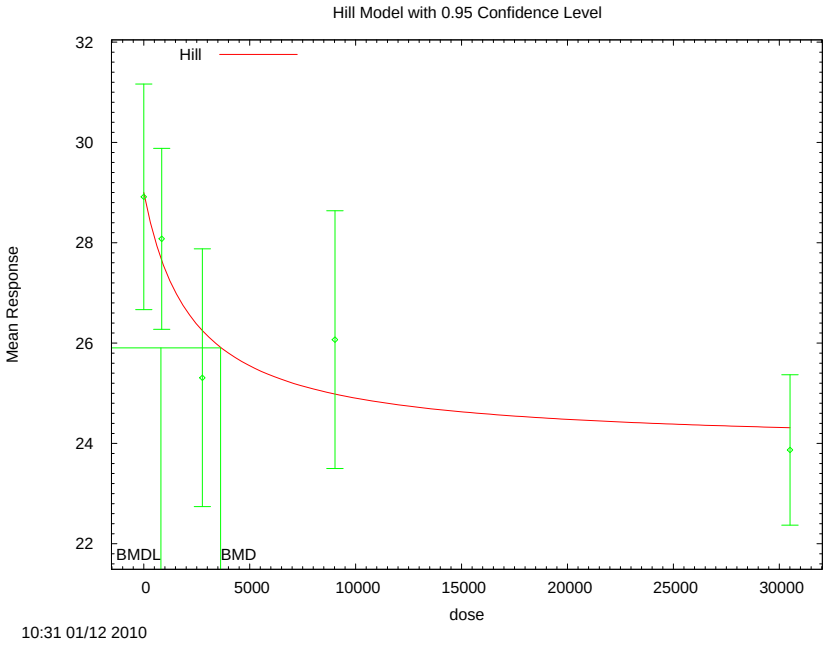
[a] Constant variance model selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model, BMDS output presented in this appendix

[d] Alternate model, BMDS output also presented in this appendix

E.2.39.2. *Figure for Selected Model: Hill*



Ohsako et al., 2001: Ano-genital distance in male pups

E.2.39.3. *Output File for Selected Model: Hill*

Ohsako et al., 2001: Ano-genital distance in male pups

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\Blood\56_Ohsako_2001_anogenital_HillCV_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\56_Ohsako_2001_anogenital_HillCV_1.plt
                                                Tue Jan 12 10:31:18 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 =      9.96434
```

```
                            rho =           0   Specified
                      intercept =     28.9146
                              v =    -5.04512
                              n =     1.64399
                              k =      2013.5


           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     4.1e-008     7.2e-008     -1e-007

  intercept     4.1e-008            1        -0.53       -0.53

          v     7.2e-008        -0.53            1       -0.27

          k      -1e-007        -0.53        -0.27           1


                                  Parameter Estimates

                                                                  95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha          9.50299          1.82885            5.91851             13.0875
       intercept           28.988         0.868025            27.2867             30.6893
               v         -5.03805          1.23954            -7.4675             -2.6086
               n                1               NA
               k          2301.52          2261.96           -2131.83             6734.88

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         3.54         3.08        -0.0824
845.3    10       28.1         27.6         2.52         3.08          0.455
 2763    10       25.3         26.2         3.59         3.08         -0.953
 9022    10       26.1           25         3.59         3.08           1.12
3.05e+004    12       23.9         24.3         2.36         3.08         -0.488


 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	-86.449919	6	184.899838
A2	-84.654549	10	189.309098
A3	-86.449919	6	184.899838
fitted	-87.793369	4	183.586738
R	-95.473923	2	194.947846

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	21.6387	8	0.005631
Test 2	3.59074	4	0.4642
Test 3	3.59074	4	0.4642
Test 4	2.6869	2	0.2609

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

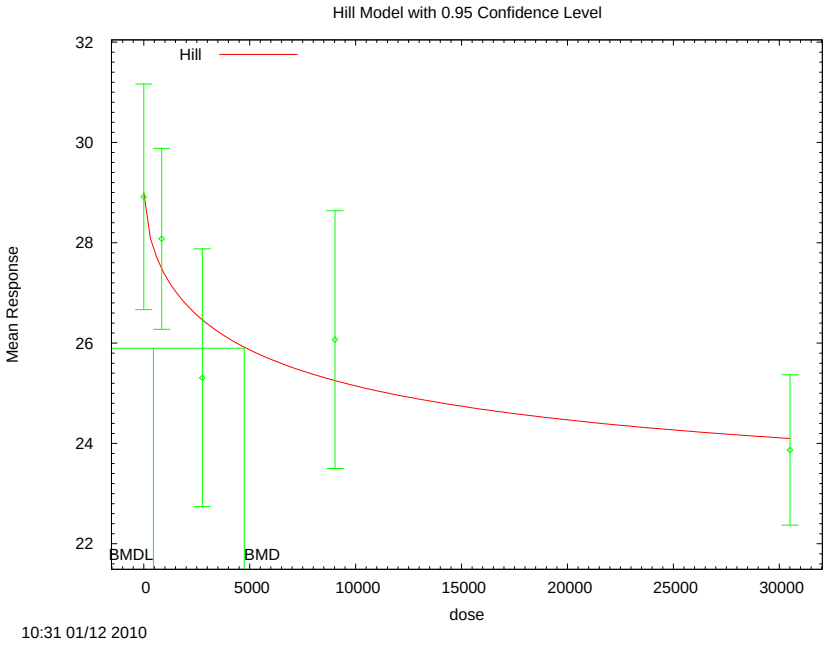
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 3628.44

BMDL = 805.33

E.2.39.4. *Figure for Unrestricted Model: Hill, Unrestricted*



Ohsako et al., 2001: Ano-genital distance in male pups

E.2.39.5. *Output File for Unrestricted Model: Hill, Unrestricted*

Ohsako et al., 2001: Ano-genital distance in male pups

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\1\Blood\56_Ohsako_2001_anogenital_HillCV_Unrest_1.(d)
         Gnuplot Plotting File:  C:\1\Blood\56_Ohsako_2001_anogenital_HillCV_Unrest_1.plt
                                                Tue Jan 12 10:31:19 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 =      9.96434
```

```
                          rho =           0   Specified
                    intercept =     28.9146
                            v =    -5.04512
                            n =     1.64399
                            k =      2013.5


          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     1.7e-008    7.5e-008    7.3e-008   -7.2e-008

 intercept    1.7e-008           1     -0.0053     -0.0089       -0.14

         v    7.5e-008     -0.0053           1        0.98       -0.99

         n    7.3e-008     -0.0089        0.98           1       -0.96

         k   -7.2e-008       -0.14       -0.99       -0.96           1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha          9.49042          1.82643            5.91068             13.0702
      intercept          28.9785         0.871908            27.2696             30.6874
              v         -6.77236           12.034           -30.3585             16.8138
              n         0.615459          1.15558           -1.64943             2.88035
              k          6361.67          43105.4           -78123.4             90846.7


     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         3.54         3.08        -0.0718
845.3    10       28.1         27.5         2.52         3.08          0.633
 2763    10       25.3         26.4         3.59         3.08          -1.16
 9022    10       26.1         25.2         3.59         3.08          0.861
3.05e+004    12       23.9         24.1         2.36         3.08         -0.231


 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          -86.449919           6     184.899838
              A2          -84.654549          10     189.309098
              A3          -86.449919           6     184.899838
           fitted         -87.757640           5     185.515280
               R          -95.473923           2     194.947846


                    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              21.6387          8        0.005631
   Test 2              3.59074          4          0.4642
   Test 3              3.59074          4          0.4642
   Test 4              2.61544          1          0.1058

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 =        4741.19

             BMDL =       451.715
```

E.2.40. Schantz et al. (1996): Maze Errors Per Block, Female

E.2.40.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
linear	1	0.71	2.38	0.12	19.76	5.1E+03	2.9E+03	nonconstant variance
polynomial	1	0.71	2.38	0.12	19.76	5.1E+03	2.9E+03	nonconstant variance
power	1	0.71	2.38	0.12	19.76	5.1E+03	2.9E+03	nonconstant variance, power restricted ≥1, bound hit
power	0	0.71	0.00	NA	19.38	1.2E+03	5.4E-08	nonconstant variance, power unrestricted
linear [c]	**1**	**0.71**	**1.99**	**0.16**	**17.95**	**5.5E+03**	**3.6E+03**	**constant variance**
polynomial	1	0.71	1.99	0.16	17.95	5.5E+03	3.6E+03	constant variance
power	1	0.71	1.99	0.16	17.95	5.5E+03	3.6E+03	constant variance, power restricted ≥1, bound hit
power [d]	0	0.71	0.00	NA	17.95	2.0E+03	8.1E-06	constant variance, power unrestricted

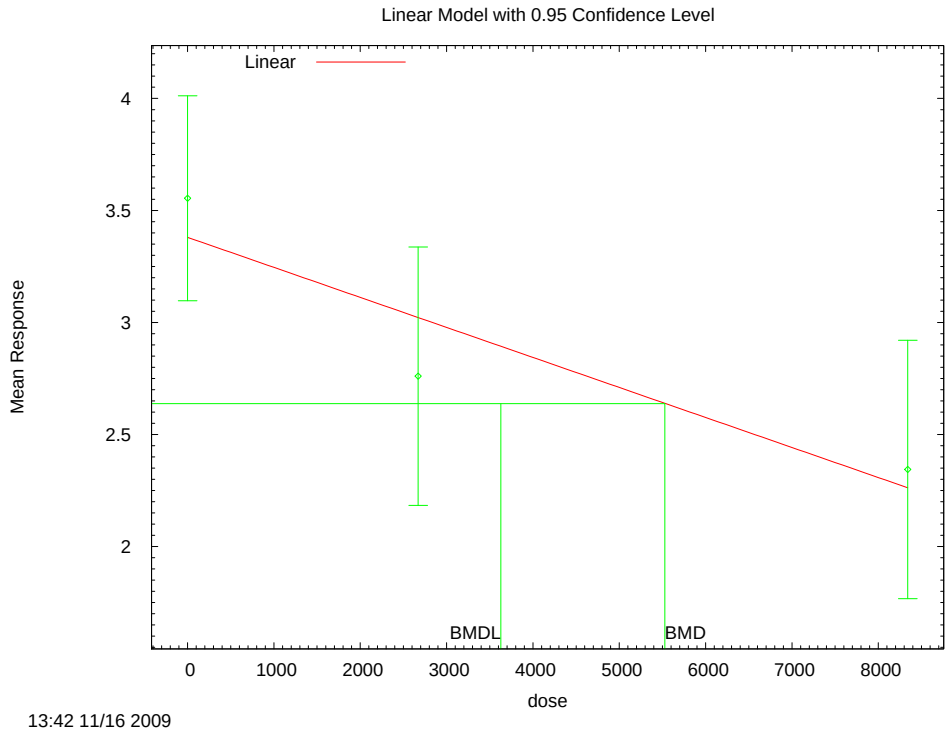
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.40.2. *Figure for Selected Model: Linear, Constant Variance*



13:42 11/16 2009

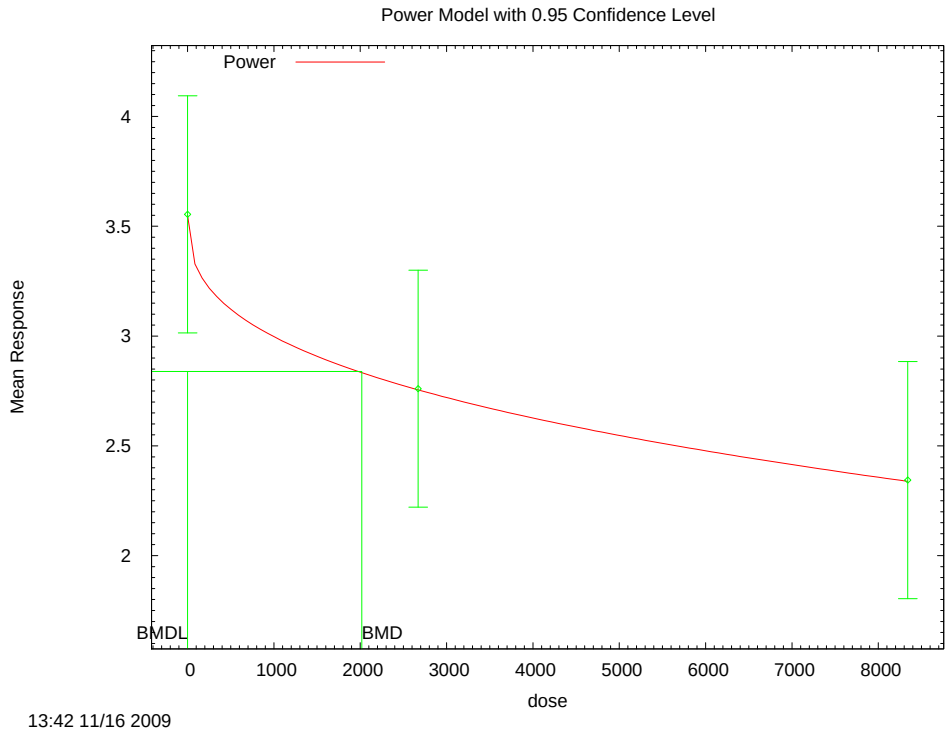
E.2.40.3. *Output File for Selected Model: Linear, Constant Variance*

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\LinearConstVar_BMR4_maze_errors.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\LinearConstVar_BMR4_maze_errors.plt
                                                 Mon Nov 16 13:42:46 2009
 ================================================================

 Rel Male Thymus wt, Tbl 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 = 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 =     0.569565
                            rho =            0   Specified
                         beta_0 =      3.37789
                         beta_1 = -0.000133906


          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     1.5e-010     7.3e-012

    beta_0     1.5e-010            1        -0.73

    beta_1     7.3e-012        -0.73            1


                                Parameter Estimates

                                                                95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha         0.547839         0.141451            0.270599            0.825079
        beta_0           3.37789         0.196469             2.99282             3.76296
        beta_1     -0.000133906     3.88571e-005       -0.000210064       -5.77472e-005


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    10       3.55         3.38        0.639         0.74          0.755
 2670    10       2.76         3.02        0.806         0.74          -1.11
 8341    10       2.34         2.26        0.806         0.74          0.355


 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          -4.976366            4      17.952732
               A2          -4.638353            6      21.276707
               A3          -4.976366            4      17.952732
           fitted          -5.973388            3      17.946777
                R         -10.975997            2      25.951993
```

```
                    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              12.6753          4         0.01298
   Test 2             0.676025          2          0.7132
   Test 3             0.676025          2          0.7132
   Test 4              1.99405          1          0.1579

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 =        5527.48


             BMDL =         3627.8
```

E.2.40.4. *Figure for Unrestricted Model: Power, Constant Variance, Power Unrestricted*



13:42 11/16 2009

E.2.40.5. *Output File for Unrestricted Model: Power, Constant Variance, Power Unrestricted*

```
 ========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\PwrConstVar_Unrest_BMR6_maze_errors.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\PwrConstVar_Unrest_BMR6_maze_errors.plt
                                                  Mon Nov 16 13:42:47 2009
 ========================================================================

 Rel Male Thymus wt, Tbl 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 0.569565
rho = 0 Specified
control = 3.55459
slope = -0.0428676
power = 0.369985

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	-6.8e-011	-1.4e-012	-1.6e-013
control	-6.8e-011	1	-0.35	-0.28
slope	-1.4e-012	-0.35	1	1
power	-1.6e-013	-0.28	1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.512609	0.132355	0.253198	0.77202
control	3.55459	0.226409	3.11084	3.99834
slope	-0.0428676	0.119074	-0.276249	0.190514
power	0.369985	0.311491	-0.240526	0.980496

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	3.55	3.55	0.639	0.716	2.62e-010
2670	10	2.76	2.76	0.806	0.716	3.09e-010
8341	10	2.34	2.34	0.806	0.716	3.32e-010

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	-4.976366	4	17.952732
A2	-4.638353	6	21.276707
A3	-4.976366	4	17.952732
fitted	-4.976366	4	17.952732
R	-10.975997	2	25.951993

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	12.6753	4	0.01298
Test 2	0.676025	2	0.7132
Test 3	0.676025	2	0.7132
Test 4	1.77636e-015	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 = 2017.9

BMDL = 8.10578e-006

E.2.41. Shi et al. (2007): Estradiol

E.2.41.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance p-Value [a]	χ^2 Test Statistic	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	3	0.05	11.41	0.01	391.64	3.8E+03	2.1E+03	nonconstant variance, power restricted ≥1
exponential (M3)	3	0.05	11.41	0.01	391.64	3.8E+03	2.1E+03	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**2**	**0.05**	**0.74**	**0.69**	**382.97**	**4.4E+02**	**2.0E+02**	**nonconstant variance, power restricted ≥1**
exponential (M5)	2	0.05	0.74	0.69	382.97	4.4E+02	2.0E+02	nonconstant variance, power restricted ≥1
exponential (M5) [d]	2	0.05	0.74	0.69	382.97	4.4E+02	2.0E+02	nonconstant variance, power unrestricted
Hill	2	0.05	0.05	0.97	382.28	4.0E+02	error	nonconstant variance, n restricted >1, bound hit
Hill [d]	1	0.05	0.02	0.90	384.24	3.9E+02	error	nonconstant variance, n unrestricted
linear	3	0.05	14.08	0.00	394.31	5.4E+03	3.7E+03	nonconstant variance
polynomial	2	0.05	5.06	0.08	387.29	1.8E+03	1.2E+03	nonconstant variance
power	3	0.05	14.08	0.00	394.31	5.4E+03	3.7E+03	nonconstant variance, power restricted ≥1, bound hit
power [d]	2	0.05	1.36	0.51	383.59	3.5E+02	1.8E+01	nonconstant variance, power unrestricted
exponential (M2)	3	0.05	9.37	0.02	392.09	2.8E+03	1.6E+03	constant variance, power restricted ≥1
exponential (M3)	3	0.05	9.37	0.02	392.09	2.8E+03	1.6E+03	constant variance, power restricted ≥1
exponential (M4)	2	0.05	0.61	0.74	385.34	3.3E+02	1.5E+02	constant variance, power restricted ≥1
exponential (M5)	2	0.05	0.61	0.74	385.34	3.3E+02	1.5E+02	constant variance, power restricted ≥1
exponential (M5)	2	0.05	0.61	0.74	385.34	3.3E+02	1.5E+02	constant variance, power unrestricted
Hill	1	0.05	0.26	0.61	386.98	3.1E+02	1.2E+02	constant variance, n restricted >1
Hill	1	0.05	0.26	0.61	386.98	3.1E+02	4.0E+01	constant variance, n unrestricted
linear	3	0.05	12.21	0.01	394.93	4.4E+03	3.2E+03	constant variance
polynomial	2	0.05	5.39	0.07	390.12	1.4E+03	9.3E+02	constant variance

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
power	3	0.05	12.21	0.01	394.93	4.4E+03	3.2E+03	constant variance, power restricted ≥1, bound hit
power	2	0.05	1.66	0.44	386.38	2.3E+02	1.2E+01	constant variance, power unrestricted

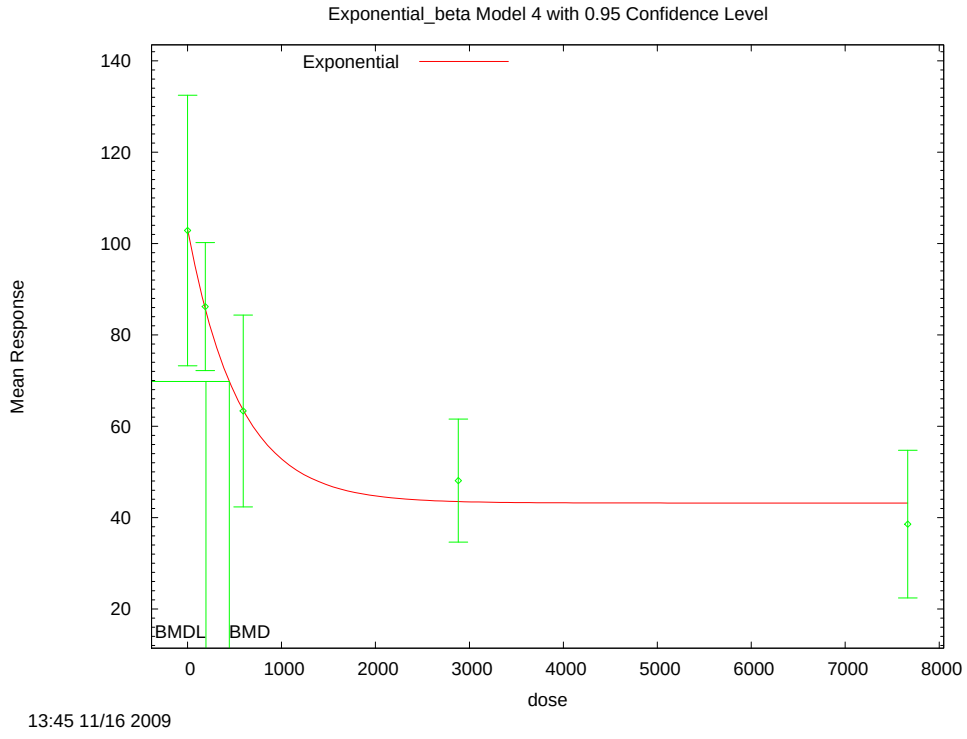
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.41.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



E.2.41.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
================================================================
        Exponential Model. (Version: 1.5;  Date: 4/23/2009)
        Input Data File: C:\USEPA\BMDS21\AD\Blood\Exp_BMR1_Shi_estradiol_17B_conc_PE9.(d)
        Gnuplot Plotting File:
                                              Mon Nov 16 13:45:19 2009
```

```
 ========================================================================

 Figure 4 PE9 only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 4
                --------          --------
                  lnalpha             2.65881
                      rho            0.913414
                        a                 108
                        b         0.000503911
                        c            0.340136
                        d                   1



                  Parameter Estimates

                 Variable          Model 4
                 --------          -------
                  lnalpha           1.66777
                      rho           1.15313
                        a           103.145
                        b        0.00182735
                        c          0.418744
                        d                 1


          Table of Stats From Input Data

     Dose      N         Obs Mean     Obs Std Dev
     -----    ---       ----------   -------------
         0     10        102.9        41.41
     188.3     10        86.19        19.58
     592.1     10        63.33        29.36
      2882     10         48.1        18.82
      7665     10        38.57        22.59
```

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	103.1	33.35	-0.02732
188.3	85.69	29.96	0.05287
592.1	63.51	25.21	-0.02235
2882	43.5	20.27	0.7167
7665	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	382.9688

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

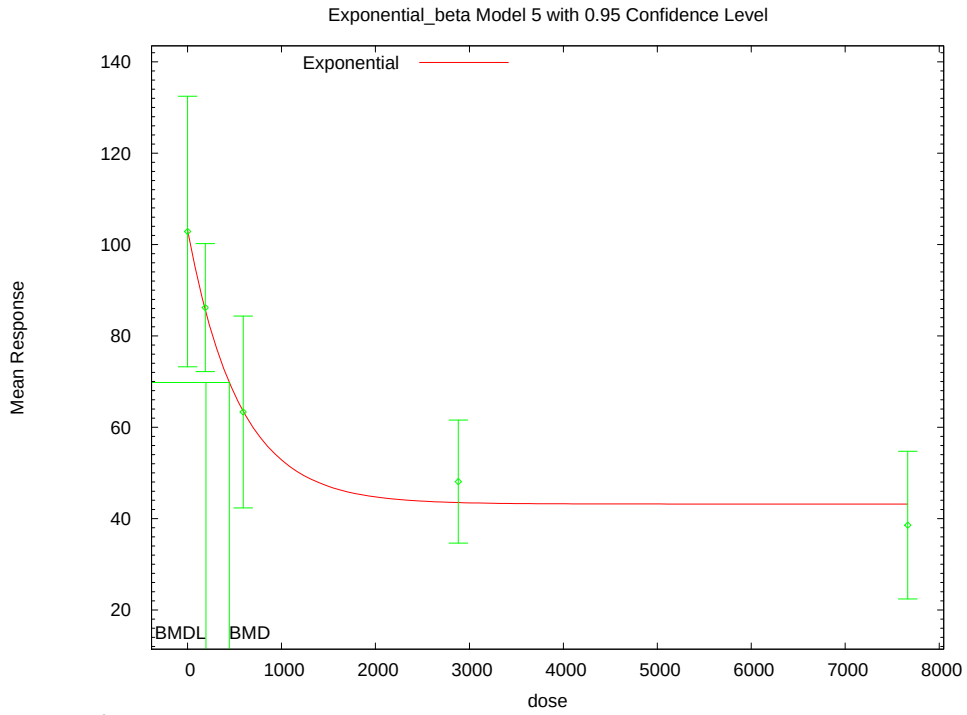
Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	39.39	8	< 0.0001
Test 2	9.389	4	0.05208
Test 3	4.892	3	0.1798
Test 6a	0.7425	2	0.6899

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 =      444.551

                  BMDL =      195.249
```

E.2.41.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



E.2.41.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
 ================================================================
          Exponential Model. (Version: 1.5;  Date: 4/23/2009)
          Input Data File:
C:\USEPA\BMDS21\AD\Blood\Exp_Unrest_BMR1_Shi_estradiol_17B_conc_PE9.(d)
          Gnuplot Plotting File:
```

Mon Nov 16 13:45:21 2009

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Figure 4 PE9 only

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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 5
lnalpha	2.65881
rho	0.913414
a	108
b	0.000503911
c	0.340136
d	1

Parameter Estimates

Variable	Model 5
lnalpha	1.66777
rho	1.15313
a	103.145
b	0.00182735
c	0.418744
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	102.9	41.41
188.3	10	86.19	19.58
592.1	10	63.33	29.36
2882	10	48.1	18.82
7665	10	38.57	22.59
~~~~~~~~~~

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	103.1	33.35	-0.02732
188.3	85.69	29.96	0.05287
592.1	63.51	25.21	-0.02235
2882	43.5	20.27	0.7167
7665	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
5	-186.4844	5	382.9688

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 7a: Does Model 5 fit the data? (A3 vs 5)

Tests of Interest

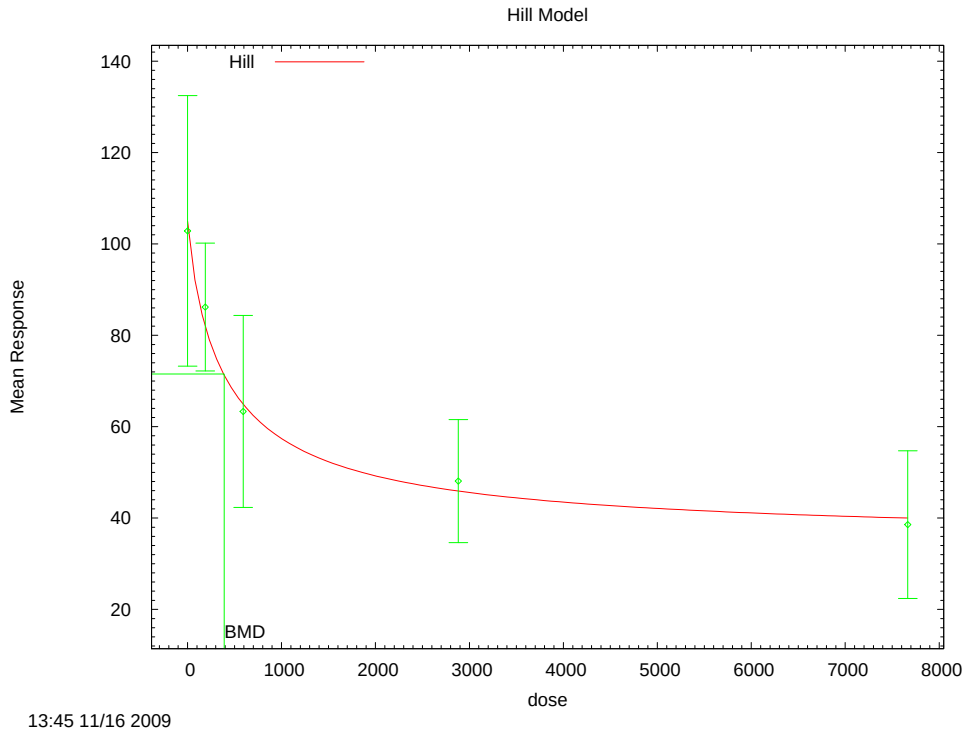
Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	39.39	8	< 0.0001
Test 2	9.389	4	0.05208
Test 3	4.892	3	0.1798
Test 7a	0.7425	2	0.6899

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 7a is greater than .1.  Model 5 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 =      444.551

                 BMDL =      195.249
```

E.2.41.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



E.2.41.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File:
C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_Shi_estradiol_17B_conc_PE9.(d)
          Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_Shi_estradiol_17B_conc_PE9.plt
                                                  Mon Nov 16 13:45:22 2009
 ================================================================
```

Figure 4 PE9 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 =	6.63982
rho =	0
intercept =	102.857
v =	-64.2856
n =	1.33525
k =	461.707

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	intercept	v	n	k
lalpha	1	-1	0.064	-0.095	0.073	0.085
rho	-1	1	-0.075	0.096	-0.074	-0.085
intercept	0.064	-0.075	1	-0.61	-0.22	-0.37
v	-0.095	0.096	-0.61	1	0.83	-0.4
n	0.073	-0.074	-0.22	0.83	1	-0.52
k	0.085	-0.085	-0.37	-0.4	-0.52	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	1.54702	2.36086	-3.08017	6.17422
rho	1.17907	0.564621	0.0724289	2.2857
intercept	105.265	10.3805	84.9191	125.61
v	-70.2058	20.1009	-109.603	-30.8086
n	0.875252	0.64467	-0.388278	2.13878
k	426.676	337.186	-234.197	1087.55

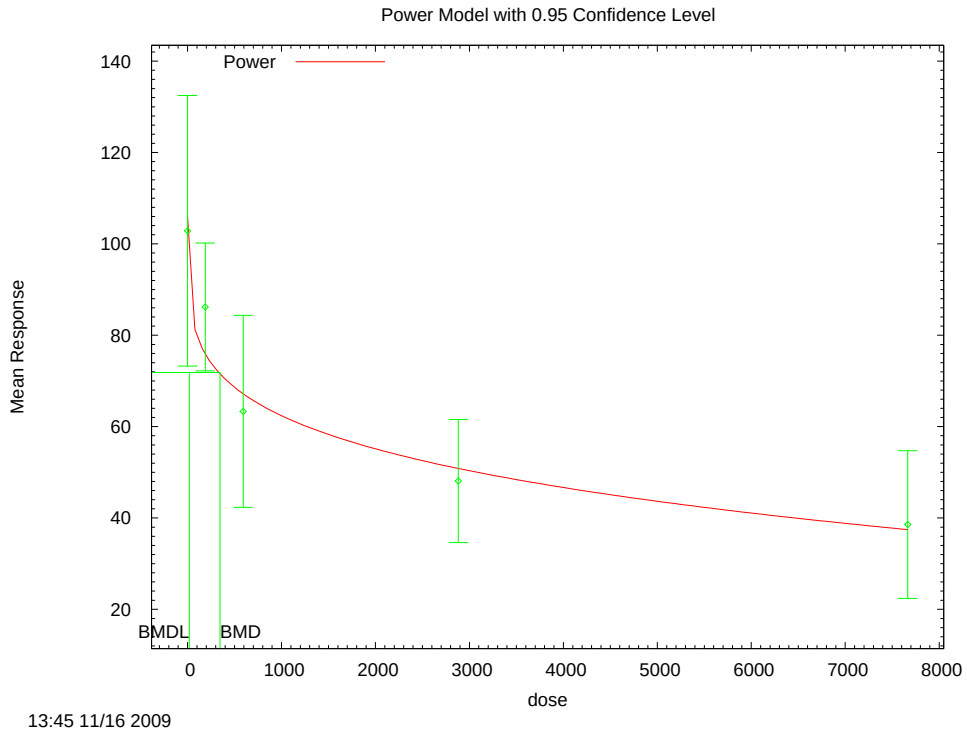
Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	103	105	41.4	33.7	-0.226
188.3	10	86.2	82.2	19.6	29.2	0.431
592.1	10	63.3	65.2	29.4	25.4	-0.227

```
2882    10       48.1         46.2         18.8         20.8          0.294
7665    10       38.6         40.2         22.6         19.1         -0.277


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         -188.361545            6     388.723090
             A2         -183.666974           10     387.333947
             A3         -186.113162            7     386.226325
          fitted        -186.121461            6     384.242922
              R         -203.360558            2     410.721116


                   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              39.3872          8          <.0001
  Test 2              9.38914          4         0.05208
  Test 3              4.89238          3          0.1798
  Test 4            0.0165976          1          0.8975

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 =        390.413


BMDL computation failed.
```

E.2.41.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



13:45 11/16 2009

E.2.41.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File:
C:\USEPA\BMDS21\AD\Blood\Power_Unrest_BMR1_Shi_estradiol_17B_conc_PE9.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\Power_Unrest_BMR1_Shi_estradiol_17B_conc_PE9.plt
                                                  Mon Nov 16 13:45:22 2009
 ================================================================

 Figure 4 PE9 only
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   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 =      6.63982
                          rho =            0
                      control =      102.857
                        slope =       -2.986
                        power =     0.343163


          Asymptotic Correlation Matrix of Parameter Estimates

                lalpha          rho      control        slope        power

    lalpha           1           -1        0.048         0.17         0.25

       rho          -1            1       -0.059        -0.17        -0.25

   control       0.048       -0.059            1        -0.74        -0.59

     slope        0.17        -0.17        -0.74            1         0.98

     power        0.25        -0.25        -0.59         0.98            1


                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha           1.5482          2.39188           -3.13979             6.23619
            rho           1.1846         0.571778          0.0639365             2.30526
        control          106.216          10.4574            85.7201             126.712
          slope         -9.40933           6.9801           -23.0901             4.27142
          power         0.221631        0.0746081          0.0754014             0.36786


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    10        103          106         41.4         34.4         -0.309
188.3    10       86.2         76.2         19.6         28.2           1.12
592.1    10       63.3         67.5         29.4         26.3           -0.5
 2882    10       48.1         51.2         18.8         22.3         -0.443
 7665    10       38.6         37.9         22.6         18.7          0.113


 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         -188.361545            6     388.723090
             A2         -183.666974           10     387.333947
             A3         -186.113162            7     386.226325
          fitted        -186.795167            5     383.590334
              R         -203.360558            2     410.721116


                   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              39.3872          8          <.0001
  Test 2              9.38914          4         0.05208
  Test 3              4.89238          3          0.1798
  Test 4              1.36401          2          0.5056

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 = 346.016


             BMDL = 18.2028
```

E.2.42. Smialowicz et al. (2008): PFC per 10^6 Cells

E.2.42.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	3	<0.0001	13.24	0.00	892.22	5.8E+03	3.9E+03	nonconstant variance, power restricted ≥1
exponential (M3)	3	<0.0001	639.80	<0.0001	1518.75	6.4E+03	error	nonconstant variance, power restricted ≥1
exponential (M4)	3	<0.0001	13.24	0.00	892.22	5.8E+03	3.9E+03	nonconstant variance, power restricted ≥1
exponential (M5)	2	<0.0001	10.69	0.00	891.67	8.4E+03	5.1E+03	nonconstant variance, power restricted ≥1
exponential (M5) [d]	2	<0.0001	10.69	0.00	891.67	8.4E+03	5.1E+03	nonconstant variance, power unrestricted
Hill	2	<.0001	9.23	0.01	890.21	8.2E+03	error	nonconstant variance, n restricted >1, bound hit
Hill [d]	1	<.0001	8.09	0.00	891.07	6.0E+03	error	nonconstant variance, n unrestricted
linear [c]	**3**	**<.0001**	**9.68**	**0.02**	**888.66**	**9.7E+03**	**7.8E+03**	**nonconstant variance**
polynomial	2	<.0001	9.28	0.01	890.26	8.4E+03	5.4E+03	nonconstant variance
power	3	<.0001	9.68	0.02	888.66	9.7E+03	7.8E+03	nonconstant variance, power restricted ≥1, bound hit
power [d]	2	<.0001	7.86	0.02	888.84	5.9E+03	1.6E+03	nonconstant variance, power unrestricted
exponential (M2)	3	<0.0001	6.23	0.10	901.90	4.6E+03	2.8E+03	constant variance, power restricted ≥1
exponential (M3)	3	<0.0001	6.23	0.10	901.90	4.6E+03	2.8E+03	constant variance, power restricted ≥1
exponential (M4)	2	<0.0001	6.23	0.04	903.90	4.6E+03	8.1E+02	constant variance, power restricted ≥1
exponential (M5)	2	<0.0001	6.23	0.04	903.90	4.6E+03	8.1E+02	constant variance, power restricted ≥1
exponential (M5)	2	<0.0001	6.23	0.04	903.90	4.6E+03	8.1E+02	constant variance, power unrestricted
Hill	2	<.0001	5.53	0.06	903.19	2.0E+03	3.8E+02	constant variance, n restricted >1, bound hit
Hill	1	<.0001	1.55	0.21	901.22	1.1E+03	1.2E+02	constant variance, n unrestricted
linear	3	<.0001	7.92	0.05	903.59	7.6E+03	5.8E+03	constant variance
polynomial	2	<.0001	6.55	0.04	904.22	5.3E+03	3.3E+03	constant variance

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
power	3	<.0001	7.92	0.05	903.59	7.6E+03	5.8E+03	constant variance, power restricted ≥1, bound hit
power	2	<.0001	1.46	0.48	899.13	1.0E+03	1.2E+02	constant variance, power unrestricted

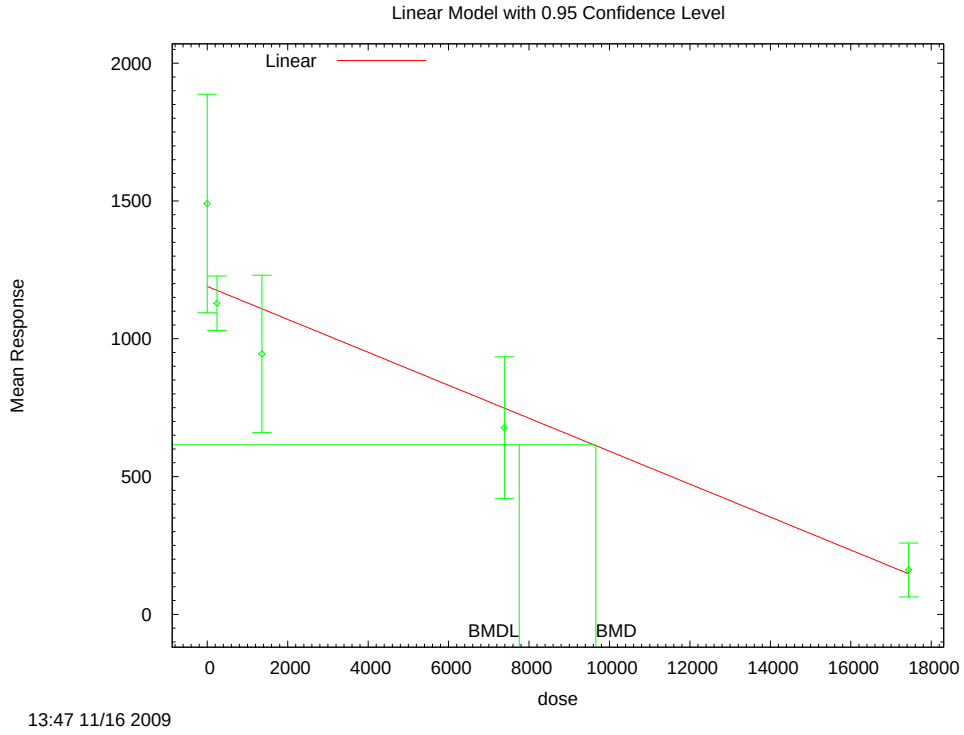
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.42.2. *Figure for Selected Model: Linear, Nonconstant Variance*



E.2.42.3. *Output File for Selected Model: Linear, Nonconstant Variance*

```
 ======================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Linear_BMR1_PFC_per_cells.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Linear_BMR1_PFC_per_cells.plt
                                                 Mon Nov 16 13:47:58 2009
 ======================================================================

 Anti Response to SRBCs, PFC per 10^6 cells, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
```

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 = 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 =	12.3562
rho =	0
beta_0 =	1213.22
beta_1 =	-0.0629452

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	beta_0	beta_1
lalpha	1	-1	0.081	-0.15
rho	-1	1	-0.08	0.15
beta_0	0.081	-0.08	1	-0.9
beta_1	-0.15	0.15	-0.9	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	1.72142	1.91282	-2.02764	5.47047
rho	1.55211	0.2835	0.99646	2.10776
beta_0	1192.68	79.6002	1036.66	1348.69
beta_1	-0.0597519	0.00532318	-0.0701851	-0.0493186

Table of Data and Estimated Values of Interest

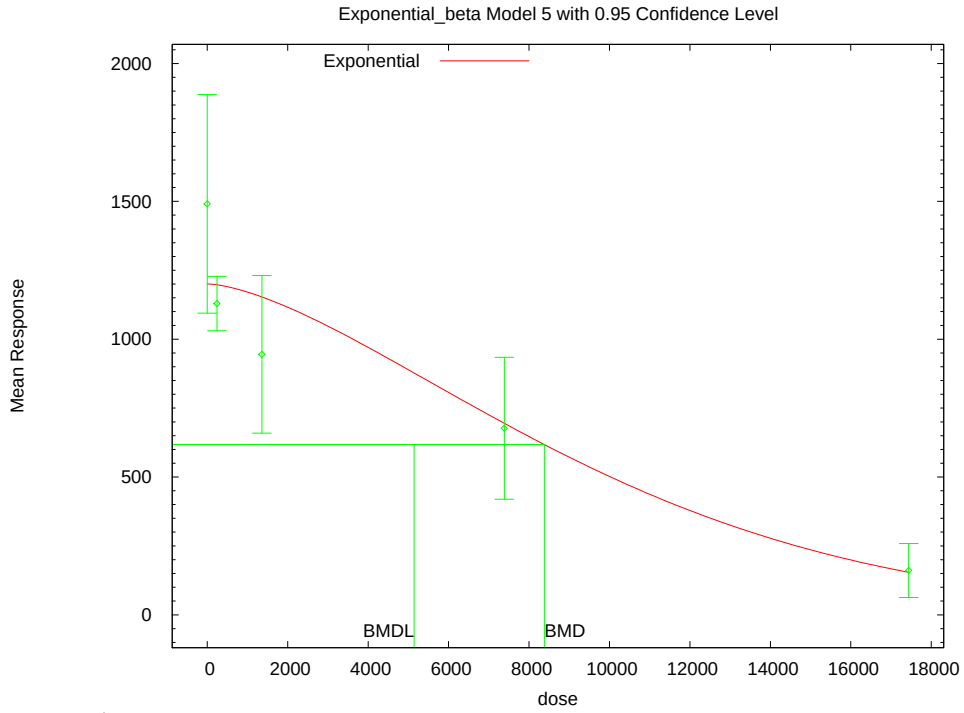
Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	15	1.49e+003	1.19e+003	716	577	2
241.3	14	1.13e+003	1.18e+003	171	572	-0.322
1358	15	945	1.11e+003	516	547	-1.18
7385	15	677	751	465	403	-0.715
1.744e+004	8	161	151	117	116	0.251

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         -444.832859           6     901.665718
             A2         -425.402825          10     870.805651
             A3         -435.489363           7     884.978727
         fitted         -440.330158           4     888.660316
              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              20.1731          3       0.0001563
  Test 4              9.68159          3         0.02148

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 =        9660.48


             BMDL =        7755.63
```

E.2.42.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



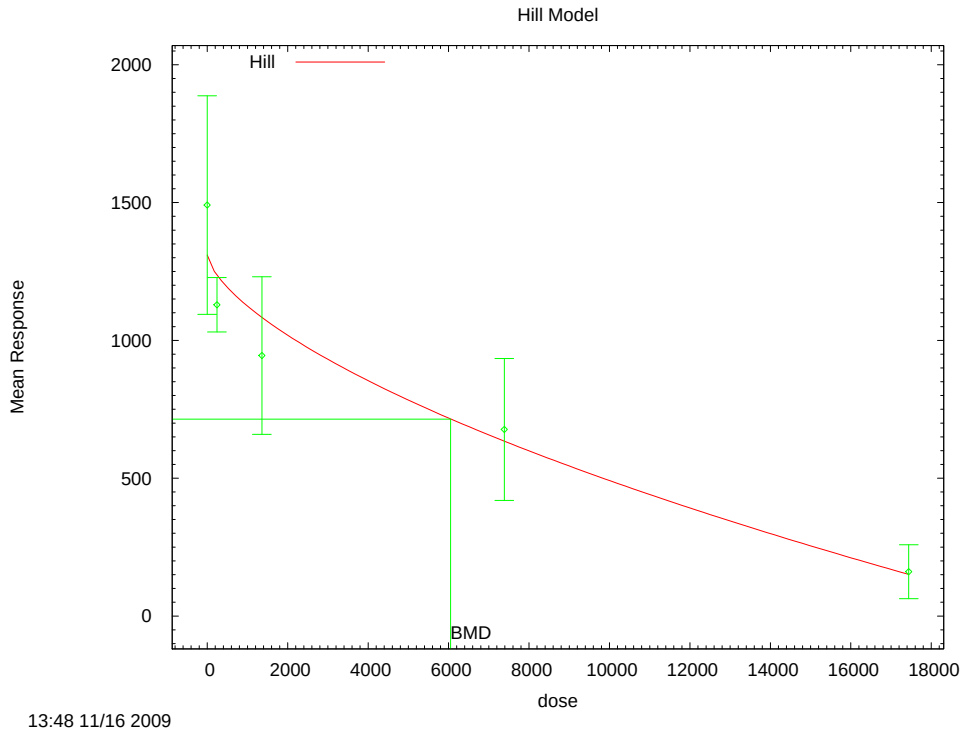
E.2.42.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Exp_Unrest_BMR1_PFC_per_cells.(d)
         Gnuplot Plotting File:
                                                  Mon Nov 16 13:48:00 2009
 ================================================================

 Anti Response to SRBCs, PFC per 10^6 cells, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 5
                --------          --------
                  lnalpha             3.29848
                      rho              1.2578
                        a             1565.55
                        b          0.000129358
                        c          0.000102839
                        d                    1



                   Parameter Estimates

                   Variable          Model 5
                   --------          -------
                    lnalpha           1.88041
                        rho           1.53102
                          a            1200.9
                          b      9.15015e-005
                          c                 0
                          d           1.53838


            Table of Stats From Input Data

      Dose      N         Obs Mean     Obs Std Dev
      -----    ---       ----------   -------------
          0     15         1491          716
      241.3     14         1129          171
       1358     15          945          516
       7385     15          677          465
   1.744e+004      8          161          117


                Estimated Values of Interest

       Dose      Est Mean      Est Std     Scaled Residual
     ------    ----------    ---------    ----------------
          0          1201        583.1             1.927
      241.3          1198        581.8           -0.4405
       1358          1153        565.3            -1.427
       7385         694.8        383.5           -0.1801
  1.744e+004         154.3        121.2            0.1566



   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       -444.8329           6      901.6657
                       A2       -425.4028          10      870.8057
                       A3       -435.4894           7      884.9787
                        R       -463.7537           2      931.5074
                        5       -440.8331           5      891.6662


Additive constant for all log-likelihoods =     -61.57.  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                        76.7            8           < 0.0001
  Test 2                       38.86            4           < 0.0001
  Test 3                       20.17            3          0.0001563
 Test 7a                       10.69            2           0.004778


  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 =      8379.86

             BMDL =      5143.92
```

E.2.42.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



E.2.42.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_PFC_per_cells.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_PFC_per_cells.plt
                                                 Mon Nov 16 13:48:01 2009
 ================================================================

 Anti Response to SRBCs, PFC per 10^6 cells, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =      12.3562
```

```
                          rho =           0
                    intercept =        1491
                            v =       -1330
                            n =    0.478435
                            k =     4033.79


          Asymptotic Correlation Matrix of Parameter Estimates

                lalpha          rho    intercept            v            n            k

    lalpha           1           -1          0.4       -0.047        -0.39         0.16

       rho          -1            1        -0.41         0.05         0.39        -0.16

 intercept         0.4        -0.41            1        -0.15        -0.77         0.36

         v      -0.047         0.05        -0.15            1         0.37        -0.95

         n       -0.39         0.39        -0.77         0.37            1        -0.65

         k        0.16        -0.16         0.36        -0.95        -0.65            1


                                Parameter Estimates

                                                                95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        lalpha           2.8564          2.65961            -2.35633             8.06913
           rho          1.38249         0.391339            0.615484              2.1495
     intercept          1309.76          139.641             1036.07             1583.45
             v         -18748.9          37661.1            -92563.2             55065.4
             n         0.659862         0.240194            0.189091             1.13063
             k     1.07302e+006     4.27003e+006       -7.29608e+006        9.44213e+006


     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    1.31e+003          716          596           1.18
241.3    14  1.13e+003    1.24e+003          171          572         -0.703
 1358    15        945    1.08e+003          516          522          -1.02
 7385    15        677          633          465          360          0.469
1.744e+004     8        161          149          117          133          0.251


 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	-444.832859	6	901.665718
A2	-425.402825	10	870.805651
A3	-435.489363	7	884.978727
fitted	-439.536553	6	891.073107
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	20.1731	3	0.0001563
Test 4	8.09438	1	0.00444

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

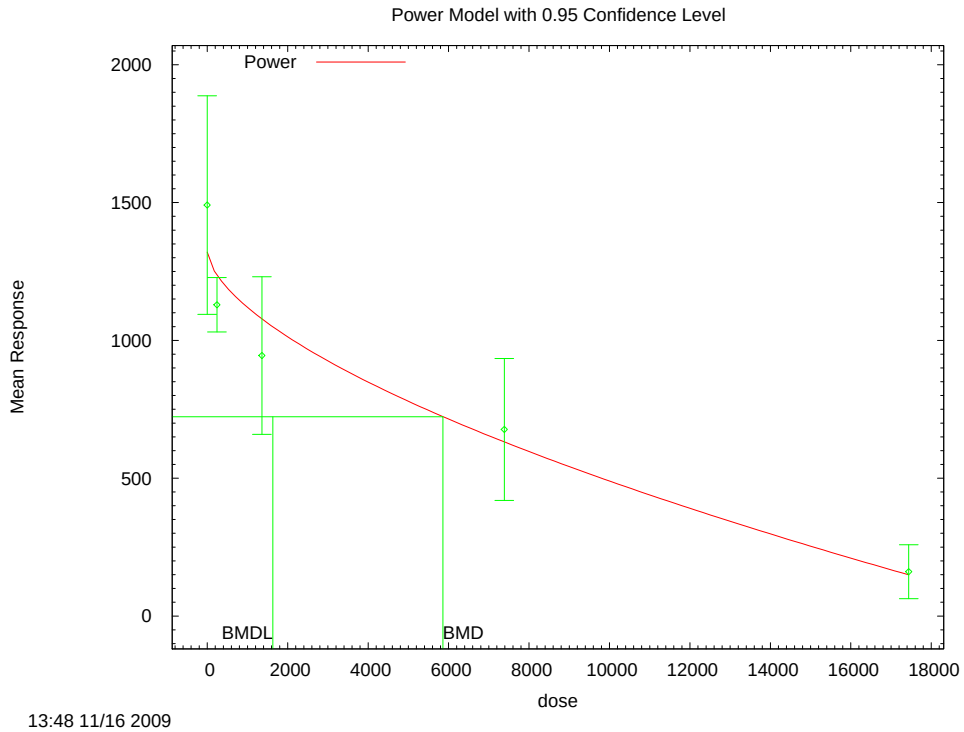
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 6049.74

BMDL computation failed.

E.2.42.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



E.2.42.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Power_Unrest_BMR1_PFC_per_cells.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Power_Unrest_BMR1_PFC_per_cells.plt
                                                Mon Nov 16 13:48:05 2009
 ================================================================

 Anti Response to SRBCs, PFC per 10^6 cells, 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 =      12.3562
                            rho =            0
                        control =         1491
                          slope =     -79.8343
                          power =     0.288026


            Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho      control        slope        power

    lalpha             1           -1         0.39        -0.42         -0.4

       rho            -1            1        -0.41         0.42          0.4

   control          0.39        -0.41            1        -0.81        -0.79

     slope         -0.42         0.42        -0.81            1            1

     power          -0.4          0.4        -0.79            1            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha          2.91272          2.64894             -2.2791             8.10454
            rho          1.37364         0.389689              0.60986             2.13741
        control           1319.7          140.669              1043.99             1595.41
          slope         -2.80443          6.05405             -14.6701             9.06128
          power         0.617853         0.211323             0.203668             1.03204


     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    1.32e+003          716          597           1.11
241.3    14  1.13e+003    1.24e+003          171          571         -0.705
 1358    15        945    1.08e+003          516          519         -0.992
 7385    15        677          631          465          359          0.494
1.744e+004     8        161          149          117          133          0.256


 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         -444.832859           6     901.665718
               A2         -425.402825          10     870.805651
               A3         -435.489363           7     884.978727
           fitted         -439.417961           5     888.835922
                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              20.1731          3       0.0001563
   Test 4              7.85719          2         0.01967

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 = 5856.4


            BMDL = 1632.55
```

E.2.43. Smialowicz et al. (2008): PFC per Spleen

E.2.43.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	3	0.00	5.76	0.12	377.56	7.4E+03	4.7E+03	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.00	5.34	0.07	379.14	8.5E+03	4.9E+03	nonconstant variance, power restricted ≥1
exponential (M4)	3	0.00	5.76	0.12	377.56	7.4E+03	4.7E+03	nonconstant variance, power restricted ≥1
exponential (M5)	1	0.00	5.34	0.02	381.14	8.5E+03	4.9E+03	nonconstant variance, power restricted ≥1
exponential (M5) [d]	1	0.00	5.34	0.02	381.14	8.5E+03	4.9E+03	nonconstant variance, power unrestricted
Hill	2	0.00	4.31	0.12	378.11	8.6E+03	error	nonconstant variance, n restricted >1, bound hit
Hill [d]	1	0.00	2.66	0.10	378.46	6.6E+03	error	nonconstant variance, n unrestricted
linear [c]	**3**	**0.00**	**5.72**	**0.13**	**377.52**	**1.1E+04**	**8.9E+03**	**nonconstant variance**
polynomial	2	0.00	4.49	0.11	378.29	8.9E+03	5.7E+03	nonconstant variance
power	3	0.00	5.72	0.13	377.52	1.1E+04	8.9E+03	nonconstant variance, power restricted ≥1, bound hit
power [d]	2	0.00	2.62	0.27	376.42	6.5E+03	2.1E+03	nonconstant variance, power unrestricted
exponential (M2)	3	0.00	4.38	0.22	391.51	5.8E+03	3.2E+03	constant variance, power restricted ≥1
exponential (M3)	3	0.00	4.38	0.22	391.51	5.8E+03	3.2E+03	constant variance, power restricted ≥1
exponential (M4)	2	0.00	4.38	0.11	393.51	5.8E+03	8.0E+02	constant variance, power restricted ≥1
exponential (M5)	2	0.00	4.38	0.11	393.51	5.8E+03	8.0E+02	constant variance, power restricted ≥1
exponential (M5)	2	0.00	4.38	0.11	393.51	5.8E+03	8.0E+02	constant variance, power unrestricted
Hill	2	0.00	3.87	0.14	393.00	2.7E+03	4.0E+02	constant variance, n restricted >1, bound hit
Hill	1	0.00	1.06	0.30	392.19	1.8E+03	1.8E+02	constant variance, n unrestricted
linear	3	0.00	5.59	0.13	392.72	9.0E+03	6.7E+03	constant variance
polynomial	2	0.00	4.61	0.10	393.74	6.5E+03	3.8E+03	constant variance

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
power	3	0.00	5.59	0.13	392.72	9.0E+03	6.7E+03	constant variance, power restricted ≥1, bound hit
power	2	0.00	1.01	0.60	390.14	1.8E+03	1.8E+02	constant variance, power unrestricted

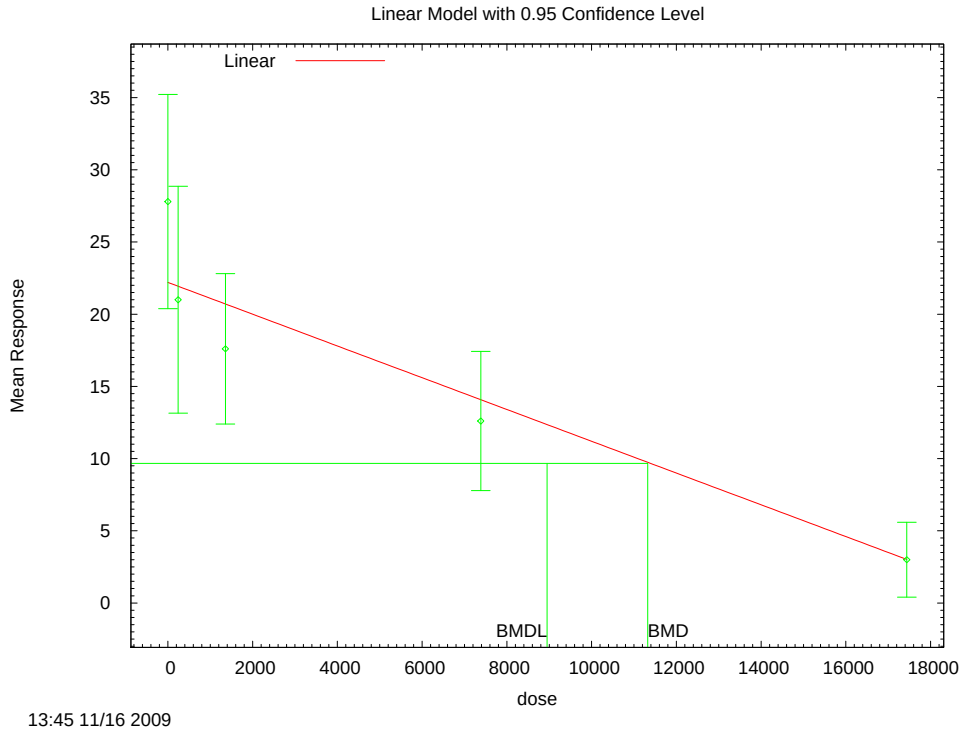
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.43.2. *Figure for Selected Model: Linear, Nonconstant Variance*



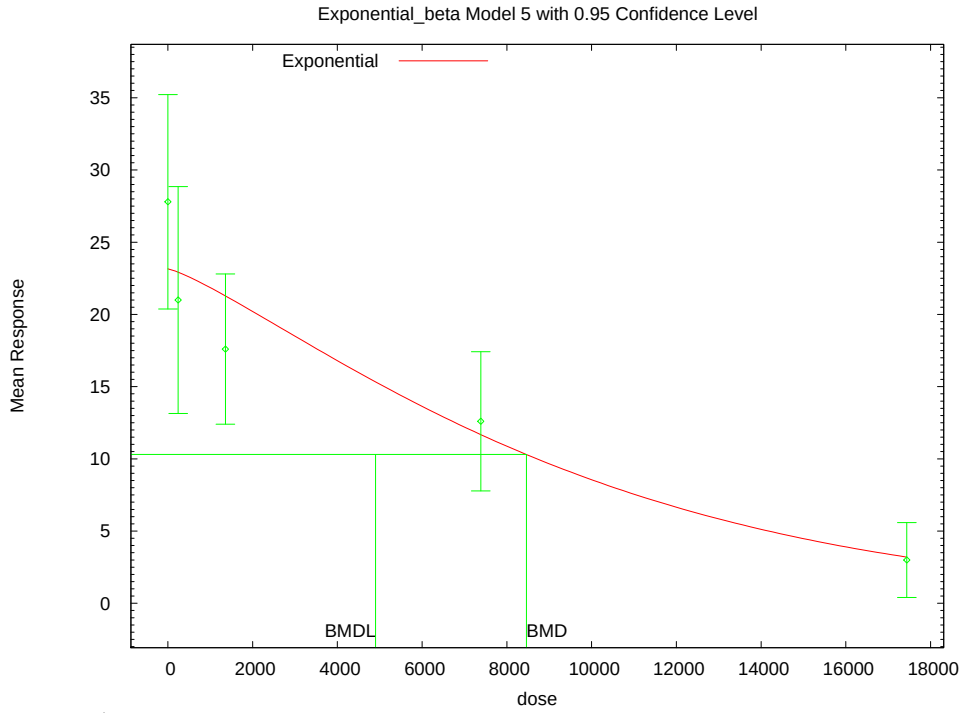
E.2.43.3. *Output File for Selected Model: Linear, Nonconstant Variance*

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Linear_BMR1_PFC_per_spleen.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Linear_BMR1_PFC_per_spleen.plt
                                                Mon Nov 16 13:45:55 2009
 ================================================================

 Anti Response to SRBCs - PFC x 10 to the 4 per spleen, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
```

```
   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 = 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
                       beta_0 =      22.5956
                       beta_1 =  -0.00117245


          Asymptotic Correlation Matrix of Parameter Estimates

                lalpha          rho       beta_0       beta_1

    lalpha           1        -0.97        0.031       -0.021

       rho        -0.97            1       -0.034        0.026

    beta_0        0.031       -0.034            1        -0.88

    beta_1       -0.021        0.026        -0.88            1


                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         0.491077         0.742891          -0.964962             1.94712
            rho          1.47094         0.264097           0.953314             1.98856
         beta_0           22.151          1.72621            18.7677             25.5343
         beta_1      -0.00110204     0.000118826         -0.00133493        -0.000869145


     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         22.2         13.4         12.5           1.75
241.3    14         21         21.9         13.6         12.4         -0.268
 1358    15       17.6         20.7          9.4         11.9         -0.998
 7385    15       12.6           14          8.7         8.91         -0.614
1.744e+004     8          3         2.93          3.1         2.82         0.0665


 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        -184.760998            4     377.521996
               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              5.72194          3           0.126

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 =        11322.2


             BMDL =        8948.34
```

E.2.43.4. *Figure for UnrestrictedModel: Exponential (M5), Nonconstant Variance, Power Unrestricted*



13:45 11/16 2009

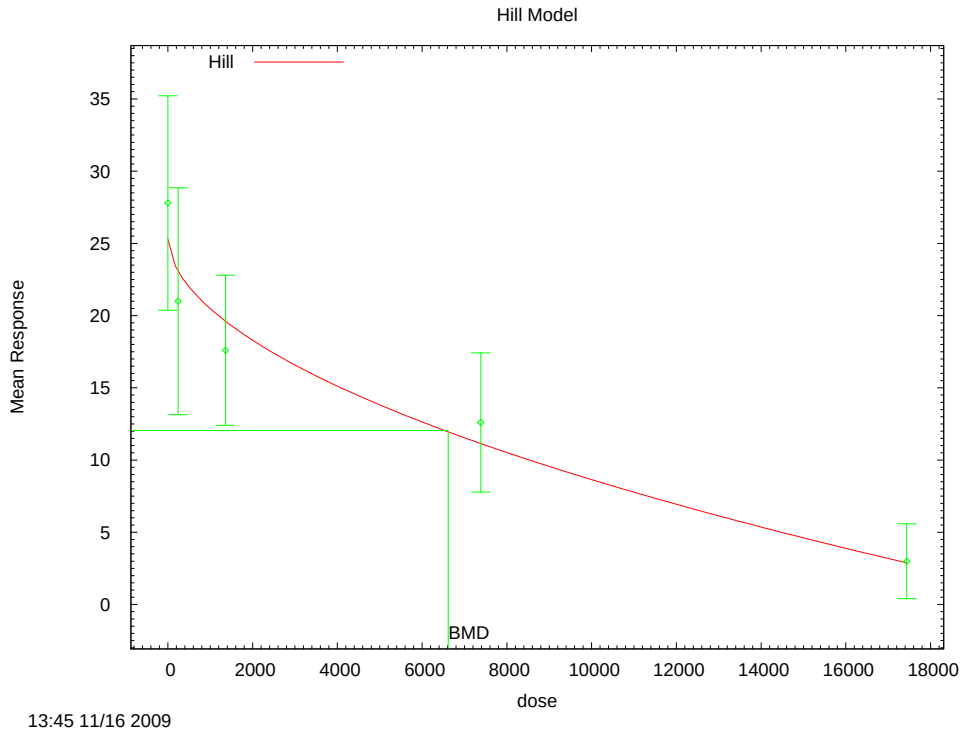
E.2.43.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Exp_Unrest_BMR1_PFC_per_spleen.(d)
         Gnuplot Plotting File:
                                                  Mon Nov 16 13:45:56 2009
 ================================================================

 Anti Response to SRBCs - PFC x 10 to the 4 per spleen, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 5
                --------          --------
                  lnalpha            0.786146
                      rho             1.36372
                        a               29.19
                        b          0.000129431
                        c          0.000102775
                        d                    1



                  Parameter Estimates

                 Variable          Model 5
                 --------          -------
                  lnalpha           0.52811
                      rho           1.45744
                        a           23.1604
                        b      9.96651e-005
                        c      6.92509e-030
                        d           1.23518


            Table of Stats From Input Data

      Dose      N         Obs Mean     Obs Std Dev
      -----    ---       ----------   -------------
          0     15         27.8         13.4
      241.3     14           21         13.6
       1358     15         17.6          9.4
       7385     15         12.6          8.7
   1.744e+004      8            3          3.1


                Estimated Values of Interest

       Dose      Est Mean      Est Std     Scaled Residual
     ------    ----------    ---------    ----------------
          0         23.16        12.86             1.397
      241.3         22.93        12.77          -0.5656
       1358         21.28        12.09            -1.18
       7385         11.68        7.807           0.4578
1.744e+004           3.2         3.04          -0.1864



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        -190.565           6        393.13
                       A2       -181.4763          10       382.9526
                       A3          -181.9           7       377.8001
                        R       -204.6365           2        413.273
                        5       -184.5689           6       381.1378


Additive constant for all log-likelihoods =     -61.57.  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                      46.32             8           < 0.0001
  Test 2                      18.18             4           0.001139
  Test 3                     0.8475             3             0.8381
 Test 7a                      5.338             1            0.02087


  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 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 =      8460.94

            BMDL =      4901.02
```

E.2.43.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



13:45 11/16 2009

E.2.43.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_PFC_per_spleen.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_PFC_per_spleen.plt
                                                  Mon Nov 16 13:45:57 2009
 ================================================================

 Anti Response to SRBCs - PFC x 10 to the 4 per spleen, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =      4.76607
```

```
                          rho =           0
                    intercept =        27.8
                            v =       -24.8
                            n =    0.476652
                            k =     4009.51


          Asymptotic Correlation Matrix of Parameter Estimates

                lalpha          rho    intercept            v            n            k

    lalpha           1        -0.98         0.24         0.03        -0.21        0.019

       rho       -0.98            1         -0.3       -0.026         0.21       -0.021

 intercept        0.24         -0.3            1        0.079        -0.73          0.1

         v        0.03       -0.026        0.079            1        0.019        -0.96

         n       -0.21         0.21        -0.73        0.019            1        -0.28

         k       0.019       -0.021          0.1        -0.96        -0.28            1


                                Parameter Estimates

                                                                95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        lalpha         0.742099          1.02085            -1.25872             2.74292
           rho          1.37015         0.355955             0.67249             2.06781
     intercept          25.3072          2.92734             19.5697             31.0447
             v         -1195.09          4993.33            -10981.8             8591.65
             n         0.543247         0.174917            0.200417            0.886078
             k     2.57198e+007     2.10767e+008       -3.87375e+008        4.38815e+008


     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         25.3         13.4         13.3          0.728
241.3    14         21         23.1         13.6         12.5         -0.629
 1358    15       17.6         19.7          9.4         11.2         -0.716
 7385    15       12.6         11.2          8.7          7.6          0.691
1.744e+004     8          3         3.03          3.1          3.1          -0.03


 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	-183.230840	6	378.461681
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	2.66162	1	0.1028

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

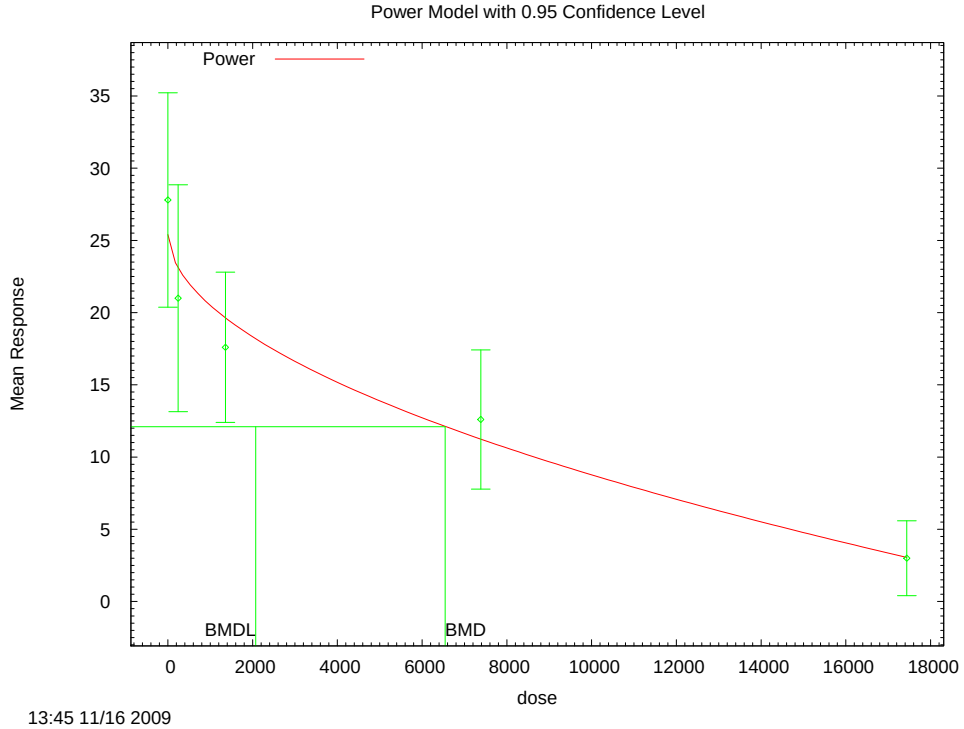
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 6615.87

BMDL computation failed.

E.2.43.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



E.2.43.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Power_Unrest_BMR1_PFC_per_spleen.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Power_Unrest_BMR1_PFC_per_spleen.plt
                                                 Mon Nov 16 13:45:57 2009
 ================================================================

 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 =	-1.51177
power =	0.286447

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.98	0.25	-0.24	-0.22
rho	-0.98	1	-0.3	0.25	0.22
control	0.25	-0.3	1	-0.78	-0.74
slope	-0.24	0.25	-0.78	1	1
power	-0.22	0.22	-0.74	1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	0.746924	1.02058	-1.25337	2.74721
rho	1.36826	0.355827	0.670849	2.06566
control	25.3818	2.96695	19.5666	31.1969
slope	-0.124774	0.226126	-0.567972	0.318425
power	0.531205	0.175723	0.186794	0.875617

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	0.705
241.3	14	21	23.1	13.6	12.4	-0.626
1358	15	17.6	19.6	9.4	11.1	-0.704
7385	15	12.6	11.2	8.7	7.6	0.702
1.744e+004	8	3	3.03	3.1	3.1	-0.0313

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         -183.210067           5     376.420134
               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              2.62008          2          0.2698

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 = 6542.48


            BMDL = 2072.46
```

E.2.44. Toth et al. (1978): Amyloidosis

E.2.44.1. *Summary Table of BMDS Modeling Results*

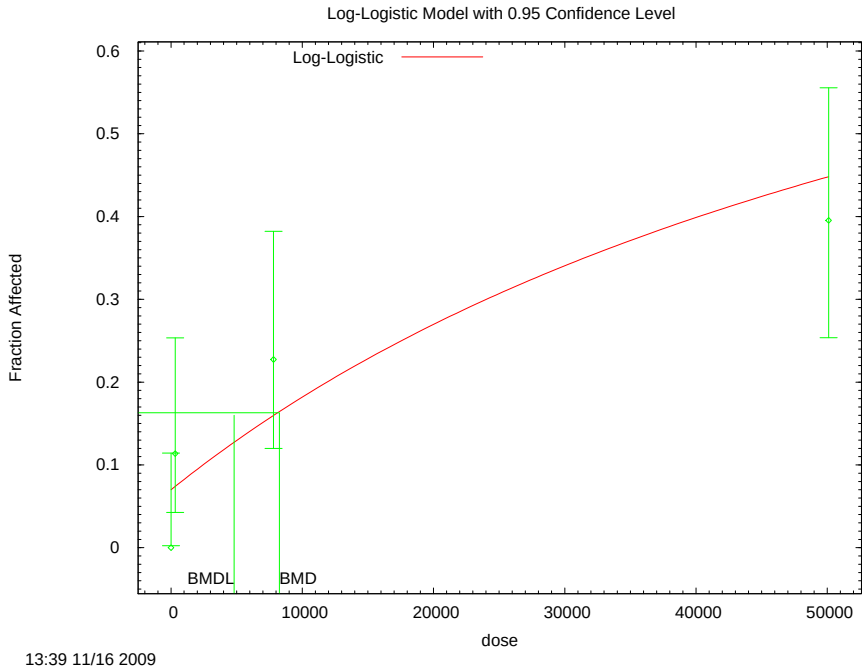
Amyloidosis (Toth et al. (1978))							
Model	**Degrees of Freedom**	**χ^2 Test Statistic**	**χ^2 p-Value [a]**	**AIC**	**BMD (ng/kg-d)**	**BMDL (ng/kg-d)**	**Model Notes**
gamma	2	6.45	0.04	149.12	1.1E+04	7.0E+03	power restricted ≥1, bound hit
logistic	2	7.91	0.02	151.34	2.0E+04	1.6E+04	
log-logistic[b]	**2**	**5.86**	**0.05**	**148.27**	**8.3E+03**	**4.8E+03**	**slope restricted ≥1, bound hit**
log-logistic [c]	2	0.20	0.90	140.24	2.7E+02	2.9E+00	slope unrestricted
log-probit	2	9.94	0.007	153.52	2.2E+04	1.5E+4	slope restricted ≥1, bound hit
log-probit	2	0.28	0.87	140.32	2.7E+02	4.0E+00	slope unrestricted
multistage	2	6.45	0.04	149.12	1.1E+04	7.0E+03	betas restricted ≥0
probit	2	7.75	0.02	151.11	1.9E+04	1.5E+04	
Weibull	2	6.45	0.04	149.12	1.1E+04	7.0E+03	power restricted ≥1, bound hit
Weibull	3	0.00	1.00	140.03	2.0E+02	1.9E+00	power unrestricted

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

[c] Alternate model also presented in this appendix

E.2.44.2. *Figure for Selected Model: Log-Logistic, Slope Restricted ≥1*



E.2.44.3. *Output File for Selected Model: Log-Logistic, Slope Restricted ≥1*

```
 ================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21\AD\Blood\LogLogistic_BMR1_Amyloidosis.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\LogLogistic_BMR1_Amyloidosis.plt
                                              Mon Nov 16 13:39:45 2009
 ================================================================

 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 = -10.8548
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

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0699641	*	*	*
intercept	-11.2157	*	*	*
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	-72.1329	2	8.23187	2	0.01631
Reduced model	-82.0119	1	27.99	3	<.0001

AIC: 148.266

Goodness of Fit

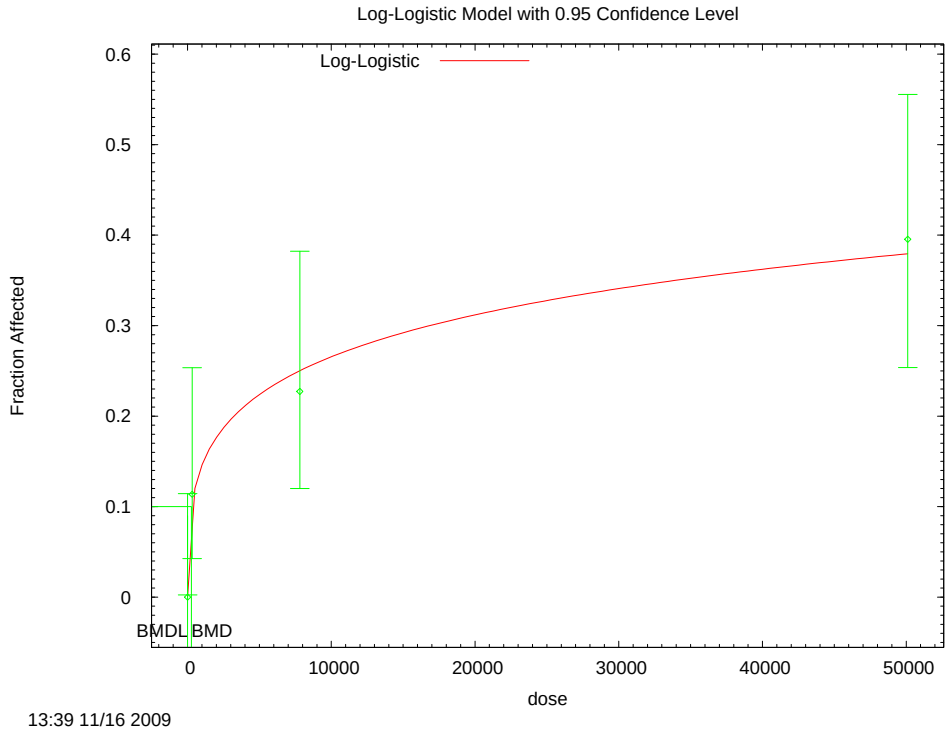
Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0700	2.659	0.000	38	-1.691
315.4949	0.0739	3.251	5.000	44	1.008
7814.0188	0.1585	6.973	10.000	44	1.250
50105.0000	0.4446	19.117	17.000	43	-0.650

Chi^2 = 5.86 d.f. = 2 P-value = 0.0535

Benchmark Dose Computation

```
Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =       8254.29

            BMDL =       4805.18
```

E.2.44.4. *Figure for Unrestricted Model: Log-Logistic, Slope Unrestricted*



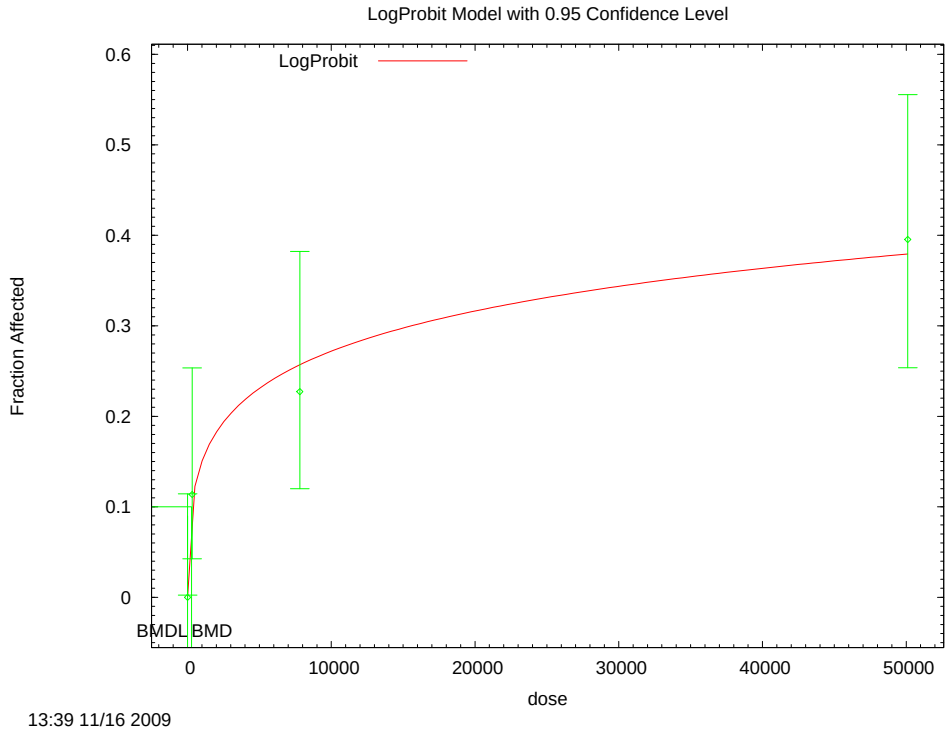
E.2.44.5. *Output File for Unrestricted Model: Log-Logistic, Slope Unrestricted*

```
 ========================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\LogLogistic_Unrest_BMR1_Amyloidosis.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\LogLogistic_Unrest_BMR1_Amyloidosis.plt
                                                  Mon Nov 16 13:39:45 2009
 ========================================================================

 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 =     -3.91243
                         slope =     0.314588


          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        -0.98

     slope        -0.98            1



                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background                0            *                *                   *
      intercept         -4.01968            *                *                   *
          slope         0.326277            *                *                   *

* - 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        -68.1202         2      0.206421      2          0.9019
   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
   315.4949     0.1051         4.623     5.000          44        0.186
  7814.0188     0.2507        11.029    10.000          44       -0.358
 50105.0000     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 =        266.567

            BMDL =        2.92895
```

E.2.44.6. *Figure for Unrestricted Model: Log-Probit, Slope Restricted ≥1*



E.2.44.7. *Output File for Unrestricted Model: Log-Probit, Slope Restricted ≥1*

```
 ========================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\LogProbit_BMR1_Amyloidosis.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\LogProbit_BMR1_Amyloidosis.plt
                                                  Mon Nov 16 13:39:45 2009
 ========================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 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 (and Specified) Parameter Values
                      background =            0
                       intercept =      -2.2812
                           slope =     0.180958


            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        -0.98

     slope        -0.98            1



                                 Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background                0               NA
      intercept          -2.3225          0.57595            -3.45134            -1.19365
          slope         0.185565        0.0628719           0.0623389            0.308792

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         -68.017         4
   Fitted model        -68.1574         2      0.280896      2           0.869
  Reduced model        -82.0119         1         27.99      3         <.0001

           AIC:         140.315


                                  Goodness  of  Fit
                                                                  Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          38        0.000
  315.4949     0.1048         4.611     5.000          44        0.192
 7814.0188     0.2549        11.216    10.000          44       -0.421
```

```
50105.0000     0.3766        16.195    17.000          43        0.253

 Chi^2 = 0.28      d.f. = 2        P-value = 0.8704


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =        273.029

            BMDL =        4.02007
```

E.2.45. Toth et al. (1978): Skin Lesions

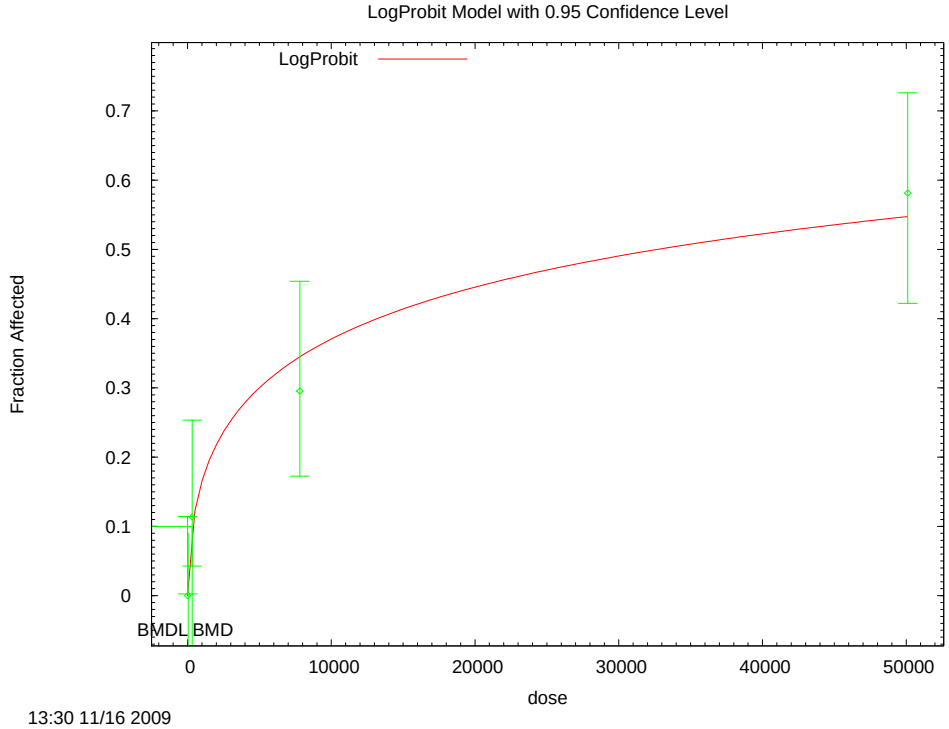
E.2.45.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	2	6.89	0.03	156.34	5.7E+03	4.1E+03	power restricted ≥1, bound hit
logistic	2	10.70	0.00	161.42	1.4E+04	1.1E+04	
log-logistic[b]	**2**	**5.09**	**0.08**	**153.96**	**3.5E+03**	**2.2E+03**	**slope restricted ≥1, bound hit**
log-logistic[c]	2	0.04	0.95	147.08	2.60E+02	3.18E+01	slope urestricted
log-probit	2	14.29	<0.001	164.79	1.24E+04	8.31E+03	slope restricted ≥1, bound hit
log-probit	2	0.80	0.67	147.84	3.3E+02	4.5E+01	slope unrestricted ≥1
multistage	2	6.89	0.03	156.34	5.7E+03	4.1E+03	betas restricted ≥0
probit	2	10.39	0.01	160.99	1.3E+04	1.0E+04	
Weibull	2	6.89	0.03	156.34	5.7E+03	4.1E+03	power restricted ≥1, bound hit
Weibull	2	0.00	1.00	147.04	2.19E+02	2.08E+01	power unrestricted

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

E.2.45.2. *Figure for Selected Model: Log-Logistic, Slope Restricted ≥1*



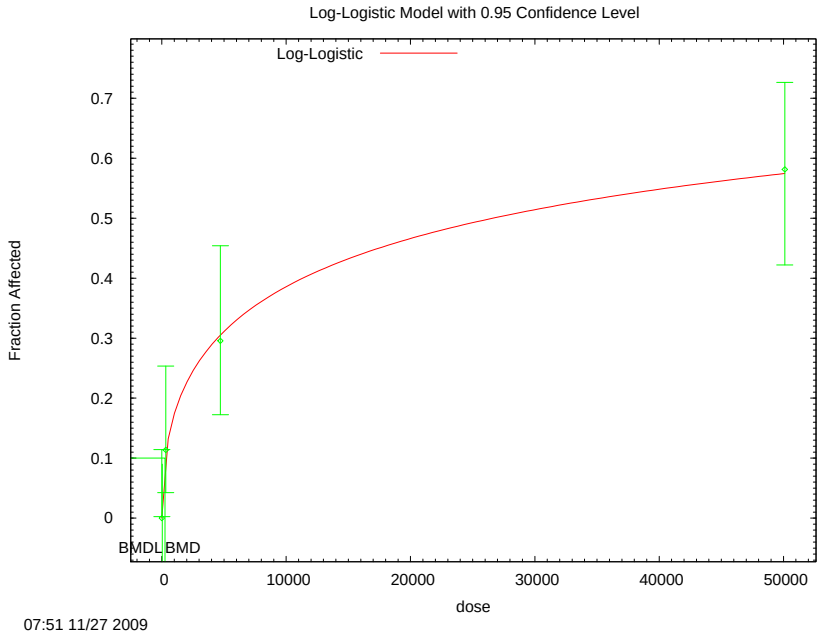
E.2.45.3. *Output File for Selected Model: Log-Logistic, Slope Restricted ≥1*

```
 ================================================================
        Logistic Model. (Version: 2.12; Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21\A\Blood\LogLogistic_BMR2_Skin_lesion_1yr.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\LogLogistic_BMR2_Skin_lesion_1yr.plt
                                          Mon Nov 16 13:30:07 2009
 ================================================================

 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 =       -10.252
                          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        0.0564295            *                *                   *
      intercept         -10.3645            *                *                   *
          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         -74.9791         2       6.92292      2         0.03138
  Reduced model         -95.8498         1       48.6642      3         <.0001

           AIC:         153.958


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0564         2.144     0.000          38       -1.508
   315.4949     0.0657         2.892     5.000          44        1.283
  7814.0188     0.2430        10.690    13.000          44        0.812
 50105.0000     0.6343        27.273    25.000          43       -0.720

 Chi^2 = 5.09      d.f. = 2        P-value = 0.0783
```

```
   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =       3523.85

            BMDL =       2211.53
```

E.2.45.4. *Figure for Unrestricted Model: Log-Logistic, Slope Unrestricted*



E.2.45.5. *Output File for Unrestricted Model: Log-Logistic, Slope Unrestricted*

```
========================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\Usepa\Bmds2\Data\LogTcdSet.(d)
         Gnuplot Plotting File:  C:\Usepa\Bmds2\Data\LogTcdSet.plt
                                              Fri Nov 27 07:51:12 2009
 ========================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]
```

```
   Dependent variable = r_skin
   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 =     -4.78342
                          slope =     0.469549


           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        -0.98

     slope        -0.98            1



                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0            *                *                   *
      intercept         -4.84059            *                *                   *
          slope         0.475472            *                *                   *

* - 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        -71.5376         2     0.0398444      2          0.9803
   Reduced model        -95.8498         1       48.6642      3         <.0001

           AIC:         147.075


                                  Goodness  of  Fit
```

```
                                                                  Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0000         0.000       0.000       38          0.000
   316.0000     0.1087         4.784       5.000       44          0.105
  4714.0000     0.3060        13.464      13.000       44         -0.152
 50105.0000     0.5756        24.753      25.000       43          0.076

  Chi^2 = 0.04      d.f. = 2        P-value = 0.9803


    Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        259.682

             BMDL =         31.788
```

E.2.46. Van Birgelen et al. (1995a): Hepatic Retinol

E.2.46.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	4	<0.0001	41.09	<0.0001	159.73	4.3E+03	2.3E+03	nonconstant variance, power restricted ≥1
exponential (M3)	4	<0.0001	40.44	<0.0001	159.09	3.4E+04	2.4E+03	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**3**	**<0.0001**	**20.80**	**0.00**	**141.45**	**1.4E+04**	**1.9E+03**	**nonconstant variance, power restricted ≥1**
exponential (M5)	3	<0.0001	20.80	0.00	141.45	1.4E+04	1.9E+03	nonconstant variance, power restricted ≥1
exponential (M5) [d]	3	<0.0001	20.80	0.00	141.45	1.4E+04	1.9E+03	nonconstant variance, power unrestricted
Hill	3	<.0001	4.22	0.24	124.86	2.9E+03	error	nonconstant variance, n restricted >1, bound hit
Hill [d]	2	<.0001	2.85	0.24	125.50	2.0E+03	error	nonconstant variance, n unrestricted
linear	4	<.0001	58.18	<.0001	176.83	1.0E+05	7.9E+04	nonconstant variance
polynomial	4	<.0001	58.18	<.0001	176.83	1.0E+05	7.9E+04	nonconstant variance
power	4	<.0001	58.18	<.0001	176.83	1.0E+05	7.9E+04	nonconstant variance, power restricted ≥1, bound hit
power [d]	3	<.0001	11.12	0.01	131.77	2.1E+02	7.7E+00	nonconstant variance, power unrestricted

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	4	<0.0001	3.87	0.42	184.19	3.0E+03	1.9E+03	constant variance, power restricted ≥1
exponential (M3)	4	<0.0001	3.87	0.42	184.19	3.0E+03	1.9E+03	constant variance, power restricted ≥1
exponential (M4)	3	<0.0001	1.84	0.61	184.15	2.7E+03	1.7E+03	constant variance, power restricted ≥1
exponential (M5)	3	<0.0001	1.84	0.61	184.15	2.7E+03	1.7E+03	constant variance, power restricted ≥1
exponential (M5)	3	<0.0001	1.84	0.61	184.15	2.7E+03	1.7E+03	constant variance, power unrestricted
Hill	3	<.0001	1.04	0.79	183.36	2.1E+03	1.1E+03	constant variance, n restricted >1, bound hit
Hill	2	<.0001	0.98	0.61	185.29	1.7E+03	4.0E+01	constant variance, n unrestricted
linear	4	<.0001	25.63	<.0001	205.94	6.8E+04	5.0E+04	constant variance
polynomial	4	<.0001	25.63	<.0001	205.94	6.8E+04	5.0E+04	constant variance
power	4	<.0001	25.63	<.0001	205.94	6.8E+04	5.0E+04	constant variance, power restricted ≥1, bound hit
power	3	<.0001	2.28	0.52	184.60	2.1E+02	6.2E+00	constant variance, power unrestricted

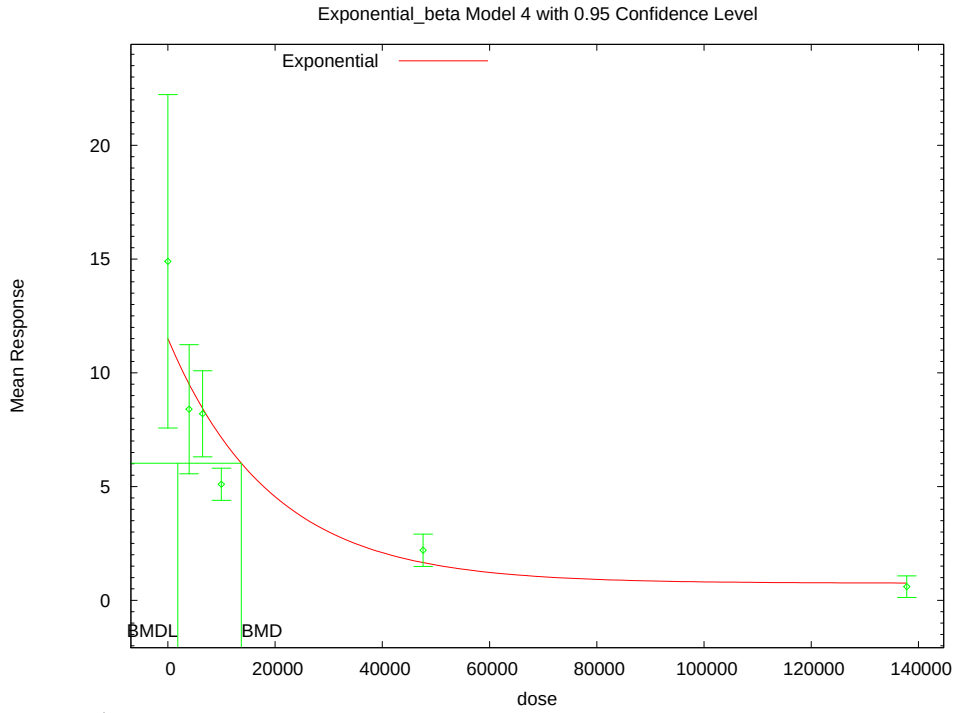
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.46.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



E.2.46.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_BMR1_hepatic_retinol.(d)
         Gnuplot Plotting File:
                                                  Fri Nov 20 12:28:01 2009
 ================================================================

 Tbl3, hepatic retinol
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   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
```
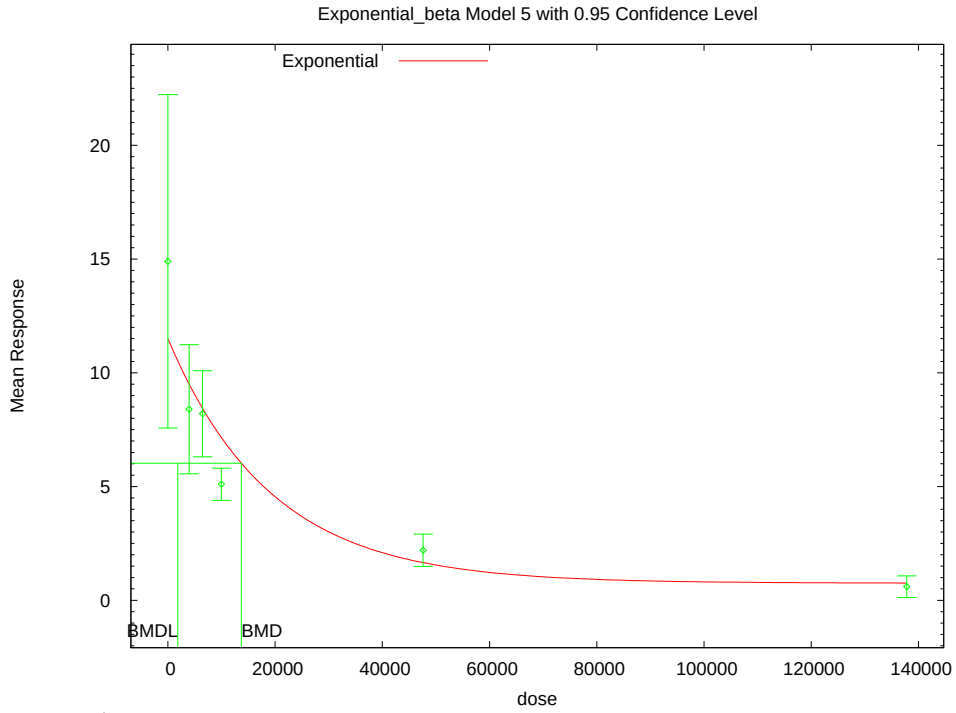

```
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 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         4.61687e-005
                        c            0.0365247
                        d                    1



                  Parameter Estimates

                 Variable          Model 4
                 --------          -------
                  lnalpha         -0.926841
                      rho           1.77261
                        a           11.5052
                        b      5.20223e-005
                        c         0.0653036
                        d                 1


            Table of Stats From Input Data

      Dose      N         Obs Mean     Obs Std Dev
      -----    ---       ----------   -------------
          0      8         14.9        8.768
       3969      8          8.4        3.394
       6479      8          8.2        2.263
       9968      8          5.1       0.8485
      4.761e+004      8          2.2       0.8485
      1.378e+005      8          0.6       0.5657


                Estimated Values of Interest

       Dose      Est Mean      Est Std     Scaled Residual
      ------    ----------    ---------    ----------------
          0         11.51        5.483            1.751
       3969         9.499        4.627          -0.6719
       6479         8.428        4.161          -0.1551
       9968         7.154        3.599           -1.614
4.761e+004         1.655       0.9832            1.568
1.378e+005        0.7596       0.4931          -0.9156


   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       -65.72639            5      141.4528


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                        20.8             3          0.0001156


  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 =      13706.9

             BMDL =      1852.89
```

E.2.46.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



12:28 11/20 2009

E.2.46.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_Unrest_BMR1_hepatic_retinol.(d)
         Gnuplot Plotting File:
                                                  Fri Nov 20 12:28:10 2009
 ========================================================================

 Tbl3, hepatic retinol
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   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
```
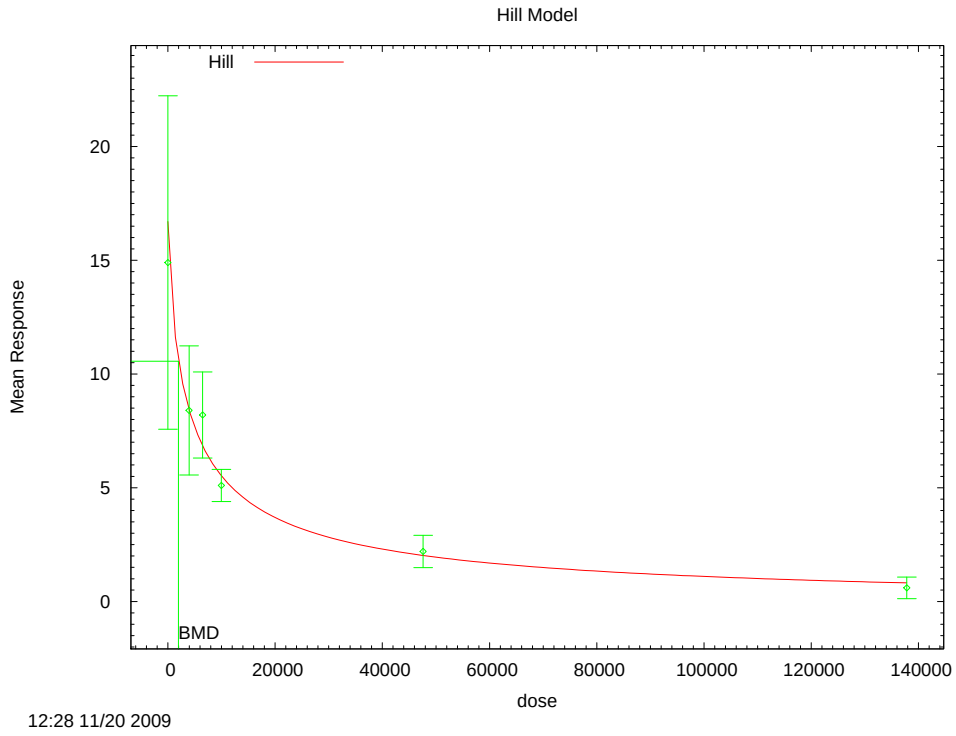

```
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 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 5
                --------          --------
                  lnalpha            -1.16065
                      rho             1.53688
                        a              15.645
                        b         4.61687e-005
                        c            0.0365247
                        d                    1



                  Parameter Estimates

                 Variable          Model 5
                 --------          -------
                  lnalpha         -0.926841
                      rho           1.77261
                        a           11.5052
                        b      5.20223e-005
                        c         0.0653036
                        d                 1


          Table of Stats From Input Data

    Dose      N         Obs Mean     Obs Std Dev
    -----    ---       ----------   -------------
        0      8         14.9        8.768
     3969      8          8.4        3.394
     6479      8          8.2        2.263
     9968      8          5.1       0.8485
    4.761e+004      8          2.2       0.8485
    1.378e+005      8          0.6       0.5657


                Estimated Values of Interest

     Dose      Est Mean      Est Std     Scaled Residual
    ------    ----------    ---------    ----------------
        0         11.51        5.483            1.751
     3969         9.499        4.627          -0.6719
     6479         8.428        4.161          -0.1551
     9968         7.154        3.599           -1.614
4.761e+004         1.655       0.9832            1.568
1.378e+005        0.7596       0.4931          -0.9156


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
                        5       -65.72639            5      141.4528


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 7a: Does Model 5 fit the data? (A3 vs 5)


                            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 7a                         20.8            3          0.0001156


  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 =      13706.9

              BMDL =      1852.89
```

E.2.46.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



E.2.46.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_hepatic_retinol.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_hepatic_retinol.plt
                                                  Fri Nov 20 12:28:12 2009
 ================================================================

 Tbl3, hepatic retinol
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   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 = 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
                     intercept =         14.9
                             v =        -14.3
                             n =      3.62162
                             k =      6985.28


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho    intercept            v            n            k

    lalpha            1        -0.78        -0.04        0.012        0.036        0.033

       rho        -0.78            1       -0.099         0.12       -0.046       -0.052

 intercept        -0.04       -0.099            1        -0.94        -0.25        -0.81

         v        0.012         0.12        -0.94            1         0.54         0.75

         n        0.036       -0.046        -0.25         0.54            1         0.31

         k        0.033       -0.052        -0.81         0.75         0.31            1



                                 Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -1.16164         0.374355            -1.89536           -0.427913
            rho          1.69911          0.18585             1.33485             2.06337
      intercept          16.6709          2.08161              12.591             20.7508
              v         -17.0495          2.32002            -21.5967            -12.5023
              n         0.763329          0.19632            0.378549             1.14811
              k          4251.89          1440.45             1428.66             7075.13



     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         16.7         8.77         6.11          -0.82
 3969     8        8.4         8.37         3.39          3.4         0.0248
 6479     8        8.2         6.79         2.26         2.85            1.4
 9968     8        5.1         5.47        0.849         2.37         -0.439
4.761e+004     8        2.2         1.95        0.849        0.987          0.716
1.378e+005     8        0.6        0.741        0.566        0.434         -0.919



 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	-56.747514	6	125.495027
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	2.84659	2	0.2409

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 = 1

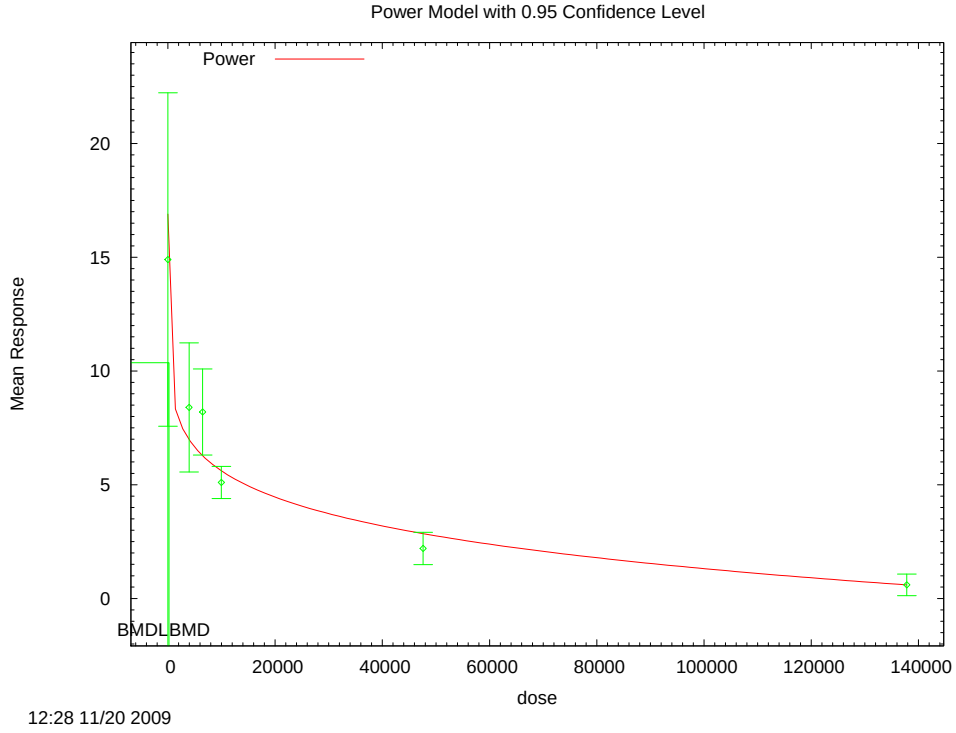
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 1980.88

BMDL computation failed.

E.2.46.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



E.2.46.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_hepatic_retinol.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_hepatic_retinol.plt
                                                  Fri Nov 20 12:28:14 2009
 ================================================================

 Tbl3, hepatic retinol
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   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 =	2.76506
rho =	0
control =	14.9
slope =	-0.92667
power =	0.231239

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.8	-0.042	0.048	0.063
rho	-0.8	1	-0.089	-0.038	-0.1
control	-0.042	-0.089	1	-0.91	-0.81
slope	0.048	-0.038	-0.91	1	0.98
power	0.063	-0.1	-0.81	0.98	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-0.986245	0.394723	-1.75989	-0.212602
rho	1.67858	0.202896	1.28091	2.07625
control	16.9266	2.23237	12.5513	21.302
slope	-3.10665	1.35883	-5.76991	-0.443384
power	0.139874	0.0269583	0.0870372	0.192712

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
3969	8	8.4	7.03	3.39	3.14	1.24
6479	8	8.2	6.32	2.26	2.87	1.85
9968	8	5.1	5.67	0.849	2.62	-0.611
4.761e+004	8	2.2	2.91	0.849	1.5	-1.34
1.378e+005	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	-60.885852	5	131.771704
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	11.1233	3	0.01108

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 = 209.498

BMDL = 7.67456

E.2.47. Van Birgelen et al. (1995a): Hepatic Retinol Palmitate

E.2.47.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	4	<0.0001	57.51	<0.0001	460.28	error	error	nonconstant variance, power restricted ≥1
exponential (M3)	4	<0.0001	57.51	<0.0001	460.28	error	error	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**3**	**<0.0001**	**42.23**	**<0.0001**	**446.99**	**7.8E+04**	**2.0E+04**	**nonconstant variance, power restricted ≥1**
exponential (M5)	3	<0.0001	42.23	<0.0001	446.99	7.8E+04	2.0E+04	nonconstant variance, power restricted ≥1
exponential (M5) [d]	3	<0.0001	42.23	<0.0001	446.99	7.8E+04	2.0E+04	nonconstant variance, power unrestricted
Hill	3	<.0001	11.47	0.01	416.23	2.0E+03	error	nonconstant variance, n restricted >1, bound hit
Hill [d]	3	<.0001	120.59	<.0001	525.36	5.0E-11	5.0E-11	nonconstant variance, n unrestricted
linear	4	<.0001	83.61	<.0001	486.37	1.9E+05	1.3E+05	nonconstant variance
polynomial	4	<.0001	128.71	<.0001	531.47	6.2E+04	5.0E+04	nonconstant variance
power	4	<.0001	83.61	<.0001	486.37	1.9E+05	1.3E+05	nonconstant variance, power restricted ≥1, bound hit
power [d]	3	<.0001	4.22	0.24	408.98	2.9E+01	3.2E-02	nonconstant variance, power unrestricted
exponential (M2)	4	<0.0001	142.00	<0.0001	649.06	error	error	constant variance, power restricted ≥1
exponential (M3)	4	<0.0001	142.00	<0.0001	649.06	error	error	constant variance, power restricted ≥1
exponential (M4)	3	<0.0001	2.84	0.42	511.95	7.9E+02	2.9E+00	constant variance, power restricted ≥1
exponential (M5)	3	<0.0001	2.84	0.42	511.95	7.9E+02	2.0E+00	constant variance, power restricted ≥1
exponential (M5)	3	<0.0001	2.84	0.42	511.95	7.9E+02	2.0E+00	constant variance, power unrestricted
Hill	3	<.0001	0.93	0.82	510.04	3.9E+02	9.5E+01	constant variance, n restricted >1, bound hit
Hill	2	<.0001	0.31	0.86	511.42	2.8E-01	2.8E-01	constant variance, n unrestricted
linear	4	<.0001	43.71	<.0001	550.82	1.1E+05	7.0E+04	constant variance
polynomial	4	<.0001	43.71	<.0001	550.82	1.1E+05	7.0E+04	constant variance
power	4	<.0001	43.71	<.0001	550.82	1.1E+05	7.0E+04	constant variance, power restricted ≥1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
power	3	<.0001	0.33	0.95	509.44	2.0E-04	2.0E-04	constant variance, power unrestricted

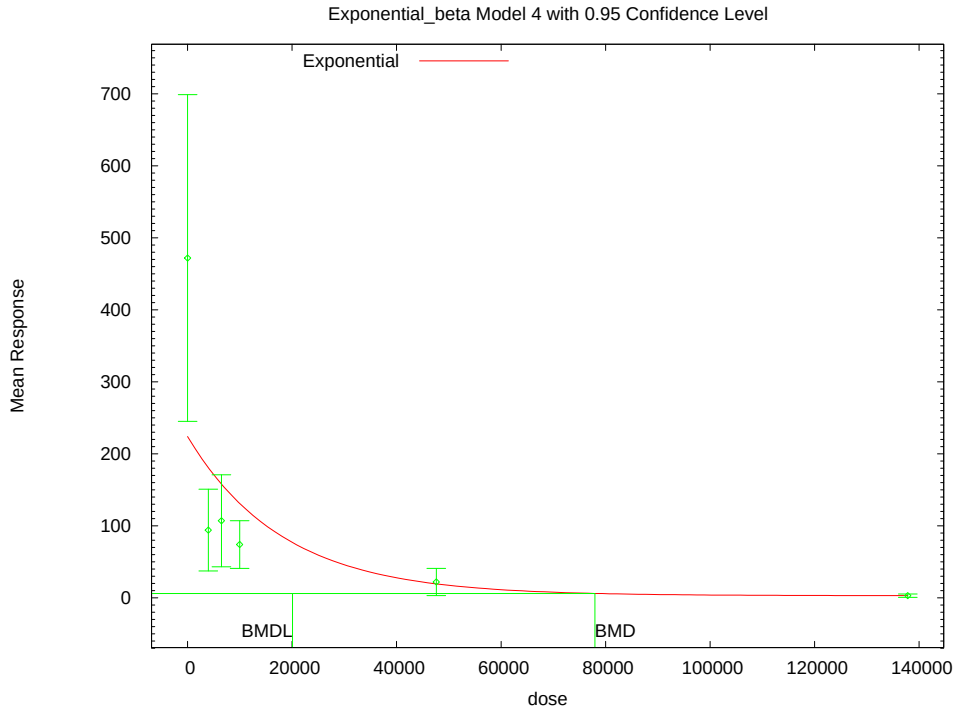
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.47.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



E.2.47.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_BMR1_hepatic_retinol_palmitate.(d)
         Gnuplot Plotting File:
                                                 Fri Nov 20 12:29:00 2009
 ================================================================

 Tbl3, hepatic retinol palmitate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
```

```
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 = 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         6.13207e-005
                       c           0.00576502
                       d                    1


                  Parameter Estimates

                Variable          Model 4
                --------          -------
                 lnalpha         -0.241584
                     rho           2.03456
                       a           223.851
                       b      5.45885e-005
                       c          0.012925
                       d                 1

  NC = No Convergence


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      8          472        271.5
   3969      8           94        67.88
   6479      8          107        76.37
   9968      8           74         39.6
  4.761e+004      8           22        22.63
  1.378e+005      8            3        2.828


               Estimated Values of Interest
```

Dose	Est Mean	Est Std	Scaled Residual
0	223.9	217.8	3.222
3969	180.8	175.3	-1.401
6479	158	152.9	-0.9443
9968	131.1	126.4	-1.278
4.761e+004	19.33	18.03	0.4197
1.378e+005	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	-218.4969	5	446.9938

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

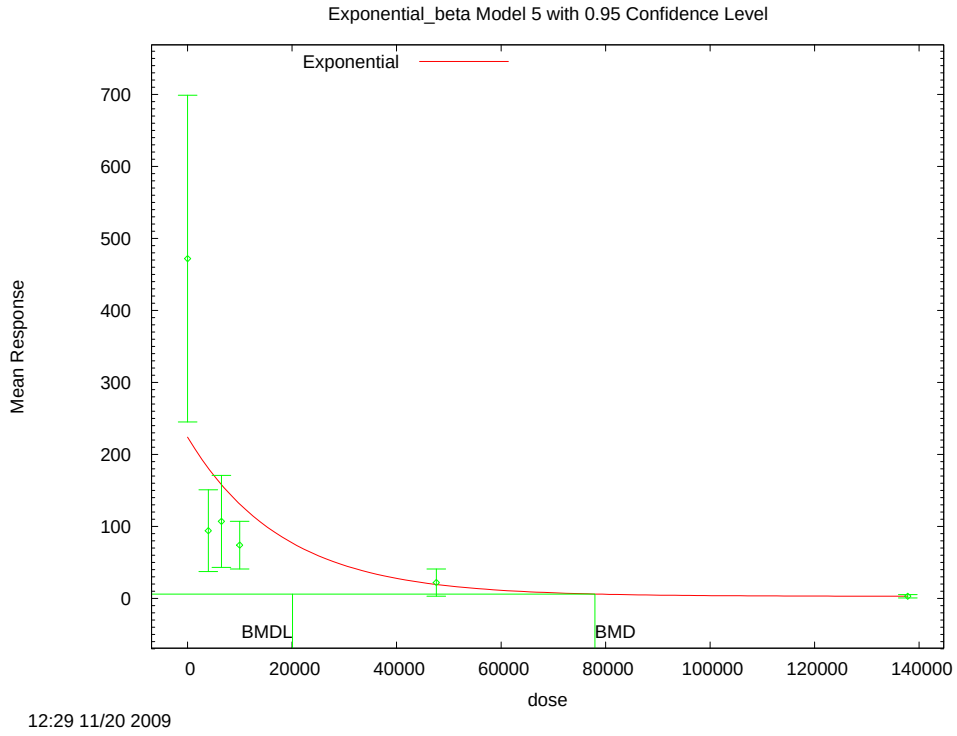
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

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 =      77948.7

                  BMDL =      20092.3
```

E.2.47.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



E.2.47.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

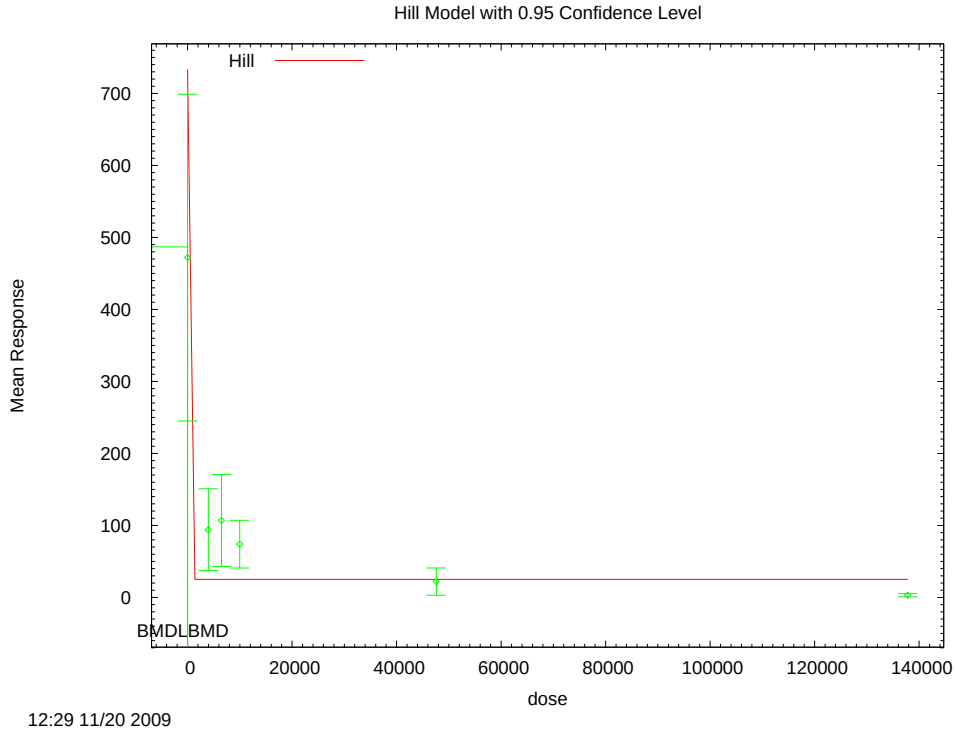
```
 ================================================================
          Exponential Model. (Version: 1.5;  Date: 4/23/2009)
          Input Data File:
C:\USEPA\BMDS21\Nov20\Blood\Exp_Unrest_BMR1_hepatic_retinol_palmitate.(d)
          Gnuplot Plotting File:
                                                 Fri Nov 20 12:29:18 2009
```

```
 ========================================================================

 Tbl3, hepatic retinol palmitate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 5
                 --------          --------
                   lnalpha            0.284674
                       rho             1.77158
                         a               495.6
                         b         6.13207e-005
                         c           0.00576502
                         d                    1



                    Parameter Estimates

                  Variable          Model 5
                  --------          -------
                   lnalpha         -0.241584
                       rho           2.03456
                         a           223.851
                         b      5.45885e-005
                         c          0.012925
                         d                 1

     NC = No Convergence


            Table of Stats From Input Data

     Dose      N         Obs Mean     Obs Std Dev
     -----    ---       ----------   -------------
         0      8          472        271.5
      3969      8           94        67.88
      6479      8          107        76.37
      9968      8           74         39.6
```

```
      4.761e+004      8           22        22.63
      1.378e+005      8            3        2.828


                  Estimated Values of Interest

       Dose      Est Mean      Est Std     Scaled Residual
     ------    ----------    ---------    ---------------
          0         223.9        217.8             3.222
       3969         180.8        175.3            -1.401
       6479           158        152.9           -0.9443
       9968         131.1        126.4            -1.278
4.761e+004         19.33        18.03            0.4197
1.378e+005         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
                        5       -218.4969           5      446.9938


   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 7a: Does Model 5 fit the data? (A3 vs 5)


                           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 7a                     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 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 =      77952.3

                  BMDL =      20092.3
```

E.2.47.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



E.2.47.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
          Hill Model. (Version: 2.14;  Date: 06/26/2008)
          Input Data File:
C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_hepatic_retinol_palmitate.(d)
```

```
          Gnuplot Plotting File:
C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_hepatic_retinol_palmitate.plt
                                                    Fri Nov 20 12:29:21 2009
 ========================================================================

 Tbl3, hepatic retinol palmitate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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
                      intercept =          472
                              v =         -469
                              n =       1.6454
                              k =      2462.18


           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         -0.9      -0.0084        -0.05      0.00043

       rho         -0.9            1         0.33        -0.25     6.2e-005

 intercept      -0.0084         0.33            1           -1      0.00089

         v        -0.05        -0.25           -1            1     -0.00081

         n      0.00043     6.2e-005      0.00089     -0.00081            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha          9.05753         0.813787             7.46254             10.6525
            rho         0.296518         0.132793           0.0362478            0.556789
      intercept           733.34          146.204             446.785             1019.89
              v         -707.607           132.71            -967.713              -447.5
              n         0.620012          31.4549            -61.0305             62.2705
              k      1.3782e-010               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	472	733	272	246	-3
3969	8	94	25.7	67.9	150	1.29
6479	8	107	25.7	76.4	150	1.53
9968	8	74	25.7	39.6	150	0.91
4.761e+004	8	22	25.7	22.6	150	-0.0704
1.378e+005	8	3	25.7	2.83	150	-0.429

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	-257.680271	5	525.360542
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	120.594	3	<.0001

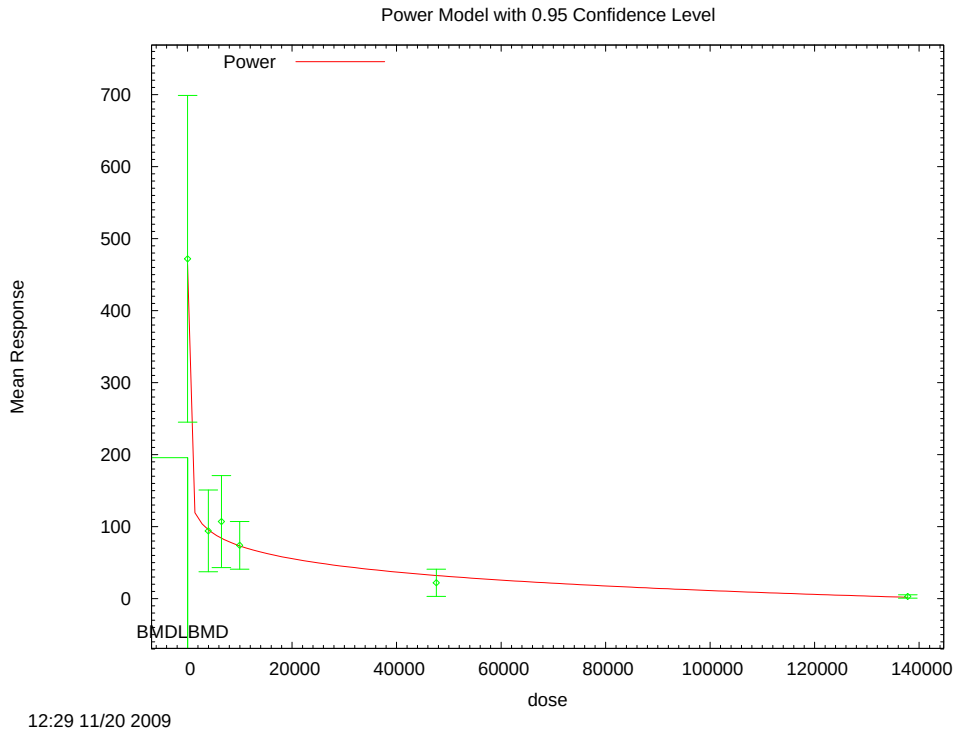
The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

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 =   5.01376e-011

            BMDL =  5.01376e-011
```

E.2.47.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



12:29 11/20 2009

E.2.47.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File:
C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_hepatic_retinol_palmitate.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_hepatic_retinol_palmitate.plt
                                                  Fri Nov 20 12:29:22 2009
```

```
 ========================================================================

 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 =     -204.597
                          power =    0.0711193


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho      control        slope        power

    lalpha            1        -0.95          0.3        -0.32         -0.3

       rho        -0.95            1        -0.41         0.37         0.29

   control          0.3        -0.41            1        -0.96        -0.82

     slope        -0.32         0.37        -0.96            1         0.95

     power         -0.3         0.29        -0.82         0.95            1


                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         0.064014         0.859473            -1.62052             1.74855
            rho          1.81132         0.197468             1.42429             2.19835
        control          464.289          87.5706             292.654             635.925
          slope         -216.594          73.4027            -360.461            -72.7275
          power        0.0639105        0.0139781           0.0365139           0.0913071


      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
 3969     8         94         96.5         67.9         64.7         -0.108
 6479     8        107         84.8         76.4         57.6           1.09
 9968     8         74         74.2         39.6           51       -0.00938
4.761e+004     8         22         33.2         22.6         24.6          -1.28
1.378e+005     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        -199.490894            5     408.981788
               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              4.21544          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 = 28.9991

BMDL = 0.0324608
```

E.2.48. Van Birgelen et al. (1995a): Plasma FT4

E.2.48.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2) [c]	**4**	**0.01**	**2.70**	**0.61**	**214.98**	**4.4E+04**	**2.8E+04**	**nonconstant variance, power restricted ≥1**
exponential (M3)	4	0.01	2.70	0.61	214.98	4.4E+04	2.8E+04	nonconstant variance, power restricted ≥1
exponential (M4)	3	0.01	1.96	0.58	216.24	3.0E+04	1.2E+04	nonconstant variance, power restricted ≥1
exponential (M5)	3	0.01	1.96	0.58	216.24	3.0E+04	1.2E+04	nonconstant variance, power restricted ≥1
exponential (M5) [d]	3	0.01	1.96	0.58	216.24	3.0E+04	1.2E+04	nonconstant variance, power unrestricted
Hill	3	0.01	1.90	0.59	216.19	2.8E+04	8.8E+03	nonconstant variance, n restricted >1, bound hit
Hill [d]	2	0.01	1.90	0.39	218.19	2.8E+04	7.9E+03	nonconstant variance, n unrestricted
linear	4	0.01	3.98	0.41	216.27	6.0E+04	4.4E+04	nonconstant variance
polynomial	4	0.01	3.98	0.41	216.27	6.0E+04	4.4E+04	nonconstant variance
power	4	0.01	3.98	0.41	216.27	6.0E+04	4.4E+04	nonconstant variance, power restricted ≥1, bound hit
power [d]	3	0.01	2.30	0.51	216.59	3.0E+04	7.2E+03	nonconstant variance, power unrestricted
exponential (M2)	4	0.01	3.21	0.52	213.50	4.1E+04	2.7E+04	constant variance, power restricted ≥1
exponential (M3)	4	0.01	3.21	0.52	213.50	4.1E+04	2.7E+04	constant variance, power restricted ≥1
exponential (M4)	3	0.01	2.47	0.48	214.76	2.7E+04	1.1E+04	constant variance, power restricted ≥1
exponential (M5)	3	0.01	2.47	0.48	214.76	2.7E+04	1.1E+04	constant variance, power restricted ≥1
exponential (M5)	3	0.01	2.47	0.48	214.76	2.7E+04	1.1E+04	constant variance, power unrestricted
Hill	3	0.01	2.35	0.50	214.64	2.4E+04	8.1E+03	constant variance, n restricted >1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
Hill	2	0.01	2.33	0.31	216.62	2.4E+04	7.0E+03	constant variance, n unrestricted
linear	4	0.01	4.50	0.34	214.79	5.7E+04	4.3E+04	constant variance
polynomial	4	0.01	4.50	0.34	214.79	5.7E+04	4.3E+04	constant variance
power	4	0.01	4.50	0.34	214.79	5.7E+04	4.3E+04	constant variance, power restricted ≥1, bound hit
power	3	0.01	2.66	0.45	214.95	2.6E+04	6.4E+03	constant variance, power unrestricted

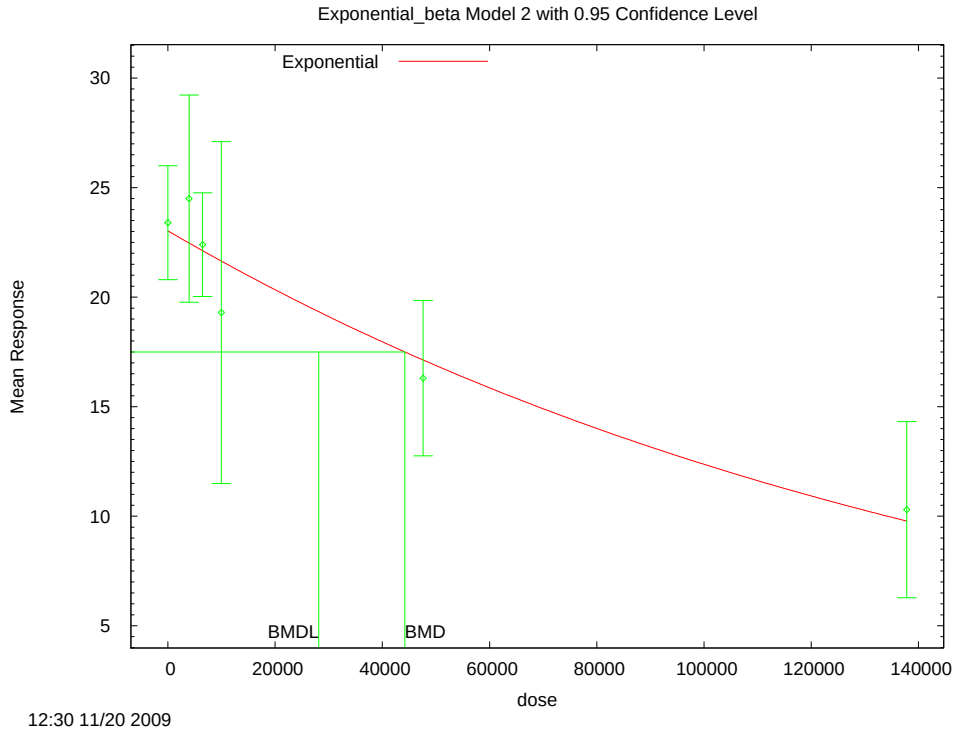
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.2.48.2. *Figure for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*



E.2.48.3. *Output File for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_BMR1_plasma_FT4.(d)
         Gnuplot Plotting File:
                                                  Fri Nov 20 12:30:05 2009
 ================================================================

 Tbl3, plasma FT4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 2
                --------          --------
                  lnalpha             4.29134
                      rho            -0.423761
                        a               25.725
                        b         2.47112e-005
                        c              0.381323
                        d                     1



                   Parameter Estimates

                 Variable          Model 2
                 --------          -------
                  lnalpha            1.7323
                      rho           0.534787
                        a            23.5975
                        b      1.50877e-005
                        c           0.358997
                        d                  1
```

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	23.4	3.111
3969	8	24.5	5.657
6479	8	22.4	2.828
9968	8	19.3	9.334
4.761e+004	8	16.3	4.243
1.378e+005	8	10.3	4.808

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	23.03	5.531	0.1896
3969	22.47	5.496	1.046
6479	22.12	5.474	0.1445
9968	21.65	5.444	-1.219
4.761e+004	17.13	5.13	-0.4583
1.378e+005	9.779	4.447	0.3314

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	-102.145	7	218.2901
A2	-94.04963	12	212.0993
A3	-102.143	8	220.286
R	-117.8175	2	239.635
2	-103.491	4	214.9821

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

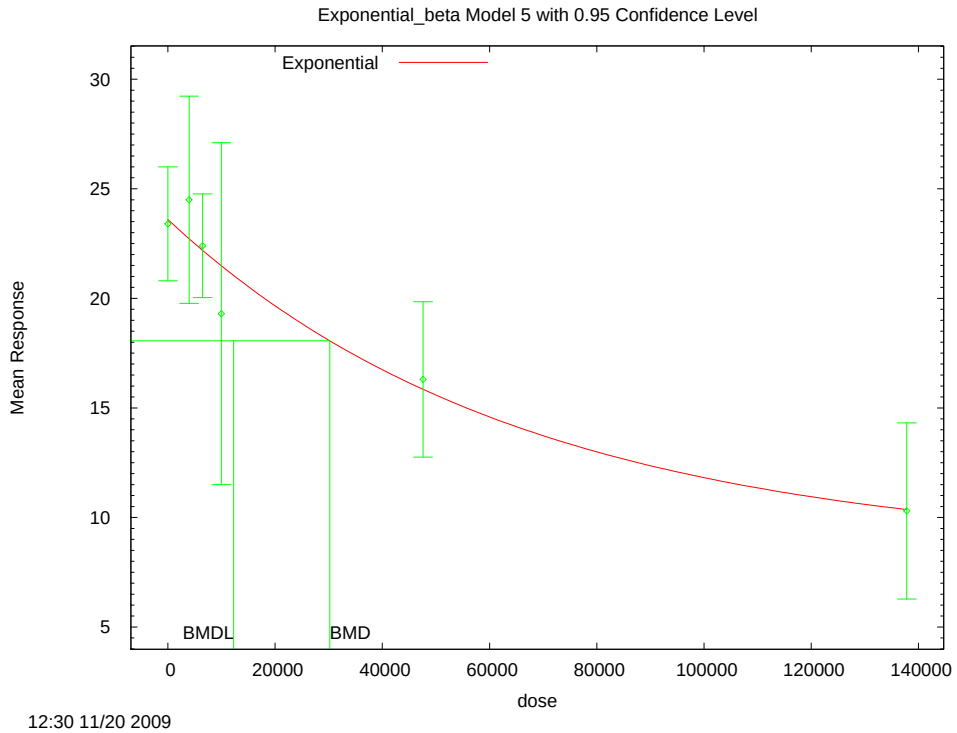
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	47.54	10	< 0.0001

```
      Test 2                        16.19          5            0.00632
      Test 3                        16.19          4           0.002778
      Test 4                        2.696          4             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 less than .1.  You may want to
      consider a different variance model.

      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 =      44193.5

                BMDL =      28156.1
```

E.2.48.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



E.2.48.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_Unrest_BMR1_plasma_FT4.(d)
         Gnuplot Plotting File:
                                                  Fri Nov 20 12:30:11 2009
 ================================================================

 Tbl3, plasma FT4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 5
                --------          --------
                  lnalpha             4.29134
                      rho            -0.423761
                        a               25.725
                        b         2.47112e-005
                        c              0.381323
                        d                     1



                   Parameter Estimates

                 Variable          Model 5
                 --------          -------
                  lnalpha            1.7323
                      rho           0.534787
                        a            23.5975
                        b      1.50877e-005
                        c           0.358997
                        d                  1
```

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	23.4	3.111
3969	8	24.5	5.657
6479	8	22.4	2.828
9968	8	19.3	9.334
4.761e+004	8	16.3	4.243
1.378e+005	8	10.3	4.808

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	23.6	5.537	-0.1009
3969	22.72	5.481	0.9194
6479	22.19	5.446	0.1096
9968	21.49	5.4	-1.145
4.761e+004	15.85	4.978	0.2575
1.378e+005	10.36	4.443	-0.03965

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	-102.145	7	218.2901
A2	-94.04963	12	212.0993
A3	-102.143	8	220.286
R	-117.8175	2	239.635
5	-103.1224	5	216.2449

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)

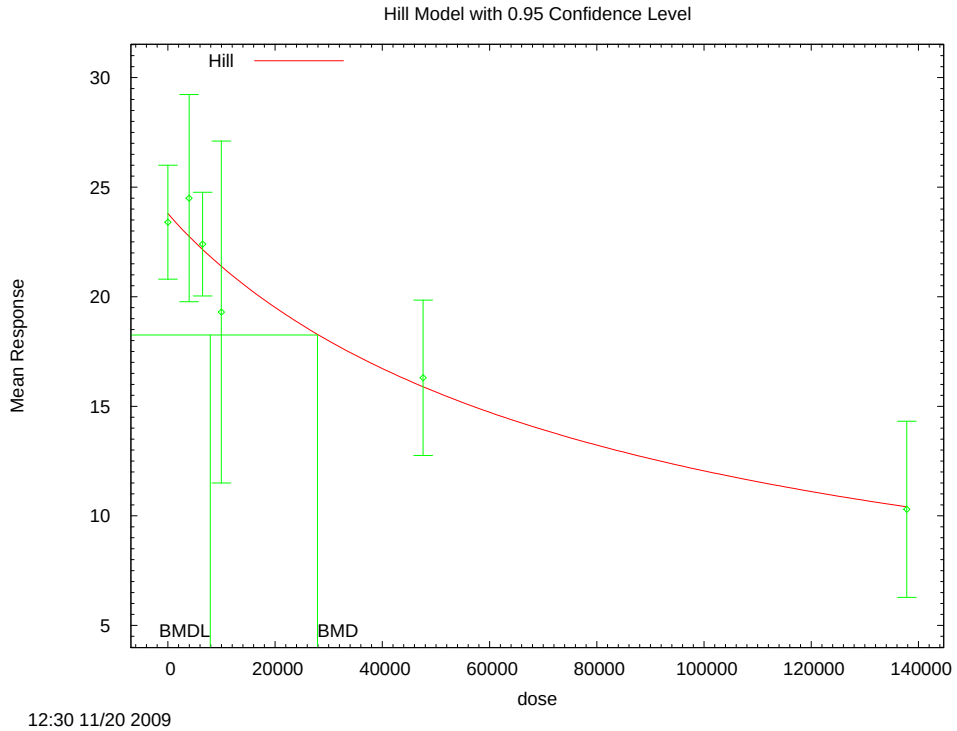
Test 7a: Does Model 5 fit the data? (A3 vs 5)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value

```
      Test 1                        47.54          10           < 0.0001
      Test 2                        16.19           5            0.00632
      Test 3                        16.19           4           0.002778
     Test 7a                        1.959           3              0.581


      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 greater than .1.  Model 5 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 =      30208.5

                BMDL =      12273.2
```

E.2.48.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



12:30 11/20 2009

E.2.48.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_plasma_FT4.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_plasma_FT4.plt
                                              Fri Nov 20 12:30:12 2009
 ================================================================

 Tbl3, plasma FT4
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   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 = 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 =      3.38957
                           rho =            0
                     intercept =         23.4
                             v =        -13.1
                             n =     0.996796
                             k =      40705.6


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho    intercept            v            n            k

    lalpha            1           -1          0.2        -0.16        -0.19         0.12

       rho           -1            1         -0.2         0.16         0.19        -0.12

 intercept          0.2         -0.2            1        -0.39        -0.59         0.22

         v        -0.16         0.16        -0.39            1          0.9        -0.98

         n        -0.19         0.19        -0.59          0.9            1        -0.85

         k         0.12        -0.12         0.22        -0.98        -0.85            1


                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha          1.81761          2.18889            -2.47254             6.10776
            rho         0.505217         0.744572           -0.954117             1.96455
      intercept          23.7748          1.72532             20.3933             27.1564
              v         -21.6283          20.8713            -62.5352             19.2786
              n         0.975863           0.6937           -0.383764             2.33549
              k          83458.4           171511              -252696              419613
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	23.4	23.8	3.11	5.52	-0.192
3969	8	24.5	22.7	5.66	5.46	0.921
6479	8	22.4	22.1	2.83	5.43	0.143
9968	8	19.3	21.4	9.33	5.38	-1.08
4.761e+004	8	16.3	15.9	4.24	4.99	0.255
1.378e+005	8	10.3	10.4	4.81	4.48	-0.0414

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	-102.145036	7	218.290071
A2	-94.049629	12	212.099258
A3	-102.143023	8	220.286046
fitted	-103.092664	6	218.185329
R	-117.817514	2	239.635028

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	47.5358	10	<.0001
Test 2	16.1908	5	0.00632
Test 3	16.1868	4	0.002778
Test 4	1.89928	2	0.3869

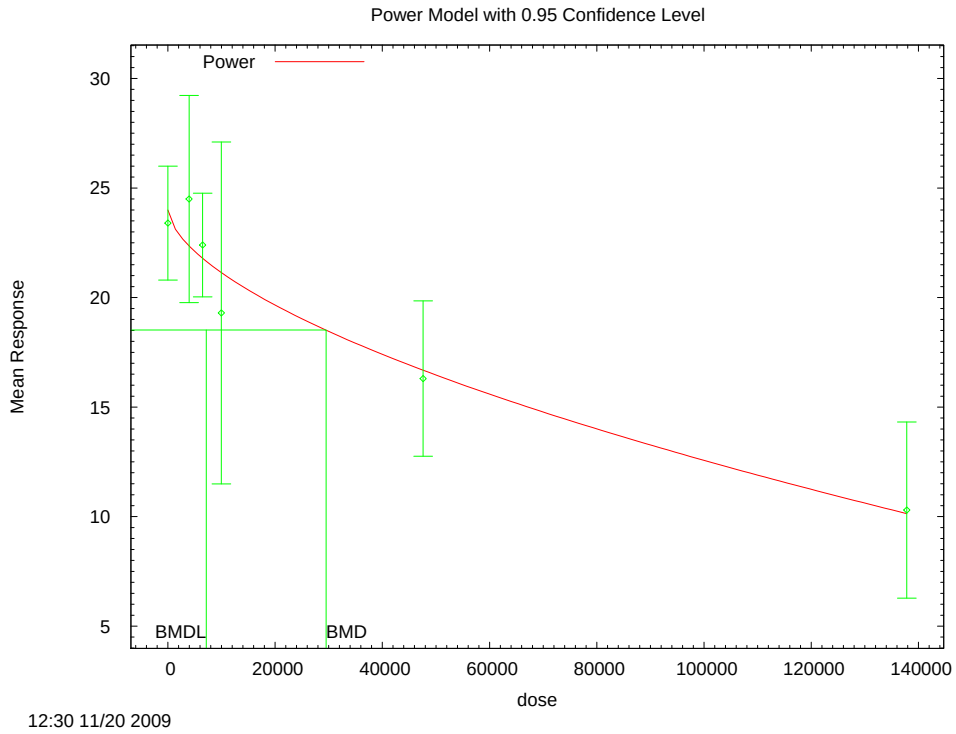
The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

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 =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        27884.5

            BMDL =       7907.26
```

E.2.48.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



E.2.48.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
=================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_plasma_FT4.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_plasma_FT4.plt
                                                Fri Nov 20 12:30:13 2009
=================================================================
```

Tbl3, plasma FT4

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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 =	3.38957
rho =	0
control =	24.5
slope =	-0.0256219
power =	0.537235

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-1	0.099	-0.069	-0.06
rho	-1	1	-0.1	0.069	0.06
control	0.099	-0.1	1	-0.78	-0.75
slope	-0.069	0.069	-0.78	1	1
power	-0.06	0.06	-0.75	1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	1.99957	2.14696	-2.20839	6.20753
rho	0.44594	0.730207	-0.98524	1.87712
control	24.0444	1.65932	20.7922	27.2966
slope	-0.0113184	0.0287697	-0.0677059	0.0450692
power	0.601415	0.209424	0.190952	1.01188

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	23.4	24	3.11	5.52	-0.33
3969	8	24.5	22.4	5.66	5.44	1.1
6479	8	22.4	21.8	2.83	5.4	0.3
9968	8	19.3	21.2	9.33	5.37	-0.985
4.761e+004	8	16.3	16.7	4.24	5.09	-0.212
1.378e+005	8	10.3	10.1	4.81	4.55	0.129
~~~~~~

```
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         -102.145036           7     218.290071
              A2          -94.049629          12     212.099258
              A3         -102.143023           8     220.286046
          fitted         -103.295375           5     216.590750
               R         -117.817514           2     239.635028


                    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              47.5358         10          <.0001
  Test 2              16.1908          5         0.00632
  Test 3              16.1868          4        0.002778
  Test 4               2.3047          3          0.5116

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 =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 29513.9
```

```
BMDL = 7158.08
```

E.2.49. Van Birgelen et al. (1995a): Plasma TT4

E.2.49.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	4	0.94	9.91	0.04	241.35	5.6E+04	3.6E+04	nonconstant variance, power restricted ≥1
exponential (M2)	4	0.94	9.91	0.04	241.35	5.6E+04	3.6E+04	nonconstant variance, power unrestricted
exponential (M3)	4	0.94	9.91	0.04	241.35	5.6E+04	3.6E+04	nonconstant variance, power restricted ≥1
exponential (M3)	4	0.94	9.91	0.04	241.35	5.6E+04	3.6E+04	nonconstant variance, power unrestricted
exponential (M4)	3	0.94	9.33	0.03	242.77	3.6E+04	6.8E+03	nonconstant variance, power restricted ≥1
exponential (M4)	3	0.94	9.33	0.03	242.77	3.6E+04	6.8E+03	nonconstant variance, power unrestricted
exponential (M5)	3	0.94	9.33	0.03	242.77	3.6E+04	5.5E+03	nonconstant variance, power restricted ≥1
exponential (M5)	3	0.94	9.33	0.03	242.77	3.6E+04	5.5E+03	nonconstant variance, power unrestricted
Hill	3	0.94	5.45	0.14	238.89	9.4E+03	error	nonconstant variance, n restricted >1, bound hit
Hill	3	0.94	5.45	0.14	238.89	9.4E+03	error	nonconstant variance, n unrestricted
linear	4	0.94	10.33	0.04	241.77	6.6E+04	4.5E+04	nonconstant variance
polynomial	4	0.94	10.33	0.04	241.77	6.6E+04	4.5E+04	nonconstant variance
power	4	0.94	10.33	0.04	241.77	6.6E+04	4.5E+04	nonconstant variance, power restricted ≥1, bound hit
power	3	0.94	8.78	0.03	242.22	2.9E+04	5.4E+03	nonconstant variance, power unrestricted
exponential (M2) [c]	**4**	**0.94**	**9.33**	**0.05**	**239.35**	**5.7E+04**	**3.9E+04**	**constant variance, power restricted ≥1**
exponential (M3)	4	0.94	9.33	0.05	239.35	5.7E+04	3.9E+04	constant variance, power restricted ≥1
exponential (M4)	3	0.94	8.75	0.03	240.78	3.7E+04	9.1E+03	constant variance, power restricted ≥1
exponential (M5)	3	0.94	8.75	0.03	240.78	3.7E+04	9.1E+03	constant variance, power restricted ≥1

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M5) [d]	3	0.94	8.75	0.03	240.78	3.7E+04	9.1E+03	constant variance, power unrestricted
Hill	3	0.94	6.31	0.10	238.33	9.5E+03	error	constant variance, n restricted >1, bound hit
Hill [d]	3	0.94	6.31	0.10	238.33	9.5E+03	error	constant variance, n unrestricted
linear	4	0.94	9.75	0.04	239.77	6.6E+04	4.8E+04	constant variance
polynomial	4	0.94	9.75	0.04	239.77	6.6E+04	4.8E+04	constant variance
power	4	0.94	9.75	0.04	239.77	6.6E+04	4.8E+04	constant variance, power restricted ≥1, bound hit
power [d]	3	0.94	8.21	0.04	240.24	3.0E+04	5.8E+03	constant variance, power unrestricted

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

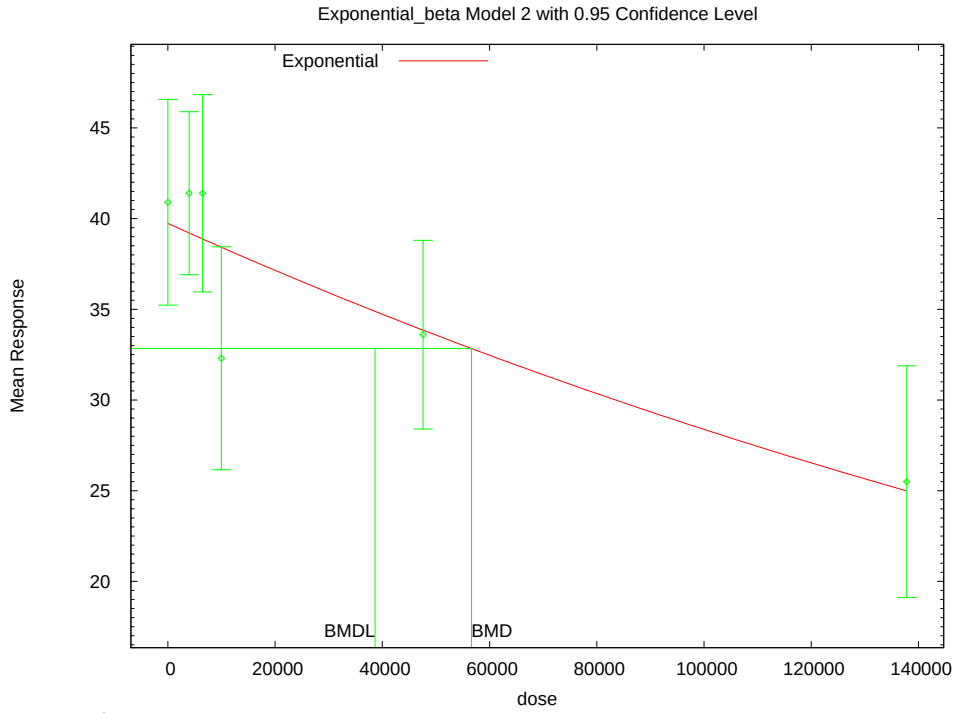
[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

1
2

E.2.49.2. *Figure for Selected Model: Exponential (M2), Constant Variance, Power Restricted ≥1*



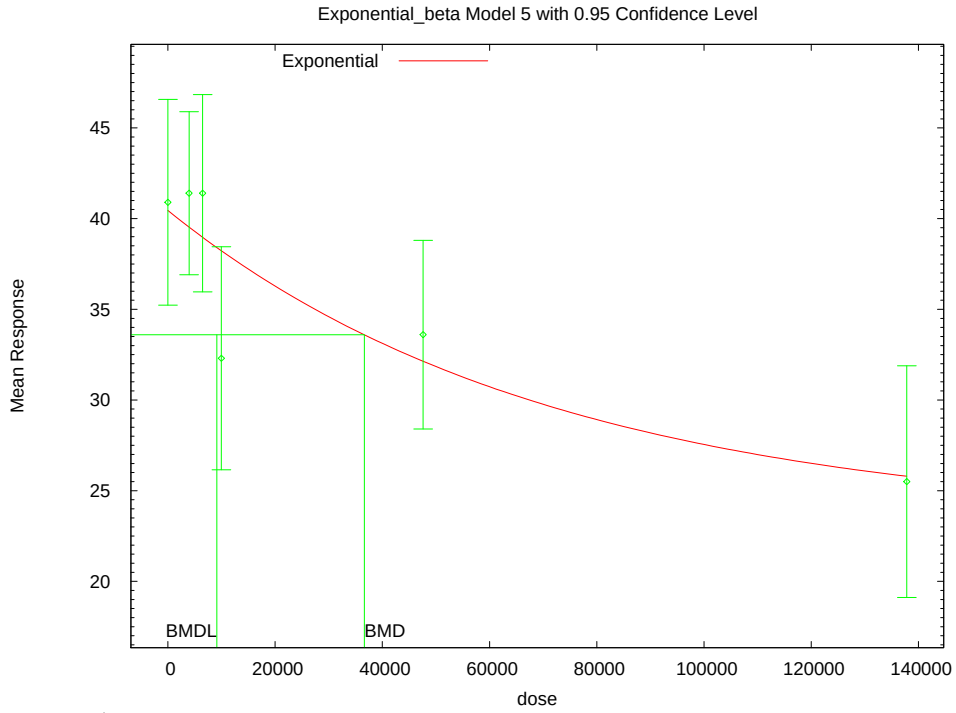
E.2.49.3. *Output File for Selected Model: Exponential (M2), Constant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_CV_BMR1_plasma_TT4.(d)
         Gnuplot Plotting File:
                                                  Fri Nov 20 12:31:00 2009
 ================================================================

 Tbl3, plasma TT4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 2
                --------          --------
                  lnalpha             3.66719
                      rho(S)                0
                        a               43.47
                        b         1.98277e-005
                        c             0.558678
                        d                    1

  (S) = Specified



                   Parameter Estimates

                  Variable          Model 2
                  --------          -------
                   lnalpha           3.84955
                       rho                 0
                         a           40.4479
                         b      1.38876e-005
                         c          0.575097
                         d                 1


            Table of Stats From Input Data

    Dose      N         Obs Mean     Obs Std Dev
    -----    ---       ----------   -------------
        0      8         40.9        6.788
     3969      8         41.4        5.374
     6479      8         41.4        6.505
     9968      8         32.3        7.354
    4.761e+004      8         33.6        6.223
    1.378e+005      8         25.5        7.637


                Estimated Values of Interest

     Dose      Est Mean      Est Std     Scaled Residual
    ------    ----------    ---------    ----------------
        0         39.73        6.895           0.4797
     3969          39.2        6.895            0.901
     6479         38.87        6.895            1.036
     9968         38.42        6.895           -2.511
4.761e+004         33.85        6.895          -0.1024
1.378e+005         24.99        6.895           0.2106


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       -112.0125           7       238.025
                       A2       -111.4015          12      246.8029
                       A3       -112.0125           7       238.025
                        R       -127.4455           2       258.891
                        2       -116.6748           3      239.3495


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 4:  Does Model 2 fit the data? (A3 vs. 2)


                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                       32.09            10          0.0003871
  Test 2                       1.222             5             0.9427
  Test 3                       1.222             5             0.9427
  Test 4                       9.325             4            0.05348


  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.  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 =      56637.1

              BMDL =      38643.8
```

E.2.49.4. *Figure for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*



E.2.49.5. *Output File for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*

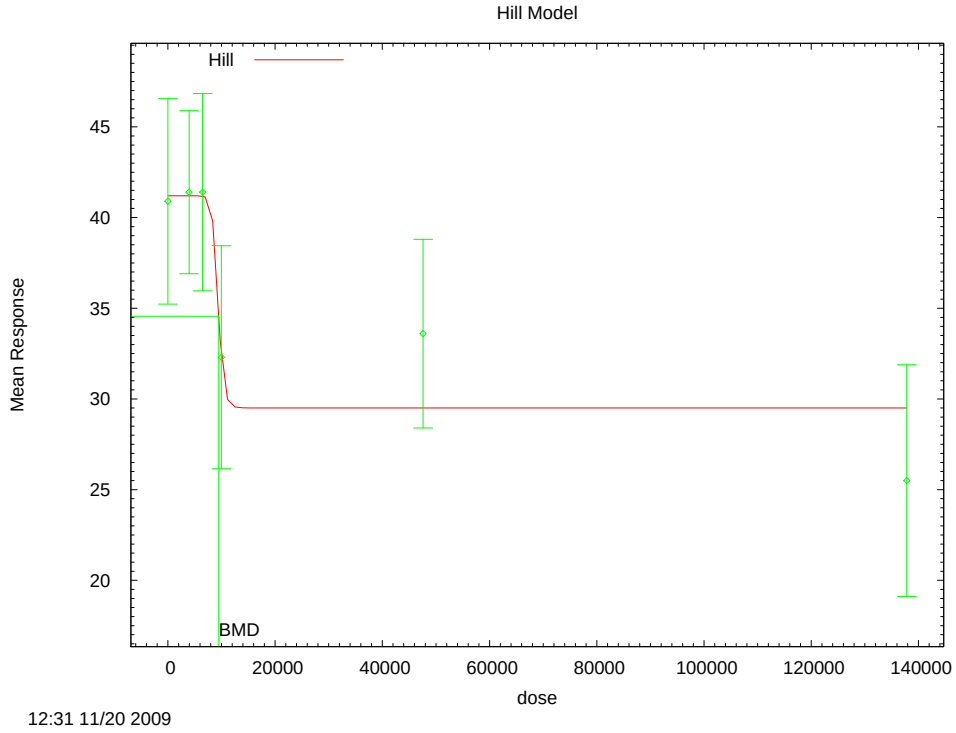
```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_CV_Unrest_BMR1_plasma_TT4.(d)
         Gnuplot Plotting File:
                                                  Fri Nov 20 12:31:08 2009
 ================================================================

 Tbl3, plasma TT4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 5
                --------          --------
                  lnalpha             3.66719
                      rho(S)                0
                        a                43.47
                        b         1.98277e-005
                        c             0.558678
                        d                    1

  (S) = Specified



                   Parameter Estimates

                  Variable          Model 5
                  --------          -------
                   lnalpha           3.84955
                       rho                 0
                         a           40.4479
                         b      1.38876e-005
                         c          0.575097
                         d                 1


            Table of Stats From Input Data

    Dose      N         Obs Mean     Obs Std Dev
    -----    ---       ----------   -------------
        0      8         40.9        6.788
     3969      8         41.4        5.374
     6479      8         41.4        6.505
     9968      8         32.3        7.354
    4.761e+004      8         33.6        6.223
    1.378e+005      8         25.5        7.637


                Estimated Values of Interest

     Dose      Est Mean      Est Std     Scaled Residual
    ------    ----------    ---------    ----------------
        0         40.45        6.854           0.1866
     3969         39.53        6.854           0.7733
     6479         38.97        6.854            1.003
     9968         38.23        6.854           -2.446
4.761e+004         32.13        6.854           0.6049
1.378e+005          25.8        6.854          -0.1223


   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       -112.0125           7       238.025
                       A2       -111.4015          12      246.8029
                       A3       -112.0125           7       238.025
                        R       -127.4455           2       258.891
                        5       -116.3891           4      240.7782


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 7a: Does Model 5 fit the data? (A3 vs 5)


                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                        32.09          10           0.0003871
  Test 2                        1.222           5              0.9427
  Test 3                        1.222           5              0.9427
 Test 7a                        8.753           3             0.03276


  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 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 =      36636.4
```

```
                 BMDL =       9124.3
```

E.2.49.6. *Figure for Unrestricted Model: Hill, Constant Variance, n Unrestricted*



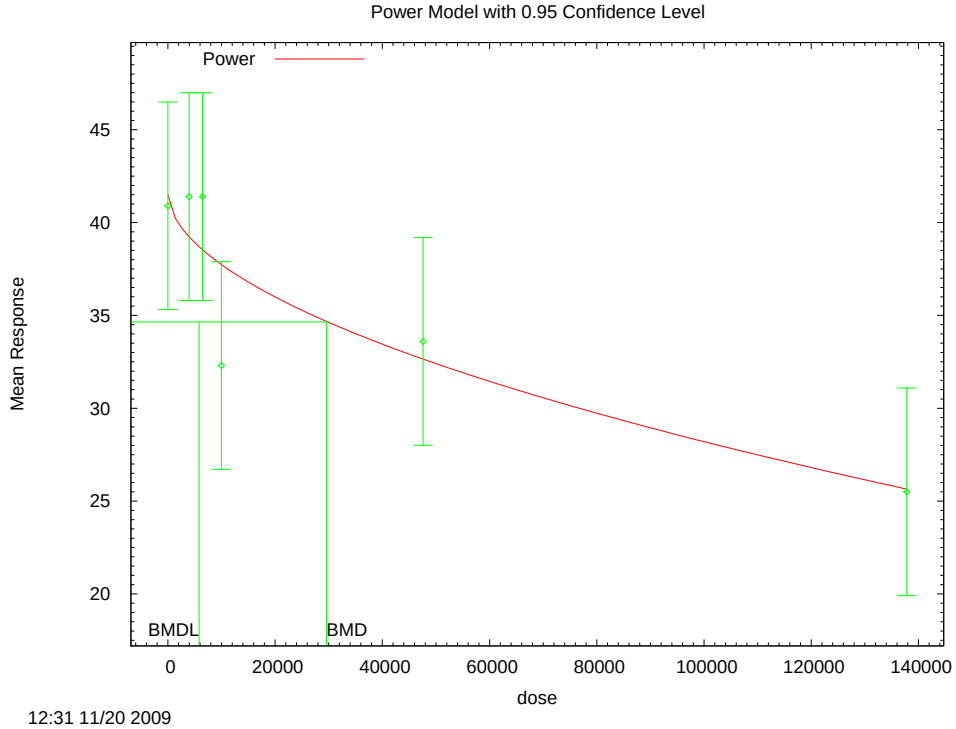
E.2.49.7. *Output File for Unrestricted Model: Hill, Constant Variance, n Unrestricted*

```
 ========================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Hill_CV_Unrest_BMR1_plasma_TT4.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Blood\Hill_CV_Unrest_BMR1_plasma_TT4.plt
                                                 Fri Nov 20 12:31:10 2009
 ========================================================================

 Tbl3, plasma TT4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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
                          alpha =      44.7333
                            rho =            0   Specified
                      intercept =         40.9
                              v =        -15.4
                              n =      3.33301
                              k =      9622.52


           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    -6.6e-008     7.9e-008    -1.5e-007

   intercept    -6.6e-008            1        -0.63        -0.12

           v     7.9e-008        -0.63            1        -0.29

           k    -1.5e-007        -0.12        -0.29            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha          44.6379          9.11167             26.7793             62.4964
       intercept          41.2386          1.36525             38.5627             43.9144
               v          -11.689           2.1552            -15.9131            -7.46484
               n               18               NA
               k          9336.14          666.631             8029.56             10642.7

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       40.9         41.2         6.79         6.68         -0.143
 3969     8       41.4         41.2         5.37         6.68         0.0683
 6479     8       41.4         41.2         6.51         6.68         0.0752
 9968     8       32.3         32.3         7.35         6.68        -0.00058
4.761e+004     8       33.6         29.5         6.22         6.68           1.71
1.378e+005     8       25.5         29.5         7.64         6.68          -1.71


 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         -112.012501            7     238.025002
              A2         -111.401462           12     246.802924
              A3         -112.012501            7     238.025002
           fitted        -115.165987            4     238.331973
               R         -127.445484            2     258.890968


                    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               32.088         10       0.0003871
   Test 2              1.22208          5          0.9427
   Test 3              1.22208          5          0.9427
   Test 4              6.30697          3         0.09759

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 =        9486.87


BMDL computation failed.
```

E.2.49.8. *Figure for Unrestricted Model: Power, Constant Variance, Power Unrestricted*



E.2.49.9. *Output File for Unrestricted Model: Power, Constant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Pwr_CV_Unrest_BMR1_plasma_TT4.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Blood\Pwr_CV_Unrest_BMR1_plasma_TT4.plt
                                                 Fri Nov 20 12:31:11 2009
 ================================================================

 Tbl3, plasma TT4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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
```

```
                          alpha =      44.7333
                            rho =            0   Specified
                        control =         41.4
                          slope =      -1.4001
                          power =     0.189211


            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    -5.9e-009      -5e-011    -3.8e-010

    control    -5.9e-009            1        -0.78        -0.75

      slope      -5e-011        -0.78            1            1

      power    -3.8e-010        -0.75            1            1



                                  Parameter Estimates

                                                          95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
           alpha          46.4461          9.48077             27.8641              65.028
         control          41.4607          2.18095             37.1861             45.7352
           slope       -0.0241896        0.0653588            -0.15229            0.103911
           power         0.547925         0.223428            0.110013            0.985836



      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     8       40.9         41.5         6.79         6.82         -0.233
 3969     8       41.4         39.2         5.37         6.82          0.916
 6479     8       41.4         38.5         6.51         6.82           1.21
 9968     8       32.3         37.7         7.35         6.82          -2.24
4.761e+004     8       33.6         32.6         6.22         6.82          0.408
1.378e+005     8       25.5         25.6         7.64         6.82        -0.0527



 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         -112.012501           7     238.025002
              A2         -111.401462          12     246.802924
              A3         -112.012501           7     238.025002
           fitted         -116.119011           4     240.238023
               R         -127.445484           2     258.890968


                    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               32.088         10       0.0003871
   Test 2              1.22208          5          0.9427
   Test 3              1.22208          5          0.9427
   Test 4              8.21302          3         0.04181

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 = 29589.5


            BMDL = 5826.38
```

E.2.50. White et al. (1986): CH50

E.2.50.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance p-Value [a]	χ^2 Test Statistic	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	5	0.09	19.19	0.00	389.66	1.1E+04	6.9E+03	nonconstant variance, power restricted ≥1
exponential (M3)	5	0.09	19.19	0.00	389.66	1.1E+04	6.9E+03	nonconstant variance, power restricted ≥1

exponential (M4)	4	0.09	18.15	0.00	390.63	7.8E+03	2.9E+03	nonconstant variance, power restricted ≥1
exponential (M5)	4	0.09	18.15	0.00	390.63	7.8E+03	2.9E+03	nonconstant variance, power restricted ≥1
Hill [c]	**4**	**0.09**	**17.12**	**0.00**	**389.60**	**4.8E+03**	**8.3E+02**	**nonconstant variance, n restricted >1, bound hit**
Hill [d]	3	0.09	7.05	0.07	381.53	8.2E+01	7.6E+01	nonconstant variance, n unrestricted
linear	5	0.09	23.97	0.00	394.45	1.9E+04	1.4E+04	nonconstant variance
polynomial	5	0.09	23.97	0.00	394.45	1.9E+04	1.4E+04	nonconstant variance
power	5	0.09	23.97	0.00	394.45	1.9E+04	1.4E+04	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	5	0.09	19.89	0.00	388.58	9.6E+03	6.5E+03	constant variance, power restricted ≥1
exponential (M3)	5	0.09	19.89	0.00	388.58	9.6E+03	6.5E+03	constant variance, power restricted ≥1
exponential (M4)	4	0.09	18.80	0.00	389.48	6.5E+03	2.2E+03	constant variance, power restricted ≥1
exponential (M5)	4	0.09	18.80	0.00	389.48	6.5E+03	2.2E+03	constant variance, power restricted ≥1
Hill	4	0.09	17.39	0.00	388.07	3.3E+03	8.4E+02	constant variance, n restricted >1, bound hit
Hill	3	0.09	7.07	0.07	379.75	1.5E+02	6.3E+00	constant variance, n unrestricted
linear	5	0.09	24.48	0.00	393.16	1.8E+04	1.4E+04	constant variance
polynomial	5	0.09	24.48	0.00	393.16	1.8E+04	1.4E+04	constant variance
power	5	0.09	24.48	0.00	393.16	1.8E+04	1.4E+04	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

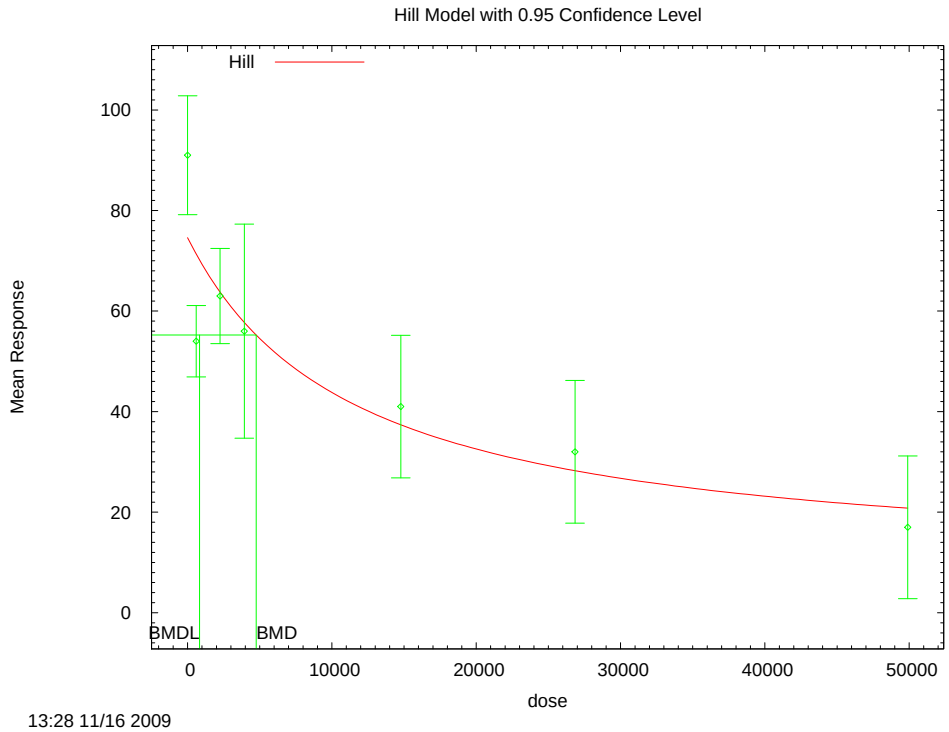
[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

1
2

E.2.50.2. *Figure for Selected Model: Hill, Nonconstant Variance, n Restricted >1, Bound Hit*



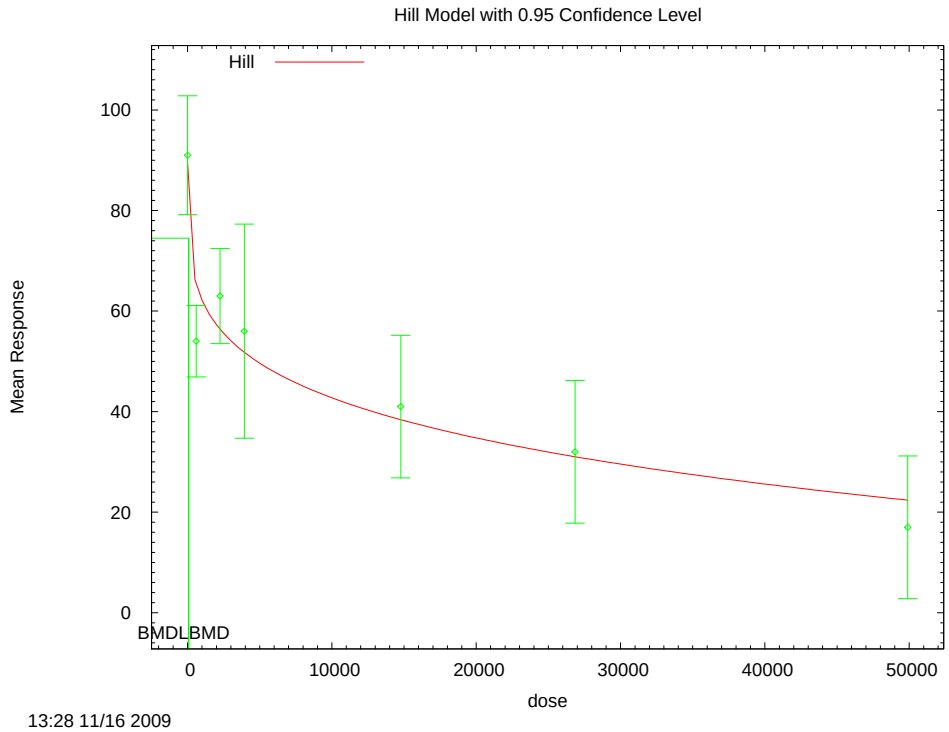
E.2.50.3. *Output File for Selected Model: Hill, Nonconstant Variance, n Restricted >1, Bound Hit*

```
 ========================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Hill_BMR1_CH50.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Hill_BMR1_CH50.plt
                                                  Mon Nov 16 13:28:23 2009
 ========================================================================

 [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 =       602.74


           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          1.66271             1.32215             7.83986
            rho         0.312931         0.431612           -0.533012             1.15887
      intercept          74.6365          6.33658              62.217              87.056
              v         -66.2095          14.7868            -95.1911            -37.2278
              n                1               NA
              k          11475.6          11747.8            -11549.6             34500.8

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
602.7     8         54         71.3         8.49         19.3          -2.54
 2250     8         63         63.8         11.3         18.9         -0.117
 3934     8         56         57.7         25.5         18.6         -0.263
1.477e+004     8         41         37.4           17         17.4          0.589
2.684e+004     8         32         28.3           17         16.7          0.636
4.99e+004     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        -189.800260            5     389.600520
                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              17.1231          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 =        4756.06

             BMDL =       825.553
```

E.2.50.4. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



13:28 11/16 2009

E.2.50.5. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_CH50.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_CH50.plt
                                                Mon Nov 16 13:28:23 2009
 ================================================================

 [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 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 =      602.74


          Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho    intercept            v            n            k

    lalpha            1           -1         0.16         0.19        -0.4       -0.013

       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       -0.011        -0.93

         n         -0.4          0.4        -0.58       -0.011            1        -0.36

         k       -0.013        0.011        0.015        -0.93        -0.36            1


                                Parameter Estimates

                                                                95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        lalpha          6.54258          2.08981           2.44663             10.6385
           rho        -0.246247         0.541898          -1.30835            0.815854
     intercept          89.6313          5.59369           78.6679             100.595
             v         -615.173          706.037          -1998.98             768.633
             n         0.246754        0.0587686           0.13157            0.361938
             k     2.44083e+008     1.35075e+009      -2.40334e+009        2.89151e+009


     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
602.7     8         54         65.2         8.49         15.8          -2.01
 2250     8         63         56.3         11.3           16           1.17
 3934     8         56         51.7         25.5         16.2          0.747
1.477e+004     8         41         38.3           17         16.8          0.453
2.684e+004     8         32         30.9           17         17.3          0.175
4.99e+004     8         17         22.3           17           18         -0.833


 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	-184.762700	6	381.525401
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	7.04802	3	0.07038

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 = 81.6596

BMDL = 75.5039

E.3. ADMINISTERED DOSE BMDS RESULTS

E.3.1. Amin et al. (2000): Saccharin Consumed, Female (0.25%)

E.3.1.1. *Summary Table of BMDS Modeling Results*

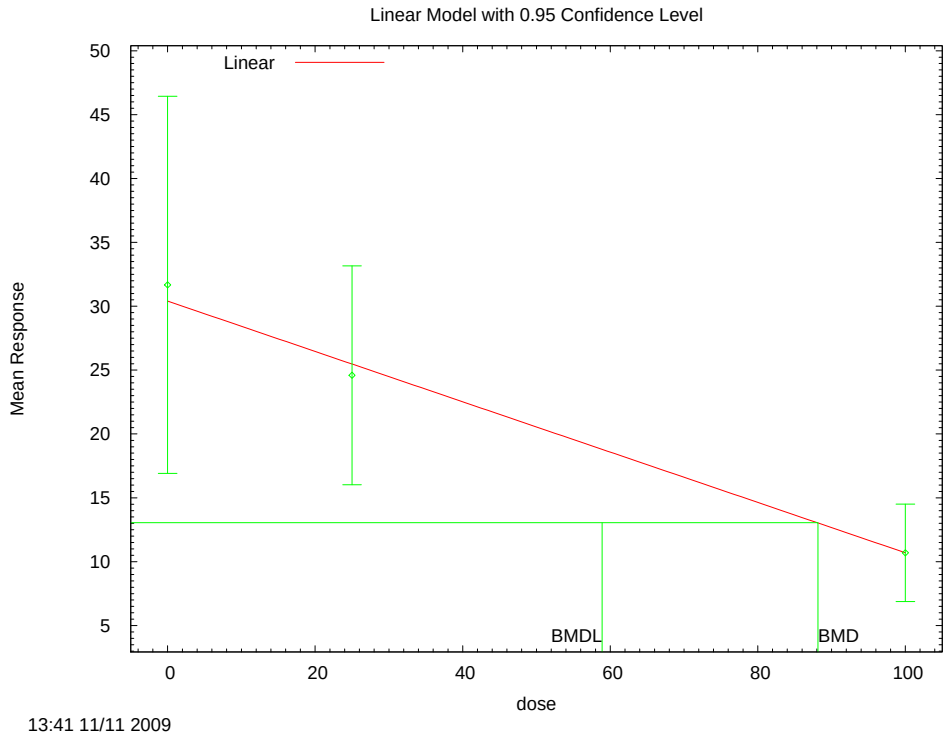
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
linear [c]	**1**	**0.00**	**0.84**	**0.36**	**179.70**	**8.8E+01**	**5.9E+01**	**nonconstant variance**
polynomial	1	0.00	0.84	0.36	179.70	8.8E+01	5.9E+01	nonconstant variance
power	1	0.00	0.84	0.36	179.70	8.8E+01	5.9E+01	nonconstant variance, power restricted ≥1, bound hit
linear	1	0.00	0.12	0.73	191.80	6.6E+01	4.3E+01	constant variance
polynomial	1	0.00	0.12	0.73	191.80	6.6E+01	4.3E+01	constant variance
power	1	0.00	0.12	0.73	191.80	6.6E+01	4.3E+01	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.1.2. *Figure for Selected Model: Linear, Nonconstant Variance*



E.3.1.3. *Output file for Selected Model: Linear, Nonconstant Variance*

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Linear_BMR1_25_s_c.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Linear_BMR1_25_s_c.plt
                                                Wed Nov 11 13:41:21 2009
 ================================================================

 Rel Male Thymus wt, Tbl 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
   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
```

E.3.2. Amin et al. (2000): Saccharin Consumed, Female (0.50%)

E.3.2.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
linear [c]	**1**	**<.0001**	**4.68**	**0.03**	**159.74**	**9.9E+01**	**6.4E+01**	**nonconstant variance**
polynomial	1	<.0001	4.68	0.03	159.74	9.9E+01	6.4E+01	nonconstant variance
power	1	<.0001	4.68	0.03	159.74	9.9E+01	6.4E+01	nonconstant variance, power restricted ≥1, bound hit
linear	1	<.0001	2.57	0.11	175.96	6.5E+01	4.3E+01	constant variance

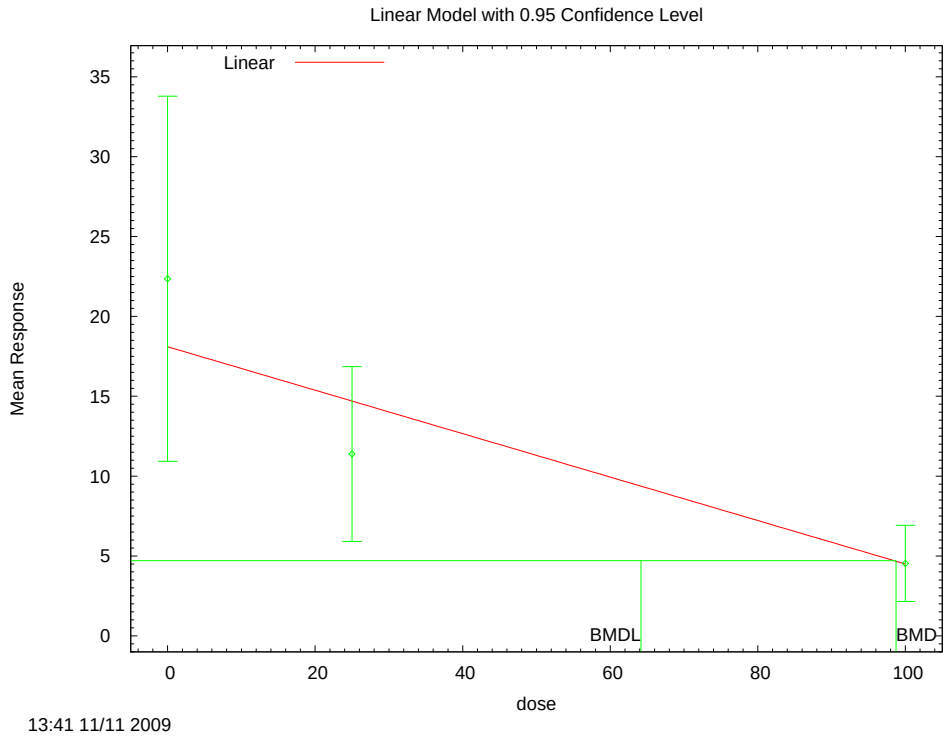
polynomial	1	<.0001	2.57	0.11	175.96	6.5E+01	4.3E+01	constant variance
power	1	<.0001	2.57	0.11	175.96	6.5E+01	4.3E+01	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] **Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix**

E.3.2.2. *Figure for Selected Model: Linear, Nonconstant Variance*



E.3.2.3. *Output File for Selected Model: Linear, Nonconstant Variance*

```
 ========================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Linear_BMR1_50_s_c.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Linear_BMR1_50_s_c.plt
                                                 Wed Nov 11 13:41:42 2009
 ========================================================================

 Rel Male Thymus wt, Tbl 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
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
```

E.3.3. Amin et al. (2000): Saccharin Preference Ratio, Female (0.25%)

E.3.3.1. *Summary Table of BMDS Modeling Results*

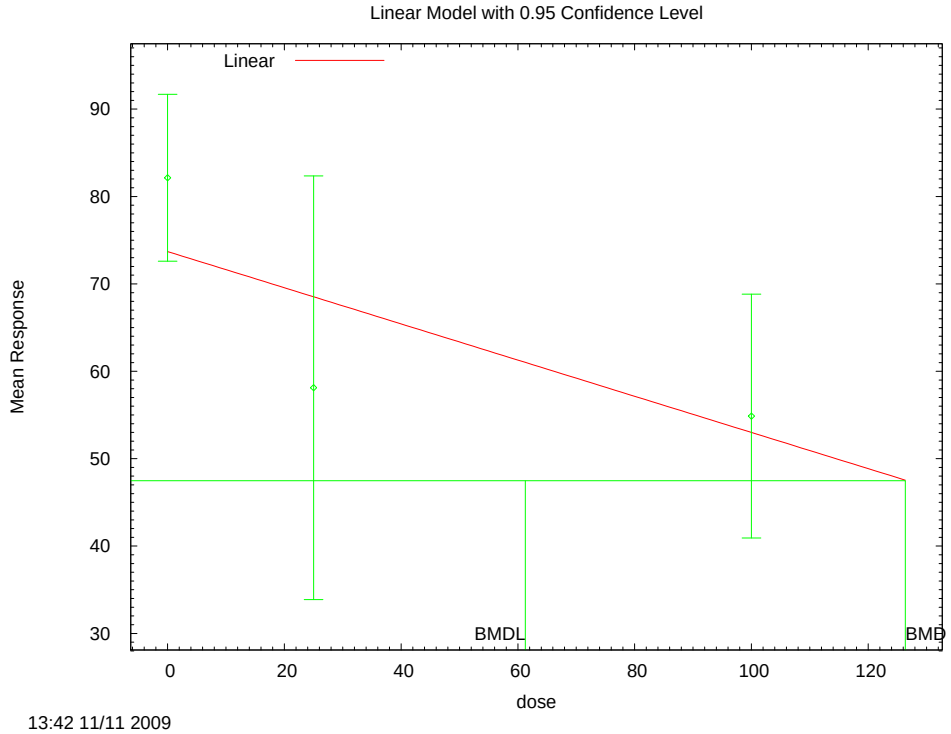
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
linear [c]	**1**	**0.01**	**9.80**	**0.00**	**228.09**	**1.3E+02**	**6.1E+01**	**nonconstant variance**
polynomial	1	0.01	9.80	0.00	228.09	1.3E+02	6.1E+01	nonconstant variance
power	1	0.01	9.80	0.00	228.09	1.3E+02	6.1E+01	nonconstant variance, power restricted ≥1, bound hit
linear	1	0.01	3.36	0.07	226.51	1.1E+02	6.1E+01	constant variance
polynomial	1	0.01	3.36	0.07	226.51	1.1E+02	6.1E+01	constant variance
power	1	0.01	3.36	0.07	226.51	1.1E+02	6.1E+01	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.3.2. *Figure for Selected Model: Linear, Nonconstant Variance*



E.3.3.3. *Output File for Selected Model: Linear, Nonconstant Variance*

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Linear_BMR1_25_s_p_f.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Linear_BMR1_25_s_p_f.plt
                                                Wed Nov 11 13:42:05 2009
 ================================================================

 Rel Male Thymus wt Tbl 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
   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
```

E.3.4. Amin et al. (2000): Saccharin Preference Ratio, Female (0.50%)

E.3.4.1. *Summary Table of BMDS Modeling Results*

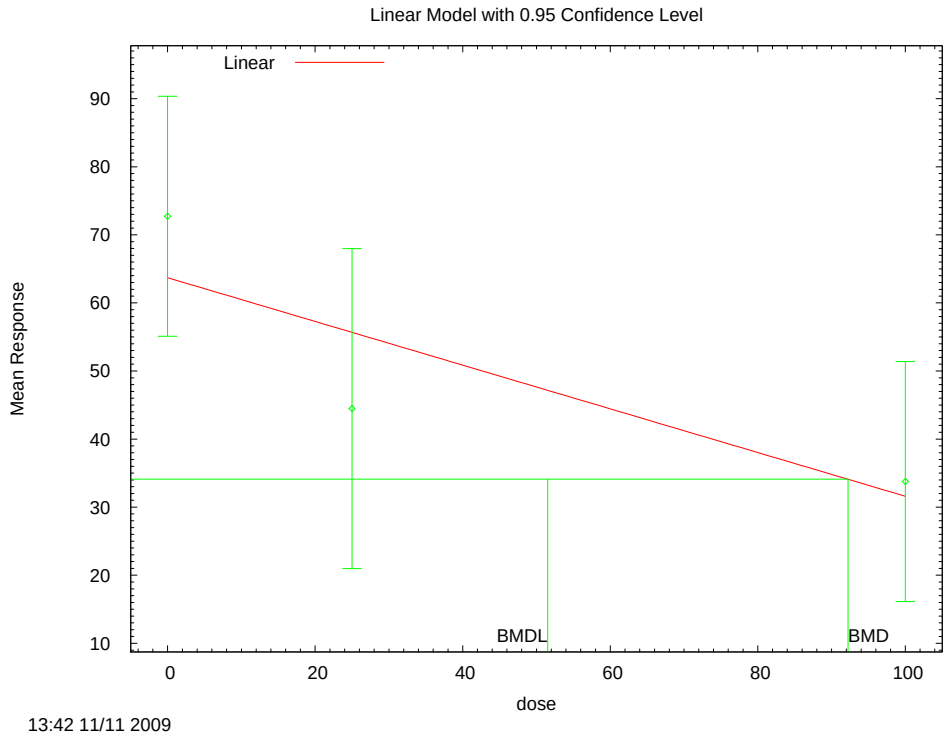
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
linear [c]	**1**	**0.56**	**2.60**	**0.11**	**236.57**	**9.2E+01**	**5.2E+01**	**nonconstant variance**
polynomial	1	0.56	2.60	0.11	236.57	9.2E+01	5.2E+01	nonconstant variance
power	1	0.56	2.60	0.11	236.57	9.2E+01	5.2E+01	nonconstant variance, power restricted ≥1, bound hit
linear	1	0.56	2.92	0.09	234.94	8.3E+01	5.1E+01	constant variance
polynomial	1	0.56	2.92	0.09	234.94	8.3E+01	5.1E+01	constant variance
power	1	0.56	2.92	0.09	234.94	8.3E+01	5.1E+01	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.4.2. *Figure for Selected Model: Linear, Nonconstant Variance*



E.3.4.3. *Output File for Selected Model: Linear, Nonconstant Variance*

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Linear_BMR1_50_s_p_f.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Linear_BMR1_50_s_p_f.plt
                                                Wed Nov 11 13:42:27 2009
 ================================================================

 Rel Male Thymus wt, Tbl 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
   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 =      6.63936
                             rho =            0
                          beta_0 =      64.1858
                          beta_1 =    -0.332668


            Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho       beta_0       beta_1

     lalpha            1           -1         0.11        -0.18

        rho           -1            1        -0.11         0.18

     beta_0         0.11        -0.11            1        -0.75

     beta_1        -0.18         0.18        -0.75            1


                                  Parameter Estimates

                                                        95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          lalpha          4.43902          3.53662           -2.49263             11.3707
             rho         0.562378         0.909867           -1.22093             2.34569
          beta_0          63.7204          7.49597            49.0286             78.4122
          beta_1        -0.320869         0.114882          -0.546034          -0.0957048


      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         63.7         24.6         29.6          0.962
   25    10       44.5         55.7         32.9         28.5          -1.24
  100    10       33.8         31.6         24.6         24.3          0.277


 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         -113.009921           4     234.019841
               A2         -112.428886           6     236.857773
               A3         -112.984528           5     235.969055
           fitted         -114.283840           4     236.567679
                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              1.11128          1          0.2918
   Test 4              2.59862          1           0.107

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.  Consider running a
homogeneous model

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 =        92.2435


             BMDL =        51.5208
```

E.3.5. Bell et al. (2007): Balano-Preputial Separation in Male Pups (10% Extra Risk)

E.3.5.1. *Summary Table of BMDS modeling results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	2	1.99	0.37	113.51	7.3E+00	4.7E+00	power restricted ≥1, bound hit
logistic	2	2.88	0.24	114.85	1.5E+01	1.1E+01	
log-logistic [b]	**2**	**1.57**	**0.46**	**112.95**	**5.2E+00**	**2.9E+00**	**slope restricted ≥1, bound hit**
log-logistic [c]	1	0.49	0.48	113.91	2.1E+00	1.4E-01	slope unrestricted

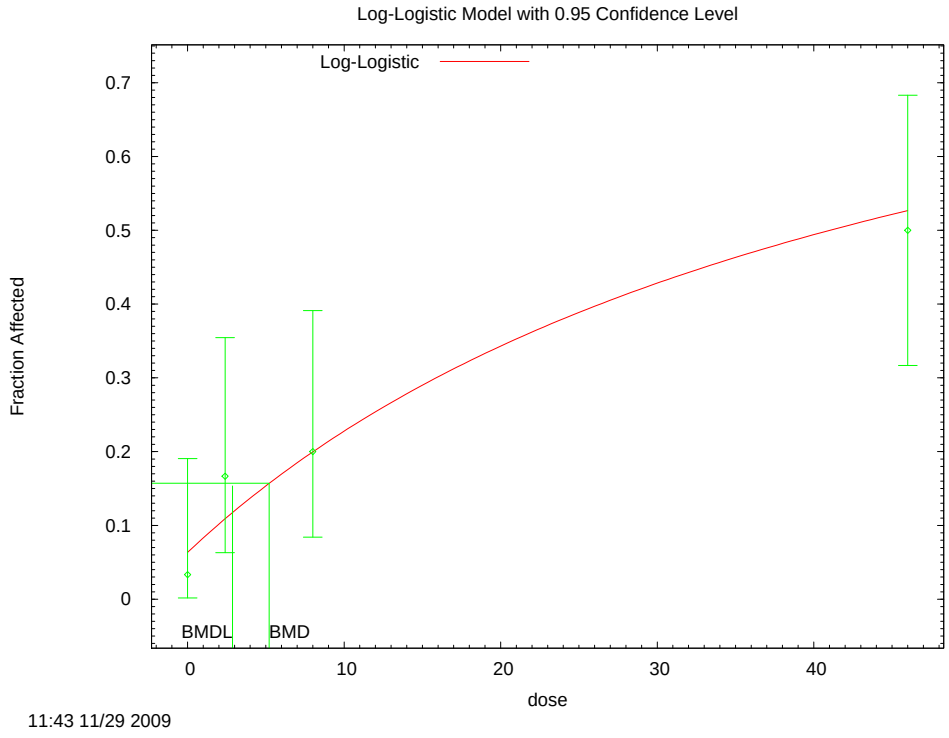
log-probit	1	0.60	0.44	114.02	2.2E+00	1.7E-01	slope restricted ≥1
multistage, 1-degree	2	1.99	0.37	113.51	7.3E+00	4.7E+00	betas restricted ≥0, bound hit
probit	2	2.79	0.25	114.72	1.4E+01	1.1E+01	
Weibull	2	1.99	0.37	113.51	7.3E+00	4.7E+00	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

[c] Alternate model also presented in this appendix

E.3.5.2. *Figure for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*



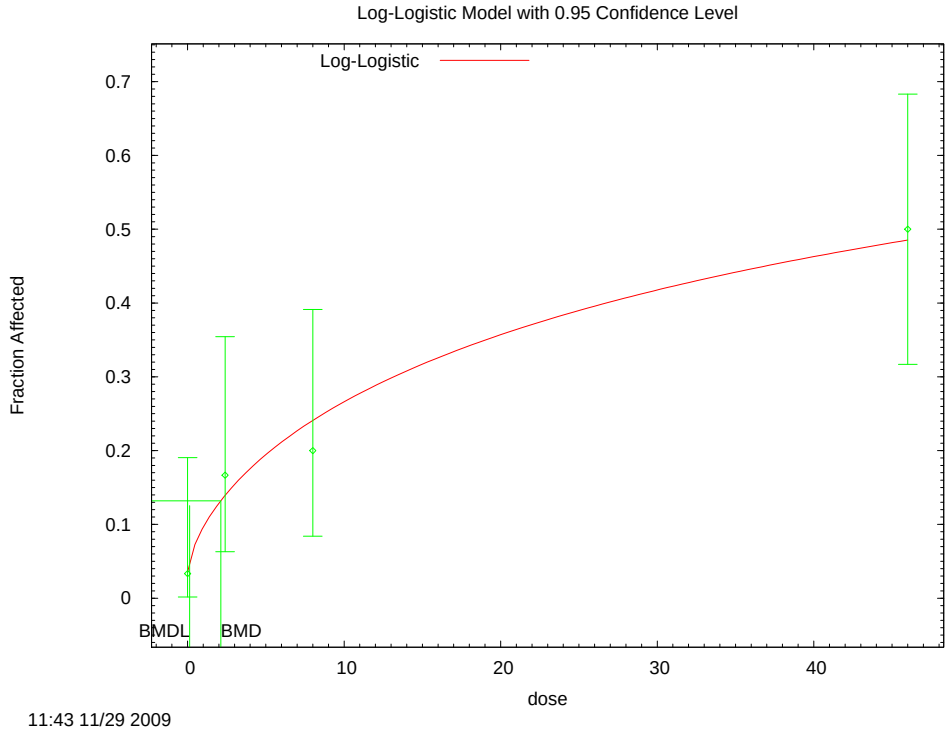
E.3.5.3. *Output File for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov29\LogLogistic_BMR2_BPS_d49.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov29\LogLogistic_BMR2_BPS_d49.plt
                                                 Sun Nov 29 11:43:52 2009
 ================================================================

 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
```

E.3.5.4. *Figure for Unrestricted Model: Log-Logistic, Slope Unrestricted*



E.3.5.5. *Output File for Unrestricted Model: Log-Logistic, Slope Unrestricted*

```
 ========================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov29\LogLogistic_Unrest_BMR2_BPS_d49.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov29\LogLogistic_Unrest_BMR2_BPS_d49.plt
                                                 Sun Nov 29 11:43:54 2009
 ========================================================================

 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 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 = -2.54947
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

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval 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

Dose	Est._Prob.	Expected	Observed	Size	Scaled 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
```

E.3.6. Bell et al. (2007): Balano-Preputial Separation in Male Pups (5% Extra Risk)

E.3.6.1. *Summary Table of BMDS Modeling Results*

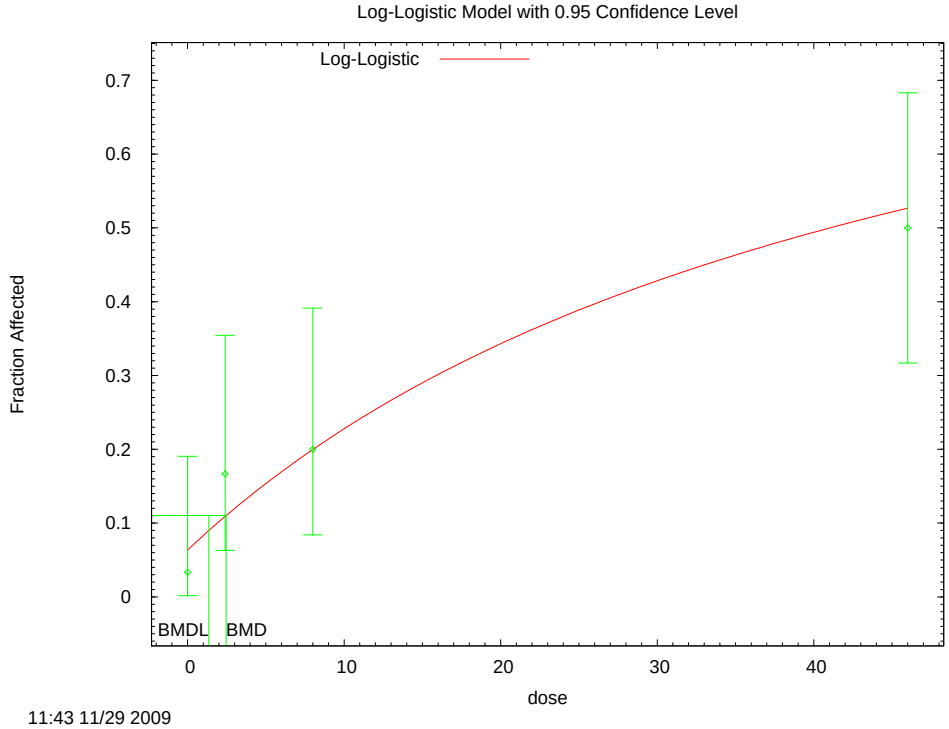
Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	2	1.99	0.37	113.51	3.6E+00	2.3E+00	power restricted ≥1, bound hit
logistic	2	2.88	0.24	114.85	8.4E+00	6.2E+00	
log-logistic [b]	**2**	**1.57**	**0.46**	**112.95**	**2.5E+00**	**1.4E+00**	**slope restricted ≥1, bound hit**
log-logistic [c]	1	0.49	0.48	113.91	7.0E-01	1.1E-02	slope unrestricted
log-probit	1	0.60	0.44	114.02	8.6E-01	2.1E-02	slope restricted ≥1
multistage, 1-degree	2	1.99	0.37	113.51	3.6E+00	2.3E+00	betas restricted ≥0, bound hit
probit	2	2.79	0.25	114.72	7.7E+00	5.7E+00	
Weibull	2	1.99	0.37	113.51	3.6E+00	2.3E+00	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

[c] Alternate model also presented in this appendix

E.3.6.2. *Figure for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*

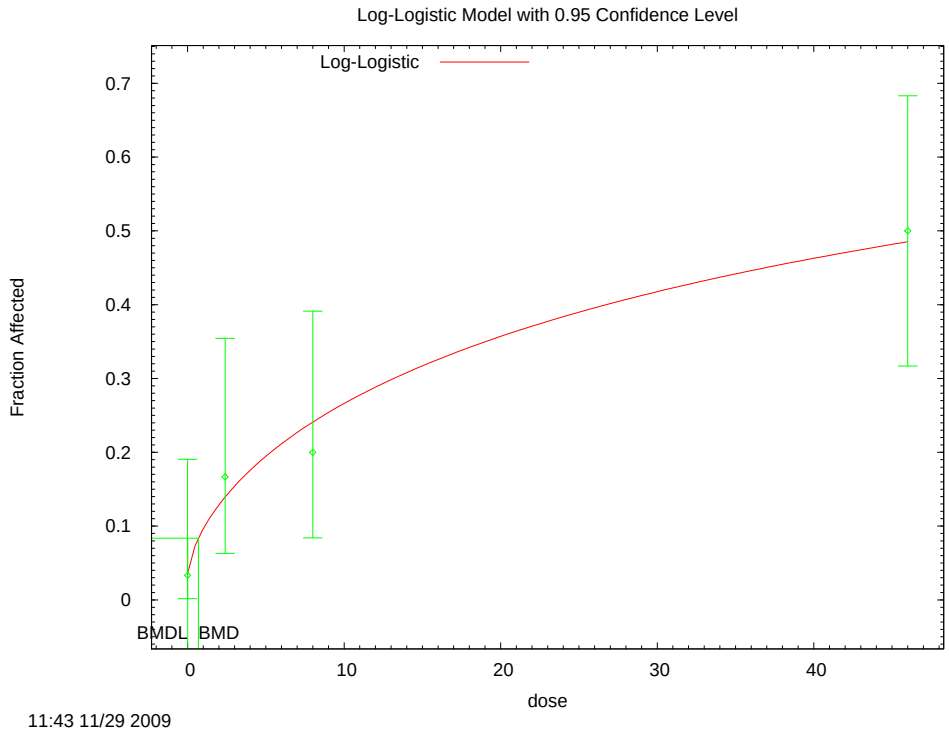


E.3.6.3. *Output File for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov29\LogLogistic_BMR1_BPS_d49.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov29\LogLogistic_BMR1_BPS_d49.plt
                                                Sun Nov 29 11:43:49 2009
 ================================================================

 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 =           0.05

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        2.46751

             BMDL =        1.35943
```

E.3.6.4. *Figure for Unrestricted Model: Log-Logistic, Slope Unrestricted*



E.3.6.5. *Output File for Unrestricted Model: Log-Logistic, Slope Unrestricted*

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov29\LogLogistic_Unrest_BMR1_BPS_d49.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov29\LogLogistic_Unrest_BMR1_BPS_d49.plt
                                                Sun Nov 29 11:43:53 2009
 ================================================================

 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 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 =     -2.54947
                          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 =           0.05

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.697474

            BMDL =      0.0111259
```

E.3.7. Cantoni et al. (1981): Urinary Copro-Porhyrins

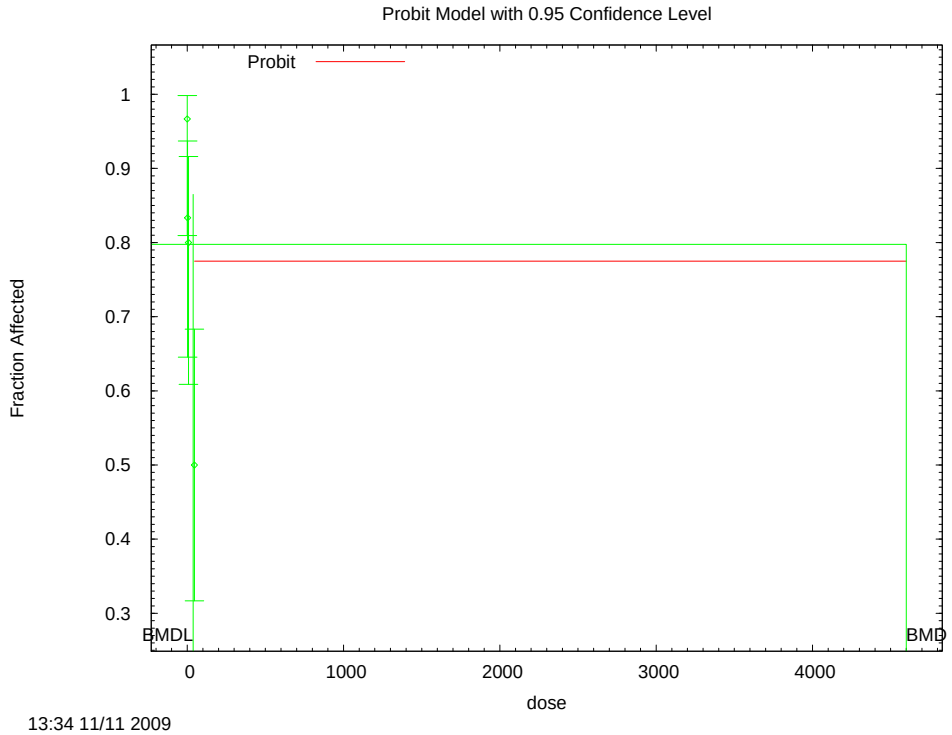
E.3.7.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
logistic	2	20.02	0.00	131.96	4.6E+03	3.8E+01	
log-logistic	2	20.02	0.00	131.96	8.0E+07	3.8E+01	slope restricted ≥1, bound hit
log-probit	2	20.02	0.00	131.96	4.6E+03	error	slope restricted ≥1
multistage, 2-degree	3	20.02	0.00	129.96	error	error	betas restricted ≥0, bound hit
probit [b]	**2**	**20.02**	**0.00**	**131.96**	**4.6E+03**	**3.8E+01**	

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

E.3.7.2. *Figure for Selected Model: Probit*



E.3.7.3. *Output File for Selected Model: Probit*

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Probit_BMR2_BPS_pnd49.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Probit_BMR2_BPS_pnd49.plt
                                              Wed Nov 11 13:34:24 2009
 ================================================================

 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 = 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 (and Specified) Parameter Values
                    background =            0   Specified
                     intercept =      1.29116
                         slope =   -0.0292594


          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        -0.64

     slope        -0.64            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
      intercept         0.755415         0.164576            0.432851             1.07798
          slope                0       0.00651162          -0.0127625           0.0127625


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -53.7077         4
    Fitted model        -63.9797         2        20.544      2      3.4588333e-005
   Reduced model        -63.9797         1        20.544      3       0.0001309

           AIC:         131.959
```

```
                                Goodness  of  Fit
                                                                  Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000     0.7750        23.250    29.000          30        2.514
    2.4000     0.7750        23.250    25.000          30        0.765
    8.0000     0.7750        23.250    24.000          30        0.328
   46.0000     0.7750        23.250    15.000          30       -3.607

 Chi^2 = 20.02     d.f. = 2        P-value = 0.0000

 Slope parameter essentially zero.  BMD set to 100 * max(Dose).


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =           4600

            BMDL =        38.2394
```

E.3.8. Cantoni et al. (1981): Urinary Porphyrins

E.3.8.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	<0.0001	19.41	<0.0001	58.75	1.2E+01	9.0E+00	nonconstant variance, power restricted ≥1
exponential (M3)	2	<0.0001	19.41	<0.0001	58.75	1.2E+01	9.0E+00	nonconstant variance, power restricted ≥1
exponential (M4)	1	<0.0001	21.80	<0.0001	63.14	2.2E-01	1.1E-01	nonconstant variance, power restricted ≥1
exponential (M5)	1	<0.0001	21.80	<0.0001	63.14	2.2E-01	1.1E-01	nonconstant variance, power restricted ≥1
Hill	0	<.0001	19.02	NA	62.36	9.4E+00	4.7E+00	nonconstant variance, n restricted >1
linear [c]	**2**	**<.0001**	**23.15**	**<.0001**	**62.49**	**7.7E-01**	**2.8E-01**	**nonconstant variance**
polynomial	1	<.0001	18.19	<.0001	59.53	6.3E+00	2.0E+00	nonconstant variance
power	2	<.0001	23.15	<.0001	62.49	7.7E-01	2.8E-01	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	2	<0.0001	0.05	0.98	108.89	7.0E+01	5.0E+01	constant variance, power restricted ≥1
exponential (M3)	2	<0.0001	0.05	0.98	108.89	7.0E+01	5.0E+01	constant variance, power restricted ≥1

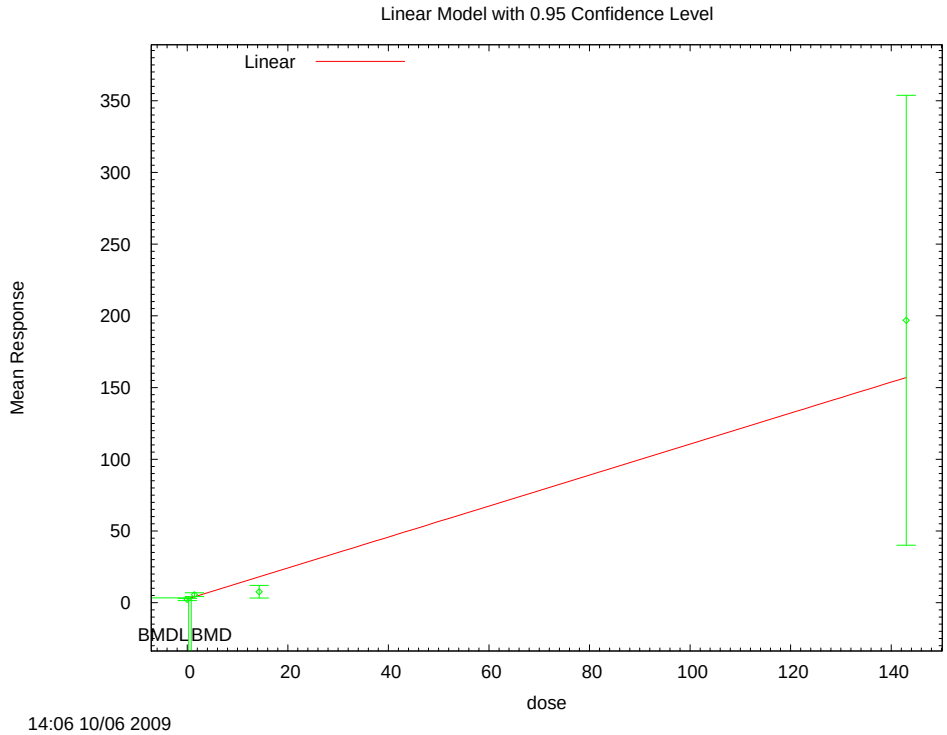
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M4)	1	<0.0001	0.86	0.35	111.70	1.8E+01	1.0E+01	constant variance, power restricted ≥1
exponential (M5)	0	<0.0001	0.04	N/A	112.88	4.2E+01	1.4E+01	constant variance, power restricted ≥1
Hill	0	<.0001	0.04	NA	112.88	4.2E+01	1.0E+01	constant variance, n restricted >1
linear	2	<.0001	0.85	0.66	109.69	1.8E+01	1.3E+01	constant variance
polynomial	1	<.0001	0.03	0.86	110.88	4.4E+01	1.1E+01	constant variance
power	1	<.0001	0.04	0.85	110.88	4.2E+01	1.4E+01	constant variance, power restricted ≥1

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.8.2. *Figure for Selected Model: Linear, Nonconstant Variance*



E.3.8.3. *Output File for Selected Model: Linear, Nonconstant Variance*

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\AniDose\Linear_BMR1_Urinary_porphyrins.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AniDose\Linear_BMR1_Urinary_porphyrins.plt
                                                Tue Oct 06 14:06:04 2009
 ================================================================

 Table 1, dose converted to ng per kg per day
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 =      6.68244
                          rho =            0
                       beta_0 =      -1.7736
                       beta_1 =      1.38238


          Asymptotic Correlation Matrix of Parameter Estimates

               lalpha          rho       beta_0       beta_1

    lalpha          1        -0.89        -0.27          0.2

       rho        -0.89            1         0.18       -0.082

    beta_0        -0.27         0.18            1        -0.31

    beta_1          0.2       -0.082        -0.31            1


                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -2.51366         0.863504            -4.2061           -0.821228
            rho          2.27539         0.314031             1.6599             2.89088
         beta_0          2.57041         0.376521            1.83244             3.30838
         beta_1          1.07729         0.234062           0.618541             1.53605


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     4       2.27         2.57         0.49        0.833         -0.721
```

```
1.43     4       5.55         4.11         0.85         1.42          2.03
14.3     3       7.62           18         1.79         7.61         -2.36
 143     3        197          157         63.1         89.4          0.78


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          -51.421748            5     112.843496
             A2          -15.312111            8      46.624223
             A3          -15.669627            6      43.339255
         fitted          -27.243469            4      62.486938
              R          -68.750584            2     141.501167


                   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              106.877          6          <.0001
  Test 2              72.2193          3          <.0001
  Test 3             0.715032          2          0.6994
  Test 4              23.1477          2          <.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 =      0.773193
            BMDL =      0.281589
```

E.3.9. Crofton et al. (2005): Serum T4

E.3.9.1. *Summary Table of BMDS Modeling Results*

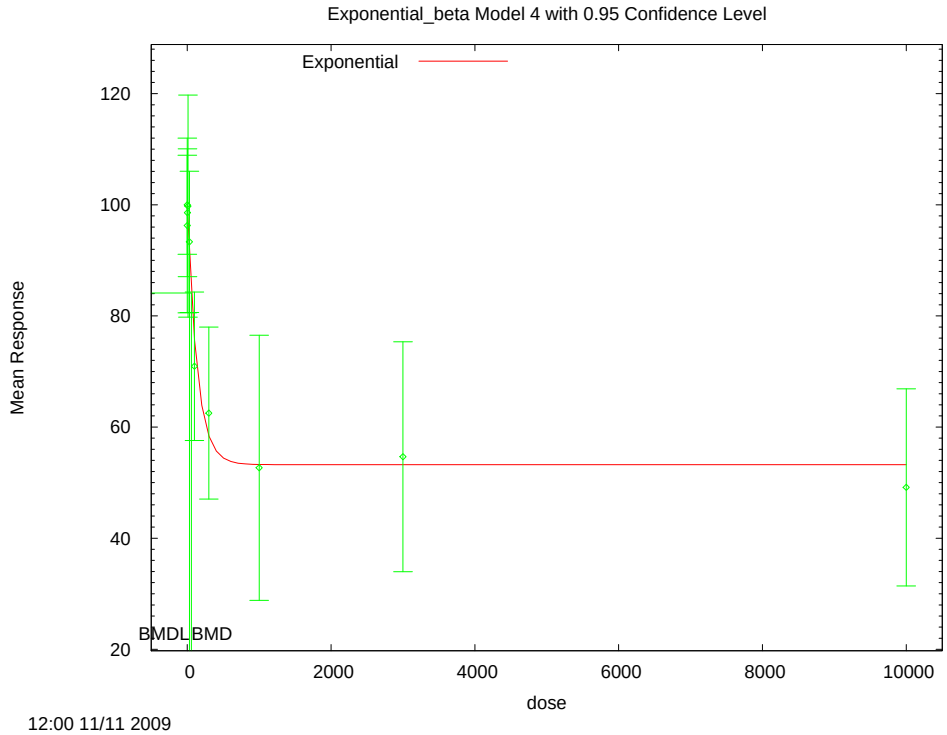
Model	Degrees of Freedom	Variance p-Value [a]	χ^2 Test Statistic	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	8	0.76	46.09	<0.0001	518.24	2.1E+03	1.2E+03	constant variance, power restricted ≥1
exponential (M3)	8	0.76	46.09	<0.0001	518.24	2.1E+03	1.2E+03	constant variance, power restricted ≥1
exponential (M4) [c]	**7**	**0.76**	**2.05**	**0.96**	**476.20**	**5.6E+01**	**3.0E+01**	**constant variance, power restricted ≥1**
exponential (M5)	7	0.76	2.05	0.96	476.20	5.6E+01	3.0E+01	constant variance, power restricted ≥1
Hill	6	0.76	1.28	0.97	477.43	5.6E+01	2.6E+01	constant variance, n restricted >1
linear	8	0.76	51.36	<.0001	523.52	4.2E+03	3.1E+03	constant variance
polynomial	8	0.76	51.36	<.0001	523.52	4.2E+03	3.1E+03	constant variance
power	8	0.76	51.36	<.0001	523.52	4.2E+03	3.1E+03	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.9.2. *Figure for Selected Model: Exponential (M4), Constant Variance, Power Restricted ≥1*



E.3.9.3. *Output File for selected Model: Exponential (M4), Constant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AD\ExpConstVar_BMR1_SerumT4.(d)
         Gnuplot Plotting File:
                                                  Wed Nov 11 12:00:47 2009
 ================================================================

 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
```

E.3.10. DeCaprio et al. (1986): Absolute Kidney Weight, Males

E.3.10.1. *Summary Table of BMDS Modeling Results*

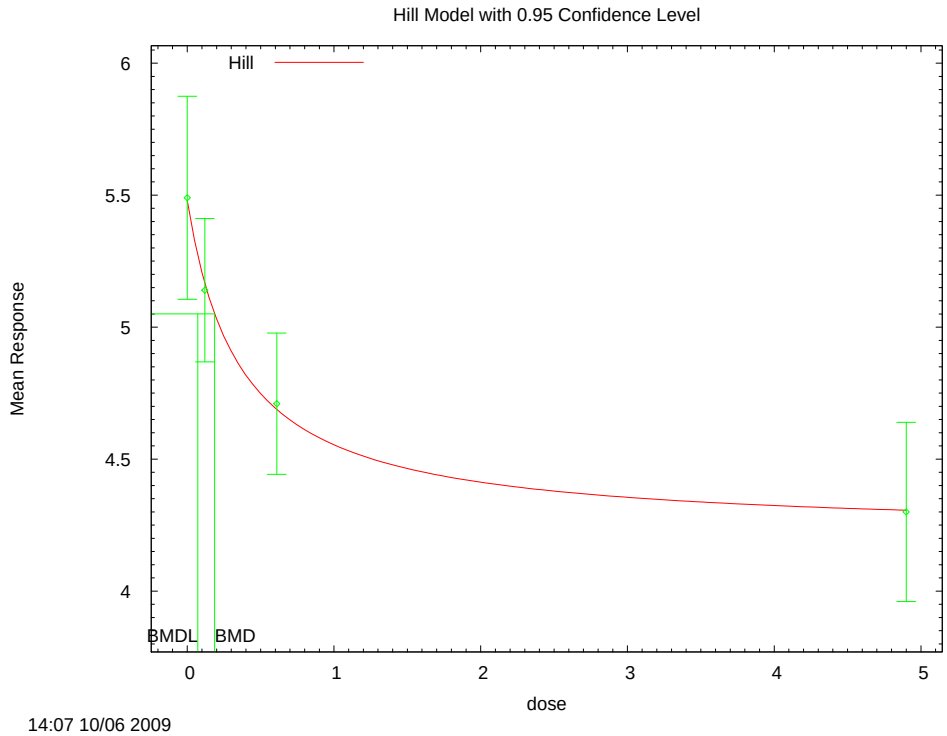
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.67	10.85	0.00	-9.87	2.6E+00	1.7E+00	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.67	10.85	0.00	-9.87	2.6E+00	1.7E+00	nonconstant variance, power restricted ≥1
exponential (M4)	1	0.67	0.54	0.46	-18.18	2.7E-01	1.2E-01	nonconstant variance, power restricted ≥1
exponential (M5)	1	0.67	0.54	0.46	-18.18	2.7E-01	1.2E-01	nonconstant variance, power restricted ≥1
Hill	1	0.67	0.08	0.78	-18.64	1.9E-01	7.3E-02	nonconstant variance, n restricted >1, bound hit
linear	2	0.67	11.14	0.00	-9.58	2.8E+00	1.9E+00	nonconstant variance
polynomial	1	0.67	1.10	0.29	-17.62	3.6E-01	2.3E-01	nonconstant variance
power	2	0.67	11.14	0.00	-9.58	2.8E+00	1.9E+00	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	2	0.67	10.90	0.00	-11.71	2.5E+00	1.7E+00	constant variance, power restricted ≥1
exponential (M3)	2	0.67	10.90	0.00	-11.71	2.5E+00	1.7E+00	constant variance, power restricted ≥1
exponential (M4)	1	0.67	0.52	0.47	-20.10	2.6E-01	1.2E-01	constant variance, power restricted ≥1
exponential (M5)	1	0.67	0.52	0.47	-20.10	2.6E-01	1.2E-01	constant variance, power restricted ≥1
Hill [c]	**1**	**0.67**	**0.07**	**0.79**	**-20.54**	**1.9E-01**	**7.1E-02**	**constant variance, n restricted >1, bound hit**
linear	2	0.67	11.21	0.00	-11.40	2.6E+00	1.9E+00	constant variance
polynomial	1	0.67	1.08	0.30	-19.53	3.5E-01	2.4E-01	constant variance
power	2	0.67	11.21	0.00	-11.40	2.6E+00	1.9E+00	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.10.2. *Figure for Selected Model: Hill, Constant Variance, n Restricted >1, Bound Hit*



E.3.10.3. *Output File for Selected Model: Hill, Constant Variance, n Restricted >1, Bound Hit*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AniDose\HillConstVar_BMR1_abs_male_kidney_wt.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AniDose\HillConstVar_BMR1_abs_male_kidney_wt.plt
                                                Tue Oct 06 14:07:06 2009
 ================================================================

 Abs Male Kidney wt, Tbl 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =     0.202865
                              rho =            0   Specified
                        intercept =         5.49
                                v =        -1.19
                                n =      1.12255
                                k =     0.399186


            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    -1.7e-009     4.6e-009      -2e-009

     intercept    -1.7e-009            1        -0.49        -0.54

             v     4.6e-009        -0.49            1        -0.27

             k      -2e-009        -0.54        -0.27            1



                                  Parameter Estimates

                                                          95.0% Wald Confidence Interval
           Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
              alpha         0.183391        0.0405044            0.104004            0.262778
          intercept          5.47882         0.130251             5.22353              5.7341
                  v         -1.25656         0.197258            -1.64318           -0.869946
                  n                1               NA
                  k         0.361009         0.220645          -0.0714485            0.793466

    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       5.49         5.48        0.538        0.428         0.0826
     0.12    10       5.14         5.17        0.379        0.428         -0.187
     0.61    11       4.71         4.69        0.398        0.428          0.159
      4.9    10        4.3         4.31        0.474        0.428        -0.0626



     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           14.306322            5     -18.612644
             A2           15.093716            8     -14.187432
             A3           14.306322            5     -18.612644
          fitted          14.270730            4     -20.541459
               R          -0.636909            2       5.273819


                    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              31.4613          6          <.0001
   Test 2              1.57479          3          0.6651
   Test 3              1.57479          3          0.6651
   Test 4            0.0711848          1          0.7896

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 =       0.186641

            BMDL =     0.0714793
```

E.3.11. DeCaprio et al. (1986): Absolute Thymus Weight, Males

E.3.11.1. *Summary Table of BMDS Modeling Results*

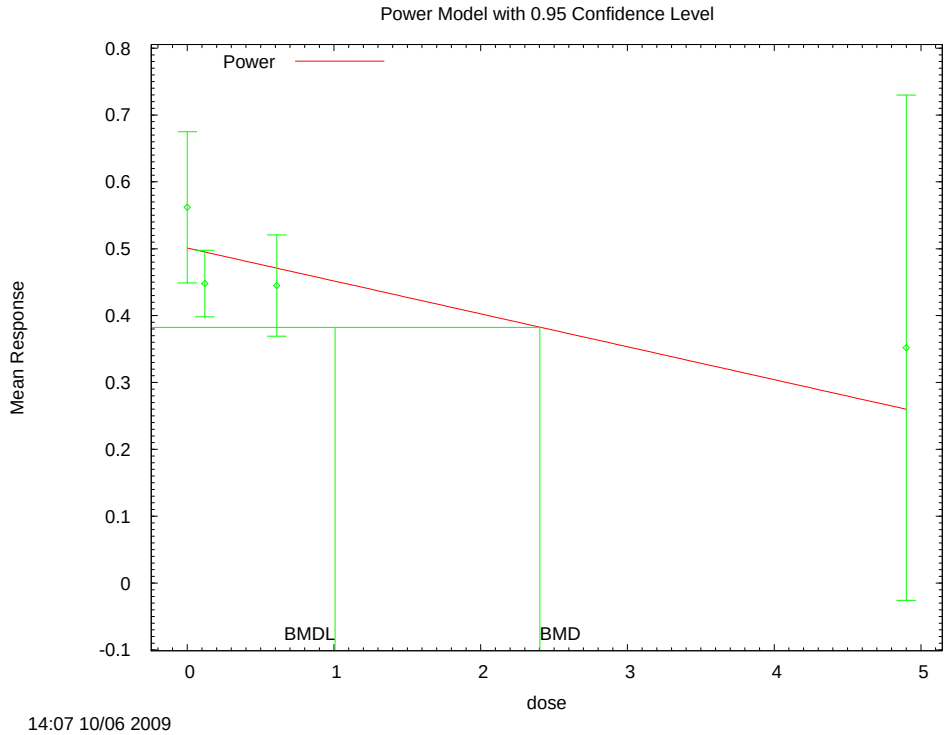
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	<0.0001	0.74	0.69	-93.74	1.8E+00	4.8E-01	nonconstant variance, power restricted ≥1
exponential (M3)	1	<0.0001	0.70	0.40	-91.78	2.4E+00	4.8E-01	nonconstant variance, power restricted ≥1
exponential (M4)	2	<0.0001	0.74	0.69	-93.74	1.8E+00	4.4E-01	nonconstant variance, power restricted ≥1
exponential (M5)	0	<0.0001	0.70	N/A	-89.78	2.4E+00	4.8E-01	nonconstant variance, power restricted ≥1
Hill	0	<.0001	0.70	NA	-89.78	8.4E-01	error	nonconstant variance, n restricted >1
linear	2	<.0001	0.69	0.71	-93.79	2.4E+00	error	nonconstant variance
polynomial	1	<.0001	0.69	0.41	-91.79	2.4E+00	error	nonconstant variance
power [c]	**2**	**<.0001**	**0.69**	**0.71**	**-93.79**	**2.4E+00**	**1.0E+00**	**nonconstant variance, power restricted ≥1, bound hit**
exponential (M2)	2	<0.0001	1.01	0.60	-60.51	1.1E+01	3.7E+00	constant variance, power restricted ≥1
exponential (M3)	2	<0.0001	1.01	0.60	-60.51	1.1E+01	3.7E+00	constant variance, power restricted ≥1
exponential (M4)	1	<0.0001	0.60	0.44	-58.92	error	error	constant variance, power restricted ≥1
exponential (M5)	1	<0.0001	0.60	0.44	-58.92	error	error	constant variance, power restricted ≥1
Hill	1	<.0001	0.40	0.53	-59.12	error	error	constant variance, n restricted >1, bound hit
linear	2	<.0001	1.04	0.59	-60.48	9.0E+00	4.2E+00	constant variance
polynomial	1	<.0001	0.67	0.41	-58.85	error	5.8E+00	constant variance
power	2	<.0001	1.04	0.59	-60.48	9.0E+00	4.2E+00	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.11.2. *Figure for Selected Model: Power, Nonconstant Variance, Power Restricted ≥1, Bound Hit*



E.3.11.3. *Output File for Selected Model: Power, Nonconstant Variance, Power Restricted ≥1, Bound Hit*

```
 ========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\AniDose\Pwr_BMR1_abs_thymus_wt.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AniDose\Pwr_BMR1_abs_thymus_wt.plt
                                                  Tue Oct 06 14:07:51 2009
 ========================================================================

 Abs Thymus wt, Tbl 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 =     -2.54423
                            rho =            0
                        control =        0.562
                          slope =    -0.216619
                          power =    -0.019526


           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         0.39        -0.97

       rho         0.99            1         0.33        -0.98

   control         0.39         0.33            1         -0.4

     slope        -0.97        -0.98         -0.4            1


                                 Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -7.29904          2.85129           -12.8875            -1.71062
            rho         -4.37824          3.97762           -12.1742             3.41775
        control         0.500643        0.0242054           0.453202            0.548085
          slope       -0.0492183        0.0335618          -0.114998           0.0165617
          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      0.562        0.501        0.158        0.118           1.64
 0.12    10      0.448        0.495       0.0696        0.121          -1.22
 0.61    11      0.445        0.471        0.113        0.135         -0.628
  4.9    10      0.352        0.259        0.528        0.498          0.587


 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           33.761192            5     -57.522384
             A2           57.094821            8     -98.189643
             A3           51.239109            6     -90.478218
         fitted           50.896393            4     -93.792785
              R           32.253943            2     -60.507885


                    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              49.6818          6          <.0001
   Test 2              46.6673          3          <.0001
   Test 3              11.7114          2        0.002863
   Test 4             0.685433          2          0.7098

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 =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

              BMD = 2.40256


             BMDL = 1.00746
```

E.3.12. DeCaprio et al. (1986): Body Weight, Females

E.3.12.1. *Summary Table of BMDS Modeling Results*

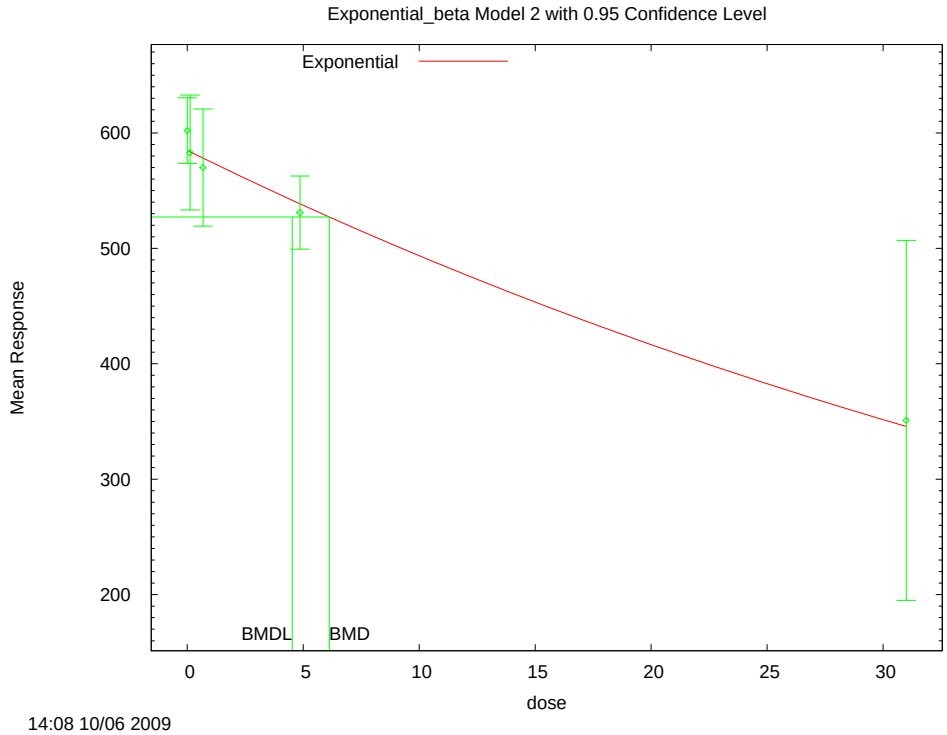
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	3	0.10	1.49	0.68	380.09	5.5E+00	3.6E+00	nonconstant variance, power restricted ≥1
exponential (M3)	3	0.10	1.49	0.68	380.09	5.5E+00	3.6E+00	nonconstant variance, power restricted ≥1
exponential (M4)	2	0.10	1.27	0.53	381.87	4.5E+00	2.4E+00	nonconstant variance, power restricted ≥1
exponential (M5)	2	0.10	1.27	0.53	381.87	4.5E+00	2.4E+00	nonconstant variance, power restricted ≥1
Hill	2	0.10	1.26	0.53	381.86	4.5E+00	error	nonconstant variance, n restricted >1, bound hit
linear	3	0.10	2.06	0.56	380.66	6.9E+00	4.7E+00	nonconstant variance
polynomial	2	0.10	1.28	0.53	381.88	4.6E+00	2.6E+00	nonconstant variance
power	3	0.10	2.06	0.56	380.66	6.9E+00	4.7E+00	nonconstant variance, power restricted ≥1, bound hit
exponential (M2) [c]	**3**	**0.10**	**1.11**	**0.78**	**379.55**	**6.1E+00**	**4.5E+00**	**constant variance, power restricted ≥1**
exponential (M3)	3	0.10	1.11	0.78	379.55	6.1E+00	4.5E+00	constant variance, power restricted ≥1
exponential (M4)	2	0.10	0.75	0.69	381.19	4.7E+00	2.6E+00	constant variance, power restricted ≥1
exponential (M5)	2	0.10	0.75	0.69	381.19	4.7E+00	2.6E+00	constant variance, power restricted ≥1
Hill	2	0.10	0.74	0.69	381.18	4.7E+00	2.4E+00	constant variance, n restricted >1, bound hit
linear	3	0.10	1.73	0.63	380.17	7.6E+00	5.9E+00	constant variance
polynomial	2	0.10	0.76	0.68	381.20	4.7E+00	2.7E+00	constant variance
power	3	0.10	1.73	0.63	380.17	7.6E+00	5.9E+00	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.12.2. *Figure for Selected Model: Exponential (M2), Constant Variance, Power Restricted ≥1*



E.3.12.3. *Output File for Selected Model: Exponential (M2), Constant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AniDose\ExpConstVar_BMR1_fem_BW.(d)
         Gnuplot Plotting File:
                                                  Tue Oct 06 14:08:53 2009
 ================================================================

 Female BW Tbl 1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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              8.08396
                      rho(S)                 0
                        a                632.1
                        b            0.0928666
                        c             0.528849
                        d                    1

  (S) = Specified


                   Parameter Estimates

                 Variable          Model 2
                 --------          -------
                  lnalpha           8.10223
                      rho                 0
                        a           588.488
                        b         0.0403005
                        c          0.434663
                        d                 1


          Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      8          602        33.94
   0.12     10          583        69.57
   0.68      9          570           66
   4.86     10          531        44.27
     31      4          351           98


                Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         584.9        57.71            0.839
   0.12         583.7        57.71          -0.0379
   0.68         578.2        57.71          -0.4248
   4.86         538.6        57.71          -0.4161
     31         345.7        57.71           0.1845


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       -186.2212           6      384.4424
                       A2       -182.3775          10       384.755
                       A3       -186.2212           6      384.4424
                        R       -204.9225           2      413.8449
                        2       -186.7751           3      379.5501


Additive constant for all log-likelihoods =     -37.68.  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                        45.09           8            < 0.0001
  Test 2                        7.687           4              0.1037
  Test 3                        7.687           4              0.1037
  Test 4                        1.108           3              0.7752


  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 = 1.000000

         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      6.12391

              BMDL =      4.52632
```

E.3.13. DeCaprio et al. (1986): Body Weight, Males

E.3.13.1. *Summary Table of BMDS Modeling Results*

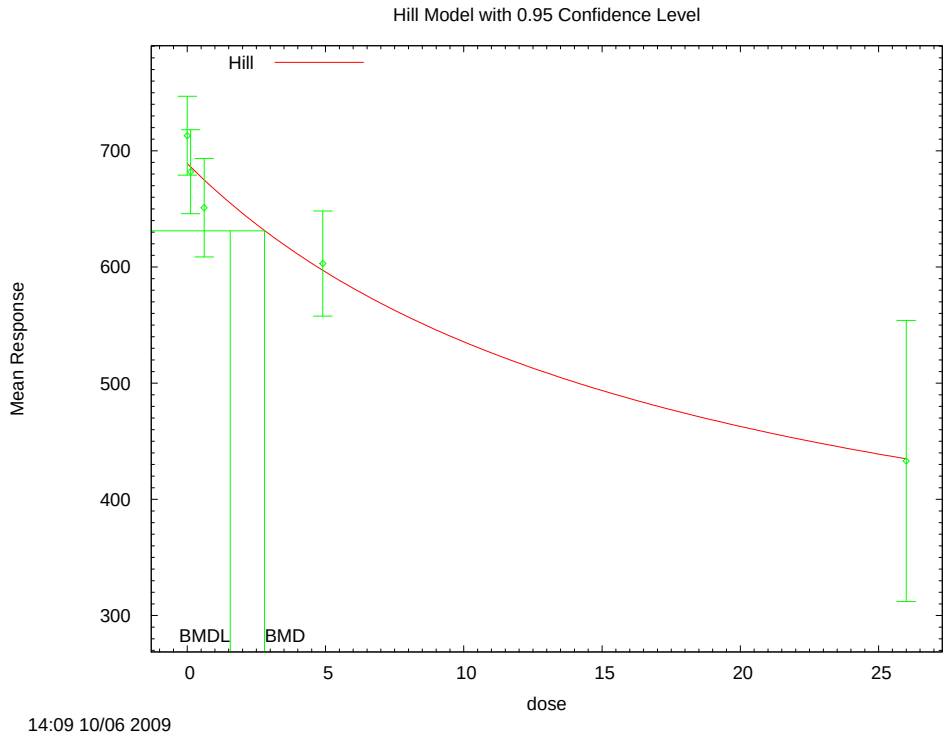
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	3	0.79	6.75	0.08	419.55	4.5E+00	2.9E+00	nonconstant variance, power restricted ≥1
exponential (M3)	3	0.79	6.75	0.08	419.55	4.5E+00	2.9E+00	nonconstant variance, power restricted ≥1
exponential (M4)	2	0.79	4.68	0.10	419.49	2.8E+00	1.5E+00	nonconstant variance, power restricted ≥1
exponential (M5)	2	0.79	4.68	0.10	419.49	2.8E+00	1.5E+00	nonconstant variance, power restricted ≥1
Hill	2	0.79	4.56	0.10	419.36	2.6E+00	error	nonconstant variance, n restricted >1, bound hit
linear	3	0.79	8.23	0.04	421.04	5.8E+00	3.9E+00	nonconstant variance
polynomial	2	0.79	4.82	0.09	419.63	2.9E+00	1.8E+00	nonconstant variance
power	3	0.79	8.23	0.04	421.04	5.8E+00	3.9E+00	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	3	0.79	6.14	0.11	417.87	4.8E+00	3.7E+00	constant variance, power restricted ≥1
exponential (M3)	3	0.79	6.14	0.11	417.87	4.8E+00	3.7E+00	constant variance, power restricted ≥1
exponential (M4)	2	0.79	4.08	0.13	417.81	2.9E+00	1.8E+00	constant variance, power restricted ≥1
exponential (M5)	2	0.79	4.08	0.13	417.81	2.9E+00	1.8E+00	constant variance, power restricted ≥1
Hill [c]	**2**	**0.79**	**3.98**	**0.14**	**417.70**	**2.8E+00**	**1.6E+00**	**constant variance, n restricted >1, bound hit**
linear	3	0.79	7.56	0.06	419.29	6.1E+00	4.8E+00	constant variance
polynomial	2	0.79	4.20	0.12	417.93	3.1E+00	2.0E+00	constant variance
power	3	0.79	7.56	0.06	419.29	6.1E+00	4.8E+00	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.13.2. *Figure for Selected Model: Hill, Constant Variance, n Restricted >1, Bound Hit*



E.3.13.3. *Output File for Selected Model: Hill, Constant Variance, n Restricted >1, Bound Hit*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AniDose\HillConstVar_BMR1_male_BW.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AniDose\HillConstVar_BMR1_male_BW.plt
                                                Tue Oct 06 14:09:41 2009
 ================================================================

 Male BW Tbl 1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =       3408.2
                              rho =            0   Specified
                        intercept =          713
                                v =         -280
                                n =       0.5774
                                k =      8.62353


            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     1.1e-008     5.5e-008    -5.8e-008

    intercept     1.1e-008            1         0.27        -0.46

            v     5.5e-008         0.27            1        -0.94

            k    -5.8e-008        -0.46        -0.94            1



                                  Parameter Estimates

                                                          95.0% Wald Confidence Interval
          Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
             alpha          3309.29          697.66             1941.9             4676.68
         intercept          688.613          11.4849             666.103             711.123
                 v         -430.869          146.654            -718.305            -143.432
                 n                1               NA
                 k          18.1326          12.6279            -6.61762             42.8828

   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        713          689         47.4         57.5           1.34
    0.12    10        682          686         50.6         57.5         -0.208
    0.61    11        651          675           63         57.5          -1.36
     4.9    10        603          597         63.2         57.5          0.333
      26     4        433          435           76         57.5        -0.0617


    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         -202.863522            6     417.727044
             A2         -202.022697           10     424.045393
             A3         -202.863522            6     417.727044
          fitted        -204.851020            4     417.702041
               R        -226.717147            2     457.434293


                    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              49.3889          8          <.0001
   Test 2              1.68165          4           0.794
   Test 3              1.68165          4           0.794
   Test 4                3.975          2           0.137

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 =        2.79396

            BMDL =       1.55261
```

E.3.14. DeCaprio et al. (1986): Relative Brain Weight, Males

E.3.14.1. *Summary Table of BMDS Modeling Results*

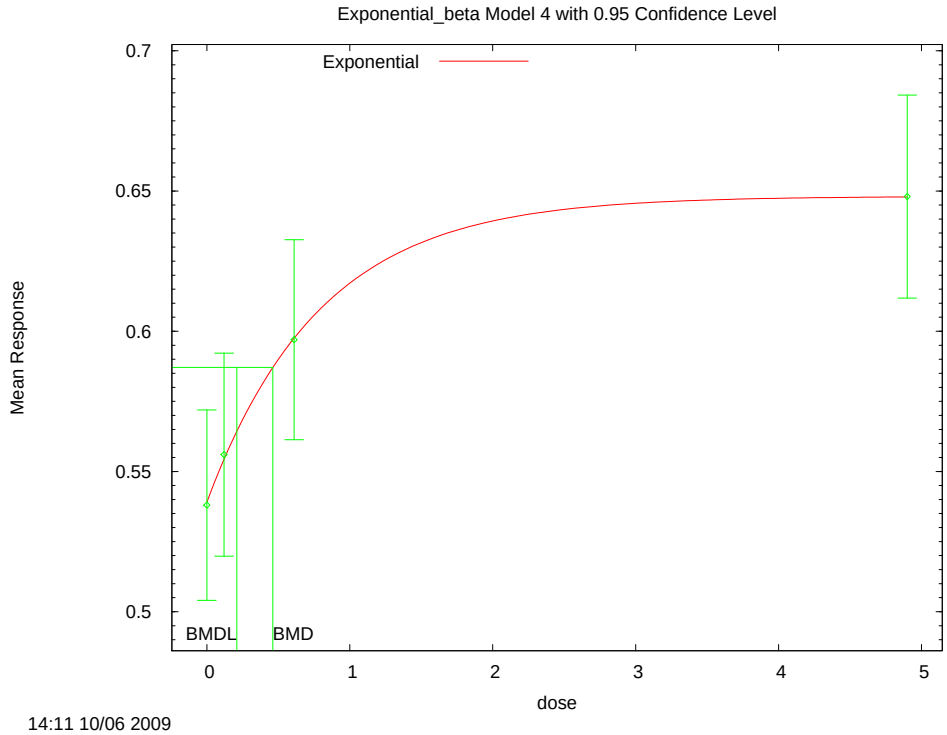
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.99	5.25	0.07	-194.78	2.9E+00	2.0E+00	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.99	5.25	0.07	-194.78	2.9E+00	2.0E+00	nonconstant variance, power restricted ≥1
exponential (M4)	1	0.99	0.02	0.89	-198.01	4.4E-01	1.8E-01	nonconstant variance, power restricted ≥1
exponential (M5)	1	0.99	0.02	0.89	-198.01	4.4E-01	1.8E-01	nonconstant variance, power restricted ≥1
Hill	0	0.99	0.00	NA	-196.03	4.1E-01	1.3E-01	nonconstant variance, n restricted >1
linear	2	0.99	5.09	0.08	-194.93	2.8E+00	1.9E+00	nonconstant variance
polynomial	1	0.99	0.08	0.78	-197.95	4.9E-01	2.7E-01	nonconstant variance
power	2	0.99	5.09	0.08	-194.93	2.8E+00	1.9E+00	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	2	0.99	5.27	0.07	-196.72	2.8E+00	2.1E+00	constant variance, power restricted ≥1
exponential (M3)	2	0.99	5.27	0.07	-196.72	2.8E+00	2.1E+00	constant variance, power restricted ≥1
exponential (M4) [c]	**1**	**0.99**	**0.02**	**0.89**	**-199.97**	**4.6E-01**	**2.1E-01**	**constant variance, power restricted ≥1**
exponential (M5)	1	0.99	0.02	0.89	-199.97	4.6E-01	2.1E-01	constant variance, power restricted ≥1
Hill	0	0.99	0.00	NA	-197.99	4.3E-01	1.5E-01	constant variance, n restricted >1
linear	2	0.99	5.10	0.08	-196.88	2.7E+00	1.9E+00	constant variance
polynomial	1	0.99	0.08	0.78	-199.91	5.0E-01	3.0E-01	constant variance
power	2	0.99	5.10	0.08	-196.88	2.7E+00	1.9E+00	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.14.2. *Figure for Selected Model: Exponential (M4), Constant Variance, Power Restricted ≥1*



E.3.14.3. *Output File for Selected Model: Exponential (M4), Constant Variance, Power Restricted ≥1*

```
 ***********************************************************************
          Exponential Model. (Version: 1.5;  Date: 4/23/2009)
          Input Data File: C:\USEPA\BMDS21\AniDose\ExpConstVar_BMR1_rel_male_brain_wt.(d)
          Gnuplot Plotting File:
                                                    Tue Oct 06 14:11:05 2009
 ***********************************************************************

 Rel Male Brain wt, Tbl 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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             -6.07283
                      rho(S)                 0
                        a              0.5111
                        b             0.351325
                        c              1.33125
                        d                    1

  (S) = Specified


                   Parameter Estimates

                 Variable          Model 4
                 --------          -------
                  lnalpha          -6.07239
                      rho                0
                        a          0.53911
                        b          1.25838
                        c          1.20224
                        d                1


          Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0     10        0.538      0.04743
   0.12     10        0.556       0.0506
   0.61     11        0.597      0.05307
    4.9     10        0.648       0.0506


                Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0        0.5391      0.04802          -0.0731
   0.12        0.5544      0.04802            0.106
   0.61        0.5975      0.04802         -0.03703
    4.9        0.6479      0.04802         0.005972


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        103.9931            5     -197.9862
                       A2        104.0646            8     -192.1293
                       A3        103.9931            5     -197.9862
                        R         92.4089            2     -180.8178
                        4        103.9841            4     -199.9682


Additive constant for all log-likelihoods =     -37.68.  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                         23.31           6           0.0006986
  Test 2                        0.1431           3              0.9862
  Test 3                        0.1431           3              0.9862
 Test 6a                       0.01798           1              0.8933


  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 =     0.461347

              BMDL =     0.209454
```

E.3.15. DeCaprio et al. (1986): Relative Liver Weight, Females

E.3.15.1. *Summary Table of BMDS Modeling Results*

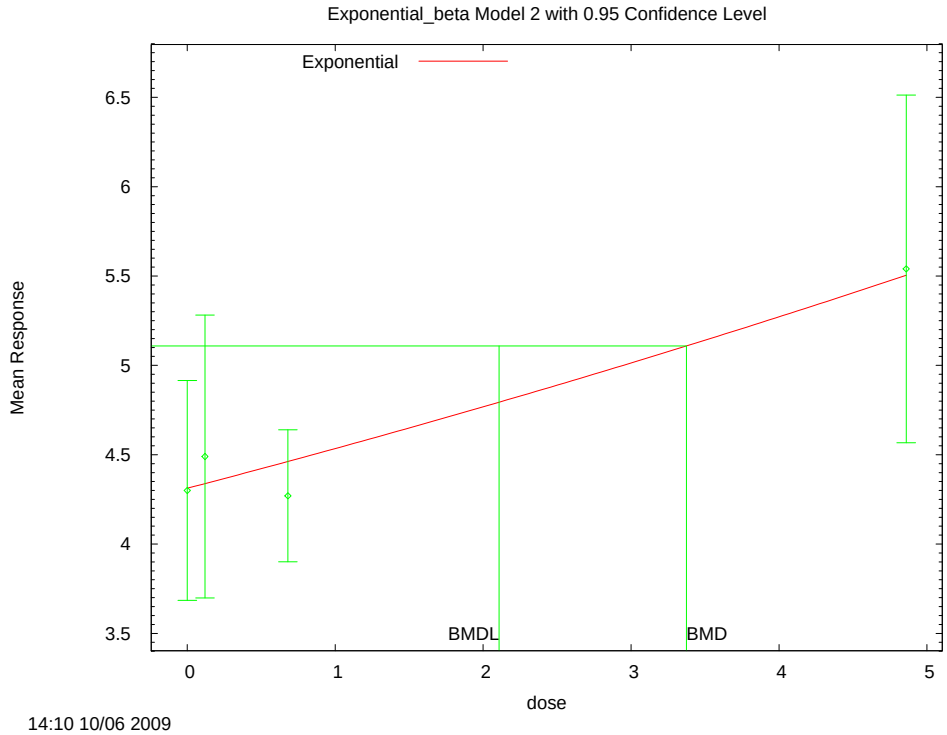
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2) [c]	**2**	**0.02**	**5.20**	**0.07**	**38.53**	**3.4E+00**	**2.1E+00**	**nonconstant variance, power restricted ≥1**
exponential (M3)	1	0.02	4.15	0.04	39.48	4.7E+00	2.3E+00	nonconstant variance, power restricted ≥1
exponential (M4)	1	0.02	5.33	0.02	40.66	3.3E+00	1.9E+00	nonconstant variance, power restricted ≥1
exponential (M5)	0	0.02	4.15	N/A	41.48	4.6E+00	7.3E-01	nonconstant variance, power restricted ≥1
Hill	0	0.02	4.15	NA	41.48	4.6E+00	7.5E-01	nonconstant variance, n restricted >1
linear	2	0.02	5.33	0.07	38.66	3.3E+00	1.9E+00	nonconstant variance
polynomial	1	0.02	2.86	0.09	38.20	4.9E+00	2.7E+00	nonconstant variance
power	1	0.02	4.15	0.04	39.48	4.7E+00	2.2E+00	nonconstant variance, power restricted ≥1
exponential (M2)	2	0.02	0.63	0.73	39.73	3.9E+00	2.7E+00	constant variance, power restricted ≥1
exponential (M3)	1	0.02	0.30	0.58	41.40	4.7E+00	2.7E+00	constant variance, power restricted ≥1
exponential (M4)	1	0.02	0.69	0.41	41.78	3.8E+00	1.2E+00	constant variance, power restricted ≥1
exponential (M5)	0	0.02	0.30	N/A	43.40	4.7E+00	7.2E-01	constant variance, power restricted ≥1
Hill	0	0.02	0.30	NA	43.40	4.7E+00	7.3E-01	constant variance, n restricted >1
linear	2	0.02	0.68	0.71	39.78	3.8E+00	2.5E+00	constant variance
polynomial	1	0.02	0.24	0.62	41.34	4.6E+00	1.2E+00	constant variance
power	1	0.02	0.30	0.58	41.40	4.7E+00	2.5E+00	constant variance, power restricted ≥1

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.15.2. *Figure for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*



E.3.15.3. *Output File for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*

```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AniDose\Exp_BMR1_rel_fem_liver_wt.(d)
         Gnuplot Plotting File:
                                                  Tue Oct 06 14:10:17 2009
 ========================================================================

 Relative Female Liver wt, Tbl 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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             -9.34924
                      rho              5.89997
                        a               4.0565
                        b             0.378048
                        c              1.43399
                        d                    1



                  Parameter Estimates

                 Variable          Model 2
                 --------          -------
                  lnalpha          -6.47175
                      rho           4.07772
                        a           4.36037
                        b          0.196303
                        c           1.57543
                        d           9.64518


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      8          4.3       0.7354
   0.12     10         4.49        1.107
   0.68      9         4.27         0.48
   4.86     10         5.54         1.36


                Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         4.312       0.7964         -0.04371
   0.12         4.338       0.8054           0.5953
   0.68         4.462       0.8483          -0.6795
   4.86         5.505         1.25          0.08976


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       -16.54794           5      43.09588
                       A2       -11.40563           8      38.81126
                       A3       -12.66678           6      37.33356
                        R       -21.58737           2      47.17474
                        2        -15.2671           4      38.53419


Additive constant for all log-likelihoods =        -34.  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                        20.36           6            0.002385
  Test 2                        10.28           3              0.0163
  Test 3                        2.522           2              0.2833
  Test 4                        5.201           2             0.07425


  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 =      3.37444

              BMDL =      2.10781
```

E.3.16. DeCaprio et al. (1986): Relative Liver Weight, Males

E.3.16.1. *Summary Table of BMDS Modeling Results*

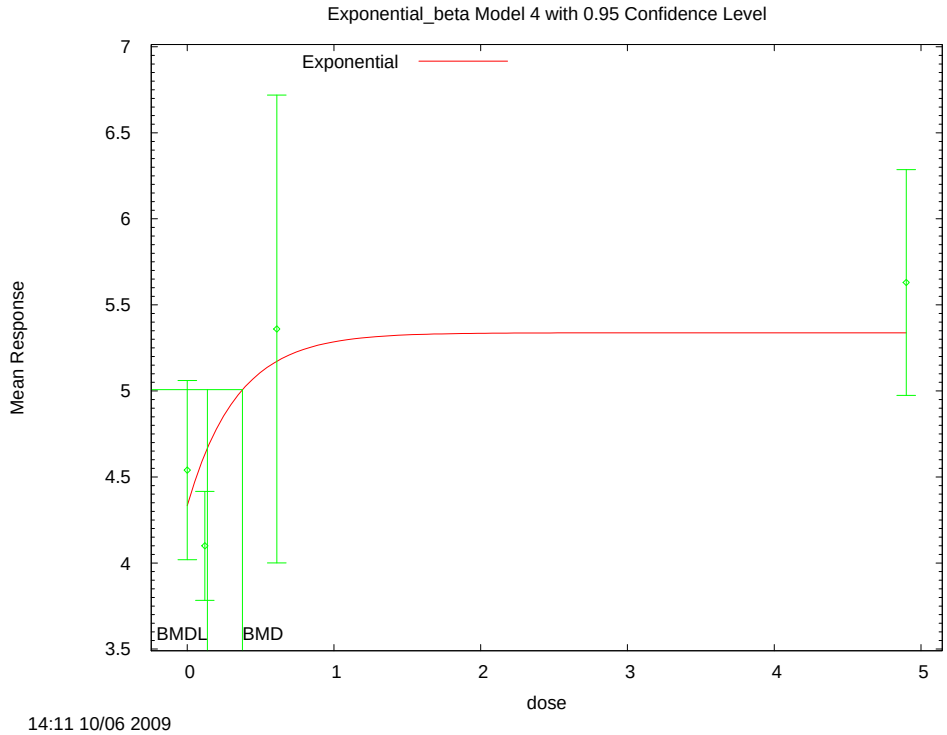
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	<0.0001	25.86	<0.0001	65.17	6.2E+00	3.7E+00	nonconstant variance, power restricted ≥1
exponential (M3)	1	<0.0001	25.30	<0.0001	66.60	5.1E+00	3.9E+00	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**1**	**<0.0001**	**16.82**	**<0.0001**	**58.12**	**3.8E-01**	**1.4E-01**	**nonconstant variance, power restricted ≥1**
exponential (M5)	0	<0.0001	7.80	N/A	51.11	3.5E-01	1.3E-01	nonconstant variance, power restricted ≥1
Hill	1	<.0001	7.80	0.01	49.11	2.8E-01	error	nonconstant variance, n restricted >1, bound hit
linear	2	<.0001	25.90	<.0001	65.20	6.3E+00	3.4E+00	nonconstant variance
polynomial	2	<.0001	25.39	<.0001	64.69	5.8E+00	4.4E+00	nonconstant variance
power	1	<.0001	25.30	<.0001	66.60	5.1E+00	3.7E+00	nonconstant variance, power restricted ≥1
exponential (M2)	2	<0.0001	5.09	0.08	64.15	5.6E+00	3.4E+00	constant variance, power restricted ≥1
exponential (M3)	2	<0.0001	5.09	0.08	64.15	5.6E+00	3.4E+00	constant variance, power restricted ≥1
exponential (M4)	1	<0.0001	2.15	0.14	63.21	1.1E+00	2.7E-01	constant variance, power restricted ≥1
exponential (M5)	0	<0.0001	0.72	N/A	63.78	6.3E-01	1.3E-01	constant variance, power restricted ≥1
Hill	0	<.0001	0.72	NA	63.78	6.5E-01	error	constant variance, n restricted >1
linear	2	<.0001	5.00	0.08	64.06	5.5E+00	3.2E+00	constant variance
polynomial	2	<.0001	5.00	0.08	64.06	5.5E+00	3.2E+00	constant variance
power	2	<.0001	5.00	0.08	64.06	5.5E+00	3.2E+00	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.16.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



E.3.16.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AniDose\Exp_BMR1_rel_male_liver_wt.(d)
         Gnuplot Plotting File:
                                                  Tue Oct 06 14:11:44 2009
 ================================================================

 Rel Male Liver wt, Tbl 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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             -10.8833
                      rho              6.71347
                        a                3.895
                        b             0.428412
                        c              1.51772
                        d                    1



                   Parameter Estimates

                 Variable          Model 4
                 --------          -------
                  lnalpha           -12.146
                      rho            7.6297
                        a              4.32
                        b           2.79927
                        c            1.2705
                        d                18


          Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0     10         4.54       0.7273
   0.12     10          4.1       0.4427
   0.61     11         5.36        2.023
    4.9     10         5.63       0.9171


                Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         4.333       0.6741           0.9699
   0.12         4.633       0.8928           -1.889
   0.61         5.172        1.417           0.4393
    4.9         5.338        1.617           0.5712



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       -26.53142           5      63.06284
                       A2        -13.9487           8      43.89739
                       A3       -15.65277           6      43.30554
                        R       -31.57211           2      67.14421
                        4       -24.06213           5      58.12426


Additive constant for all log-likelihoods =     -37.68.  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                        35.25           6            < 0.0001
  Test 2                        25.17           3            < 0.0001
  Test 3                        3.408           2              0.1819
 Test 6a                        16.82           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 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 =     0.376095

              BMDL =     0.137425
```

E.3.17. DeCaprio et al. (1986): Relative Thymus Weight, Males

E.3.17.1. *Summary Table of BMDS Modeling Results*

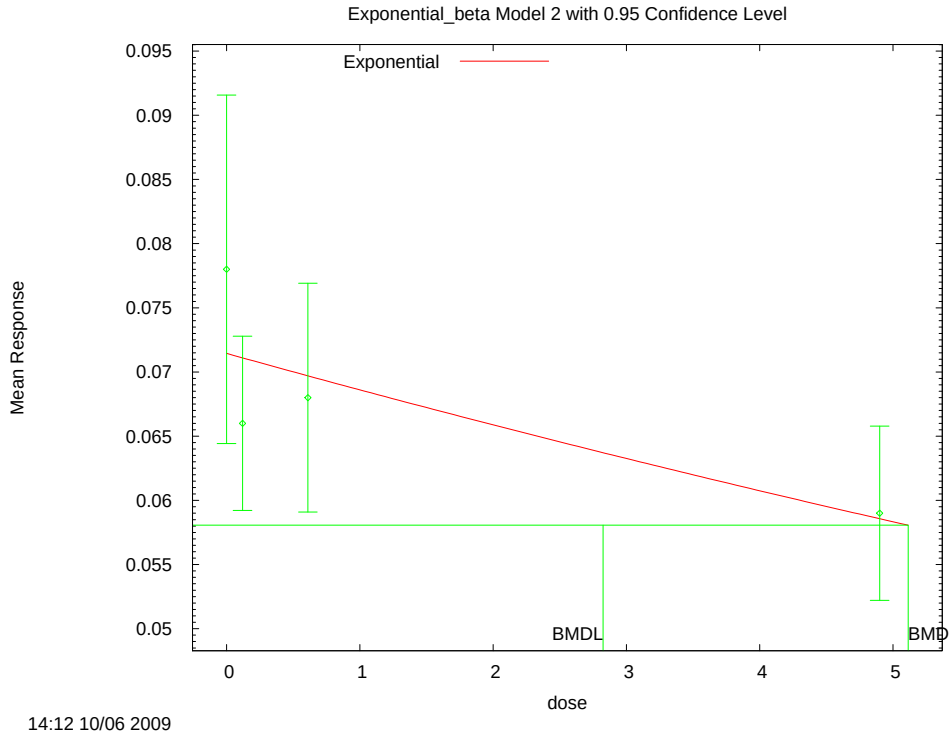
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.07	7.12	0.03	-308.01	6.0E+00	3.4E+00	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.07	7.12	0.03	-308.01	6.0E+00	3.4E+00	nonconstant variance, power restricted ≥1
exponential (M4)	1	0.07	5.77	0.02	-307.36	error	error	nonconstant variance, power restricted ≥1
exponential (M5)	1	0.07	5.77	0.02	-307.36	error	error	nonconstant variance, power restricted ≥1
Hill	1	0.07	4.71	0.03	-308.42	error	error	nonconstant variance, n restricted >1, bound hit
linear	2	0.07	7.19	0.03	-307.94	5.9E+00	3.6E+00	nonconstant variance
polynomial	1	0.07	5.98	0.01	-307.16	2.0E+00	6.8E-01	nonconstant variance
power	2	0.07	7351250	<0.0001	7350937	error	error	nonconstant variance, power restricted ≥1, bound hit
exponential (M2) [c]	**2**	**0.07**	**4.25**	**0.12**	**-306.73**	**5.1E+00**	**2.8E+00**	**constant variance, power restricted ≥1**
exponential (M3)	2	0.07	4.25	0.12	-306.73	5.1E+00	2.8E+00	constant variance, power restricted ≥1
exponential (M4)	1	0.07	3.29	0.07	-305.69	1.8E+00	7.6E-03	constant variance, power restricted ≥1
exponential (M5)	1	0.07	3.29	0.07	-305.69	1.8E+00	7.1E-03	constant variance, power restricted ≥1
Hill	1	0.07	2.10	0.15	-306.88	3.2E-01	5.1E-07	constant variance, n restricted >1, bound hit
linear	2	0.07	4.30	0.12	-306.68	5.2E+00	3.1E+00	constant variance
polynomial	1	0.07	3.48	0.06	-305.50	1.4E+00	5.1E-01	constant variance
power	2	0.07	4.30	0.12	-306.68	5.2E+00	3.1E+00	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.17.2. *Figure for selected Model: Exponential (M2), Constant Variance, Power Restricted ≥1*



E.3.17.3. *Output File for Selected Model: Exponential (M2), Constant Variance, Power Restricted ≥1*

```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AniDose\ExpConstVar_BMR1_rel_male_thymus_wt.(d)
         Gnuplot Plotting File:
                                                  Tue Oct 06 14:12:33 2009
 ========================================================================

 Rel Male Thymus wt, Tbl 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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             -8.73123
                      rho(S)                 0
                        a              0.0819
                        b             0.468839
                        c             0.686086
                        d                    1

  (S) = Specified


                   Parameter Estimates

                 Variable          Model 2
                 --------          -------
                  lnalpha          -8.65107
                      rho                 0
                        a         0.0739582
                        b           1.27978
                        c           0.80201
                        d                 1


          Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0     10        0.078      0.01897
   0.12     10        0.066     0.009487
   0.61     11        0.068      0.01327
    4.9     10        0.059     0.009487


                Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0       0.07145      0.01338            1.548
   0.12        0.0711      0.01338           -1.205
   0.61        0.0697      0.01338          -0.4219
    4.9       0.05857      0.01338           0.1014


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        158.4903            5     -306.9805
                      A2        161.9563            8     -307.9126
                      A3        158.4903            5     -306.9805
                       R        153.4442            2     -302.8885
                       2        156.3648            3     -306.7296


Additive constant for all log-likelihoods =     -37.68.  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                      17.02             6            0.009195
  Test 2                      6.932             3             0.07409
  Test 3                      6.932             3             0.07409
  Test 4                      4.251             2              0.1194


  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.  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 =      5.11373

              BMDL =      2.82487
```

E.3.18. Hojo et al. (2002): DRL Reinforce per Min

E.3.18.1. *Summary Table of BMDS Modeling Results*

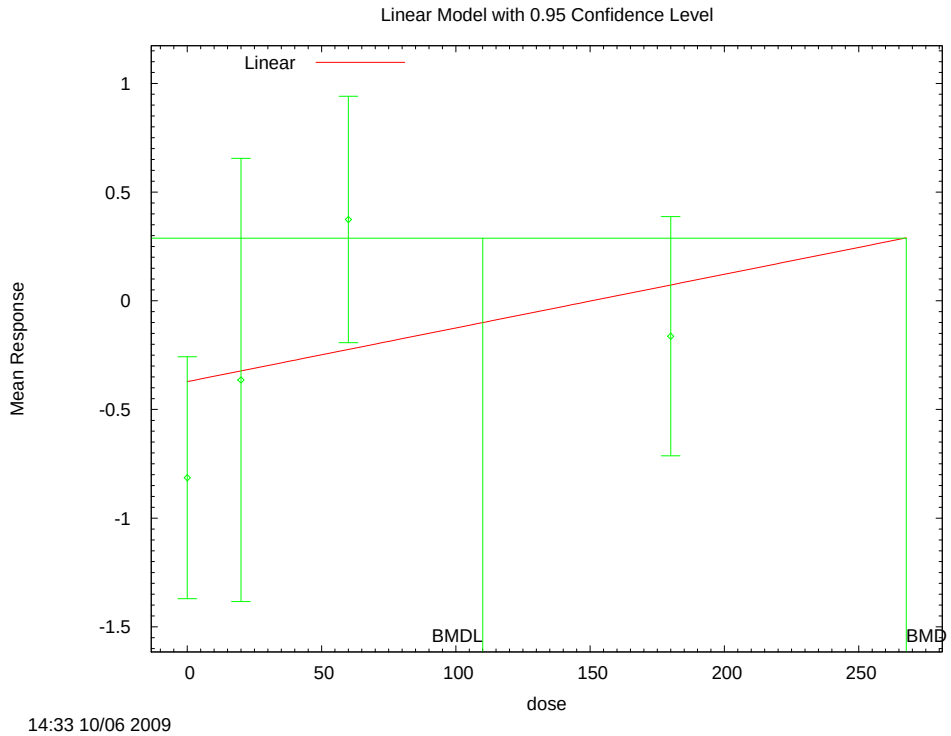
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.43	9.01	0.01	10.48	6.9E+02	1.7E+02	nonconstant variance, power restricted ≥1
exponential (M3)	1	0.43	8.95	0.00	12.43	3.9E+02	1.8E+02	nonconstant variance, power restricted ≥1
exponential (M4)	1	0.43	2.92	0.09	6.39	1.0E+01	1.5E-01	nonconstant variance, power restricted ≥1
exponential (M5)	0	0.43	2.31	N/A	7.78	2.0E+01	error	nonconstant variance, power restricted ≥1
Hill	1	0.43	1.#QNAN	<.0001	7.60	error	error	nonconstant variance, n restricted >1
linear	2	0.43	9.21	0.01	11.02	error	error	nonconstant variance
polynomial	2	0.43	8.79	0.01	10.60	error	4.4E+02	nonconstant variance
power	2	0.43	8.28	0.02	9.98	error	error	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	2	0.43	10.12	0.01	9.89	3.0E+02	1.5E+02	constant variance, power restricted ≥1
exponential (M3)	2	0.43	10.12	0.01	9.89	3.0E+02	1.5E+02	constant variance, power restricted ≥1
exponential (M4)	**1**	**0.43**	**3.47**	**0.06**	**5.24**	**1.7E+01**	**3.8E-02**	**constant variance, power restricted ≥1**
exponential (M5)	0	0.43	2.70	N/A	6.46	2.1E+01	1.2E-05	constant variance, power restricted ≥1
Hill	0	0.43	2.70	NA	6.46	2.1E+01	1.7E-05	constant variance, n restricted >1
linear [c]	2	0.43	9.78	0.01	9.55	2.7E+02	1.1E+02	constant variance
polynomial	2	0.43	9.78	0.01	9.55	2.7E+02	1.1E+02	constant variance
power	2	0.43	9.78	0.01	9.55	2.7E+02	1.1E+02	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.18.2. *Figure for Selected Model: Linear, Constant Variance*



E.3.18.3. *Output File for Selected Model: Linear, Constant Variance*

```
 ========================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\AniDose\LinearConstVar_BMR1_DRL_reinforce_per_min.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AniDose\LinearConstVar_BMR1_DRL_reinforce_per_min.plt
                                                  Tue Oct 06 14:33:14 2009
 ========================================================================

 Table 5
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =     0.337763
                              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
 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 =        267.718


             BMDL =        110.032
```

E.3.19. Hojo et al. (2002): DRL Response per Min

E.3.19.1. *Summary Table of BMDS Modeling Results*

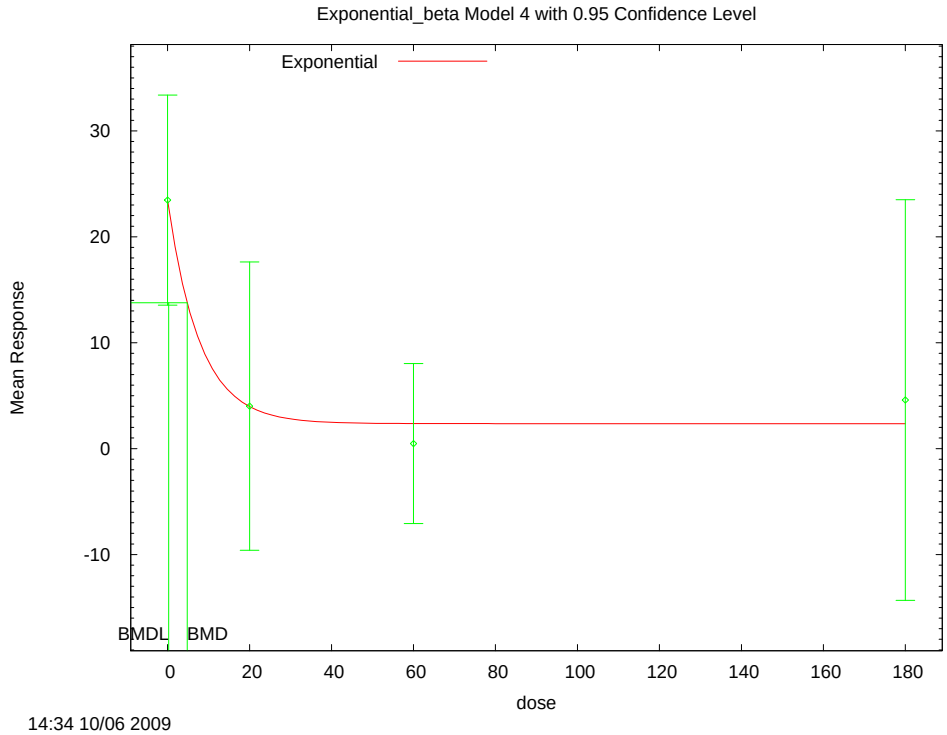
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.30	-0.14	N/A	122.33	4.3E+00	error	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.30	25.76	<0.0001	148.23	error	error	nonconstant variance, power restricted ≥1
exponential (M4)	2	0.30	-0.12	N/A	122.35	4.7E+00	3.2E-01	nonconstant variance, power restricted ≥1
exponential (M5)	1	0.30	0.16	0.69	124.63	6.4E+00	4.1E-01	nonconstant variance, power restricted ≥1
Hill	0	0.30	1.#QNAN	NA	127.53	1.3E+01	1.8E-13	nonconstant variance, n restricted >1
linear	2	0.30	11.09	0.00	133.30	2.1E+02	9.9E+01	nonconstant variance
polynomial	2	0.30	11.09	0.00	133.30	2.1E+02	error	nonconstant variance
power	2	0.30	12.33	0.00	133.30	2.2E+02	9.6E+01	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	2	0.30	1.13	0.57	122.98	6.2E+00	error	constant variance, power restricted ≥1
exponential (M3)	2	0.30	1.13	0.57	122.98	6.2E+00	error	constant variance, power restricted ≥1
exponential (M4) [c]	**1**	**0.30**	**0.50**	**0.48**	**124.36**	**4.8E+00**	**2.7E-01**	**constant variance, power restricted ≥1**
exponential (M5)	0	0.30	0.50	N/A	126.35	1.1E+01	2.1E-01	constant variance, power restricted ≥1
Hill	0	0.30	0.50	NA	126.35	1.6E+01	1.8E-13	constant variance, n restricted >1
linear	2	0.30	10.97	0.00	132.83	2.1E+02	9.8E+01	constant variance
polynomial	2	0.30	10.97	0.00	132.83	2.1E+02	9.8E+01	constant variance
power	2	0.30	10.97	0.00	132.83	2.1E+02	9.8E+01	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.19.2. *Figure for Selected Model: Exponential (M4), Constant Variance, Power Restricted ≥1*



E.3.19.3. *Output File for Selected Model: Exponential (M4), Constant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AniDose\ExpConstVar_BMR1_DRL_response_per_min.(d)
         Gnuplot Plotting File:
                                                  Tue Oct 06 14:34:01 2009
 ================================================================

 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              4.51689
                      rho(S)                 0
                        a               24.6362
                        b             0.0212679
                        c             0.0184785
                        d                     1

  (S) = Specified


                   Parameter Estimates

                  Variable          Model 4
                  --------          -------
                   lnalpha           4.54064
                       rho                 0
                         a            23.463
                         b          0.073228
                         c          0.100111
                         d           2.44375


          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
```

E.3.20. Kattainen et al. (2001): 3rd Molar Mesio-Distal Length (Molar Development)

E.3.20.1. *Summary Table of BMDS Modeling Results*

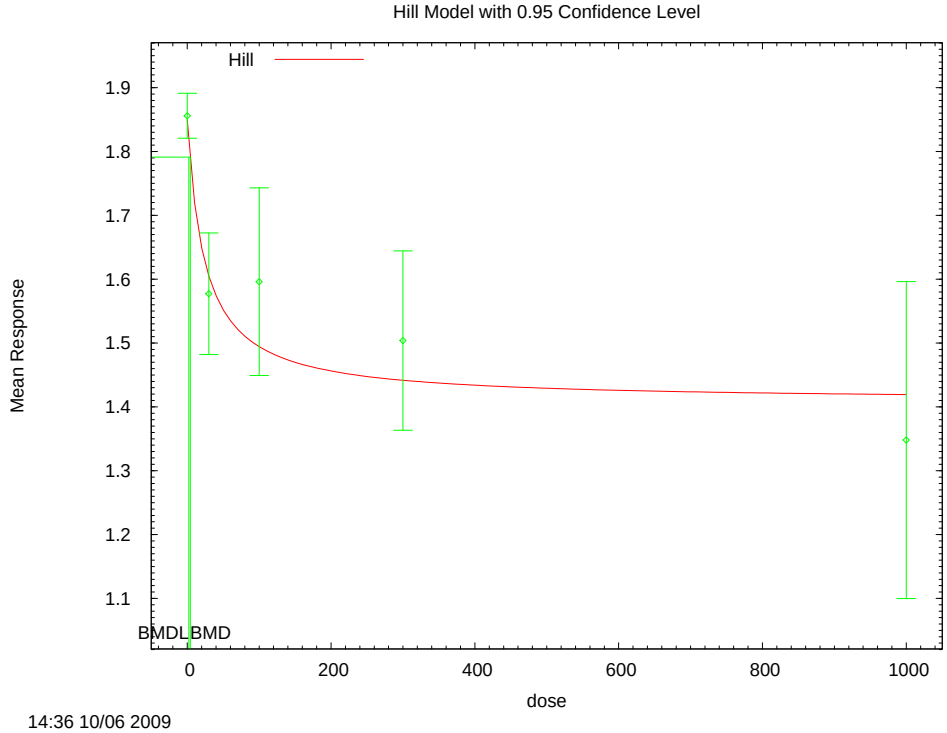
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	3	<0.0001	38.91	<0.0001	-122.95	4.0E+02	2.4E+02	nonconstant variance, power restricted ≥1
exponential (M3)	3	<0.0001	38.91	<0.0001	-122.95	4.0E+02	2.4E+02	nonconstant variance, power restricted ≥1
exponential (M4)	2	<0.0001	79.12	<0.0001	-80.75	error	error	nonconstant variance, power restricted ≥1
exponential (M5)	1	<0.0001	79.12	<0.0001	-78.75	error	error	nonconstant variance, power restricted ≥1
Hill [c]	**2**	**<.0001**	**8.72**	**0.01**	**-151.15**	**4.1E+00**	**2.1E+00**	**nonconstant variance, n restricted >1, bound hit**
linear	3	<.0001	39.54	<.0001	-122.33	4.7E+02	3.0E+02	nonconstant variance
polynomial	2	<.0001	36.57	<.0001	-123.30	1.9E+02	9.0E+01	nonconstant variance
power	3	<.0001	39.54	<.0001	-122.33	4.7E+02	3.0E+02	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	3	<0.0001	7.81	0.05	-99.70	8.5E+02	5.6E+02	constant variance, power restricted ≥1
exponential (M3)	3	<0.0001	7.81	0.05	-99.70	8.5E+02	5.6E+02	constant variance, power restricted ≥1
exponential (M4)	2	<0.0001	5.05	0.08	-100.47	2.3E+02	1.0E+00	constant variance, power restricted ≥1
exponential (M5)	2	<0.0001	5.05	0.08	-100.47	2.3E+02	8.1E-01	constant variance, power restricted ≥1
Hill	2	<.0001	3.23	0.20	-102.29	8.1E+01	1.1E+01	constant variance, n restricted >1, bound hit
linear	3	<.0001	8.07	0.04	-99.45	8.8E+02	6.2E+02	constant variance
polynomial	2	<.0001	5.88	0.05	-99.64	3.7E+02	1.8E+02	constant variance
power	3	<.0001	8.07	0.04	-99.45	8.8E+02	6.2E+02	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.20.2. *Figure for Selected Model: Hill, Nonconstant Variance, n Restricted >1, Bound Hit*



E.3.20.3. *Output File for Selected Model: Hill, Nonconstant Variance, n Restricted >1, Bound Hit*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AniDose\Hill_BMR1_3rd_molar.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AniDose\Hill_BMR1_3rd_molar.plt
                                                Tue Oct 06 14:36:22 2009
 ================================================================

 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 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 = 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

(*** 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

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval 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
```

E.3.21. Kattainen et al. (2001): Females 3rd Molar Eruption

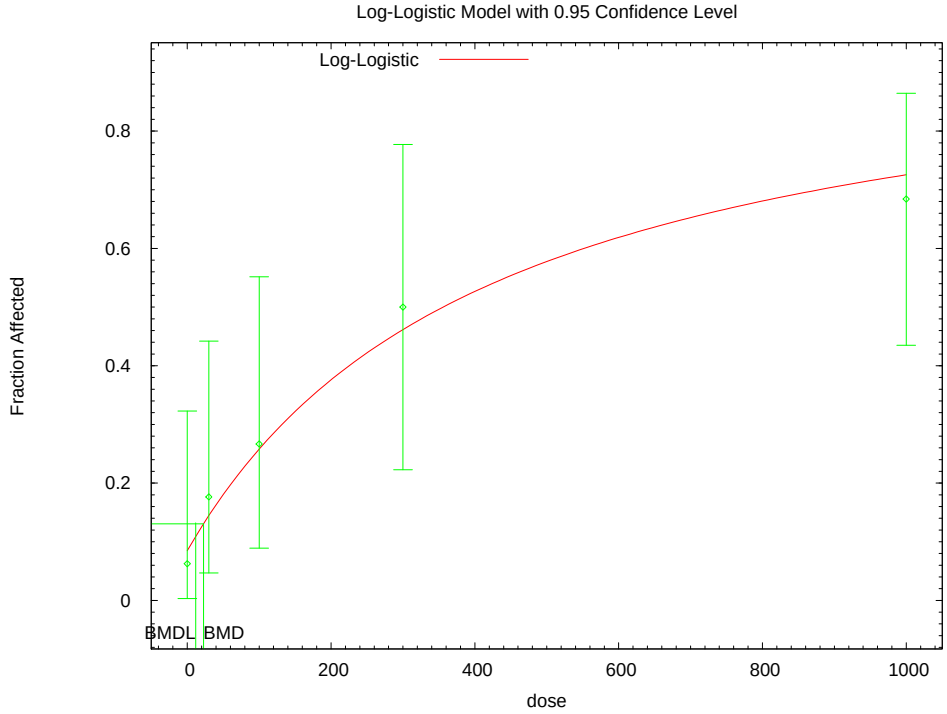
E.3.21.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
logistic	3	3.73	0.29	89.06	1.0E+02	7.3E+01	
logistic	3	3.73	0.29	89.06	1.9E+02	1.4E+02	
log-logistic [b]	**3**	**0.48**	**0.92**	**85.53**	**2.3E+01**	**1.2E+01**	**slope restricted ≥1, bound hit**
log-logistic	3	0.48	0.92	85.53	4.8E+01	2.5E+01	slope restricted ≥1, bound hit
log-probit	2	0.12	0.94	87.18	1.3E+01	5.2E-01	slope restricted ≥1
log-probit	2	0.12	0.94	87.18	2.8E+01	2.3E+00	slope restricted ≥1
multistage, 1-degree	3	1.68	0.64	86.80	4.2E+01	2.7E+01	betas restricted ≥0
multistage, 1-degree	3	1.68	0.64	86.80	8.7E+01	5.5E+01	betas restricted ≥0
probit	3	3.62	0.31	88.92	9.8E+01	7.1E+01	
probit	3	3.62	0.31	88.92	1.9E+02	1.4E+02	

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

E.3.21.2. *Figure for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*



E.3.21.3. *Output File for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File:
C:\USEPA\BMDS21\AniDose2\LogLogistic_BMR1_Female_3rd_molar_eruption.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AniDose2\LogLogistic_BMR1_Female_3rd_molar_eruption.plt
                                                Thu Oct 15 11:05:20 2009
 ================================================================

 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

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval 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

Dose	Est._Prob.	Expected	Observed	Size	Scaled 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 = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 22.5603

BMDL = 11.7531

E.3.22. Keller et al. (2006): Missing Mandibular Molars in CBA J Mice

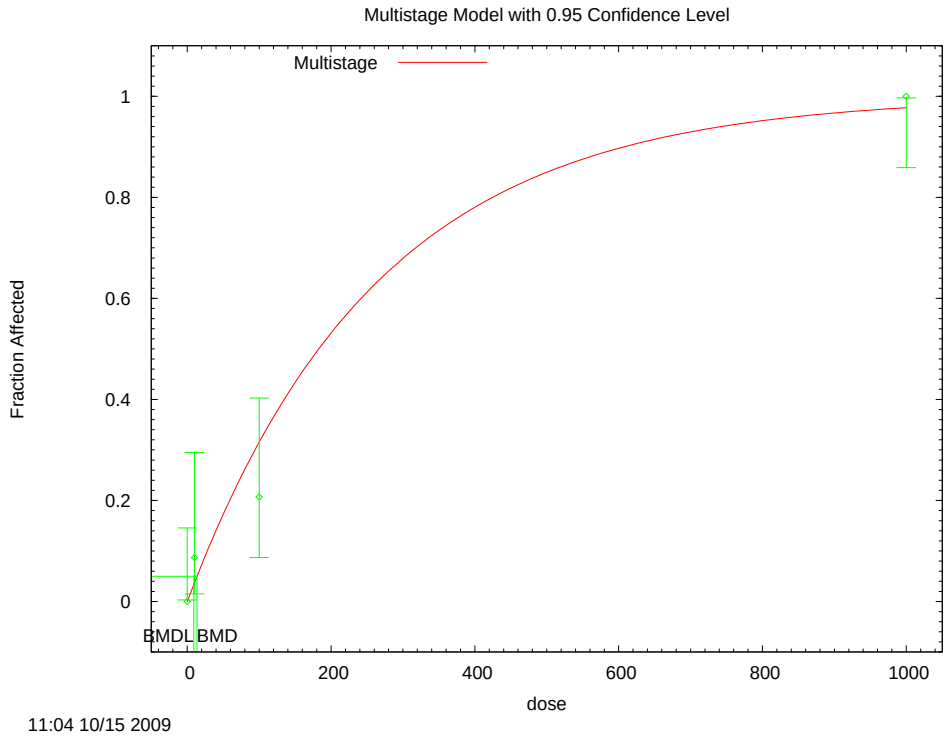
E.3.22.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	1	2.63	0.10	52.49	5.2E+01	9.9E+00	power restricted ≥1
gamma	1	2.63	0.10	52.49	7.3E+01	2.0E+01	power restricted ≥1
logistic	2	2.28	0.32	50.10	4.6E+01	3.1E+01	
logistic	2	2.28	0.32	50.10	7.2E+01	5.1E+01	
log-logistic	1	2.62	0.11	52.52	8.5E+01	3.6E+01	slope restricted ≥1
log-logistic	1	2.62	0.11	52.52	9.3E+01	5.3E+01	slope restricted ≥1
log-probit	1	2.62	0.11	52.52	7.8E+01	3.9E+01	slope restricted ≥1
log-probit	1	2.62	0.11	52.52	8.9E+01	5.3E+01	slope restricted ≥1
multistage, 2-degree	1	2.34	0.13	51.52	2.4E+01	1.1E+01	betas restricted ≥0
multistage, 1-degree [b]	**3**	**3.87**	**0.28**	**49.41**	**1.4E+01**	**9.2E+00**	**betas restricted ≥0**
multistage, 2-degree	1	2.34	0.13	51.52	4.6E+01	2.2E+01	betas restricted ≥0
multistage, 1-degree	3	3.87	0.28	49.41	2.8E+01	1.9E+01	betas restricted ≥0
probit	2	2.25	0.32	50.03	4.3E+01	2.8E+01	
probit	2	2.25	0.32	50.03	6.8E+01	4.8E+01	
Weibull	1	2.58	0.11	52.22	3.7E+01	1.0E+01	power restricted ≥1
Weibull	1	2.58	0.11	52.22	6.1E+01	2.1E+01	power restricted ≥1

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

E.3.22.2. *Figure for Selected Model: Multistage, 1-Degree, Betas Restricted ≥0*



E.3.22.3. *Output File for Selected Model: Multistage, 1-Degree, Betas Restricted ≥0*

```
 ========================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AniDose2\Multi1st_BMR1_CBA_J_mandibular.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AniDose2\Multi1st_BMR1_CBA_J_mandibular.plt
                                                  Thu Oct 15 11:04:49 2009
 ========================================================================

 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 =           0.05

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        13.5244

             BMDL =        9.17426

             BMDU =        20.3135

Taken together, (9.17426, 20.3135) is a 90     % two-sided confidence
```

interval for the BMD

E.3.23. Kociba et al. (1978): Urinary Coproporphyrins, Females (Table 2)

E.3.23.1. *Summary Table of BMDS Modeling Results*

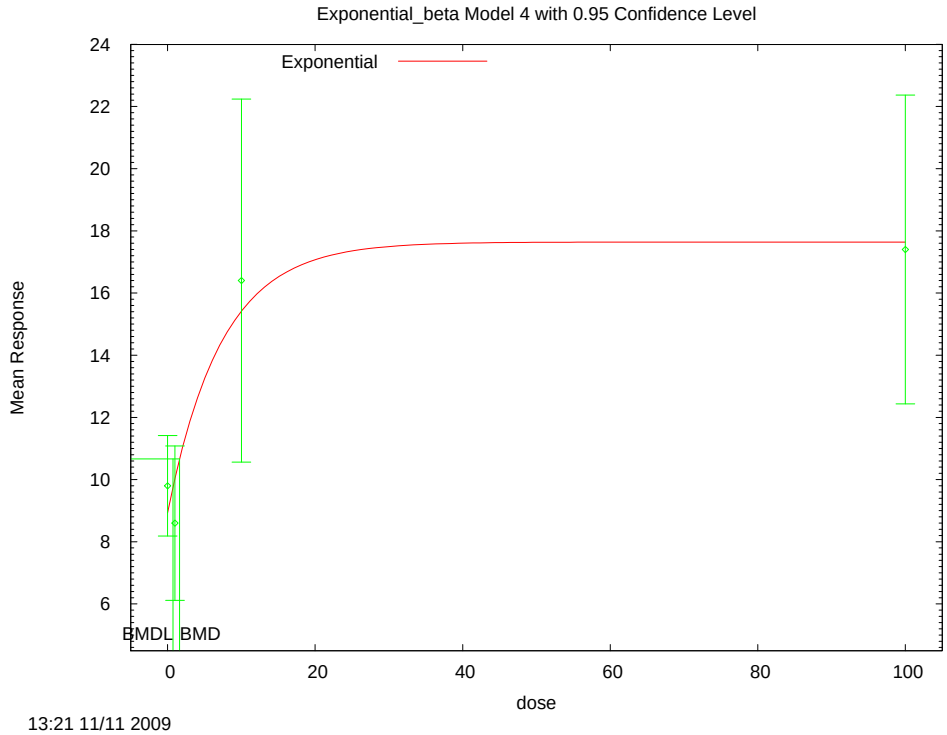
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.03	19.68	<0.0001	84.01	7.1E+01	4.3E+01	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.03	19.68	<0.0001	84.01	7.1E+01	4.3E+01	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**1**	**0.03**	**4.23**	**0.04**	**70.56**	**1.6E+00**	**7.3E-01**	**nonconstant variance, power restricted ≥1**
exponential (M5)	0	0.03	0.76	N/A	69.09	3.1E+00	1.0E+00	nonconstant variance, power restricted ≥1
linear	2	0.03	19.38	<.0001	83.71	6.2E+01	3.1E+01	nonconstant variance
polynomial	2	0.03	19.38	<.0001	83.71	6.2E+01	3.1E+01	nonconstant variance
power	2	0.03	19.38	<.0001	83.71	6.2E+01	3.1E+01	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	2	0.03	12.65	0.00	82.04	6.9E+01	4.7E+01	constant variance, power restricted ≥1
exponential (M3)	2	0.03	12.65	0.00	82.04	6.9E+01	4.7E+01	constant variance, power restricted ≥1
exponential (M4)	1	0.03	1.96	0.16	73.36	2.7E+00	1.1E+00	constant variance, power restricted ≥1
exponential (M5)	0	0.03	0.41	N/A	73.80	8.3E+00	1.0E+00	constant variance, power restricted ≥1
Hill	0	0.03	0.41	NA	73.80	7.6E+00	error	constant variance, n restricted >1
linear	2	0.03	12.32	0.00	81.72	6.1E+01	3.8E+01	constant variance
polynomial	2	0.03	12.32	0.00	81.72	6.1E+01	3.8E+01	constant variance
power	2	0.03	12.32	0.00	81.72	6.1E+01	3.8E+01	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.23.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



E.3.23.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AD\Exp_BMR1_urin_copropor_f.(d)
         Gnuplot Plotting File:
                                                  Wed Nov 11 13:21:02 2009
 ================================================================

 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          -5.49254
                      rho           2.91176
                        a               9.2
                        b          0.295128
                        c           1.83696
                        d                18


          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
```

E.3.24. Kociba et al. (1978): Uroporphyrin per Creatinine, Females

E.3.24.1. *Summary Table of BMDS Modeling Results*

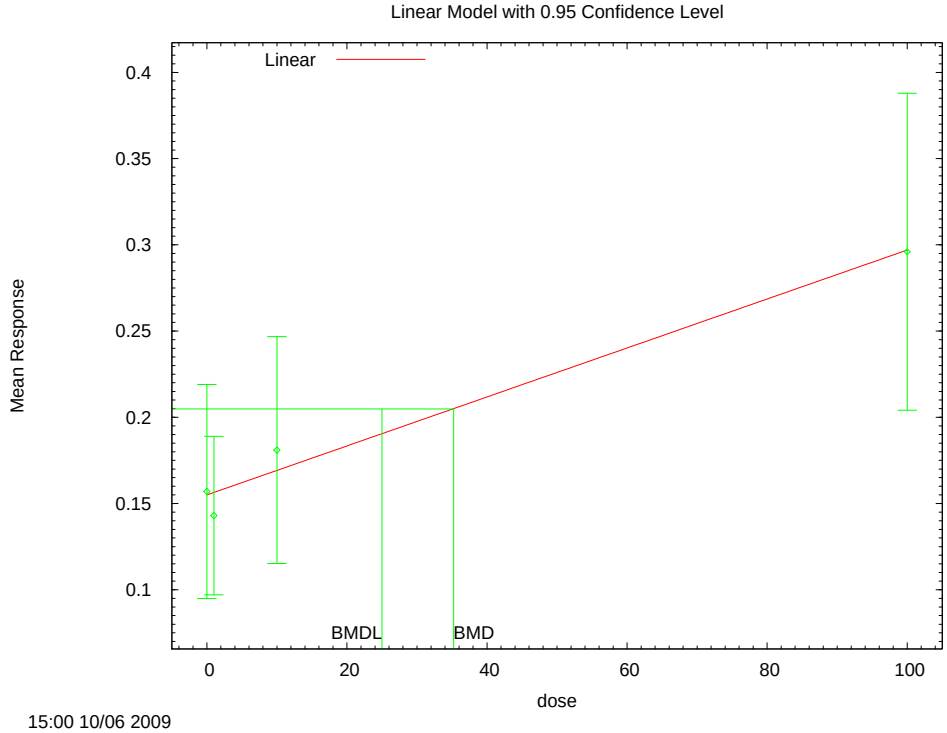
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.49	1.45	0.48	-93.10	3.8E+01	2.6E+01	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.49	1.45	0.48	-93.10	3.8E+01	2.6E+01	nonconstant variance, power restricted ≥1
exponential (M4)	1	0.49	0.73	0.39	-91.82	1.4E+01	4.4E+00	nonconstant variance, power restricted ≥1
exponential (M5)	0	0.49	0.51	N/A	-90.03	1.0E+01	4.5E+00	nonconstant variance, power restricted ≥1
Hill	0	0.49	0.51	NA	-90.03	1.0E+01	7.7E+00	nonconstant variance, n restricted >1
linear	2	0.49	1.20	0.55	-93.35	2.9E+01	1.8E+01	nonconstant variance
polynomial	1	0.49	0.72	0.40	-91.83	1.3E+01	4.8E+00	nonconstant variance
power	2	0.49	1.20	0.55	-93.35	2.9E+01	1.8E+01	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	2	0.49	0.83	0.66	-93.56	4.4E+01	3.3E+01	constant variance, power restricted ≥1
exponential (M3)	2	0.49	0.83	0.66	-93.56	4.4E+01	3.3E+01	constant variance, power restricted ≥1
exponential (M4)	1	0.49	0.31	0.58	-92.08	1.7E+01	5.5E+00	constant variance, power restricted ≥1
exponential (M5)	0	0.49	0.20	N/A	-90.19	1.1E+01	5.6E+00	constant variance, power restricted ≥1
linear [c]	**2**	**0.49**	**0.66**	**0.72**	**-93.73**	**3.5E+01**	**2.5E+01**	**constant variance**
polynomial	1	0.49	0.31	0.58	-92.08	1.7E+01	6.1E+00	constant variance

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.24.2. *Figure for Selected Model: Linear, Constant Variance*



E.3.24.3. *Output File for Selected Model: Linear, Constant Variance*

```
 ========================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File:
C:\USEPA\BMDS21\AniDose\LinearConstVar_BMR1_Females_uroporphyrin_per_creatinine.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AniDose\LinearConstVar_BMR1_Females_uroporphyrin_per_creatinine.plt
                                                  Tue Oct 06 15:00:16 2009
 ========================================================================

 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 =     0.154759
                           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

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 =        35.2176


             BMDL =        25.0024
```

E.3.25. Latchoumycandane and Mathur (2002): Daily sperm Production

E.3.25.1. *Summary Table of BMDS Modeling Results*

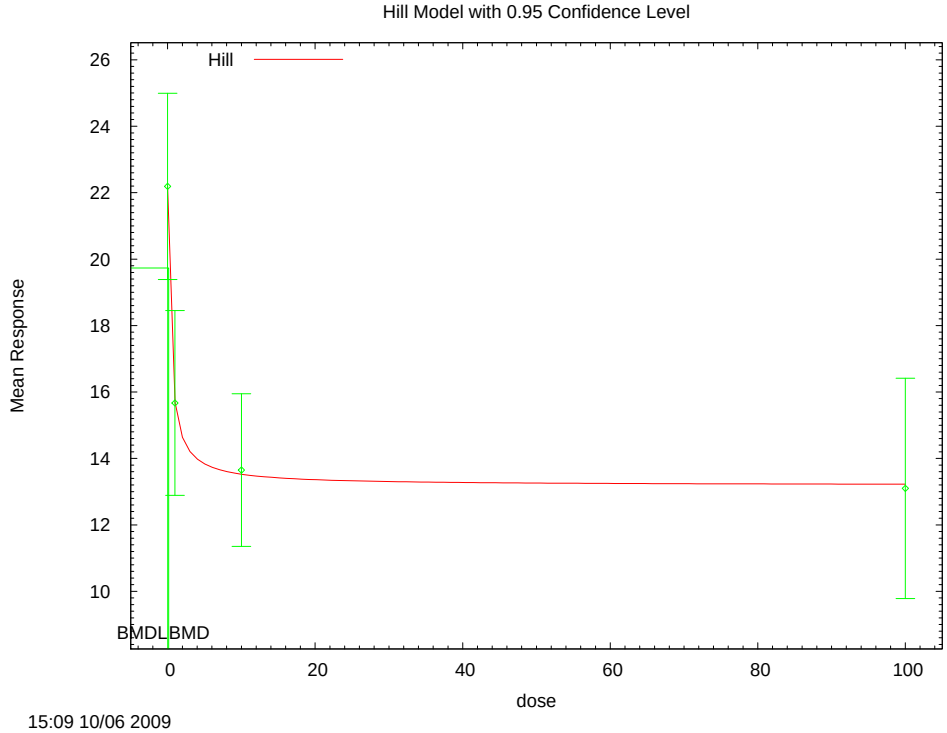
Model	Degrees of Freedom	Variance p-Value [a]	χ^2 Test Statistic	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.85	20.91	<0.0001	96.01	9.2E+01	4.5E+01	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.85	20.91	<0.0001	96.01	9.2E+01	4.5E+01	nonconstant variance, power restricted ≥1
exponential (M4)	1	0.85	0.16	0.69	77.26	2.4E-01	8.8E-02	nonconstant variance, power restricted ≥1
exponential (M5)	0	0.85	0.16	N/A	79.26	2.9E-01	8.8E-02	nonconstant variance, power restricted ≥1
Hill	1	0.85	0.04	0.85	77.14	1.4E-01	1.3E-02	nonconstant variance, n restricted >1, bound hit
linear	2	0.85	21.07	<.0001	96.18	9.5E+01	5.4E+01	nonconstant variance
polynomial	1	0.85	10.98	0.00	88.08	6.2E+00	3.7E+00	nonconstant variance
power	2	0.85	21.07	<.0001	96.18	9.5E+01	5.4E+01	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	2	0.85	21.99	<0.0001	95.11	7.6E+01	4.0E+01	constant variance, power restricted ≥1
exponential (M3)	2	0.85	21.99	<0.0001	95.11	7.6E+01	4.0E+01	constant variance, power restricted ≥1
exponential (M4)	1	0.85	0.15	0.70	75.26	2.4E-01	1.0E-01	constant variance, power restricted ≥1
exponential (M5)	0	0.85	0.15	N/A	77.26	3.7E-01	1.0E-01	constant variance, power restricted ≥1
Hill [c]	**1**	**0.85**	**0.03**	**0.86**	**75.14**	**1.4E-01**	**1.6E-02**	**constant variance, n restricted >1, bound hit**
linear	2	0.85	22.20	<.0001	95.31	8.3E+01	4.9E+01	constant variance
polynomial	1	0.85	12.98	0.00	88.09	5.0E+00	3.2E+00	constant variance
power	2	0.85	22.20	<.0001	95.31	8.3E+01	4.9E+01	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.25.2. *Figure for Selected Model: Hill, Constant Variance, n Restricted >1, Bound Hit*



E.3.25.3. *Output File for Selected Model: Hill, Constant Variance, n Restricted >1, Bound Hit*

```
 ========================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AniDose\HillConstVar_BMR1_sperm_prod.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AniDose\HillConstVar_BMR1_sperm_prod.plt
                                                Tue Oct 06 15:09:27 2009
 ========================================================================

 (x10^6) Table 1 without Vitamin E
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =      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
```

E.3.26. Li et al. (2006): Hormone Levels (Estradiol)

E.3.26.1. *Summary Table of BMDS Modeling Results*

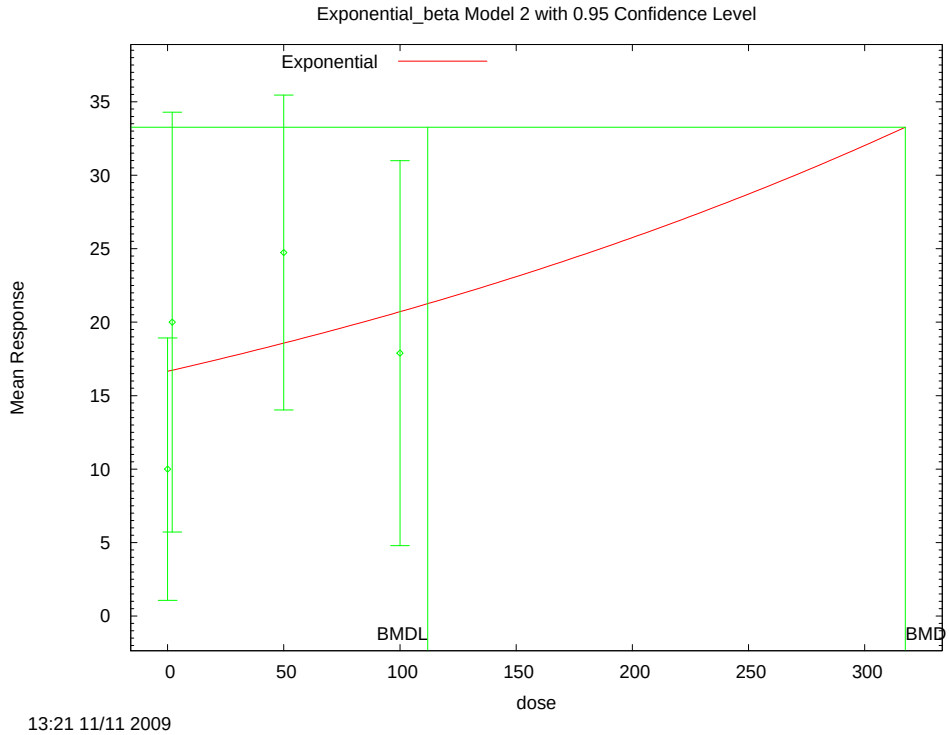
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.47	4.98	0.08	272.78	3.0E+02	1.0E+02	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.47	4.98	0.08	272.78	3.0E+02	1.0E+02	nonconstant variance, power restricted ≥1
exponential (M4)	1	0.47	0.32	0.57	270.12	error	error	nonconstant variance, power restricted ≥1
exponential (M5)	0	0.47	0.32	N/A	272.12	error	error	nonconstant variance, power restricted ≥1
Hill	1	0.47	0.32	0.57	270.12	error	error	nonconstant variance, n restricted >1, bound hit
linear	2	0.47	4.92	0.09	272.72	3.4E+02	9.7E+01	nonconstant variance
polynomial	2	0.47	4.92	0.09	272.72	3.4E+02	9.7E+01	nonconstant variance
power	2	0.47	4.92	0.09	272.72	3.4E+02	9.7E+01	nonconstant variance, power restricted ≥1, bound hit
exponential (M2) [c]	**2**	**0.47**	**3.84**	**0.15**	**270.81**	**3.2E+02**	**1.1E+02**	**constant variance, power restricted ≥1**
exponential (M3)	2	0.47	3.84	0.15	270.81	3.2E+02	1.1E+02	constant variance, power restricted ≥1
exponential (M4)	1	0.47	0.92	0.34	269.90	error	error	constant variance, power restricted ≥1
exponential (M5)	0	0.47	0.92	N/A	271.90	error	error	constant variance, power restricted ≥1
Hill	0	0.47	0.92	NA	271.90	error	error	constant variance, n restricted >1
linear	2	0.47	3.78	0.15	270.75	3.6E+02	1.1E+02	constant variance
polynomial	2	0.47	3.78	0.15	270.75	3.6E+02	1.1E+02	constant variance
power	2	0.47	3.78	0.15	270.75	3.6E+02	1.1E+02	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.26.2. *Figure for Selected Model: Exponential (M2), Constant Variance, Power Restricted ≥1*



E.3.26.3. *Output File for Selected Model: Exponential (M2), Constant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AD\ExpConst_BMR1_Li_Estradiol.(d)
         Gnuplot Plotting File:
                                                  Wed Nov 11 13:21:55 2009
 ================================================================

 Figure 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             5.52431
                      rho(S)                0
                        a                 9.5
                        b           0.0162139
                        c             2.73407
                        d                   1

  (S) = Specified


                   Parameter Estimates

                 Variable          Model 2
                 --------          -------
                  lnalpha           5.54738
                      rho                 0
                        a                10
                        b          0.842953
                        c           2.13158
                        d           1.46715

  NC = No Convergence


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0     10           10        12.48
      2     10           20        19.97
     50     10        24.74        14.98
    100     10        17.89        18.31


                Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         16.66        16.61           -1.267
      2         16.73        16.61           0.6227
     50         18.57        16.61            1.173
    100         20.71        16.61          -0.5362


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       -130.4861           5      270.9723
                       A2       -129.2199           8      274.4398
                       A3       -130.4861           5      270.9723
                        R       -132.6269           2      269.2537
                        2        -132.404           3      270.8079


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 4:  Does Model 2 fit the data? (A3 vs. 2)


                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                      6.814           6              0.3384
  Test 2                      2.533           3              0.4694
  Test 3                      2.533           3              0.4694
  Test 4                      3.836           2              0.1469


  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 =      317.497

              BMDL =      111.954
```

E.3.27. Li et al. (2006): Hormone Levels (Progesterone)

E.3.27.1. *Summary Table of BMDS Modeling Results*

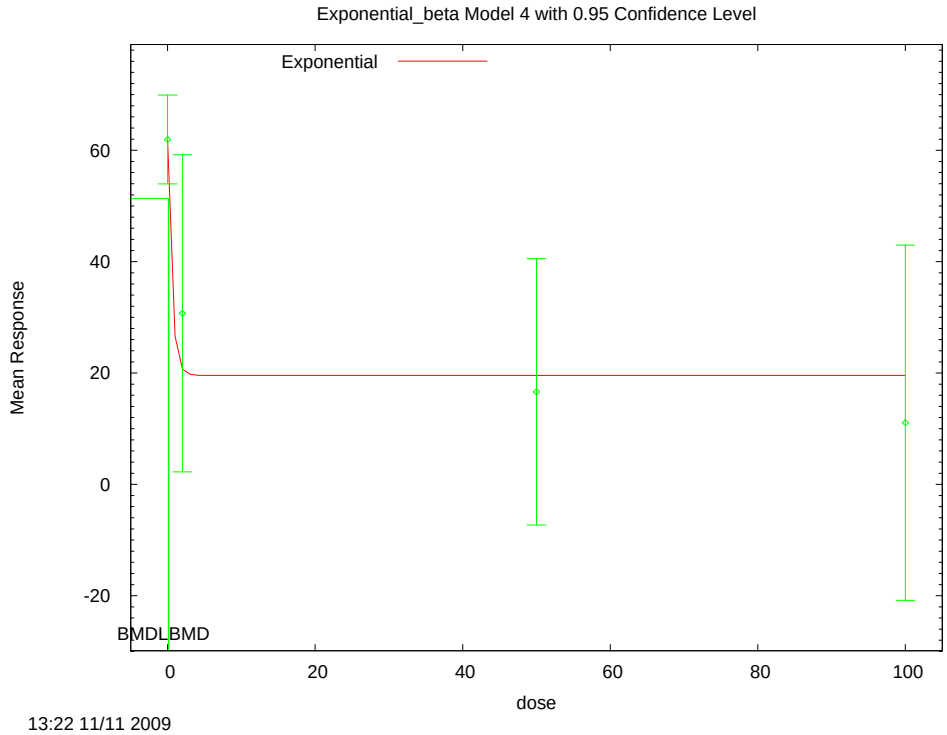
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.00	16.99	0.00	330.20	4.9E+01	error	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.00	16.99	0.00	330.20	4.9E+01	error	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**1**	**0.00**	**0.82**	**0.37**	**316.03**	**1.6E-01**	**1.0E-01**	**nonconstant variance, power restricted ≥1**
exponential (M5)	0	0.00	0.82	N/A	318.03	4.9E-01	7.9E-02	nonconstant variance, power restricted ≥1
Hill	1	0.00	0.81	0.37	316.02	2.2E-02	6.4E-05	nonconstant variance, n restricted >1, bound hit
linear	2	0.00	17.93	0.00	331.13	7.5E+01	5.2E+01	nonconstant variance
polynomial	2	0.00	17.93	0.00	331.13	7.5E+01	5.2E+01	nonconstant variance
power	2	0.00	17.93	0.00	331.13	7.5E+01	4.5E+01	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	2	0.00	3.97	0.14	329.50	6.8E+01	error	constant variance, power restricted ≥1
exponential (M3)	2	0.00	3.97	0.14	329.50	6.8E+01	error	constant variance, power restricted ≥1
exponential (M4)	1	0.00	0.14	0.71	327.66	2.2E+00	1.3E-01	constant variance, power restricted ≥1
exponential (M5)	0	0.00	0.14	N/A	329.66	2.2E+00	2.8E-01	constant variance, power restricted ≥1
Hill	1	0.00	0.12	0.73	327.64	2.4E+00	3.5E-05	constant variance, n restricted >1, bound hit
linear	2	0.00	4.97	0.08	330.49	9.2E+01	5.7E+01	constant variance
polynomial	2	0.00	4.97	0.08	330.49	9.2E+01	5.7E+01	constant variance
power	2	0.00	4.97	0.08	330.49	9.2E+01	5.7E+01	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.27.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



E.3.27.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AD\Exp_BMR1_Li_Progesterone.(d)
         Gnuplot Plotting File:
                                                  Wed Nov 11 13:22:19 2009
 ================================================================

 Figure 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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              11.2757
                      rho             -1.43319
                        a              65.0395
                        b            0.0460242
                        c             0.162232
                        d                    1



                   Parameter Estimates

                 Variable          Model 4
                 --------          -------
                  lnalpha           14.0852
                      rho          -2.26856
                        a           61.9568
                        b           1.02041
                        c          0.315961
                        d           1.78188


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0     10        61.94        11.15
      2     10        30.72        39.81
     50     10        16.62        33.44
    100     10        11.08        44.59


                Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         61.96        10.61           -0.0043
      2         20.78        36.65             0.858
     50         19.58        39.21           -0.2385
    100         19.58        39.21           -0.6853


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       -159.7613           5      329.5225
                         A2       -151.9206           8      319.8412
                         A3       -152.6038           6      317.2077
                          R       -165.9023           2      335.8046
                          4       -153.0132           5      316.0265


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                        27.96           6            < 0.0001
  Test 2                        15.68           3            0.001318
  Test 3                        1.366           2               0.505
 Test 6a                       0.8188           1              0.3655


  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 =     0.161712

              BMDL =     0.100383
```

E.3.28. Markowski et al. (2001): FR10 Run Opp

E.3.28.1. *Summary Table of BMDS Modeling Results*

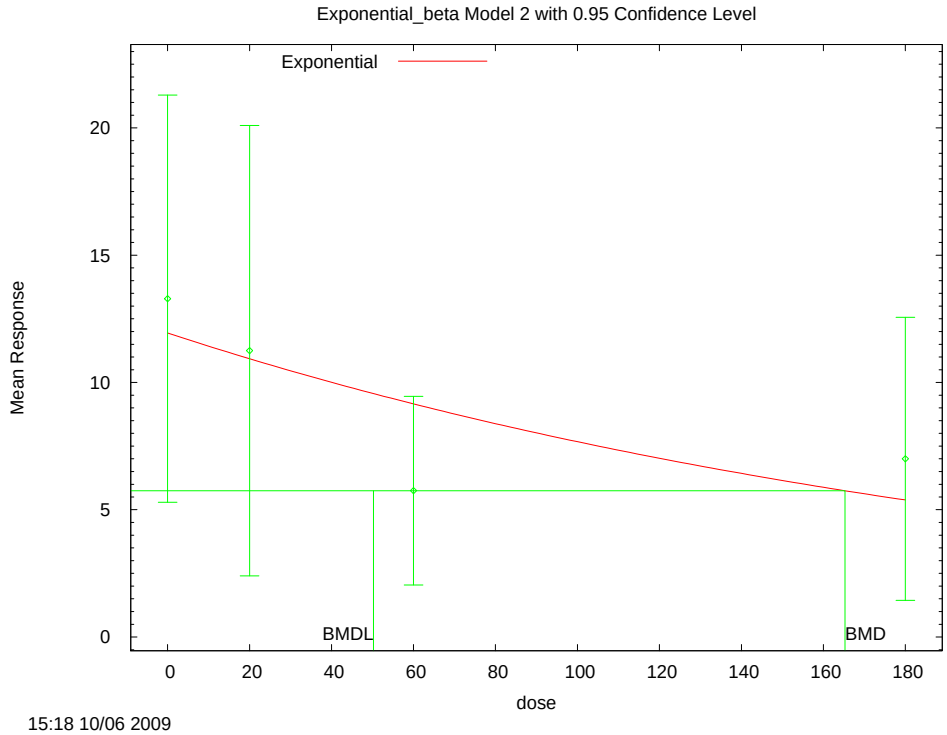
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.17	6.17	0.05	119.08	2.3E+02	5.3E+01	nonconstant variance, power restricted ≥1
exponential (M3)	1	0.17	10.00	0.00	124.91	1.6E+05	1.8E+02	nonconstant variance, power restricted ≥1
exponential (M4)	1	0.17	2.09	0.15	117.00	error	error	nonconstant variance, power restricted ≥1
exponential (M5)	0	0.17	1.52	N/A	118.43	error	error	nonconstant variance, power restricted ≥1
Hill	0	0.17	1.51	NA	118.43	error	error	nonconstant variance, n restricted >1
linear	2	0.17	6.66	0.04	119.57	2.5E+02	1.1E+02	nonconstant variance
polynomial	1	0.17	0.00	1.00	114.91	6.2E+01	2.7E+01	nonconstant variance
power	2	0.17	6.66	0.04	119.57	2.5E+02	1.1E+02	nonconstant variance, power restricted ≥1, bound hit
exponential (M2) [c]	**2**	**0.17**	**2.79**	**0.25**	**117.56**	**1.7E+02**	**5.0E+01**	**constant variance, power restricted ≥1**
exponential (M3)	2	0.17	2.79	0.25	117.56	1.7E+02	5.0E+01	constant variance, power restricted ≥1
exponential (M4)	1	0.17	0.67	0.41	117.44	4.7E+01	1.7E-01	constant variance, power restricted ≥1
exponential (M5)	0	0.17	0.15	N/A	118.92	3.2E+01	4.0E-05	constant variance, power restricted ≥1
Hill	0	0.17	0.15	NA	118.92	2.3E+01	6.7E-06	constant variance, n restricted >1
linear	2	0.17	3.32	0.19	118.09	2.1E+02	1.1E+02	constant variance
polynomial	2	0.17	3.32	0.19	118.09	2.1E+02	1.1E+02	constant variance
power	2	0.17	3.32	0.19	118.09	2.1E+02	1.1E+02	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.28.2. *Figure for Selected Model: Exponential (M2), Constant Variance, Power Restricted ≥1*



E.3.28.3. *Output File for Selected Model: Exponential (M2), Constant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AniDose\ExpConstVar_BMR1_FR10_run_opp.(d)
         Gnuplot Plotting File:
                                                 Tue Oct 06 15:18:28 2009
 ================================================================

 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             13.9545
                        b           0.0143568
                        c            0.392432
                        d                   1

  (S) = Specified


                   Parameter Estimates

                 Variable          Model 2
                 --------          -------
                  lnalpha           3.53824
                      rho                 0
                        a             13.29
                        b         0.0376253
                        c          0.483301
                        d           3.66691


          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
```

E.3.29. Markowski et al. (2001): FR2 Revolutions

E.3.29.1. *Summary Table of BMDS Modeling Results*

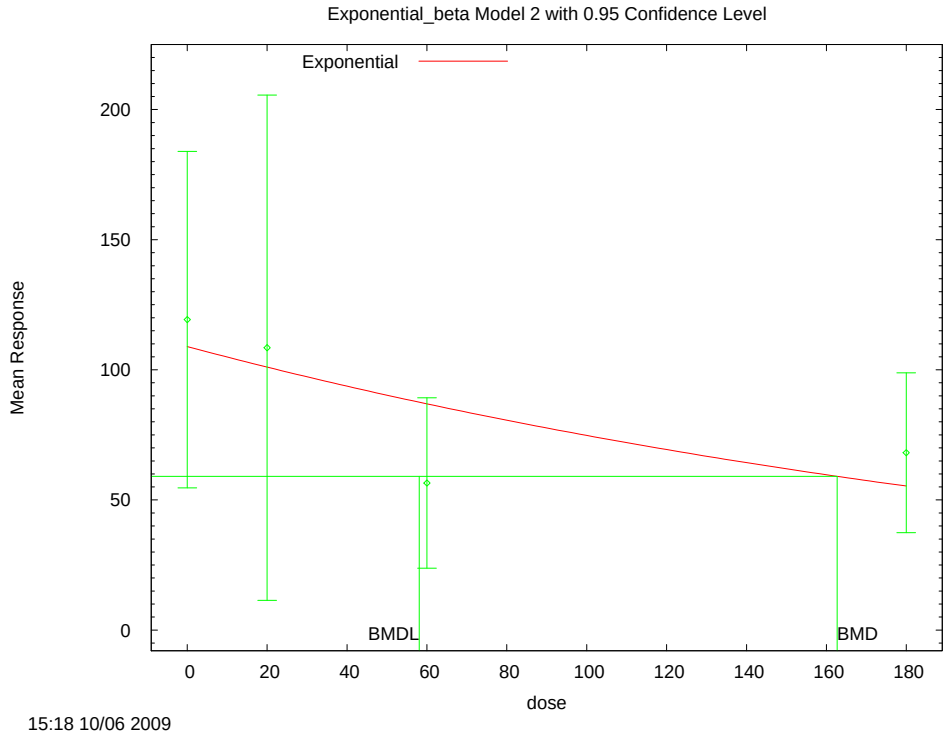
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.11	5.71	0.06	216.09	3.6E+02	1.1E+02	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.11	5.71	0.06	216.09	3.6E+02	1.1E+02	nonconstant variance, power restricted ≥1
exponential (M4)	1	0.11	1.94	0.16	214.33	error	error	nonconstant variance, power restricted ≥1
exponential (M5)	0	0.11	0.45	N/A	214.83	error	error	nonconstant variance, power restricted ≥1
Hill	1	0.11	0.45	0.50	212.83	error	error	nonconstant variance, n restricted >1, bound hit
linear	2	0.11	6.08	0.05	216.46	3.3E+02	1.4E+02	nonconstant variance
polynomial	2	0.11	6.08	0.05	216.46	3.3E+02	1.4E+02	nonconstant variance
power	2	0.11	6.08	0.05	216.46	3.3E+02	1.4E+02	nonconstant variance, power restricted ≥1, bound hit
exponential (M2) [c]	**2**	**0.11**	**3.31**	**0.19**	**217.64**	**1.6E+02**	**5.8E+01**	**constant variance, power restricted ≥1**
exponential (M3)	2	0.11	3.31	0.19	217.64	1.6E+02	5.8E+01	constant variance, power restricted ≥1
exponential (M4)	1	0.11	1.08	0.30	217.41	4.7E+01	2.0E-01	constant variance, power restricted ≥1
exponential (M5)	0	0.11	0.20	N/A	218.53	3.3E+01	1.2E+01	constant variance, power restricted ≥1
Hill	0	0.11	0.20	NA	218.53	2.4E+01	7.3E+00	constant variance, n restricted >1, bound hit
linear	2	0.11	3.80	0.15	218.13	2.0E+02	1.0E+02	constant variance
polynomial	2	0.11	3.80	0.15	218.13	2.0E+02	1.0E+02	constant variance
power	2	0.11	3.80	0.15	218.13	2.0E+02	1.0E+02	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.29.2. *Figure for Selected Model: Exponential (M2), Constant Variance, Power Restricted ≥1*



E.3.29.3. *Output File for Selected Model: Exponential (M2), Constant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AniDose\ExpConstVar_BMR1_FR2_revolutions.(d)
         Gnuplot Plotting File:
                                                  Tue Oct 06 15:18:54 2009
 ================================================================

 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              7.68046
                      rho(S)                 0
                        a              125.255
                        b            0.0134965
                        c             0.429602
                        d                    1

  (S) = Specified


                   Parameter Estimates

                  Variable          Model 2
                  --------          -------
                   lnalpha           7.68885
                       rho                 0
                         a            119.29
                         b         0.0345516
                         c          0.526177
                         d           4.19941


          Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      7        119.3         69.9
     20      4        108.5           61
     60      6         56.5         31.21
    180      7        68.14         33.23


                Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         108.9        49.85           0.5497
     20           101        49.85           0.2994
     60         86.93        49.85           -1.495
    180         55.35        49.85           0.6786


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       -104.1655            5       218.331
                       A2       -101.1402            8      218.2803
                       A3       -104.1655            5       218.331
                        R       -107.5993            2      219.1985
                        2       -105.8179            3      217.6357


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                        12.92           6             0.04435
  Test 2                        6.051           3              0.1092
  Test 3                        6.051           3              0.1092
  Test 4                        3.305           2              0.1916


  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 = 1.000000

         Risk Type = Estimated standard deviations from control

  Confidence Level = 0.950000

               BMD =      162.682

              BMDL =      58.0677
```

E.3.30. Markowski et al. (2001): FR5 Run Opp

E.3.30.1. *Summary Table of BMDS Modeling Results*

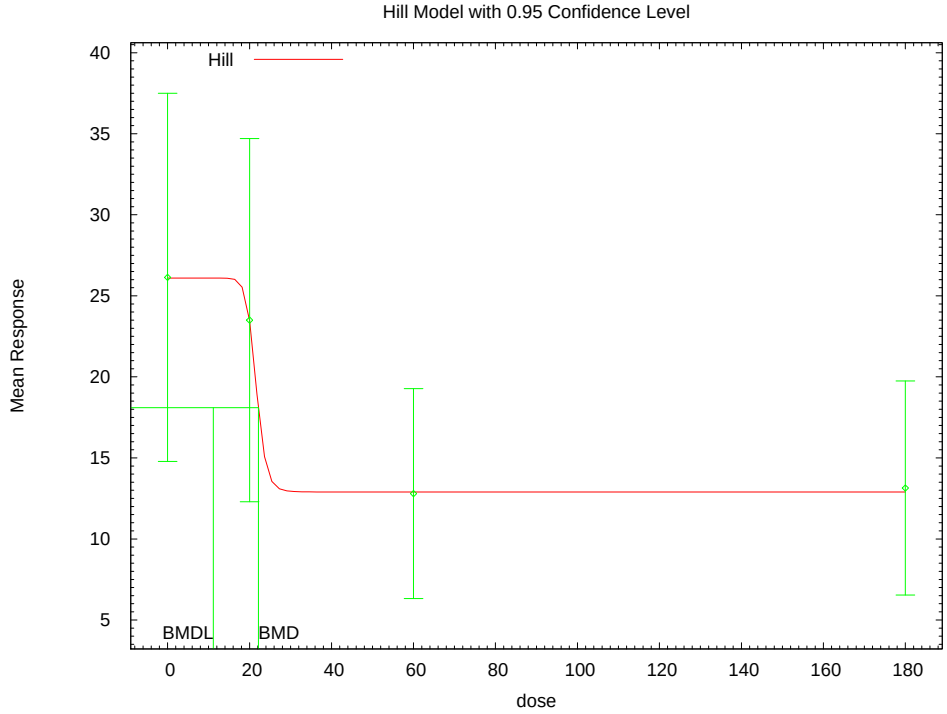
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	2	0.23	5.55	0.06	134.53	1.4E+02	5.3E+01	nonconstant variance, power restricted ≥1
exponential (M3)	2	0.23	5.55	0.06	134.53	1.4E+02	5.3E+01	nonconstant variance, power restricted ≥1
exponential (M4)	1	0.23	1.05	0.31	132.03	3.6E+01	1.2E+01	nonconstant variance, power restricted ≥1
exponential (M5)	0	0.23	0.08	N/A	133.06	2.8E+01	1.4E+01	nonconstant variance, power restricted ≥1
Hill	0	0.23	0.08	NA	133.06	2.2E+01	error	nonconstant variance, n restricted >1
linear	2	0.23	6.35	0.04	135.33	1.8E+02	9.3E+01	nonconstant variance
polynomial	1	0.23	0.06	0.81	131.04	4.0E+01	2.2E+01	nonconstant variance
power	2	0.23	6.35	0.04	135.33	1.8E+02	9.3E+01	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	2	0.23	3.80	0.15	133.83	9.5E+01	4.3E+01	constant variance, power restricted ≥1
exponential (M3)	2	0.23	3.80	0.15	133.83	9.5E+01	4.3E+01	constant variance, power restricted ≥1
exponential (M4)	1	0.23	1.06	0.30	133.09	3.0E+01	9.4E+00	constant variance, power restricted ≥1
exponential (M5)	0	0.23	0.01	N/A	134.03	2.9E+01	1.2E+01	constant variance, power restricted ≥1
Hill [c]	**1**	**0.23**	**0.01**	**0.94**	**132.03**	**2.2E+01**	**1.1E+01**	**constant variance, n restricted >1, bound hit**
linear	2	0.23	4.80	0.09	134.82	1.3E+02	8.1E+01	constant variance
polynomial	1	0.23	0.36	0.55	132.39	3.1E+01	1.8E+01	constant variance
power	2	0.23	4.80	0.09	134.82	1.3E+02	8.1E+01	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.30.2. *Figure for Selected Model: Hill, Constant Variance, n Restricted >1, Bound Hit*



E.3.30.3. *Output File for Selected Model: Hill, Constant Variance, n Restricted >1, Bound Hit*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AniDose\HillConstVar_BMR1_FR5_run_opp.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AniDose\HillConstVar_BMR1_FR5_run_opp.plt
                                                Tue Oct 06 15:22:42 2009
 ================================================================

 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
```

E.3.31. Mietinnin et al. (2006): Caries

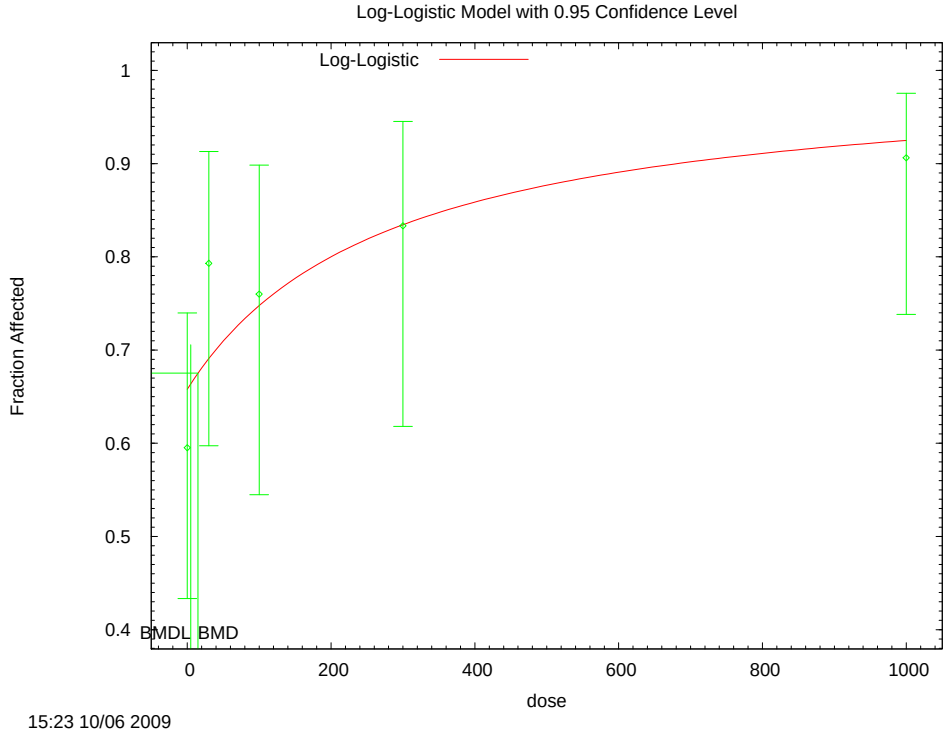
E.3.31.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	3	3.32	0.34	162.70	3.7E+01	2.0E+01	power restricted ≥1, bound hit
gamma	3	3.32	0.34	162.70	7.5E+01	4.1E+01	power restricted ≥1, bound hit
logistic	3	3.54	0.32	162.91	4.4E+01	2.6E+01	
logistic	3	3.54	0.32	162.91	9.0E+01	5.2E+01	
log-logistic [b]	**3**	**2.33**	**0.51**	**161.77**	**1.5E+01**	**5.0E+00**	**slope restricted ≥1, bound hit**
log-logistic	3	2.33	0.51	161.77	3.1E+01	1.1E+01	slope restricted ≥1, bound hit
log-probit	2	0.64	0.73	161.99	1.2E-01	error	slope restricted ≥1
log-probit	2	0.64	0.73	161.99	5.1E-01	error	slope restricted ≥1
multistage, 2-degree	3	3.32	0.34	162.70	3.7E+01	2.0E+01	betas restricted ≥0, bound hit
multistage, 2-degree	3	3.32	0.34	162.70	7.5E+01	4.1E+01	betas restricted ≥0, bound hit
probit	3	3.67	0.30	163.03	4.9E+01	3.1E+01	
probit	3	3.67	0.30	163.03	9.9E+01	6.2E+01	
Weibull	3	3.32	0.34	162.70	3.7E+01	2.0E+01	power restricted ≥1, bound hit
Weibull	3	3.32	0.34	162.70	7.5E+01	4.1E+01	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

E.3.31.2. *Figure for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*



E.3.31.3. *Output File for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AniDose\LogLogistic_BMR1_Caries.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AniDose\LogLogistic_BMR1_Caries.plt
                                                Tue Oct 06 15:23:23 2009
 ================================================================

 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 =           0.05

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =         14.824

             BMDL =        4.99044
```

E.3.32. National Toxicology Program (1982): Male Mice, Toxic Hepatitis

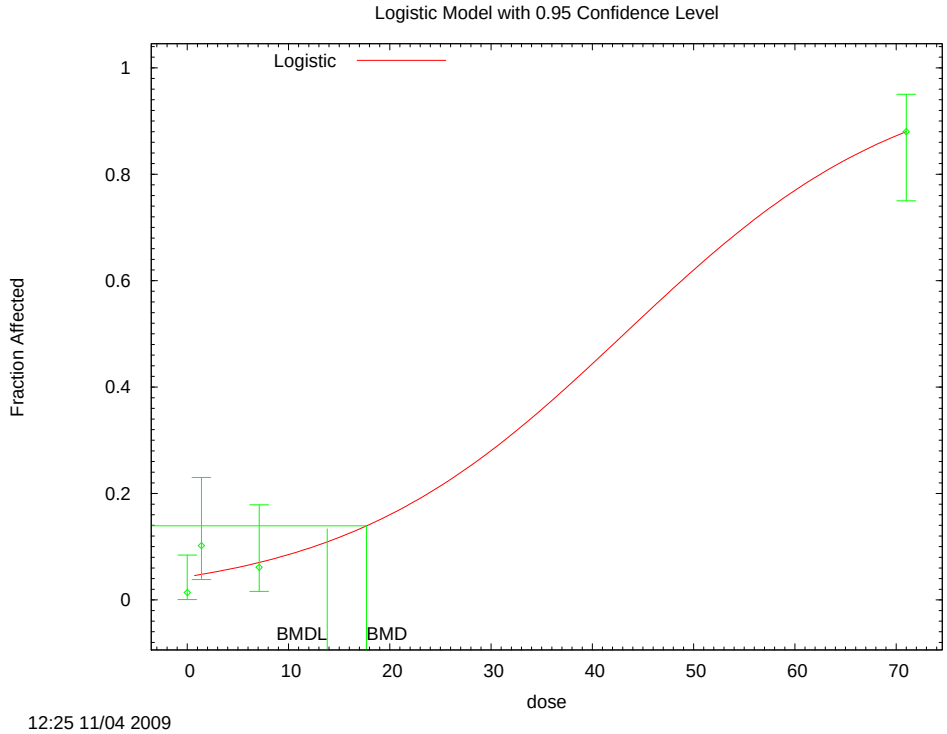
E.3.32.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	1	4.93	0.03	113.10	1.6E+01	5.2E+00	power restricted ≥1
logistic [b]	**2**	**4.76**	**0.09**	**110.71**	**1.8E+01**	**1.4E+01**	
log-logistic	1	4.93	0.03	113.09	1.5E+01	6.6E+00	slope restricted ≥1
log-probit	1	4.89	0.03	113.11	1.4E+01	7.2E+00	slope restricted ≥1
multistage, 2-degree	1	5.18	0.02	112.86	1.2E+01	4.6E+00	betas restricted ≥0
probit	2	4.86	0.09	110.70	1.6E+01	1.3E+01	
Weibull	1	4.99	0.03	113.06	1.6E+01	4.9E+00	power restricted ≥1

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

E.3.32.2. *Figure for Selected Model: Logistic*



E.3.32.3. *Output file for Selected Model: Logistic*

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AniDose\Logistic_BMR2_Toxic_hepatitis.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AniDose\Logistic_BMR2_Toxic_hepatitis.plt
                                                 Wed Nov 04 12:25:18 2009
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = 1/[1+EXP(-intercept-slope*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



                 Default Initial Parameter Values
                    background =           0   Specified
                     intercept =    -3.05581
                         slope =   0.0703319


          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        -0.66

     slope        -0.66            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
      intercept         -3.08708         0.358526           -3.78978            -2.38438
          slope          0.07156       0.00813416          0.0556174           0.0875027


                         Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -51.0633         4
    Fitted model       -53.3562         2       4.58581      2           0.101
  Reduced model        -121.743         1       141.358      3         <.0001

          AIC:         110.712
```

```
                                Goodness  of  Fit
                                                                  Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000     0.0436         3.186     1.000          73       -1.252
    1.4000     0.0480         2.353     5.000          49        1.769
    7.1000     0.0705         3.455     3.000          49       -0.254
   71.0000     0.8801        44.007    44.000          50       -0.003

 Chi^2 = 4.76      d.f. = 2        P-value = 0.0925


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        17.6885

            BMDL =        13.8272
```

E.3.33. National Toxicology Program (2006): Alveolar Metaplasia

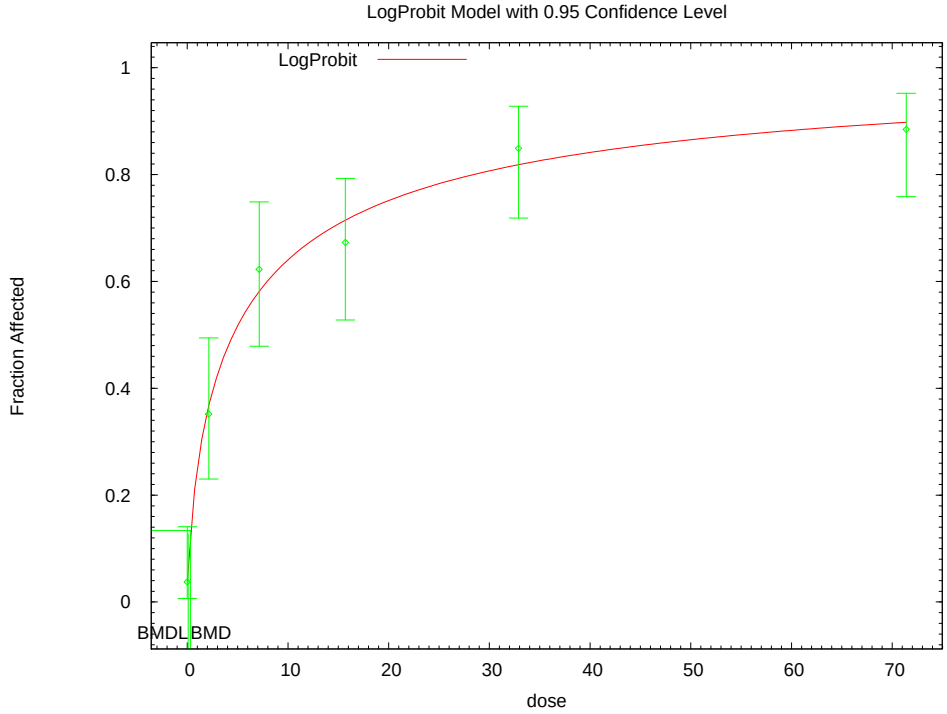
E.3.33.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	34.09	0.00	340.13	2.2E+00	1.8E+00	power restricted ≥1, bound hit
logistic	4	45.56	0.00	358.35	5.0E+00	4.1E+00	
log-logistic	4	3.98	0.41	312.97	6.6E-01	5.0E-01	slope restricted ≥1, bound hit
log-probit [b]	**3**	**1.31**	**0.73**	**312.54**	**3.3E-01**	**9.0E-02**	**slope restricted ≥1**
multistage, 2-degree	4	34.09	0.00	340.13	2.2E+00	1.8E+00	betas restricted ≥0, bound hit
probit	4	46.73	0.00	362.18	5.7E+00	4.8E+00	
Weibull	4	34.09	0.00	340.13	2.2E+00	1.8E+00	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

E.3.33.2. *Figure for Selected Model: Log-Probit, Slope Restricted ≥1*



E.3.33.3. *Output File for Selected Model: Log-Probit, Slope Restricted ≥1*

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AniDose\LogProbit_BMR2_Alveolar_metaplasia.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AniDose\LogProbit_BMR2_Alveolar_metaplasia.plt
                                                Wed Nov 04 12:26:52 2009
 ================================================================

 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 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 (and Specified) Parameter Values
background = 0.0377358
intercept = -0.759264
slope = 0.469642

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.24	0.12
intercept	-0.24	1	-0.9
slope	0.12	-0.9	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0374101	0.0259232	-0.0133985	0.0882186
intercept	-0.761678	0.210613	-1.17447	-0.348885
slope	0.471021	0.0755121	0.32302	0.619022

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-152.615	6			
Fitted model	-153.271	3	1.31226	3	0.7262
Reduced model	-216.802	1	128.374	5	<.0001

AIC: 312.543

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0374	1.983	2.000	53	0.012
2.1400	0.3679	19.868	19.000	54	-0.245
7.1400	0.5815	30.819	33.000	53	0.607
15.7000	0.7149	37.174	35.000	52	-0.668
32.9000	0.8187	43.389	45.000	53	0.574
71.4000	0.8981	46.701	46.000	52	-0.321

Chi^2 = 1.31 d.f. = 3 P-value = 0.7272

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.331636

BMDL = 0.0896842

E.3.34. National Toxicology Program (2006): Gingival Hyperplasia Squamous, 2 Years

E.3.34.1. *Summary Table of BMDS Modeling Results*

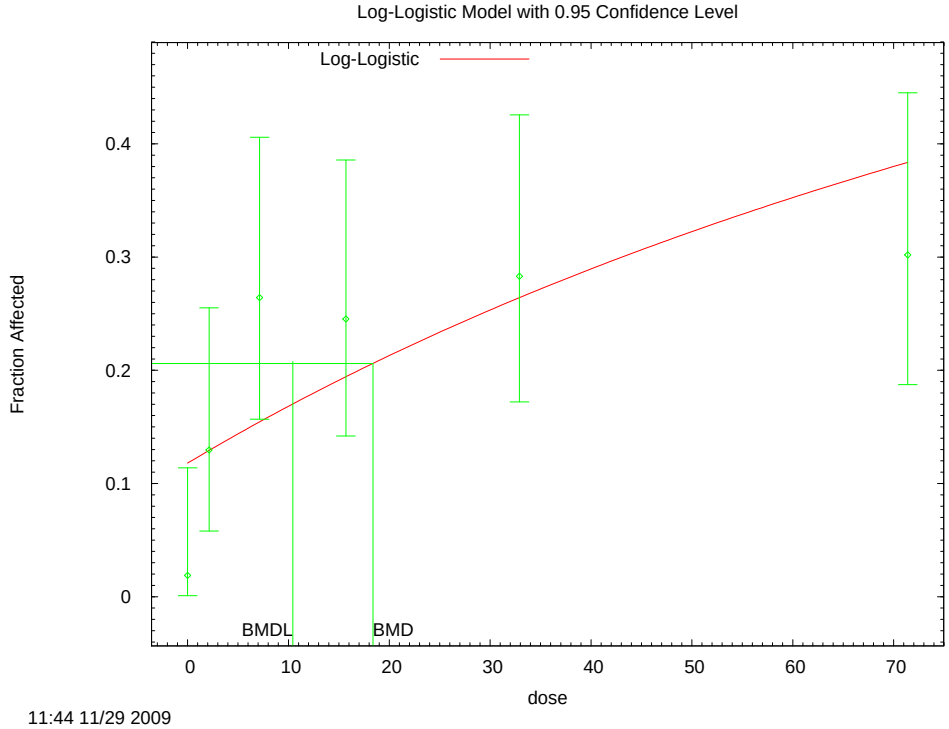
Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	12.82	0.01	318.87	2.3E+01	1.4E+01	power restricted ≥1, bound hit
logistic	4	13.78	0.01	320.91	3.6E+01	2.6E+01	
log-logistic [b]	**4**	**12.38**	**0.01**	**317.97**	**1.8E+01**	**1.0E+01**	**slope restricted ≥1, bound hit**
log-logistic [c]	3	1.53	0.68	307.42	3.7E-01	1.5E-07	slope unrestricted
log-probit	3	1.47	0.69	307.35	4.7E-01	8.9E-07	slope restricted ≥1
multistage, 1-degree	4	12.82	0.01	318.87	2.3E+01	1.4E+01	betas restricted ≥0, bound hit
probit	4	13.67	0.01	320.69	3.4E+01	2.4E+01	
Weibull	4	12.82	0.01	318.87	2.3E+01	1.4E+01	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

[c] Alternate model also presented in this appendix

E.3.34.2. *Figure for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*



E.3.34.3. *Output File for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*

```
 ===============================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov29\LogLogistic_BMR2_Ging_Hyp_2yr.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov29\LogLogistic_BMR2_Ging_Hyp_2yr.plt
                                                 Sun Nov 29 11:44:28 2009
 ===============================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 0.0188679
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

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval 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

Dose	Est._Prob.	Expected	Observed	Size	Scaled 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

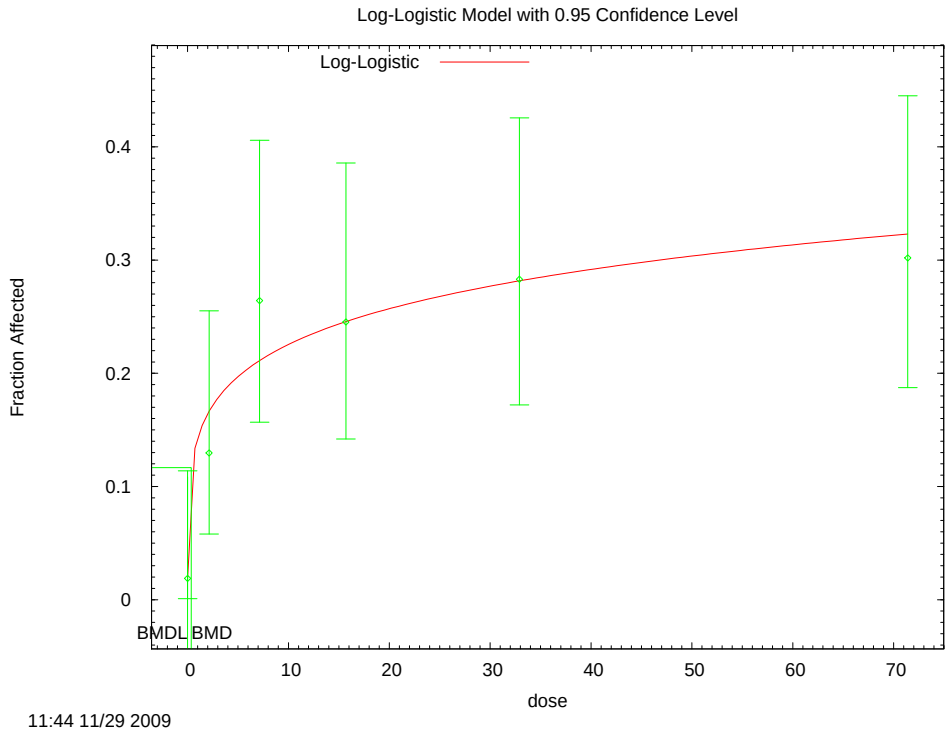
Risk Type = Extra risk

Confidence level = 0.95

BMD = 18.3832

BMDL = 10.4359

E.3.34.4. *Figure for Unrestricted Model: Log-Logistic, Slope Unrestricted*



E.3.34.5. *Output File for Unrestricted Model: Log-Logistic, Slope Unrestricted*

```
 ===================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov29\LogLogistic_Unrest_BMR2_Ging_Hyp_2yr.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov29\LogLogistic_Unrest_BMR2_Ging_Hyp_2yr.plt
                                                 Sun Nov 29 11:44:31 2009
 ===================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval 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

Dose	Est._Prob.	Expected	Observed	Size	Scaled 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

E.3.35. National Toxicology Program (2006): Heart, Cardiomyopathy

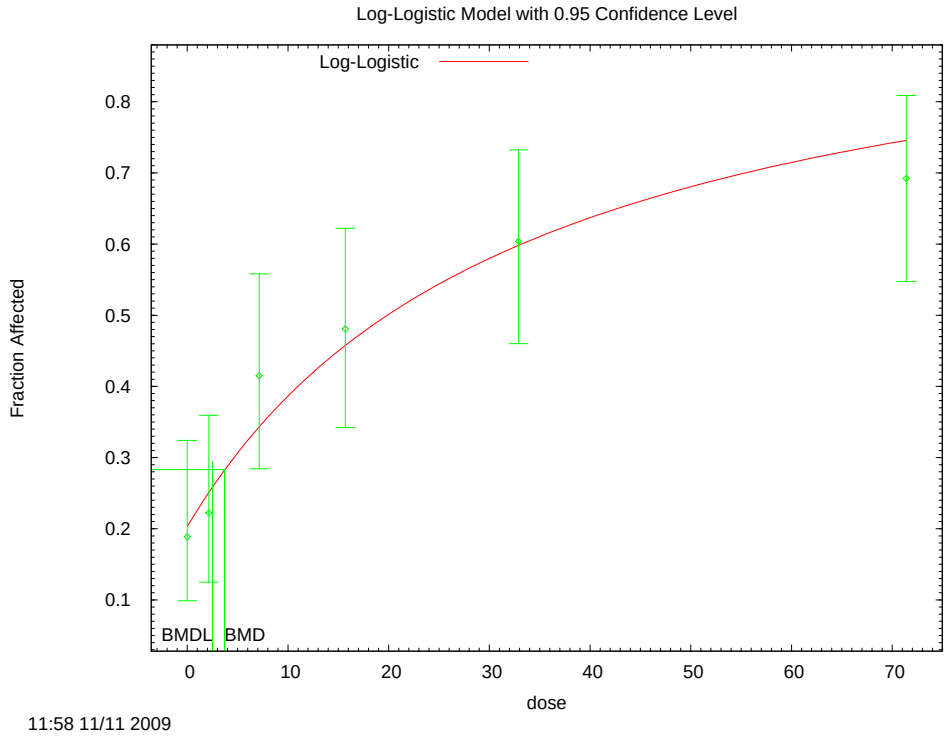
E.3.35.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	6.23	0.18	398.01	6.5E+00	4.8E+00	power restricted ≥1, bound hit
logistic	4	10.70	0.03	402.78	1.1E+01	9.2E+00	
log-logistic [b]	**4**	**2.42**	**0.66**	**394.22**	**3.7E+00**	**2.5E+00**	**slope restricted ≥1, bound hit**
log-probit	3	0.93	0.82	394.80	2.1E+00	5.1E-01	slope restricted ≥1
multistage, 2-degree	4	6.23	0.18	398.01	6.5E+00	4.8E+00	betas restricted ≥0, bound hit
probit	4	10.72	0.03	402.80	1.1E+01	9.3E+00	
Weibull	4	6.23	0.18	398.01	6.5E+00	4.8E+00	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

E.3.35.2. *Figure for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*



E.3.35.3. *Output File for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\LogLogistic_BMR2_Cardiomyopathy.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\LogLogistic_BMR2_Cardiomyopathy.plt
                                                Wed Nov 11 11:58:41 2009
 ================================================================

 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 = 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 =     0.188679
                     intercept =     -3.47661
                         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        -0.65

 intercept        -0.65            1



                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     background          0.20346            *                *                   *
      intercept         -3.50681            *                *                   *
          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         -193.93         6
```

```
   Fitted model        -195.111         2       2.36161      4          0.6696
  Reduced model        -216.802         1       45.7449      5         <.0001

           AIC:         394.221


                                  Goodness  of  Fit
                                                                        Scaled
      Dose     Est._Prob.    Expected    Observed     Size        Residual
   ----------------------------------------------------------------------------
     0.0000     0.2035        10.783    10.000          53       -0.267
     2.1400     0.2515        13.581    12.000          54       -0.496
     7.1400     0.3440        18.229    22.000          53        1.090
    15.7000     0.4585        23.840    25.000          52        0.323
    32.9000     0.5991        31.751    32.000          53        0.070
    71.4000     0.7464        38.815    36.000          52       -0.897

 Chi^2 = 2.42      d.f. = 4        P-value = 0.6589


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =        3.70462

            BMDL =        2.50223
```

E.3.36. National Toxicology Program (2006): Hepatocyte Hypertrophy, 2 Years

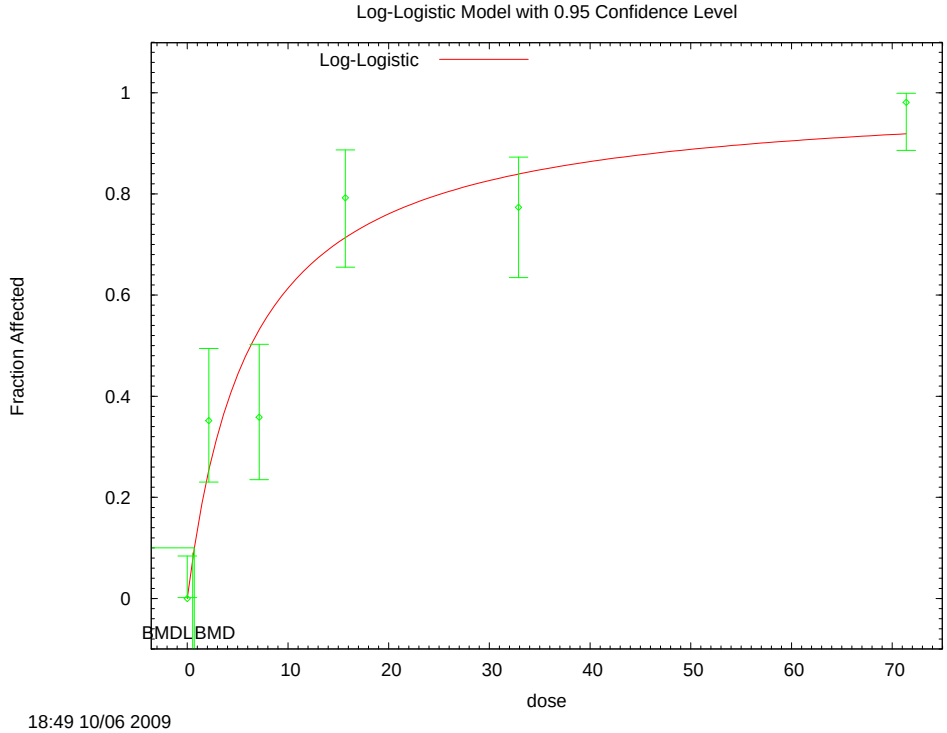
E.3.36.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	26.48	0.00	290.37	1.6E+00	1.3E+00	power restricted ≥1, bound hit
logistic	4	35.54	0.00	310.49	4.3E+00	3.6E+00	
log-logistic [b]	**5**	**15.18**	**0.01**	**278.08**	**7.0E-01**	**5.5E-01**	**slope restricted ≥1, bound hit**
log-probit	4	14.46	0.01	279.20	7.2E-01	3.3E-01	slope restricted ≥1
multistage, 2-degree	4	26.48	0.00	290.37	1.6E+00	1.3E+00	betas restricted ≥0, bound hit
probit	4	41.23	0.00	313.84	4.6E+00	3.9E+00	
Weibull	4	26.48	0.00	290.37	1.6E+00	1.3E+00	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

E.3.36.2. *Figure for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*



E.3.36.3. *Output File for Selected Model: Log-Logistic, Slope Restricted ≥1, Bound Hit*

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File:
C:\USEPA\BMDS21\AniDose\LogLogistic_BMR2_Hepatocyte_hypertrophy_2years.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AniDose\LogLogistic_BMR2_Hepatocyte_hypertrophy_2years.plt
                                                  Tue Oct 06 18:49:36 2009
 ================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = -2.2119
slope = 1.23746

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background -slope
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	intercept
intercept	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	*	*	*
intercept	-1.83737	*	*	*
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	-129.986	6			
Fitted model	-138.041	1	16.1104	5	0.006536
Reduced model	-219.97	1	179.968	5	<.0001

AIC: 278.082

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	53	0.000
2.1400	0.2542	13.724	19.000	54	1.649
7.1400	0.5320	28.198	19.000	53	-2.532
15.7000	0.7143	37.857	42.000	53	1.260
32.9000	0.8397	44.505	41.000	53	-1.312
71.4000	0.9192	48.715	52.000	53	1.655

Chi^2 = 15.18 d.f. = 5 P-value = 0.0096

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.697776

BMDL = 0.545416

E.3.37. National Toxicology Program (2006): Liver, Eosinophilic Focus, Multiple

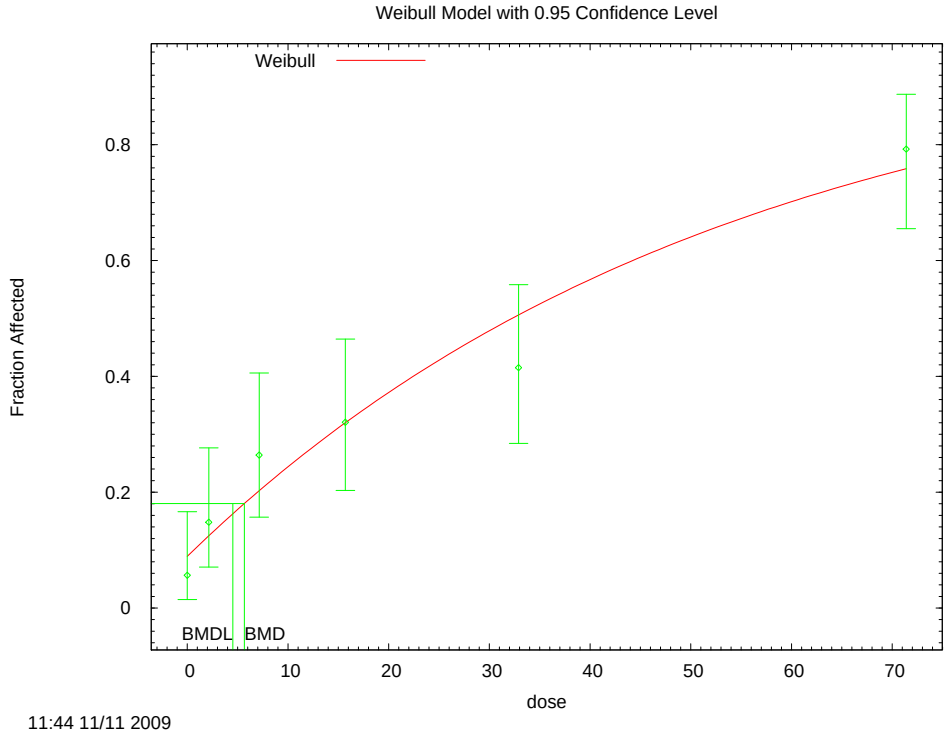
E.3.37.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	4.30	0.37	330.46	5.7E+00	4.5E+00	power restricted ≥1, bound hit
logistic	4	6.46	0.17	333.34	1.3E+01	1.1E+01	
log-logistic	3	5.90	0.12	334.15	4.7E+00	2.9E+00	slope restricted ≥1
log-probit	3	6.58	0.09	334.85	4.8E+00	1.8E+00	slope restricted ≥1
multistage, 2-degree	3	4.18	0.24	332.36	6.2E+00	4.5E+00	betas restricted ≥0
probit	4	6.16	0.19	332.96	1.2E+01	1.0E+01	
Weibull [b]	**4**	**4.30**	**0.37**	**330.46**	**5.7E+00**	**4.5E+00**	**power restricted ≥1, bound hit**

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

E.3.37.2. *Figure for Selected Model: Weibull, Power Restricted ≥1, Bound Hit*



E.3.37.3. *Output File for Selected Model: Weibull, Power Restricted ≥1, Bound Hit*

```
 ================================================================
         Weibull Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Weibull_BMR2_liver_eosin_focus.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Weibull_BMR2_liver_eosin_focus.plt
                                                Wed Nov 11 11:44:27 2009
 ================================================================

 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 =    0.0648148
                         Slope =   0.00246576
                         Power =      1.49873


           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 )

             Background        Slope

Background            1        -0.49

     Slope        -0.49            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0893152        0.0297295           0.0310464            0.147584
          Slope        0.0185641       0.00270697           0.0132586           0.0238697
          Power                1               NA

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         -161.07         6
   Fitted model        -163.229         2       4.31726      4          0.3648
```

```
  Reduced model        -202.816         1       83.4925      5         <.0001

           AIC:         330.457


                                  Goodness  of  Fit
                                                                        Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0893         4.734     3.000          53       -0.835
     2.1400     0.1248         6.738     8.000          54        0.520
     7.1400     0.2024        10.725    14.000          53        1.120
    15.7000     0.3196        16.937    17.000          53        0.019
    32.9000     0.5056        26.794    22.000          53       -1.317
    71.4000     0.7581        40.177    42.000          53        0.585

 Chi^2 = 4.30      d.f. = 4        P-value = 0.3672


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =        5.67549

            BMDL =        4.5323
```

E.3.38. National Toxicology Program (2006): Liver, Fatty Change, Diffuse

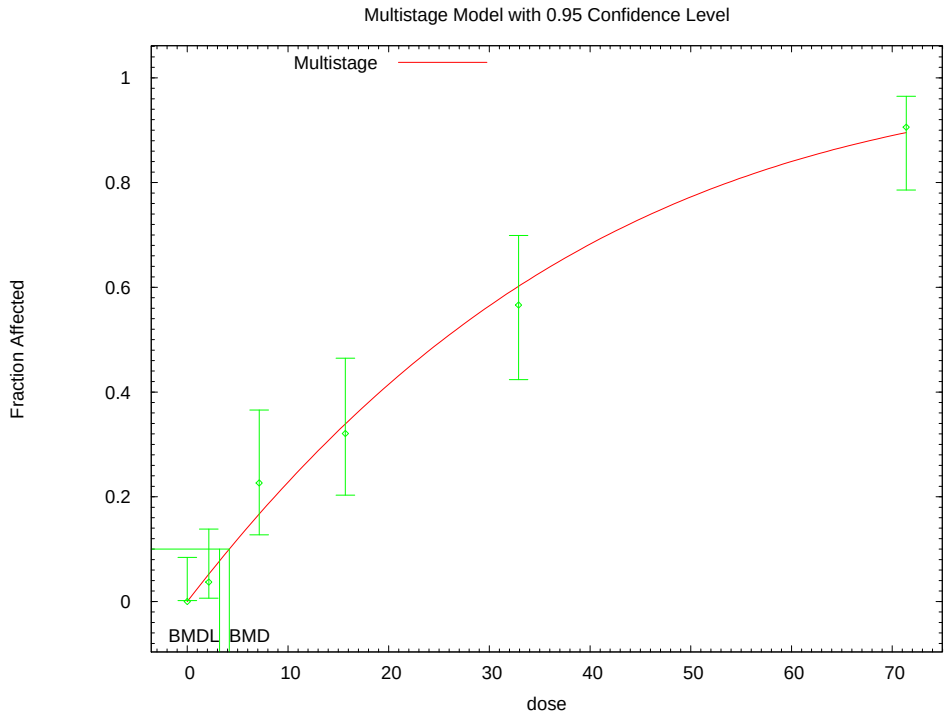
E.3.38.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	2.37	0.67	252.29	4.2E+00	3.2E+00	power restricted ≥1
logistic	4	15.06	0.00	269.83	1.1E+01	9.3E+00	
log-logistic	4	4.96	0.29	255.08	4.7E+00	3.2E+00	slope restricted ≥1
log-probit	4	5.05	0.28	255.26	4.6E+00	3.2E+00	slope restricted ≥1
multistage, 2-degree [b]	**4**	**2.03**	**0.73**	**251.93**	**4.2E+00**	**3.2E+00**	**betas restricted ≥0**
probit	4	14.92	0.00	269.43	1.1E+01	9.1E+00	
Weibull	4	2.31	0.68	252.22	4.3E+00	3.2E+00	power restricted ≥1

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

E.3.39. Figure for Selected Model: Multistage, 2-Degree, Betas Restricted ≥0



E.3.40. Output File for Selected Model: Multistage, 2-Degree, Betas Restricted ≥0

```
 ========================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Multistage_BMR2_liver_fatty_change_diff.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Multistage_BMR2_liver_fatty_change_diff.plt
                                                 Wed Nov 11 11:44:50 2009
 ========================================================================

 NTP_liver_fatty_change_diffuse
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 6
 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 =      0.02888
                        Beta(1) =    0.0193083
                        Beta(2) =  0.000185869


           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(2)

   Beta(1)            1        -0.89

   Beta(2)        -0.89            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
      Background                0            *               *                   *
         Beta(1)        0.0248561            *               *                   *
         Beta(2)     9.42857e-005            *               *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -122.992         6
   Fitted model         -123.966         2       1.94705      4          0.7455
  Reduced model         -204.846         1       163.708      5         <.0001

           AIC:          251.932


                                Goodness  of  Fit
                                                                      Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0000         0.000       0.000          53        0.000
     2.1400     0.0522         2.819       2.000          54       -0.501
     7.1400     0.1666         8.831      12.000          53        1.168
    15.7000     0.3387        17.949      17.000          53       -0.275
    32.9000     0.6014        31.875      30.000          53       -0.526
    71.4000     0.8952        47.444      48.000          53        0.249

 Chi^2 = 2.03      d.f. = 4        P-value = 0.7302


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =       4.17277
```

```
              BMDL =        3.20452

              BMDU =        5.73352

Taken together, (3.20452, 5.73352) is a 90     % two-sided confidence
interval for the BMD
```

E.3.41. National Toxicology Program (2006): Liver Necrosis

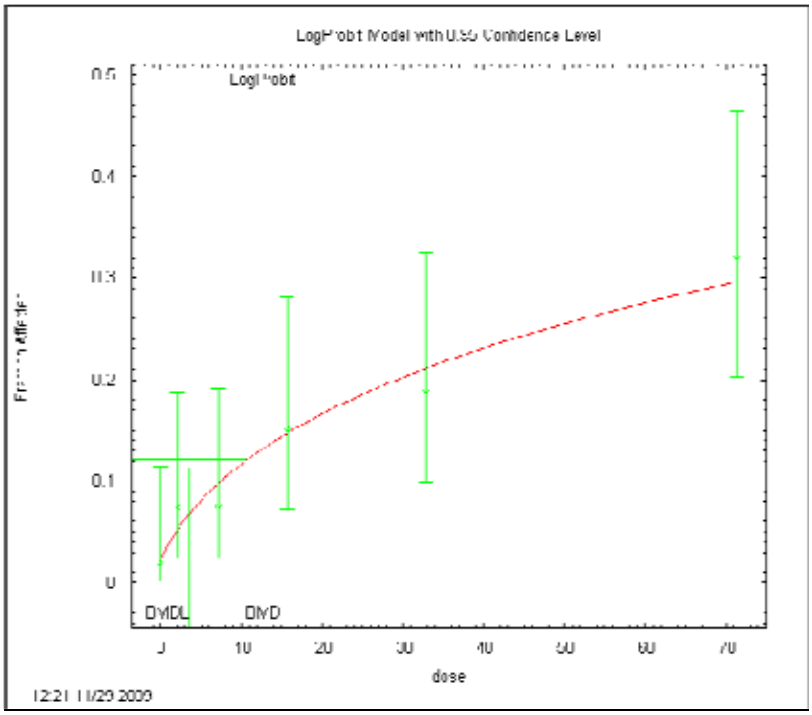
E.3.41.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	1.85	0.76	235.58	2.0E+01	1.4E+01	power restricted ≥1, bound hit
logistic	4	4.07	0.40	238.31	3.5E+01	2.8E+01	
log-logistic	4	1.60	0.81	235.27	1.8E+01	1.2E+01	slope restricted ≥1, bound hit
log-probit [b]	**3**	**1.14**	**0.77**	**236.74**	**1.1E+01**	**3.5E+00**	**slope restricted ≥1**
multistage, 2-degree	4	1.85	0.76	235.58	2.0E+01	1.4E+01	betas restricted ≥0, bound hit
probit	4	3.72	0.45	237.89	3.3E+01	2.6E+01	
Weibull	4	1.85	0.76	235.58	2.0E+01	1.4E+01	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

E.3.41.2. *Figure for Selected Model: LogProbit*



E.3.41.3. *Output File for Selected Model: Log-Probit*

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov29\LogProbit_BMR2_liver_necrosis.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov29\LogProbit_BMR2_liver_necrosis.plt
                                                 Sun Nov 29 12:24:51 2009
 ================================================================

 NTP_liver_necrosis
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 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 (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

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval 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

Dose	Est._Prob.	Expected	Observed	Size	Scaled 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

E.3.42. National Toxicology Program (2006): Liver, Pigmentation

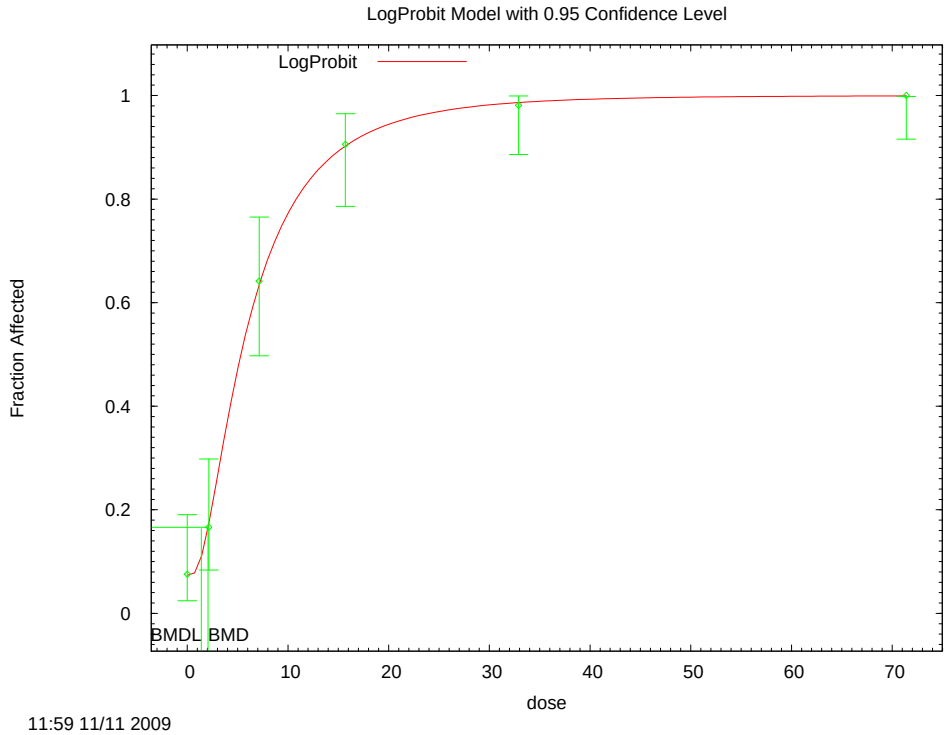
E.3.42.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	3	3.05	0.38	197.66	1.5E+00	8.1E-01	power restricted ≥1
logistic	4	29.12	0.00	203.52	2.3E+00	1.9E+00	
log-logistic	3	0.19	0.98	195.60	2.2E+00	1.5E+00	slope restricted ≥1
log-probit [b]	**3**	**0.18**	**0.98**	**195.45**	**2.1E+00**	**1.4E+00**	**slope restricted ≥1**
multistage, 2-degree	3	4.53	0.21	199.85	9.4E-01	7.1E-01	betas restricted ≥0
probit	4	131.22	0.00	210.31	2.3E+00	1.9E+00	
Weibull	3	3.75	0.29	198.49	1.3E+00	7.5E-01	power restricted ≥1

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

E.3.42.2. *Figure for Selected Model: Log-Probit, Slope Restricted ≥1*



E.3.42.3. *Output File for Selected Model: Log-Probit, Slope Restricted ≥1*

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\LogProbit_BMR2_Pigmentation.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\LogProbit_BMR2_Pigmentation.plt
                                              Wed Nov 11 11:59:31 2009
 ================================================================

 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 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 (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
```

E.3.43. National Toxicology Program (2006): Lung, Alveolar to Bronchiolar Epithelial Metaplasia (Alveolar Epithelium, Metaplasia, Bronchiolar)

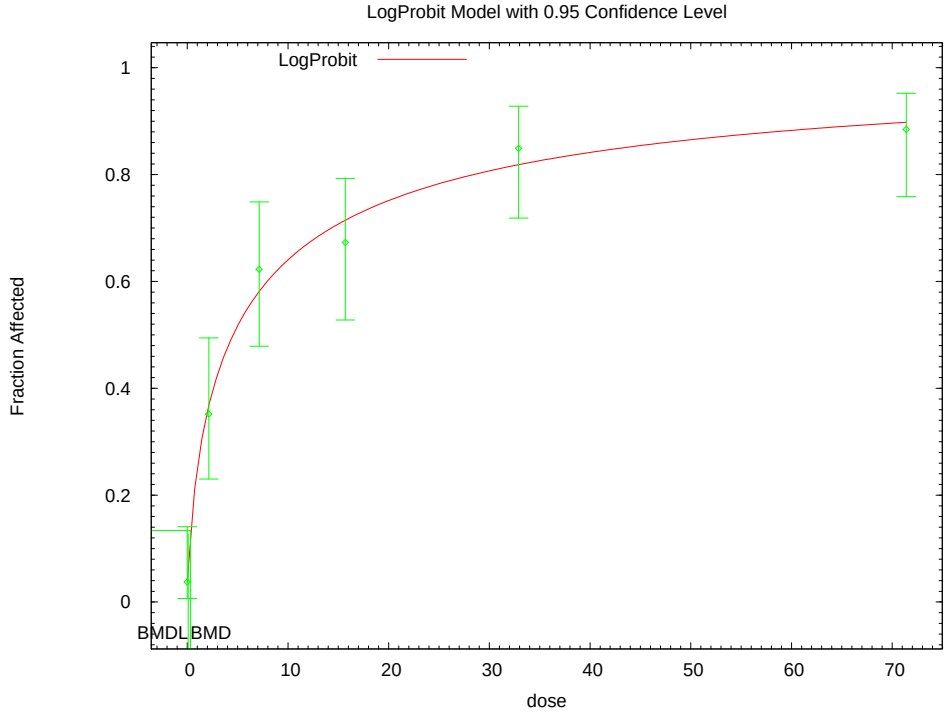
E.3.43.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	4	34.09	0.00	340.13	2.2E+00	1.8E+00	power restricted ≥1, bound hit
logistic	4	45.56	0.00	358.35	5.0E+00	4.1E+00	
log-logistic	4	3.98	0.41	312.97	6.6E-01	5.0E-01	slope restricted ≥1, bound hit
log-probit [b]	**3**	**1.31**	**0.73**	**312.54**	**3.3E-01**	**9.0E-02**	**slope restricted ≥1**
multistage, 2-degree	4	34.09	0.00	340.13	2.2E+00	1.8E+00	betas restricted ≥0, bound hit
probit	4	46.73	0.00	362.18	5.7E+00	4.8E+00	
Weibull	4	34.09	0.00	340.13	2.2E+00	1.8E+00	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

E.3.43.2. *Figure for Selected Model: Log-Probit, Slope Restricted ≥1*



E.3.43.3. *Output File for Selected Model: Log-Probit, Slope Restricted ≥1*

```
 ================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\LogProbit_BMR2_Alv_bronch_epith_metapl.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\LogProbit_BMR2_Alv_bronch_epith_metapl.plt
                                                Wed Nov 11 12:00:22 2009
 ================================================================

 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 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 (and Specified) Parameter Values
background = 0.0377358
intercept = -0.759264
slope = 0.469642

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.24	0.12
intercept	-0.24	1	-0.9
slope	0.12	-0.9	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0374101	0.0259232	-0.0133985	0.0882186
intercept	-0.761678	0.210613	-1.17447	-0.348885
slope	0.471021	0.0755121	0.32302	0.619022

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-152.615	6			
Fitted model	-153.271	3	1.31226	3	0.7262
Reduced model	-216.802	1	128.374	5	<.0001

AIC: 312.543

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0374	1.983	2.000	53	0.012
2.1400	0.3679	19.868	19.000	54	-0.245
7.1400	0.5815	30.819	33.000	53	0.607
15.7000	0.7149	37.174	35.000	52	-0.668
32.9000	0.8187	43.389	45.000	53	0.574
71.4000	0.8981	46.701	46.000	52	-0.321

Chi^2 = 1.31 d.f. = 3 P-value = 0.7272

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.331636

BMDL = 0.0896842

E.3.44. National Toxicology Program (2006): Oval Cell Hyperplasia, 2 Years

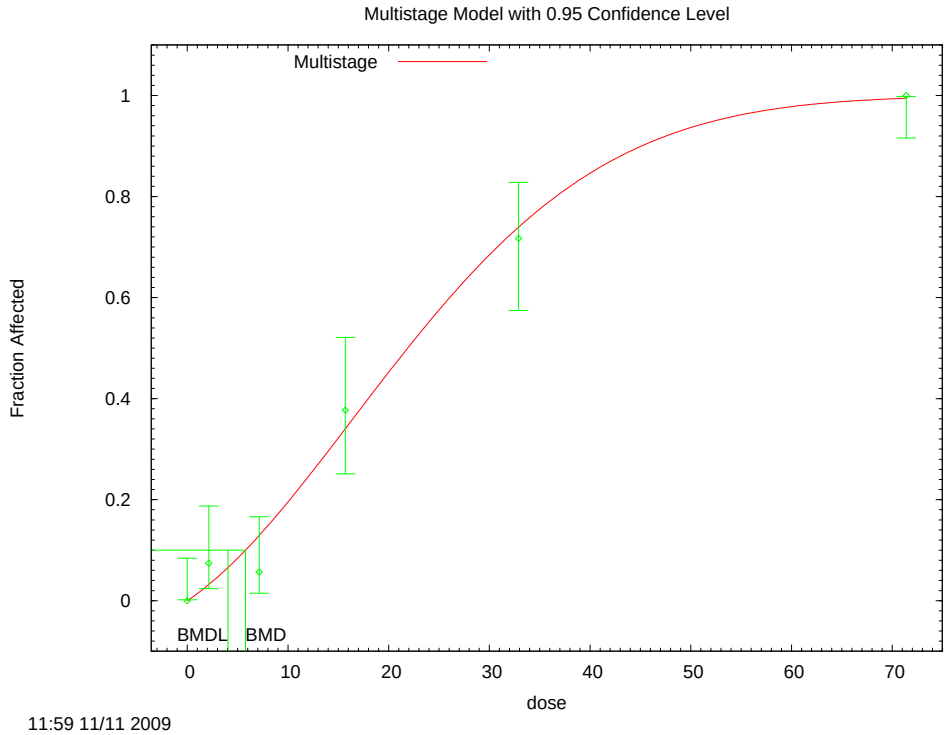
E.3.44.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	3	7.00	0.07	199.45	9.0E+00	5.5E+00	power restricted ≥1
logistic	4	8.72	0.07	199.88	9.8E+00	8.2E+00	
log-logistic	3	8.38	0.04	202.01	9.7E+00	7.2E+00	slope restricted ≥1
log-probit	3	7.12	0.07	200.42	1.0E+01	7.8E+00	slope restricted ≥1
multistage, 2-degree [b]	**4**	**6.33**	**0.18**	**195.33**	**5.8E+00**	**4.0E+00**	**betas restricted ≥0**
probit	4	7.50	0.11	198.17	9.1E+00	7.7E+00	
Weibull	3	6.92	0.07	198.69	7.7E+00	4.7E+00	power restricted ≥1

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

E.3.44.2. *Figure for Selected Model: Multistage, 2-Degree, Betas Restricted ≥0*



E.3.44.3. *Output File for Selected Model: Multistage, 2-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Multistage_BMR2_Oval_cell_hyperplasia.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Multistage_BMR2_Oval_cell_hyperplasia.plt
                                                Wed Nov 11 11:59:06 2009
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 6
 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
                        Beta(1) =           0
                        Beta(2) = 1.98687e+016


           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(2)

   Beta(1)            1        -0.89

   Beta(2)        -0.89            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background                0           *               *                   *
        Beta(1)        0.0133632           *               *                   *
        Beta(2)       0.00083535           *               *                   *

* - Indicates that this value is not calculated.
```

```
                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
       Full model        -92.4898         6
      Fitted model       -95.6669         2       6.35417      4          0.1742
    Reduced model        -210.191         1       235.402      5         <.0001

             AIC:         195.334


                                  Goodness  of  Fit
                                                                        Scaled
       Dose     Est._Prob.    Expected    Observed     Size       Residual
    ----------------------------------------------------------------------
      0.0000     0.0000         0.000     0.000          53        0.000
      2.1400     0.0319         1.723     4.000          54        1.763
      7.1400     0.1289         6.832     3.000          53       -1.571
     15.7000     0.3401        18.027    20.000          53        0.572
     32.9000     0.7392        39.175    38.000          53       -0.368
     71.4000     0.9946        52.711    53.000          53        0.539

 Chi^2 = 6.33      d.f. = 4        P-value = 0.1759


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        5.78926

             BMDL =        4.04553

             BMDU =        9.63861

Taken together, (4.04553, 9.63861) is a 90     % two-sided confidence
interval for the BMD
```

E.3.45. National Toxicology Program (2006): Toxic Hepatopathy

E.3.45.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma [b]	**4**	**1.80**	**0.77**	**185.63**	**4.7E+00**	**3.3E+00**	**power restricted ≥1**
logistic	4	12.79	0.01	198.45	7.1E+00	5.9E+00	
log-logistic	3	3.20	0.36	190.06	5.7E+00	4.0E+00	slope restricted ≥1
log-probit	3	3.09	0.38	189.86	6.1E+00	4.1E+00	slope restricted ≥1
multistage, 2-degree	4	2.89	0.58	186.52	4.2E+00	2.7E+00	betas restricted ≥0
multistage, 2-degree	4	2.89	0.58	186.52	4.2E+00	2.7E+00	betas unrestricted

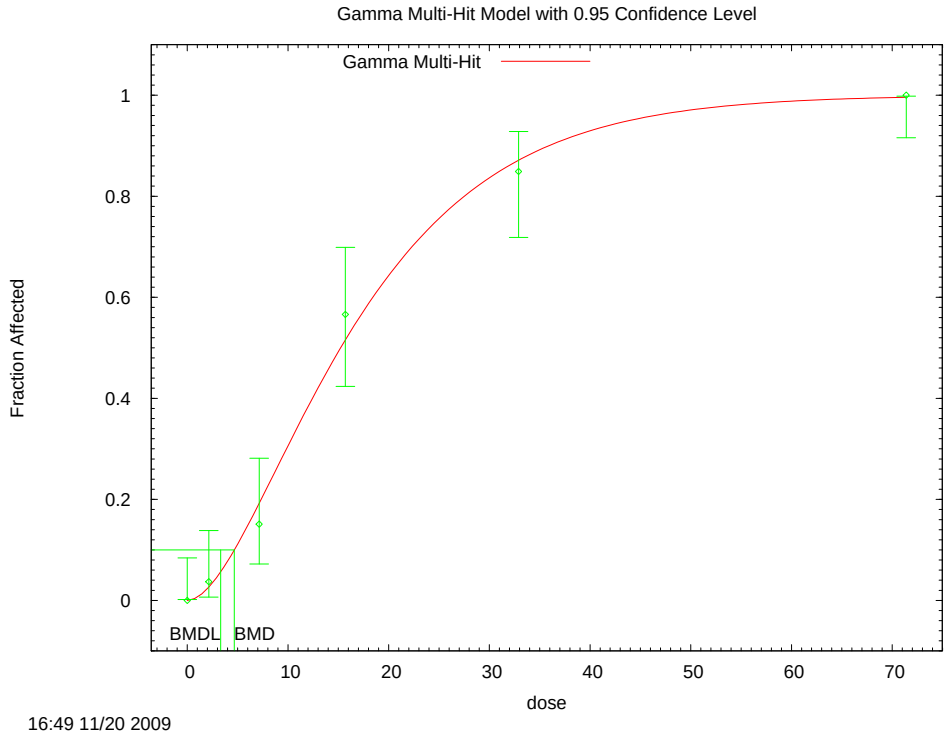
Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
multistage, 1-degree	5	10.28	0.07	194.94	2.1E+00	1.8E+00	betas unrestricted
probit	4	11.78	0.02	197.16	6.8E+00	5.7E+00	
Weibull [c]	4	1.95	0.75	185.66	4.5E+00	3.2E+00	power restricted ≥1

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

[c] Alternate model also presented in this appendix

E.3.45.2. *Figure for Selected Model: Gamma, Power Restricted ≥1*



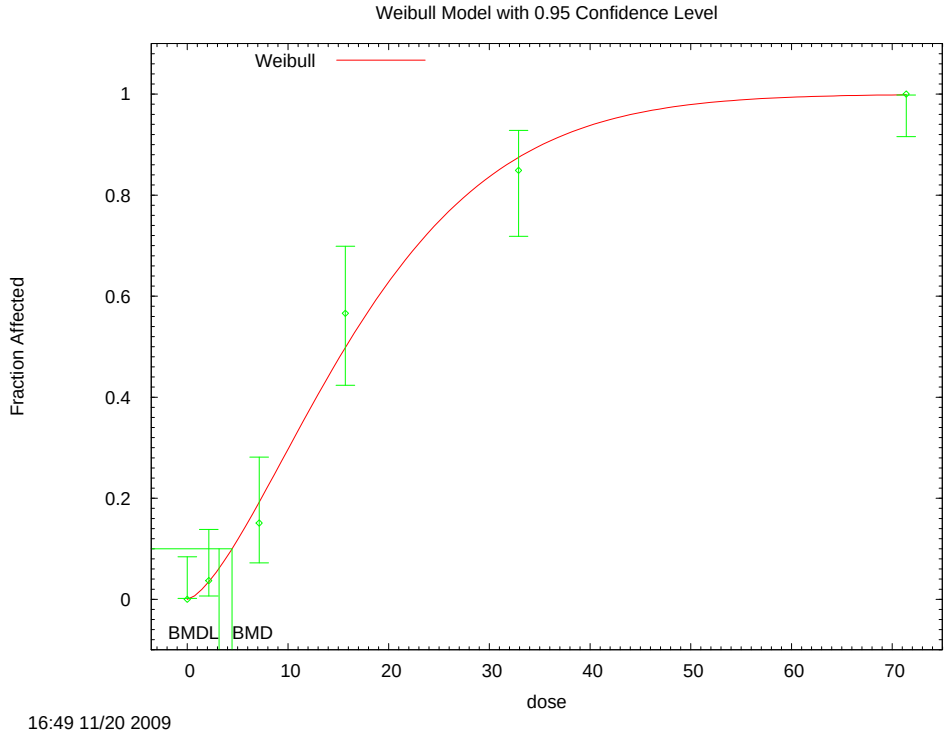
E.3.45.3. *Output file for Selected Model: Gamma, Power Restricted ≥1*

```
 ========================================================================
         Gamma Model. (Version: 2.13;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Gamma_BMR2_Toxic_hepatopathy.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Gamma_BMR2_Toxic_hepatopathy.plt
                                                 Fri Nov 20 16:49:26 2009
 ========================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
```

```
The form of the probability function is:

P[response]= background+(1-background)*CumGamma[slope*dose,power],
where CumGamma(.) is the cummulative Gamma distribution function


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 =    0.0683125
                         Power =          1.3


          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         0.94

    Power         0.94            1



                               Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
    Background                0               NA
         Slope         0.105412        0.0237428           0.0588765            0.151947
         Power          1.92239         0.361359             1.21414             2.63064

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        -89.8076         6
  Fitted model        -90.8168         2       2.01832      4          0.7324
 Reduced model        -218.207         1       256.799      5         <.0001

          AIC:         185.634


                                 Goodness  of  Fit
                                                                  Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
   0.0000     0.0000         0.000     0.000          53        0.000
   2.1400     0.0265         1.429     2.000          54        0.484
   7.1400     0.1926        10.205     8.000          53       -0.768
```

```
    15.7000     0.5170        27.403    30.000          53        0.714
    32.9000     0.8723        46.232    45.000          53       -0.507
    71.4000     0.9960        52.788    53.000          53        0.462

 Chi^2 = 1.80      d.f. = 4        P-value = 0.7716


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =       4.66805

            BMDL =       3.31743
```

E.3.45.4. *Figure for Unrestricted Model: Weibull, Power Restricted ≥1*



E.3.45.5. *Output File for Unrestricted Model: Weibull, Power Restricted ≥1*

```
 ========================================================================
         Weibull Model using Weibull Model (Version: 2.12;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Weibull_BMR2_Toxic_hepatopathy.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Weibull_BMR2_Toxic_hepatopathy.plt
                                                 Fri Nov 20 16:49:32 2009
 ========================================================================
```

```
 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 =    0.0286401
                         Power =      1.19362


          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        0.0113696       0.00592954       -0.000252127           0.0229912
          Power           1.4905         0.169532            1.15823             1.82278

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        -89.8076         6
    Fitted model       -90.8285         2       2.04181      4          0.7281
   Reduced model       -218.207         1       256.799      5         <.0001

          AIC:         185.657


                                  Goodness  of  Fit
                                                                 Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          53        0.000
     2.1400     0.0347         1.875     2.000          54        0.093
```

```
      7.1400     0.1918        10.164     8.000          53       -0.755
     15.7000     0.4979        26.391    30.000          53        0.992
     32.9000     0.8745        46.349    45.000          53       -0.559
     71.4000     0.9986        52.927    53.000          53        0.270

 Chi^2 = 1.95      d.f. = 4        P-value = 0.7454


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         4.4538

            BMDL =        3.15886
```

E.3.46. Ohsako et al. (2001): Anogenital PND120

E.3.46.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	3	0.46	5.02	0.17	185.44	7.5E+02	4.8E+02	nonconstant variance, power restricted ≥1
exponential (M3)	3	0.46	5.02	0.17	185.44	7.5E+02	4.8E+02	nonconstant variance, power restricted ≥1
exponential (M4)	2	0.46	4.29	0.12	186.72	4.8E+02	1.1E+01	nonconstant variance, power restricted ≥1
exponential (M5)	2	0.46	4.29	0.12	186.72	4.8E+02	1.1E+01	nonconstant variance, power restricted ≥1
Hill	2	0.46	3.11	0.21	185.54	7.1E+01	1.3E+01	nonconstant variance, n restricted >1, bound hit
linear	3	0.46	5.09	0.17	185.52	7.6E+02	5.1E+02	nonconstant variance
polynomial	2	0.46	4.45	0.11	186.88	4.8E+02	1.5E+02	nonconstant variance
power	3	0.46	5.09	0.17	185.52	7.6E+02	5.1E+02	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	3	0.46	7.00	0.07	185.90	6.5E+02	4.2E+02	constant variance, power restricted ≥1
exponential (M3)	3	0.46	7.00	0.07	185.90	6.5E+02	4.2E+02	constant variance, power restricted ≥1
exponential (M4)	2	0.46	3.17	0.20	184.07	4.1E+01	1.2E+01	constant variance, power restricted ≥1
exponential (M5)	1	0.46	2.84	0.09	185.74	3.8E+01	1.3E+01	constant variance, power restricted ≥1
Hill [c]	**2**	**0.46**	**2.74**	**0.25**	**183.64**	**6.0E+01**	**1.2E+01**	**constant variance, n restricted >1, bound**

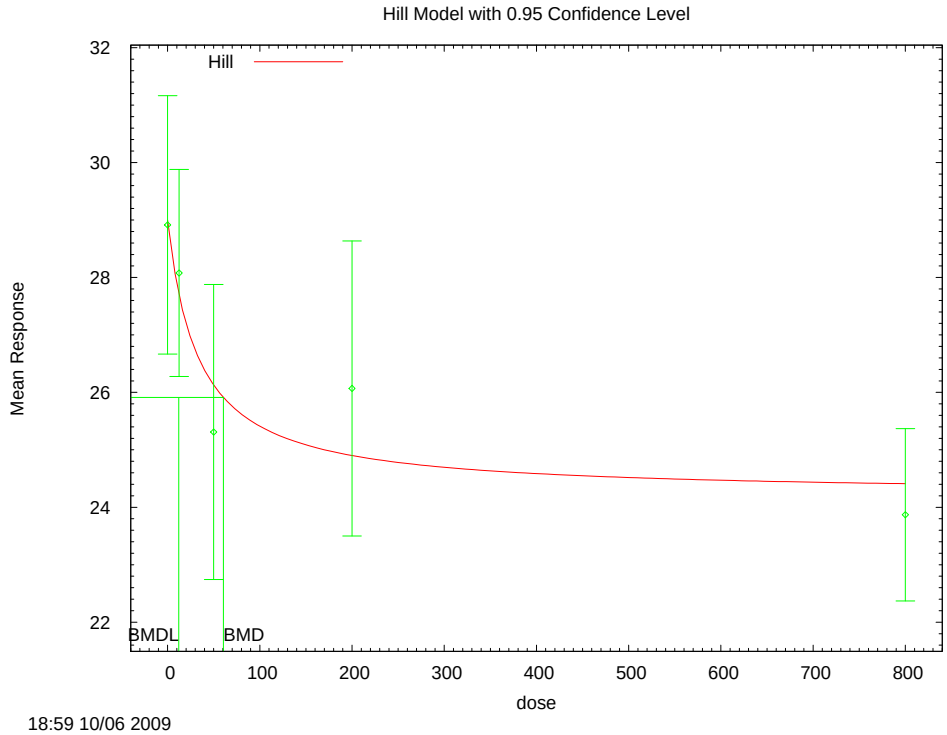
Model	Degrees of Freedom	Variance p-Value [a]	χ^2 Test Statistic	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
								hit
linear	3	0.46	7.12	0.07	186.02	6.6E+02	4.4E+02	constant variance
polynomial	2	0.46	5.55	0.06	186.45	2.7E+02	1.3E+02	constant variance
power	3	0.46	7.12	0.07	186.02	6.6E+02	4.4E+02	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.46.2. *Figure for Selected Model: Hill, Constant Variance, n Restricted >1, Bound Hit*



E.3.46.3. *Output File for Selected Model: Hill, Constant Variance, n Restricted >1, Bound Hit*

```
=================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
```

```
          Input Data File: C:\USEPA\BMDS21\AniDose\HillConstVar_BMR1_Anogenital_PND120.(d)
          Gnuplot Plotting File:  C:\USEPA\BMDS21\AniDose\HillConstVar_BMR1_Anogenital_PND120.plt
                                                  Tue Oct 06 18:59:02 2009
 ================================================================

 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 =      9.96434
                          rho =            0   Specified
                    intercept =      28.9146
                            v =     -5.04512
                            n =      1.44913
                            k =      35.3408


           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    -4.2e-009    -3.6e-008     2.3e-008

 intercept    -4.2e-009            1        -0.63        -0.52

         v    -3.6e-008        -0.63            1        -0.13

         k     2.3e-008        -0.52        -0.13            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha          9.51224          1.83063            5.92427             13.1002
      intercept          28.9963         0.861586            27.3077              30.685
              v         -4.77893          1.14548           -7.02403            -2.53384
              n                1               NA
              k          33.2115            32.41           -30.3109             96.7338

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	3.54	3.08	-0.0918
12.5	10	28.1	27.7	2.52	3.08	0.399
50	10	25.3	26.1	3.59	3.08	-0.836
200	10	26.1	24.9	3.59	3.08	1.2
800	12	23.9	24.4	2.36	3.08	-0.605

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	-86.449919	6	184.899838
A2	-84.654549	10	189.309098
A3	-86.449919	6	184.899838
fitted	-87.819648	4	183.639297
R	-95.473923	2	194.947846

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	21.6387	8	0.005631
Test 2	3.59074	4	0.4642
Test 3	3.59074	4	0.4642
Test 4	2.73946	2	0.2542

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 =       60.4402
            BMDL =       12.1546
```

E.3.47. Schantz et al. (1996): Maze Errors Per Block, Female

E.3.47.1. *Summary Table of BMDS Modeling Results*

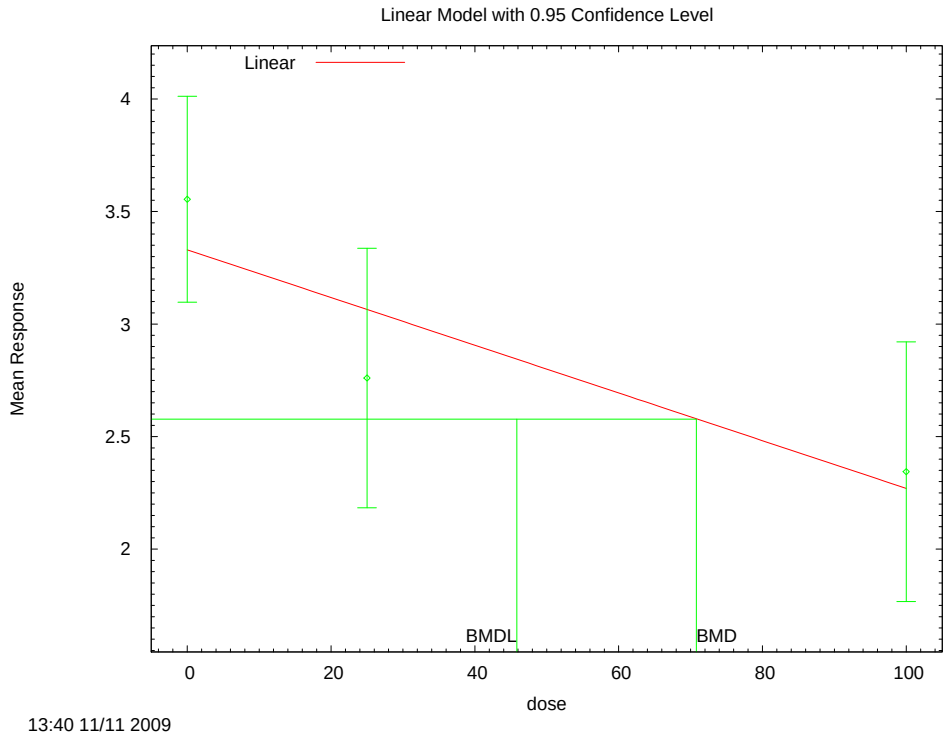
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
linear	1	0.71	3.25	0.07	20.63	6.7E+01	3.8E+01	nonconstant variance
polynomial	1	0.71	3.25	0.07	20.63	6.7E+01	3.8E+01	nonconstant variance
power	1	0.71	3.25	0.07	20.63	6.7E+01	3.8E+01	nonconstant variance, power restricted ≥1, bound hit
linear [c]	**1**	**0.71**	**2.77**	**0.10**	**18.72**	**7.1E+01**	**4.6E+01**	**constant variance**
polynomial	1	0.71	2.77	0.10	18.72	7.1E+01	4.6E+01	constant variance
power	1	0.71	2.77	0.10	18.72	7.1E+01	4.6E+01	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.47.2. *Figure for Selected Model: Linear, Constant Variance*



E.3.47.3. *Output File for Selected Model: Linear, Constant Variance*

```
 ========================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\AD\LinearConstVar_BMR4_maze_errors.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\LinearConstVar_BMR4_maze_errors.plt
                                                 Wed Nov 11 13:40:58 2009
 ========================================================================

 Rel Male Thymus wt, Tbl 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 = 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 =     0.569565
                            rho =            0   Specified
                         beta_0 =      3.32773
                         beta_1 =   -0.0105912


          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     1.3e-010     3.9e-011

    beta_0     1.3e-010            1         -0.7

    beta_1     3.9e-011         -0.7            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha         0.562168         0.145151            0.277677            0.846659
        beta_0           3.32773         0.191722             2.95196              3.7035
        beta_1       -0.0105912       0.00322157          -0.0169054         -0.00427705


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

   0    10       3.55         3.33        0.639         0.75          0.957
  25    10       2.76         3.06        0.806         0.75          -1.28
 100    10       2.34         2.27        0.806         0.75          0.319


 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          -4.976366            4      17.952732
              A2          -4.638353            6      21.276707
              A3          -4.976366            4      17.952732
          fitted          -6.360686            3      18.721371
               R         -10.975997            2      25.951993
```

```
                    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              12.6753          4         0.01298
   Test 2             0.676025          2          0.7132
   Test 3             0.676025          2          0.7132
   Test 4              2.76864          1         0.09613

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 =        70.7926


            BMDL =        45.8305
```

E.3.48. Shi et al. (2007): Estradiol

E.3.48.1. *Summary Table of BMDS Modeling Results*

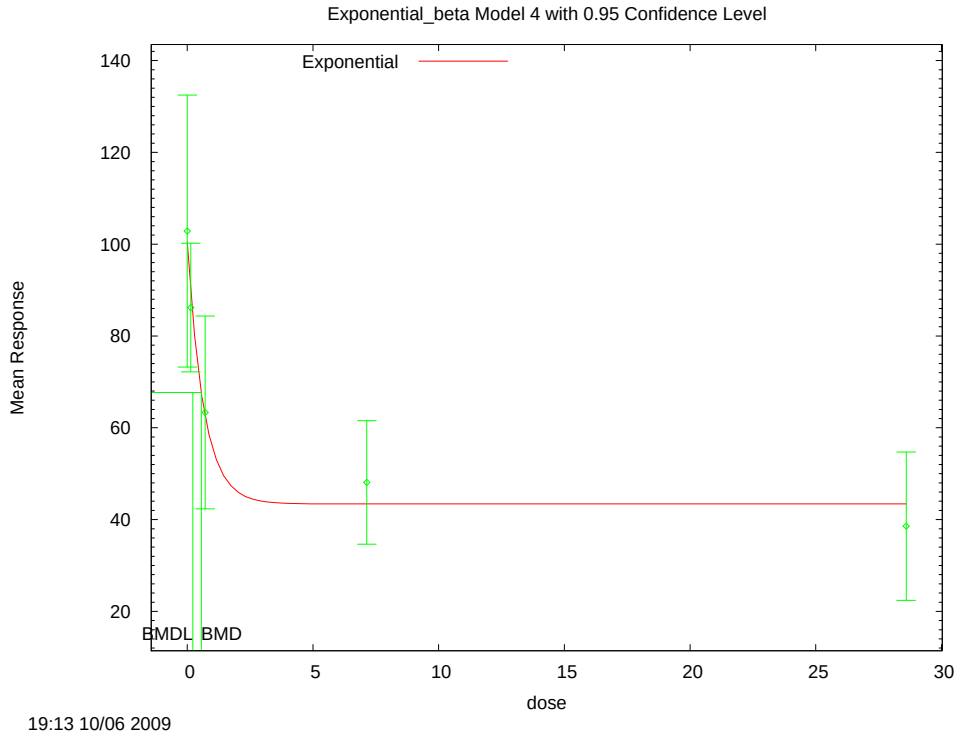
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	3	0.05	15.48	0.00	395.70	1.7E+01	9.0E+00	nonconstant variance, power restricted ≥1
exponential (M3)	3	0.05	15.48	0.00	395.70	1.7E+01	9.0E+00	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**2**	**0.05**	**1.41**	**0.49**	**383.64**	**5.6E-01**	**2.2E-01**	**nonconstant variance, power restricted ≥1**

exponential (M5)	2	0.05	1.41	0.49	383.64	5.6E-01	2.2E-01	nonconstant variance, power restricted ≥1
Hill	2	0.05	0.52	0.77	382.74	4.4E-01	error	nonconstant variance, n restricted >1, bound hit
linear	3	0.05	17.26	0.00	397.48	2.2E+01	1.5E+01	nonconstant variance
polynomial	2	0.05	7.34	0.03	389.57	5.4E+00	3.6E+00	nonconstant variance
power	3	0.05	17.26	0.00	397.48	2.2E+01	1.5E+01	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	3	0.05	13.33	0.00	396.06	1.2E+01	6.6E+00	constant variance, power restricted ≥1
exponential (M3)	3	0.05	13.33	0.00	396.06	1.2E+01	6.6E+00	constant variance, power restricted ≥1
exponential (M4)	2	0.05	0.87	0.65	385.59	3.9E-01	1.5E-01	constant variance, power restricted ≥1
exponential (M5)	2	0.05	0.87	0.65	385.59	3.9E-01	1.5E-01	constant variance, power restricted ≥1
Hill	2	0.05	0.37	0.83	385.09	3.1E-01	1.0E-01	constant variance, n restricted >1, bound hit
linear	3	0.05	15.40	0.00	398.12	1.9E+01	1.3E+01	constant variance
polynomial	2	0.05	8.10	0.02	392.82	4.5E+00	2.9E+00	constant variance
power	3	0.05	15.40	0.00	398.12	1.9E+01	1.3E+01	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected
[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria
[c] **Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix**

1

E.3.48.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



19:13 10/06 2009

E.3.48.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AniDose\Exp_BMR1_Shi_estradiol_17B_conc_PE9.(d)
         Gnuplot Plotting File:
                                                  Tue Oct 06 19:13:28 2009
 ================================================================

 Figure 4 PE9 only
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 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
```

E.3.49. Smialowicz et al. (2008): PFC per 10^6 Cells

E.3.49.1. *Summary Table of BMDS Modeling Results*

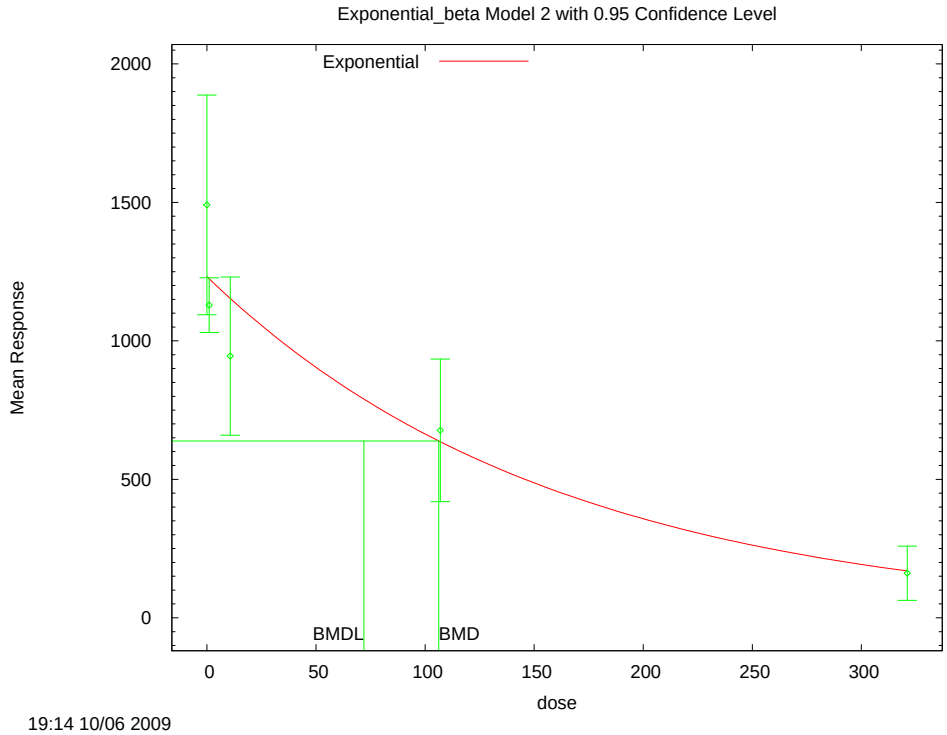
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2) [c]	**3**	**<0.0001**	**11.58**	**0.01**	**890.56**	**1.1E+02**	**7.2E+01**	**nonconstant variance, power restricted ≥1**
exponential (M3)	2	<0.0001	10.85	0.00	891.83	1.3E+02	7.6E+01	nonconstant variance, power restricted ≥1
exponential (M4)	3	<0.0001	11.58	0.01	890.56	1.1E+02	7.2E+01	nonconstant variance, power restricted ≥1
exponential (M5)	2	<0.0001	10.85	0.00	891.83	1.3E+02	7.6E+01	nonconstant variance, power restricted ≥1
Hill	2	<.0001	10.26	0.01	891.23	1.3E+02	error	nonconstant variance, n restricted >1, bound hit
linear	3	<.0001	11.79	0.01	890.77	1.8E+02	1.5E+02	nonconstant variance
polynomial	2	<.0001	10.36	0.01	891.34	1.3E+02	8.4E+01	nonconstant variance
power	3	<.0001	11.79	0.01	890.77	1.8E+02	1.5E+02	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	3	<0.0001	7.92	0.05	903.59	8.2E+01	4.8E+01	constant variance, power restricted ≥1
exponential (M3)	3	<0.0001	7.92	0.05	903.59	8.2E+01	4.8E+01	constant variance, power restricted ≥1
exponential (M4)	2	<0.0001	7.91	0.02	905.58	8.0E+01	6.2E+00	constant variance, power restricted ≥1
exponential (M5)	2	<0.0001	7.91	0.02	905.58	8.0E+01	6.2E+00	constant variance, power restricted ≥1
Hill	2	<.0001	7.31	0.03	904.98	1.6E+01	2.2E+00	constant variance, n restricted >1, bound hit
linear	3	<.0001	10.33	0.02	905.99	1.5E+02	1.1E+02	constant variance
polynomial	2	<.0001	8.14	0.02	905.80	8.8E+01	5.5E+01	constant variance
power	3	<.0001	10.33	0.02	905.99	1.5E+02	1.1E+02	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.49.2. *Figure for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*



E.3.49.3. *Output File for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AniDose\Exp_BMR1_PFC_per_cells.(d)
         Gnuplot Plotting File:
                                                  Tue Oct 06 19:14:43 2009
 ================================================================

 Anti Response to SRBCs, PFC per 10^6 cells, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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              3.29848
                      rho               1.2578
                        a              1565.55
                        b           0.00725727
                        c           0.00205679
                        d                    1



                   Parameter Estimates

                 Variable          Model 2
                 --------          -------
                  lnalpha           1.84544
                      rho           1.53651
                        a           1195.73
                        b        0.00560912
                        c                 0
                        d           1.22053


          Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0     15         1491          716
   1.07     14         1129          171
   10.7     15          945          516
    107     15          677          465
    321      8          161          117


                Estimated Values of Interest

  Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0          1232        593.6            1.688
   1.07          1224        590.7          -0.6027
   10.7          1153          565           -1.428
    107         635.7          362            0.442
    321         169.2        134.6          -0.1716


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       -444.8329            6      901.6657
                       A2       -425.4028           10      870.8057
                       A3       -435.4894            7      884.9787
                        R       -463.7537            2      931.5074
                        2       -441.2778            4      890.5555


Additive constant for all log-likelihoods =     -61.57.  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                         76.7           8            < 0.0001
  Test 2                        38.86           4            < 0.0001
  Test 3                        20.17           3           0.0001563
  Test 4                        11.58           3            0.008983


  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 =      106.252

              BMDL =      71.9153
```

E.3.50. Smialowicz et al. (2008): PFC per Spleen

E.3.50.1. *Summary Table of BMDS Modeling Results*

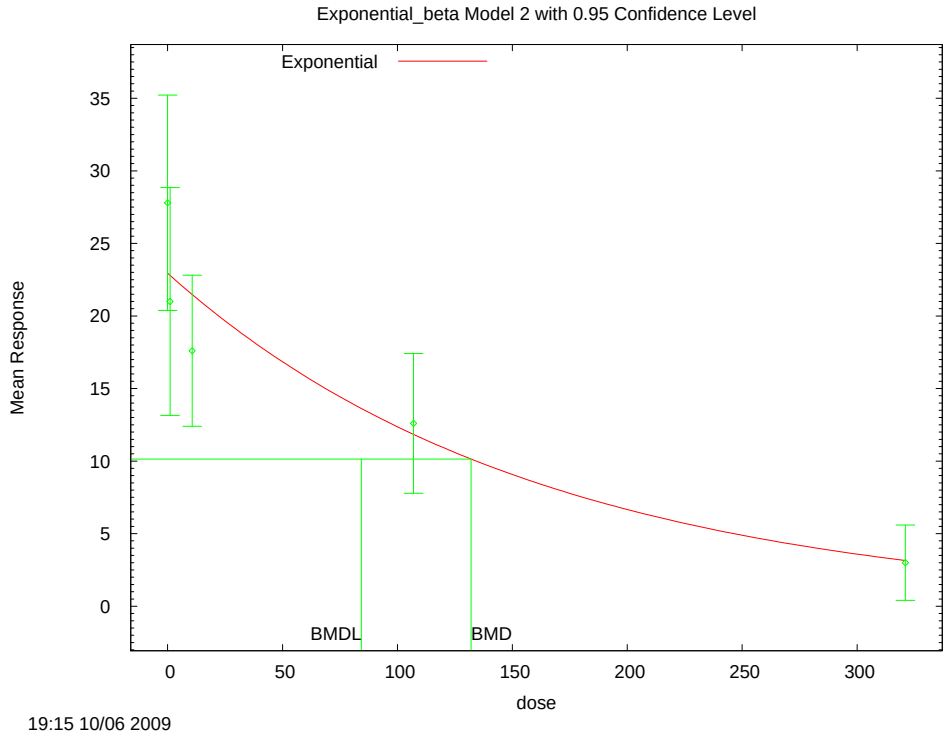
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2) [c]	**3**	**0.00**	**5.60**	**0.13**	**377.40**	**1.3E+02**	**8.4E+01**	**nonconstant variance, power restricted ≥1**
exponential (M3)	3	0.00	5.60	0.13	377.40	1.3E+02	8.4E+01	nonconstant variance, power restricted ≥1
exponential (M4)	3	0.00	5.60	0.13	377.40	1.3E+02	8.2E+01	nonconstant variance, power restricted ≥1
exponential (M5)	2	0.00	5.60	0.06	379.40	1.3E+02	8.2E+01	nonconstant variance, power restricted ≥1
Hill	2	0.00	5.35	0.07	379.15	1.4E+02	error	nonconstant variance, n restricted >1, bound hit
linear	3	0.00	8.09	0.04	379.89	2.2E+02	1.7E+02	nonconstant variance
polynomial	2	0.00	5.58	0.06	379.38	1.4E+02	8.9E+01	nonconstant variance
power	3	0.00	8.09	0.04	379.89	2.2E+02	1.7E+02	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	3	0.00	5.58	0.13	392.71	1.0E+02	5.5E+01	constant variance, power restricted ≥1
exponential (M3)	3	0.00	5.58	0.13	392.71	1.0E+02	5.5E+01	constant variance, power restricted ≥1
exponential (M4)	2	0.00	5.58	0.06	394.71	1.0E+02	6.5E+00	constant variance, power restricted ≥1
exponential (M5)	2	0.00	5.58	0.06	394.71	1.0E+02	6.5E+00	constant variance, power restricted ≥1
Hill	2	0.00	5.36	0.07	394.49	8.4E+01	1.7E+00	constant variance, n restricted >1, bound hit
linear	3	0.00	7.31	0.06	394.44	1.7E+02	1.3E+02	constant variance
polynomial	2	0.00	5.74	0.06	394.87	1.1E+02	6.3E+01	constant variance
power	3	0.00	7.31	0.06	394.44	1.7E+02	1.3E+02	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.50.2. *Figure for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*



E.3.50.3. *Output File for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AniDose\Exp_BMR1_PFC_per_spleen.(d)
         Gnuplot Plotting File:
                                                  Tue Oct 06 19:15:26 2009
 ================================================================

 Anti Response to SRBCs - PFC x 10 to the 4 per spleen, Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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             0.786146
                      rho              1.36372
                        a                29.19
                        b            0.00907371
                        c             0.0513875
                        d                     1



                   Parameter Estimates

                 Variable          Model 2
                 --------          -------
                  lnalpha          0.525138
                      rho           1.45988
                        a           22.9464
                        b        0.00618274
                        c                 0
                        d                 1


          Table of Stats From Input Data

    Dose      N         Obs Mean     Obs Std Dev
    -----    ---       ----------   -------------
        0     15         27.8         13.4
     1.07     14           21         13.6
     10.7     15         17.6          9.4
      107     15         12.6          8.7
      321      8            3          3.1


                Estimated Values of Interest

    Dose      Est Mean      Est Std     Scaled Residual
   ------    ----------    ---------    ----------------
        0         22.95         12.8             1.468
     1.07          22.8        12.74           -0.5272
     10.7         21.48         12.2            -1.231
      107         11.84        7.899            0.3719
      321         3.153        3.007           -0.1444


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        -190.565            6        393.13
                       A2       -181.4763           10      382.9526
                       A3          -181.9            7      377.8001
                        R       -204.6365            2       413.273
                        2       -184.6977            4      377.3954


Additive constant for all log-likelihoods =     -61.57.  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                        46.32           8            < 0.0001
  Test 2                        18.18           4            0.001139
  Test 3                       0.8475           3              0.8381
  Test 4                        5.595           3               0.133


  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.  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 =      132.016

              BMDL =      84.3108
```

E.3.51. Toth et al. (1978): Amyloidosis

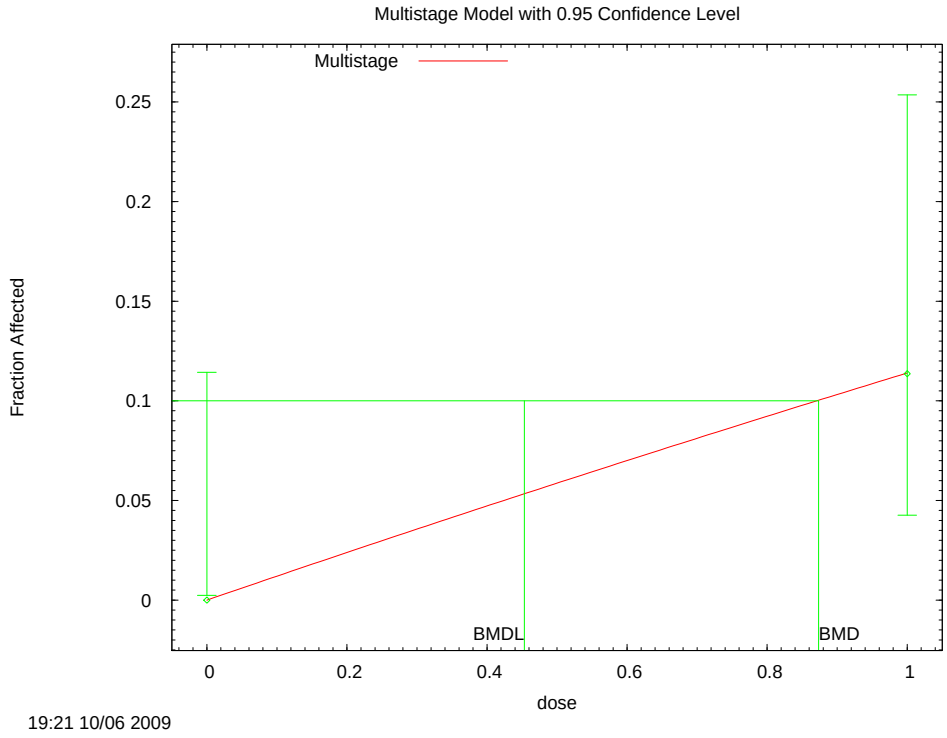
E.3.51.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
multistage, 1-degree [b]	**1**	**0.00**	**1.00**	**33.16**	**8.7E-01**	**4.5E-01**	**betas restricted ≥0**

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

E.3.51.2. *Figure for Selected Model: Multistage, 1-Degree, Betas Restricted ≥0*



E.3.51.3. *Output File for Selected Model: Multistage, 1-Degree, Betas Restricted ≥0*

```
 ========================================================================
         Multistage Model. (Version: 3.0;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AniDose\mult2_0.1_amyloidosis_1yr.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AniDose\mult2_0.1_amyloidosis_1yr.plt
                                                Tue Oct 06 19:21:03 2009
 ========================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 2
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) =     0.120628


           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)         0.120628            *               *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -15.5783         2
   Fitted model         -15.5783         1  1.42109e-014      1               1
  Reduced model         -18.8308         1       6.50504      1         0.01076

           AIC:          33.1565


                                  Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          38        0.000
     1.0000     0.1136         5.000     5.000          44       -0.000

 Chi^2 = 0.00      d.f. = 1        P-value = 1.0000
```

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =       0.873433

             BMDL =       0.453242

             BMDU =        2.10749

Taken together, (0.453242, 2.10749) is a 90     % two-sided confidence
interval for the BMD
```

E.3.52. Toth et al. (1978): Skin Lesions

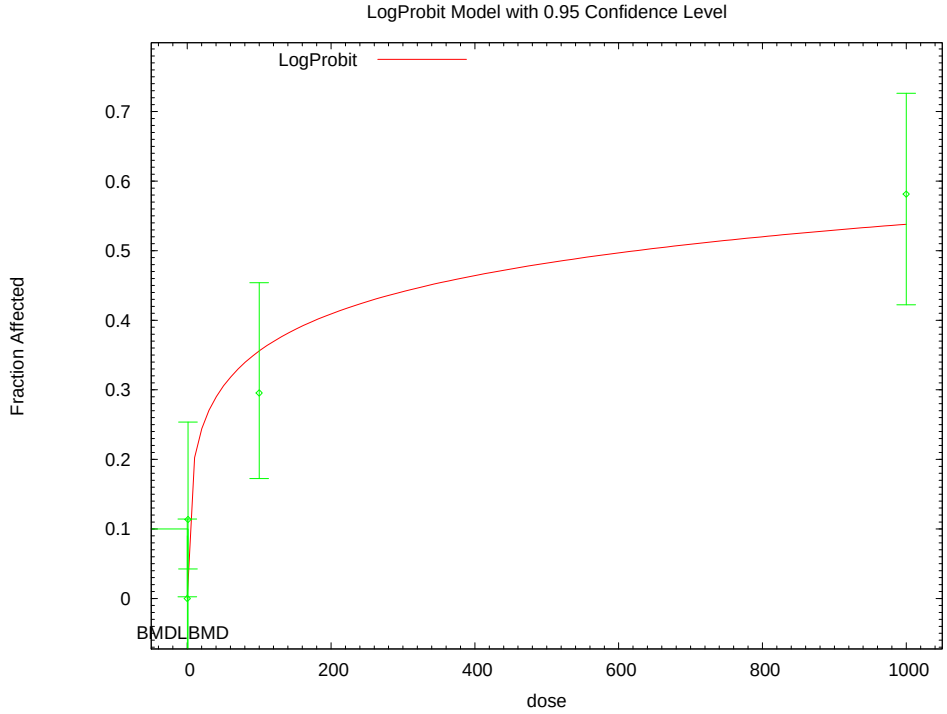
E.3.52.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 *p*-Value [a]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
gamma	2	9.35	0.01	159.22	1.2E+02	8.3E+01	power restricted ≥1, bound hit
logistic	2	12.19	0.00	162.97	2.7E+02	2.1E+02	
log-logistic	2	7.10	0.03	156.57	6.7E+01	4.1E+01	slope restricted ≥1, bound hit
log-probit [b]	**2**	**1.17**	**0.56**	**148.22**	**1.1E+00**	**6.8E-02**	**slope restricted ≥1**
multistage, 2-degree	2	9.35	0.01	159.22	1.2E+02	8.3E+01	betas restricted ≥0, bound hit
probit	2	11.98	0.00	162.68	2.5E+02	2.0E+02	
Weibull	2	9.35	0.01	159.22	1.2E+02	8.3E+01	power restricted ≥1, bound hit

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[b] **Best-fitting model as assessed by lowest-AIC criterion, bolded**

E.3.52.2. *Figure for Selected Model: Log-Probit, Slope Restricted ≥1*



E.3.52.3. *Output File for Selected Model: Log-Probit, Slope Restricted ≥1*

```
 ========================================================================
         Probit Model. (Version: 3.1;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\AniDose\LogProbit_BMR2_Skin_lesion_1yr.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AniDose\LogProbit_BMR2_Skin_lesion_1yr.plt
                                                 Tue Oct 06 19:21:47 2009
 ========================================================================

 Table 2
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 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 (and Specified) Parameter Values
                     background =            0
                      intercept =     -1.26532
                          slope =     0.195762


           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
     background               0               NA
      intercept         -1.30013         0.240943            -1.77237           -0.827887
          slope         0.202414        0.0463497            0.111571            0.293258

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        -71.5177         4
   Fitted model        -72.1089         2       1.18249      2          0.5536
  Reduced model        -95.8498         1       48.6642      3         <.0001

           AIC:         148.218


                                  Goodness  of  Fit
                                                                  Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          38        0.000
    1.0000     0.0968         4.258     5.000          44        0.378
  100.0000     0.3564        15.684    13.000          44       -0.845
 1000.0000     0.5391        23.180    25.000          43        0.557

 Chi^2 = 1.17      d.f. = 2        P-value = 0.5581


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        1.09611
```

```
BMDL =      0.0684731
```

E.3.53. Van Birgelen et al. (1995a): Hepatic Retinol

E.3.53.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	4	<0.0001	45.69	<0.0001	164.34	2.9E+02	error	nonconstant variance, power restricted ≥1
exponential (M3)	4	<0.0001	45.69	<0.0001	164.34	2.9E+02	error	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**3**	**<0.0001**	**27.40**	**<0.0001**	**148.05**	**1.2E+02**	**7.1E+01**	**nonconstant variance, power restricted ≥1**
exponential (M5)	3	<0.0001	27.40	<0.0001	148.05	1.2E+02	7.1E+01	nonconstant variance, power restricted ≥1
exponential (M5) [d]	3	<0.0001	27.40	<0.0001	148.05	1.2E+02	7.1E+01	nonconstant variance, power unrestricted
Hill	3	<.0001	8.11	0.04	128.76	1.3E+01	error	nonconstant variance, n restricted >1, bound hit
Hill [d]	2	<.0001	2.62	0.27	125.27	5.6E+00	error	nonconstant variance, n unrestricted
linear	4	<.0001	60.09	<.0001	178.73	7.8E+02	6.0E+02	nonconstant variance
polynomial	4	<.0001	60.09	<.0001	178.73	7.8E+02	6.0E+02	nonconstant variance
power	4	<.0001	60.09	<.0001	178.73	7.8E+02	6.0E+02	nonconstant variance, power restricted ≥1, bound hit
power [d]	3	<.0001	9.34	0.03	129.99	4.2E-01	8.5E-03	nonconstant variance, power unrestricted
exponential (M2)	4	<0.0001	141.80	<0.0001	322.09	error	error	constant variance, power restricted ≥1
exponential (M3)	4	<0.0001	141.80	<0.0001	322.09	error	error	constant variance, power restricted ≥1
exponential (M4)	3	<0.0001	2.71	0.44	185.03	1.2E+01	7.0E+00	constant variance, power restricted ≥1
exponential (M5)	3	<0.0001	2.71	0.44	185.03	1.2E+01	7.0E+00	constant variance, power restricted ≥1
exponential (M5)	3	<0.0001	2.71	0.44	185.03	1.2E+01	7.0E+00	constant variance, power unrestricted
Hill	3	<.0001	1.37	0.71	183.68	8.3E+00	4.2E+00	constant variance, n restricted >1, bound hit
Hill	2	<.0001	0.89	0.64	185.20	4.5E+00	5.8E-02	constant variance, n unrestricted
linear	4	<.0001	27.00	<.0001	207.31	5.3E+02	3.9E+02	constant variance

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
polynomial	4	<.0001	27.00	<.0001	207.31	5.3E+02	3.9E+02	constant variance
power	4	<.0001	27.00	<.0001	207.31	5.3E+02	3.9E+02	constant variance, power restricted ≥1, bound hit
power	3	<.0001	1.92	0.59	184.23	4.4E-01	6.6E-03	constant variance, power unrestricted

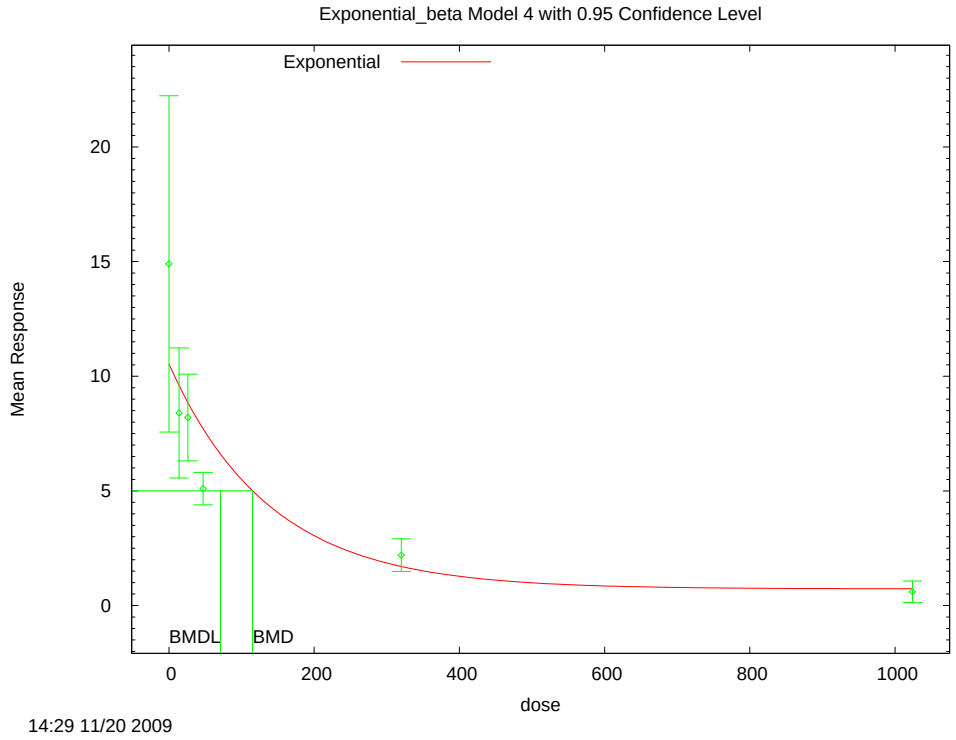
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.3.53.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



E.3.53.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_BMR1_hepatic_retinol.(d)
         Gnuplot Plotting File:
                                                  Fri Nov 20 14:29:52 2009
 ================================================================

 Tbl3, hepatic retinol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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         -0.882224
                      rho           1.82707
                        a           10.5294
                        b        0.00720346
                        c          0.068866
                        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)

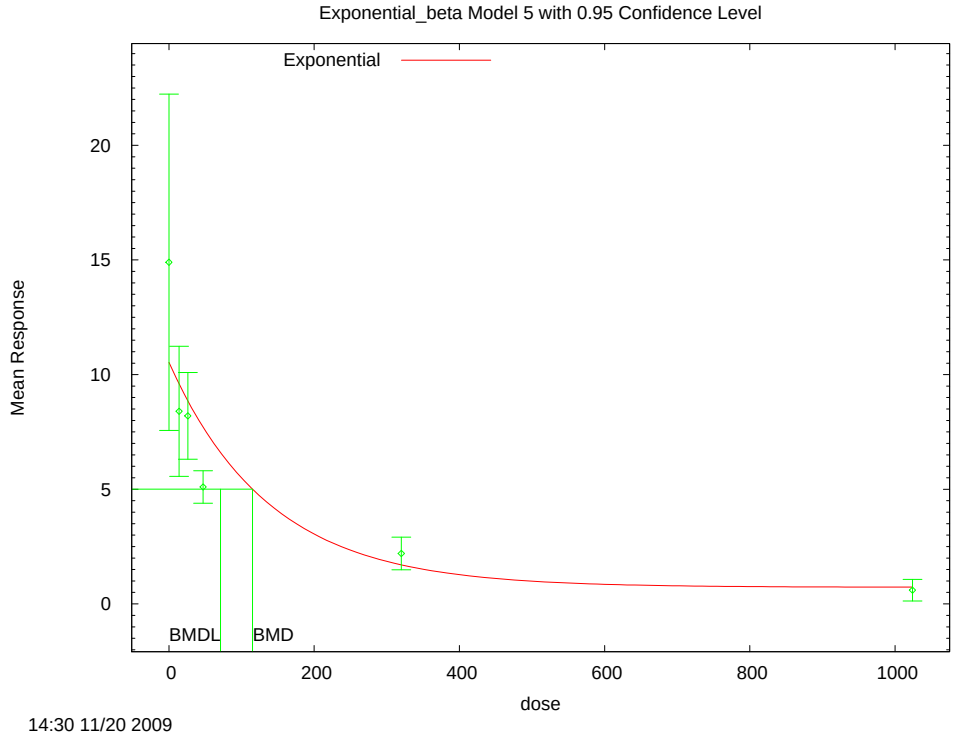
Test 6a: Does Model 4 fit the data? (A3 vs 4)

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
```

E.3.53.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



E.3.53.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
================================================================
        Exponential Model. (Version: 1.5;  Date: 4/23/2009)
        Input Data File: C:\USEPA\BMDS21\Nov20\Exp_Unrest_BMR1_hepatic_retinol.(d)
        Gnuplot Plotting File:
                                                  Fri Nov 20 14:30:05 2009
================================================================

Tbl3, hepatic retinol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  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 = 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 5
              --------        --------
               lnalpha          -1.16065
                  rho           1.53688
                    a           15.645
                    b         0.00625117
                    c          0.0365247
                    d                  1



               Parameter Estimates

              Variable         Model 5
              --------        -------
               lnalpha        -0.882224
                  rho          1.82707
                    a          10.5294
                    b        0.00720346
                    c         0.068866
                    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
5	-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 7a: Does Model 5 fit the data? (A3 vs 5)

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 7a	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 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

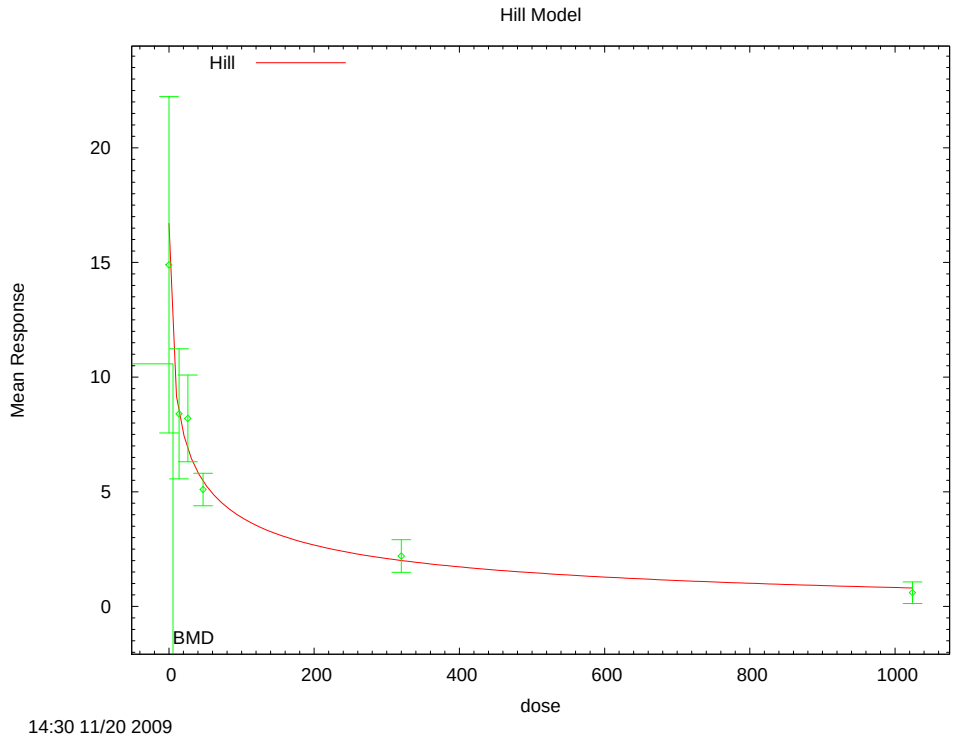
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 115.128

BMDL = 70.981

E.3.53.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



E.3.53.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
            Hill Model. (Version: 2.14;  Date: 06/26/2008)
            Input Data File: C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_hepatic_retinol.(d)
            Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_hepatic_retinol.plt
                                                        Fri Nov 20 14:30:12 2009
 ================================================================

Tbl3, hepatic retinol
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  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 = 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
              intercept =        14.9
                      v =       -14.3
                      n =     2.92354
                      k =     29.0484


       Asymptotic Correlation Matrix of Parameter Estimates

            lalpha       rho    intercept         v         n         k

 lalpha          1     -0.78     -0.041     0.015     0.037     0.029

   rho       -0.78         1     -0.098      0.11    -0.047    -0.046

intercept    -0.041    -0.098          1      -0.9     -0.25      -0.8

     v       0.015      0.11       -0.9         1      0.63      0.63

     n       0.037    -0.047      -0.25      0.63         1      0.15

     k       0.029    -0.046       -0.8      0.63      0.15         1


                    Parameter Estimates

                                          95.0% Wald Confidence Interval
     Variable        Estimate      Std. Err.    Lower Conf. Limit   Upper Conf. Limit
      lalpha        -1.16547       0.373814          -1.89813          -0.432809
        rho         1.69882       0.185479           1.33529           2.06235
   intercept         16.6759        2.07841           12.6023           20.7495
           v        -17.4464        2.46627          -22.2801          -12.6126
           n        0.570647       0.161383          0.254343          0.886951
           k         16.5364        7.36467           2.10191           30.9709
```

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	16.7	8.77	6.1	-0.824
14	8	8.4	8.37	3.39	3.39	0.0276
26	8	8.2	6.83	2.26	2.86	1.35
47	8	5.1	5.43	0.849	2.35	-0.394
320	8	2.2	1.95	0.849	0.983	0.732
1024	8	0.6	0.742	0.566	0.434	-0.929

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	-56.636555	6	125.273110
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	2.62467	2	0.2692

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 = 1

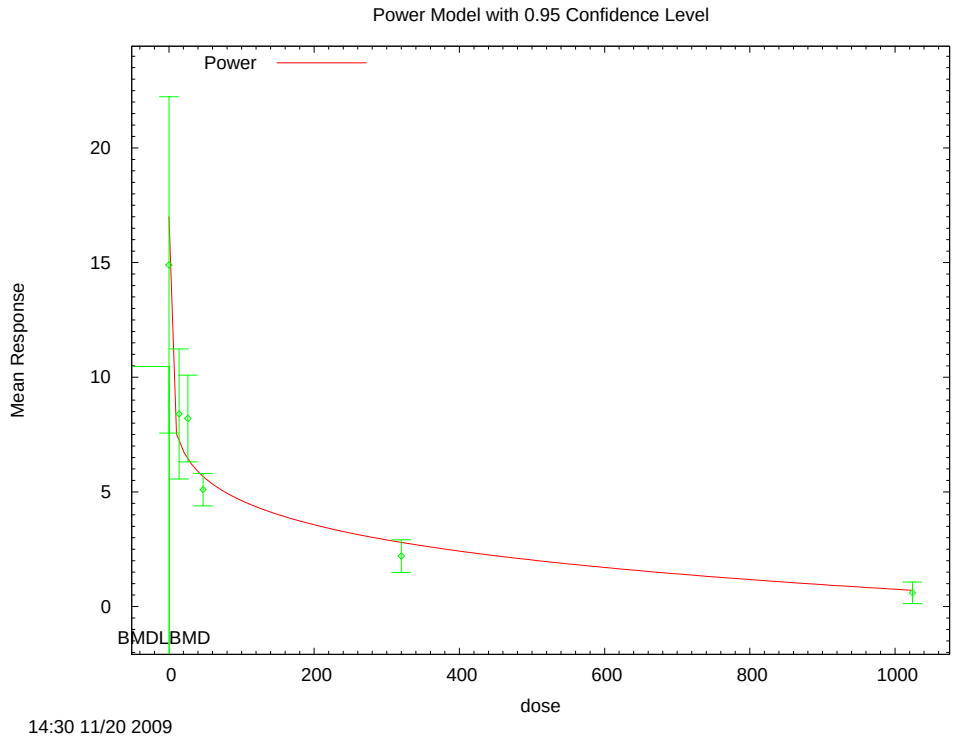
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 5.56122

BMDL computation failed.

E.3.53.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



14:30 11/20 2009

E.3.53.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_hepatic_retinol.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_hepatic_retinol.plt
                                                    Fri Nov 20 14:30:13 2009
================================================================

Tbl3, hepatic retinol
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  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 =     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

E.3.54. Van Birgelen et al. (1995a): Hepatic Retinol Palmitate

E.3.54.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	4	<0.0001	64.68	<0.0001	467.45	error	error	nonconstant variance, power restricted ≥1
exponential (M3)	4	<0.0001	64.68	<0.0001	467.45	error	error	nonconstant variance, power restricted ≥1
exponential (M4)	3	<0.0001	49.32	<0.0001	454.09	error	error	nonconstant variance, power restricted ≥1
exponential (M5)	3	<0.0001	49.32	<0.0001	454.09	error	error	nonconstant variance, power restricted ≥1
exponential (M5)	3	<0.0001	49.32	<0.0001	454.09	error	error	nonconstant variance, power unrestricted
Hill	3	<.0001	158.81	<.0001	563.58	error	error	nonconstant variance, n restricted >1
Hill [d]	3	<.0001	117.56	<.0001	522.32	2.4E-12	2.4E-12	nonconstant variance, n unrestricted
linear [c]	**4**	**<.0001**	**85.68**	**<.0001**	**488.45**	**1.4E+03**	**9.9E+02**	**nonconstant variance**
polynomial	4	<.0001	85.68	<.0001	488.45	1.4E+03	9.9E+02	nonconstant variance
power	4	<.0001	85.68	<.0001	488.45	1.4E+03	9.9E+02	nonconstant variance, power restricted ≥1, bound hit
power [d]	3	<.0001	3.30	0.35	408.06	3.8E-02	1.2E-05	nonconstant variance, power unrestricted
exponential (M2)	4	<0.0001	140.00	<0.0001	647.15	error	error	constant variance, power restricted ≥1
exponential (M3)	4	<0.0001	140.00	<0.0001	647.15	error	error	constant variance, power restricted ≥1

Model	Degrees of Freedom	Variance p-Value [a]	χ^2 Test Statistic	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M4)	3	<0.0001	3.50	0.32	512.61	2.5E+00	9.0E-03	constant variance, power restricted ≥1
exponential (M5)	3	<0.0001	3.50	0.32	512.61	2.5E+00	9.0E-03	constant variance, power restricted ≥1
exponential (M5) [d]	3	<0.0001	3.50	0.32	512.61	2.5E+00	9.0E-03	constant variance, power unrestricted
Hill	3	<.0001	1.33	0.72	510.44	1.3E+00	2.5E-01	constant variance, n restricted >1, bound hit
Hill	2	<.0001	0.29	0.86	511.40	7.9E-06	7.9E-06	constant variance, n unrestricted
linear	4	<.0001	44.59	<.0001	551.70	8.7E+02	5.5E+02	constant variance
polynomial	4	<.0001	44.59	<.0001	551.70	8.7E+02	5.5E+02	constant variance
power	4	<.0001	44.59	<.0001	551.70	8.7E+02	5.5E+02	constant variance, power restricted ≥1, bound hit
power	3	<.0001	0.29	0.96	509.40	2.2E-08	2.2E-08	constant variance, power unrestricted

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

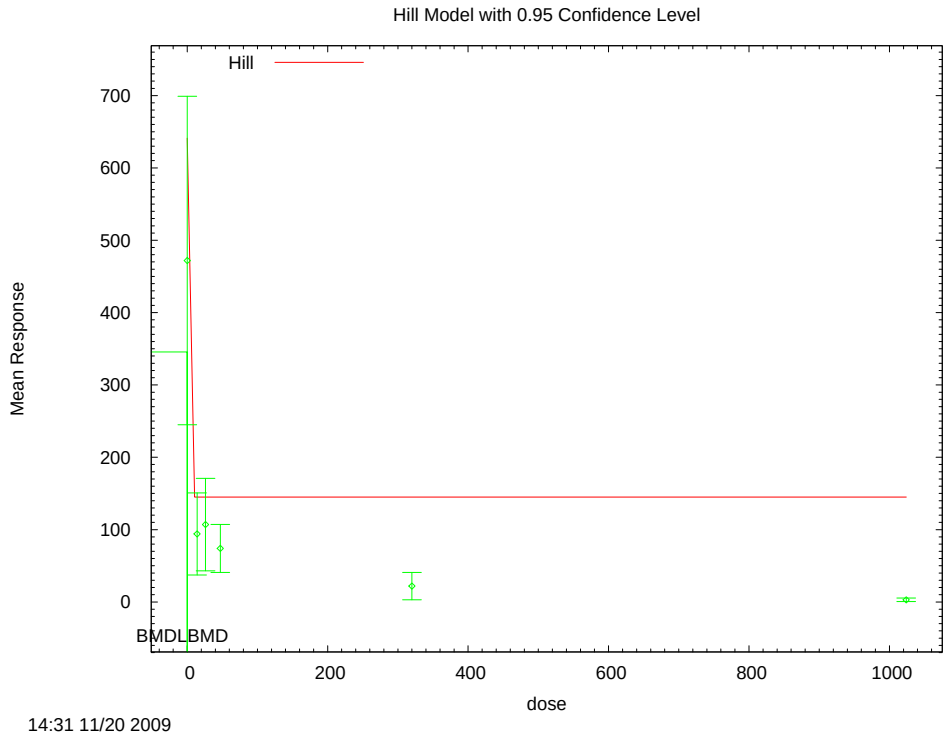
[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

1

E.3.54.2. *Figure for Selected Model: Hill, Nonconstant Variance, n Unrestricted*



E.3.54.3. *Output File for Selected Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_hepatic_retinol_palmitate.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_hepatic_retinol_palmitate.plt
                                                  Fri Nov 20 14:31:05 2009
 ================================================================

 Tbl3, hepatic retinol palmitate
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   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 = 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
intercept =	472
v =	-469
n =	1.50651
k =	8.68519

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	-1	-0.43	0.39	-0.014
rho	-1	1	0.44	-0.41	0.015
intercept	-0.43	0.44	1	-1	0.027
v	0.39	-0.41	-1	1	-0.026
n	-0.014	0.015	0.027	-0.026	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	2.09439	1.99191	-1.80969	5.99847
rho	1.43616	0.388229	0.675242	2.19707
intercept	640.986	167.573	312.548	969.423
v	-495.665	166.074	-821.163	-170.167
n	0.451934	0.597514	-0.719171	1.62304
k	1.024e-012	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	472	641	272	295	-1.62
14	8	94	145	67.9	102	-1.43
26	8	107	145	76.4	102	-1.07
47	8	74	145	39.6	102	-1.98
320	8	22	145	22.6	102	-3.43
1024	8	3	145	2.83	102	-3.96

Model Descriptions for likelihoods calculated

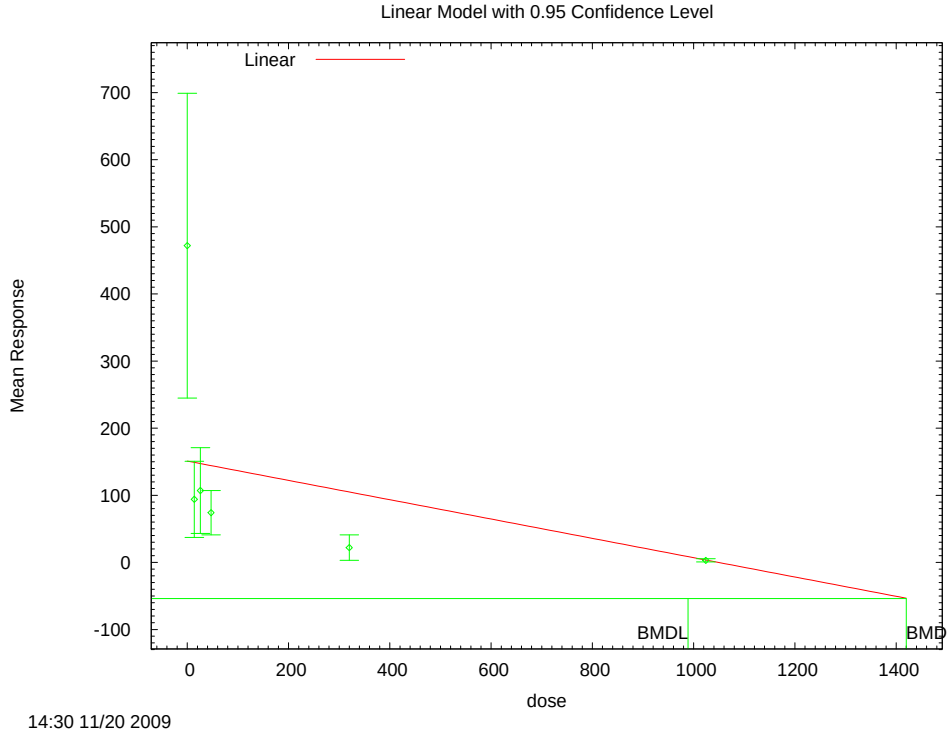
Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

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        -256.161039            5     522.322077
               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              117.556          3          <.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 =   2.41754e-012

            BMDL =  2.41754e-012
```

E.3.54.4. *Figure for Unrestricted Model: Linear, Nonconstant Variance*



14:30 11/20 2009

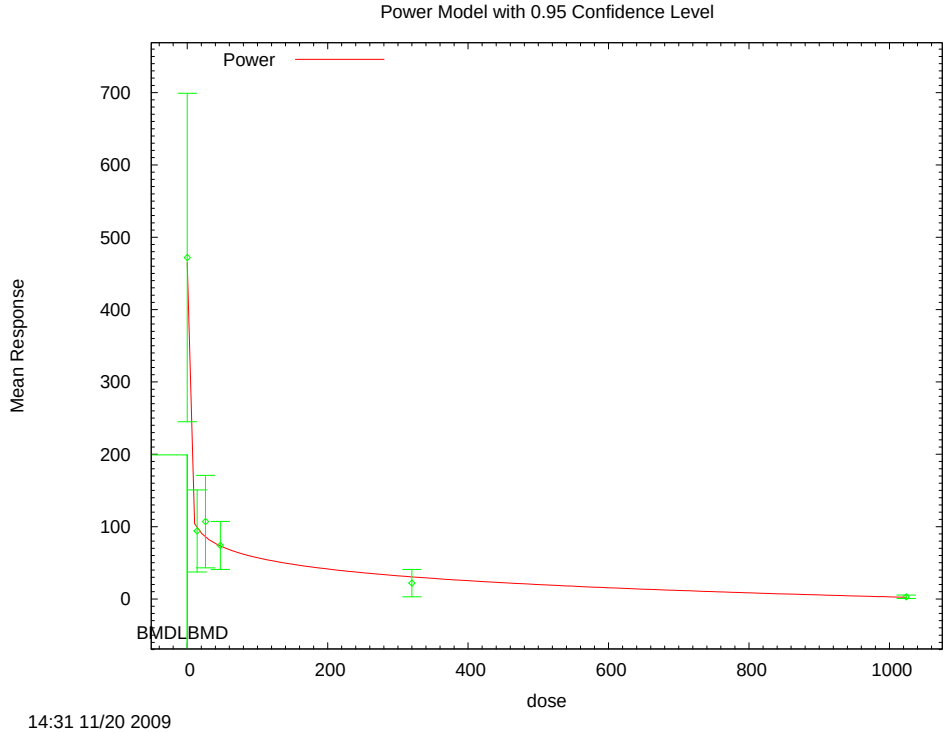
E.3.54.5. *Output File for Unrestricted Model: Linear, Nonconstant Variance*

```
 ================================================================
         Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Linear_BMR1_hepatic_retinol_palmitate.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Linear_BMR1_hepatic_retinol_palmitate.plt
                                                 Fri Nov 20 14:30:57 2009
 ================================================================

 Tbl3, hepatic retinol palmitate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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
                          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
```

E.3.54.6. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



E.3.54.7. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_hepatic_retinol_palmitate.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_hepatic_retinol_palmitate.plt
                                                  Fri Nov 20 14:31:06 2009
 ================================================================

 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

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval 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

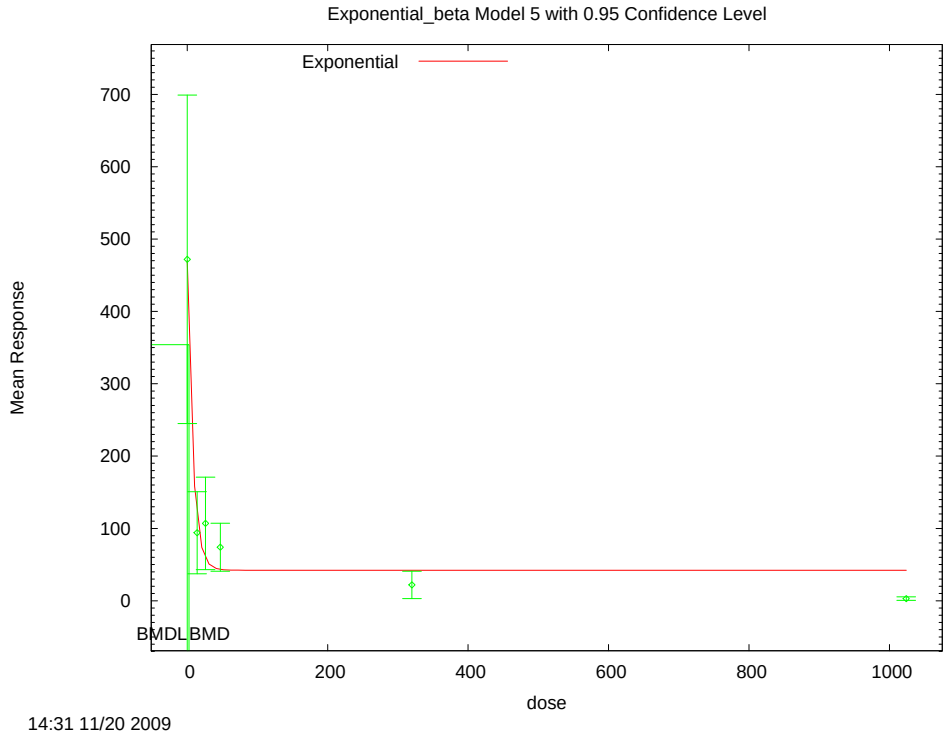
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 0.0376489

BMDL = 1.20769e-005

E.3.54.8. *Figure for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*



14:31 11/20 2009

E.3.54.9. *Output File for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*

```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_CV_Unrest_BMR1_hepatic_retinol_palmitate.(d)
         Gnuplot Plotting File:
                                                  Fri Nov 20 14:31:06 2009
 ========================================================================

 Tbl3, hepatic retinol palmitate
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 5
                --------          --------
                  lnalpha              9.43978
                      rho(S)                 0
                        a                495.6
                        b            0.00826283
                        c            0.00576502
                        d                     1

  (S) = Specified


                  Parameter Estimates

                 Variable          Model 5
                 --------          -------
                  lnalpha           9.51279
                      rho                 0
                        a           470.237
                        b          0.126105
                        c         0.0898547
                        d                 1

  NC = No Convergence


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      8          472        271.5
     14      8           94        67.88
     26      8          107        76.37
     47      8           74         39.6
    320      8           22        22.63
   1024      8            3        2.828


               Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
  ------    ----------    ---------    ----------------
      0         470.2        116.3          0.04286
     14         115.5        116.3          -0.5224
     26         58.38        116.3            1.182
     47         43.39        116.3           0.7442
    320         42.25        116.3          -0.4924
   1024         42.25        116.3          -0.9544


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       -250.5548            7      515.1096
                      R       -276.7896            2      557.5793
                      5       -252.3071            4      512.6141


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 7a: Does Model 5 fit the data? (A3 vs 5)


                          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                      107.6             5           < 0.0001
 Test 7a                      3.504             3             0.3202


  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 7a is greater than .1.  Model 5 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 =       2.5152

BMDL =   0.00902578
```

E.3.55. Van Birgelen et al. (1995a): Plasma FT4

E.3.55.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance p-Value [a]	χ^2 Test Statistic	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2) [c]	**4**	**0.01**	**3.18**	**0.53**	**215.46**	**3.4E+02**	**2.2E+02**	**nonconstant variance, power restricted ≥1**
exponential (M3)	4	0.01	3.18	0.53	215.46	3.4E+02	2.2E+02	nonconstant variance, power restricted ≥1
exponential (M4)	3	0.01	2.13	0.55	216.42	2.2E+02	8.3E+01	nonconstant variance, power restricted ≥1
exponential (M5)	3	0.01	2.13	0.55	216.42	2.2E+02	8.3E+01	nonconstant variance, power restricted ≥1
exponential (M5) [d]	3	0.01	2.13	0.55	216.42	2.2E+02	8.3E+01	nonconstant variance, power unrestricted
Hill	3	0.01	2.02	0.57	216.30	1.9E+02	4.2E+01	nonconstant variance, n restricted >1, bound hit
Hill [d]	2	0.01	1.87	0.39	218.16	1.7E+02	3.5E+01	nonconstant variance, n unrestricted
linear	4	0.01	4.52	0.34	216.81	4.6E+02	3.3E+02	nonconstant variance
polynomial	4	0.01	4.52	0.34	216.81	4.6E+02	3.3E+02	nonconstant variance
power	4	0.01	4.52	0.34	216.81	4.6E+02	3.3E+02	nonconstant variance, power restricted ≥1, bound hit
power [d]	3	0.01	2.09	0.55	216.38	1.8E+02	3.2E+01	nonconstant variance, power unrestricted
exponential (M2)	4	0.01	3.77	0.44	214.06	3.1E+02	2.1E+02	constant variance, power restricted ≥1
exponential (M3)	4	0.01	3.77	0.44	214.06	3.1E+02	2.1E+02	constant variance, power restricted ≥1
exponential (M4)	3	0.01	2.79	0.43	215.08	1.9E+02	6.7E+01	constant variance, power restricted ≥1
exponential (M5)	3	0.01	2.79	0.43	215.08	1.9E+02	6.7E+01	constant variance, power restricted ≥1
exponential (M5)	3	0.01	2.79	0.43	215.08	1.9E+02	6.7E+01	constant variance, power unrestricted
Hill	3	0.01	2.58	0.46	214.87	1.6E+02	3.7E+01	constant variance, n restricted >1, bound hit
Hill	2	0.01	2.29	0.32	216.58	1.4E+02	3.0E+01	constant variance, n unrestricted

linear	4	0.01	5.11	0.28	215.40	4.3E+02	3.3E+02	constant variance
polynomial	4	0.01	5.11	0.28	215.40	4.3E+02	3.3E+02	constant variance
power	4	0.01	5.11	0.28	215.40	4.3E+02	3.3E+02	constant variance, power restricted ≥1, bound hit
power	3	0.01	2.46	0.48	214.75	1.5E+02	2.8E+01	constant variance, power unrestricted

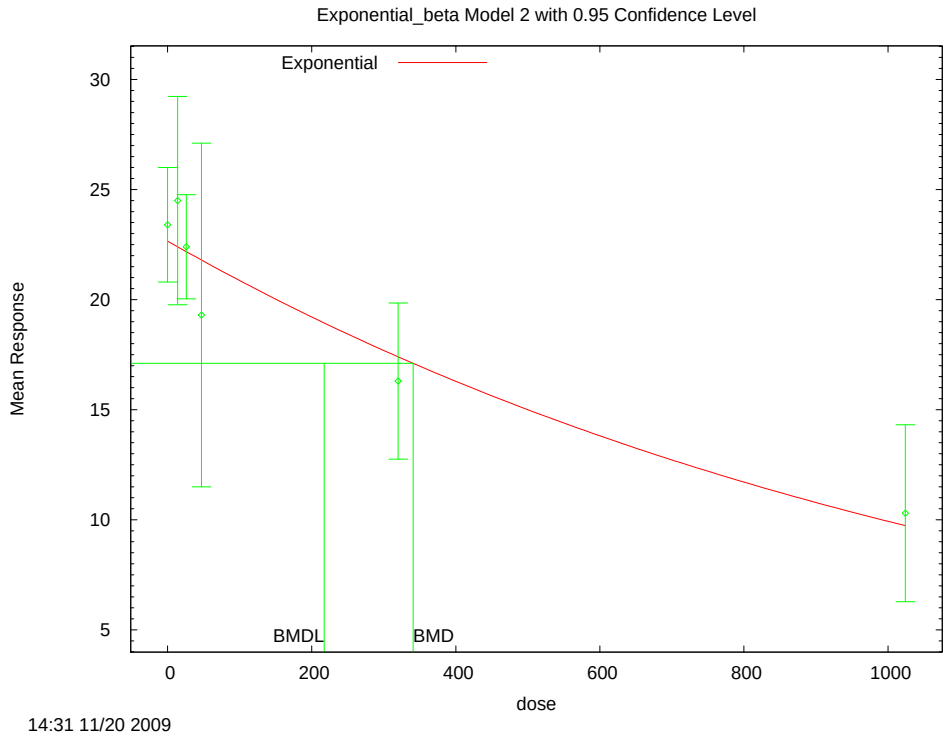
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.3.55.2. *Figure for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*



E.3.55.3. *Output File for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_BMR1_plasma_FT4.(d)
         Gnuplot Plotting File:
                                                  Fri Nov 20 14:31:57 2009
 ================================================================

 Tbl3, plasma FT4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 2
                --------          --------
                  lnalpha             4.29134
                      rho            -0.423761
                        a               25.725
                        b            0.00336354
                        c              0.381323
                        d                     1


                   Parameter Estimates

                 Variable          Model 2
                 --------          -------
                  lnalpha           1.55298
                      rho           0.59724
                        a           23.1888
                        b        0.00232277
                        c          0.391713
                        d                 1
```

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	23.4	3.111
14	8	24.5	5.657
26	8	22.4	2.828
47	8	19.3	9.334
320	8	16.3	4.243
1024	8	10.3	4.808

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	22.66	5.554	0.3768
14	22.4	5.536	1.073
26	22.18	5.521	0.1131
47	21.8	5.495	-1.286
320	17.4	5.17	-0.6029
1024	9.735	4.417	0.3618

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	-102.145	7	218.2901
A2	-94.04963	12	212.0993
A3	-102.143	8	220.286
R	-117.8175	2	239.635
2	-103.7322	4	215.4645

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

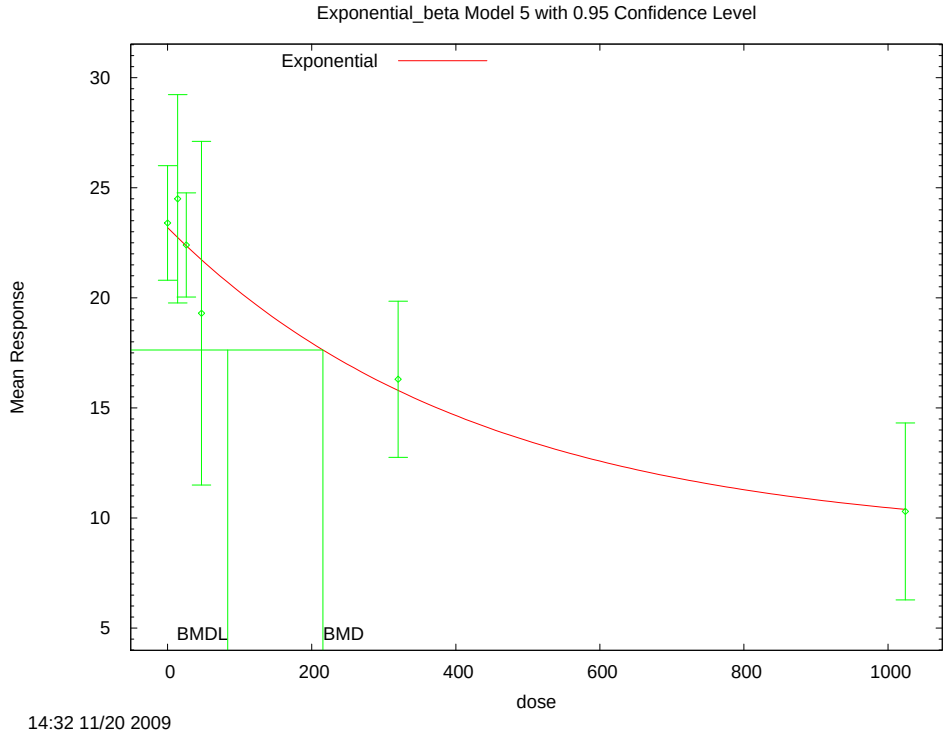
Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	47.54	10	< 0.0001

```
      Test 2                        16.19          5            0.00632
      Test 3                        16.19          4           0.002778
      Test 4                        3.178          4             0.5284


      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.  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 =      340.749

               BMDL =      217.397
```

E.3.55.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



E.3.55.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_Unrest_BMR1_plasma_FT4.(d)
         Gnuplot Plotting File:
                                                  Fri Nov 20 14:32:02 2009
 ================================================================

 Tbl3, plasma FT4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 5
                --------          --------
                  lnalpha             4.29134
                      rho           -0.423761
                        a              25.725
                        b           0.00336354
                        c             0.381323
                        d                    1


                   Parameter Estimates

                 Variable          Model 5
                 --------          -------
                  lnalpha           1.55298
                      rho           0.59724
                        a           23.1888
                        b        0.00232277
                        c          0.391713
                        d                 1
```

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	8	23.4	3.111
14	8	24.5	5.657
26	8	22.4	2.828
47	8	19.3	9.334
320	8	16.3	4.243
1024	8	10.3	4.808

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	23.19	5.558	0.1075
14	22.74	5.526	0.9022
26	22.36	5.498	0.01946
47	21.73	5.451	-1.261
320	15.79	4.956	0.2904
1024	10.39	4.373	-0.0587

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	-102.145	7	218.2901
A2	-94.04963	12	212.0993
A3	-102.143	8	220.286
R	-117.8175	2	239.635
5	-103.2077	5	216.4154

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)

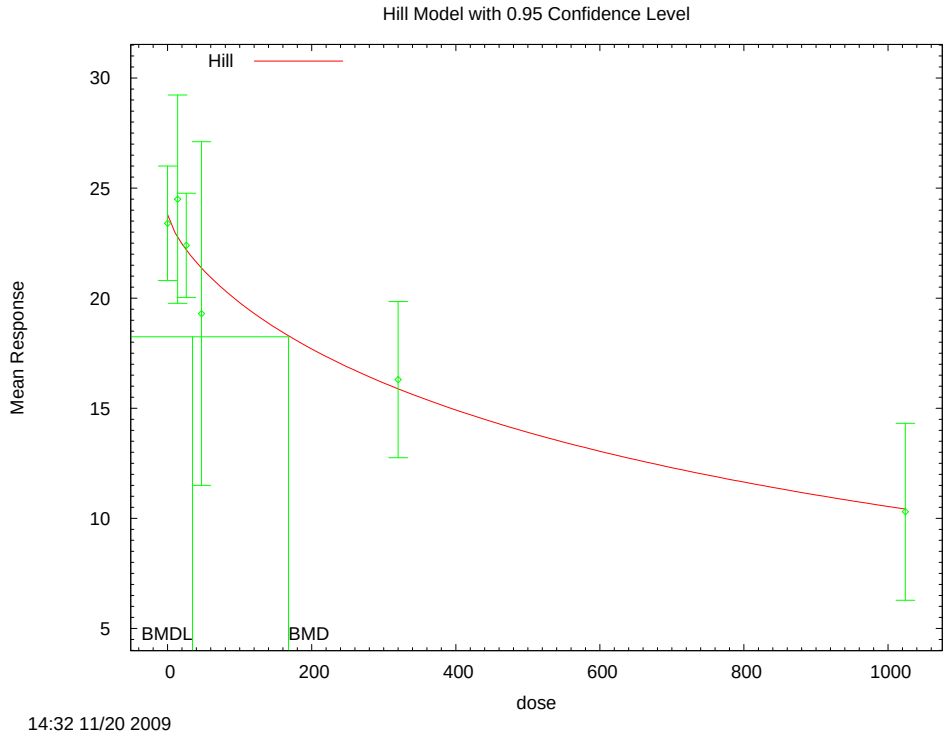
Test 7a: Does Model 5 fit the data? (A3 vs 5)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value

```
      Test 1                        47.54          10           < 0.0001
      Test 2                        16.19           5            0.00632
      Test 3                        16.19           4           0.002778
     Test 7a                        2.129           3              0.546


      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 greater than .1.  Model 5 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 =      215.664

                BMDL =      83.4225
```

E.3.55.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



E.3.55.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_plasma_FT4.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_plasma_FT4.plt
                                              Fri Nov 20 14:32:03 2009
 ================================================================

 Tbl3, plasma FT4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 =      3.38957
                           rho =            0
                     intercept =         23.4
                             v =        -13.1
                             n =     0.834965
                             k =       269.95


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho    intercept            v            n            k

    lalpha            1           -1          0.2        -0.14        -0.19         0.12

       rho           -1            1         -0.2         0.14         0.19        -0.12

 intercept          0.2         -0.2            1        -0.35        -0.58         0.27

         v        -0.14         0.14        -0.35            1          0.9        -0.99

         n        -0.19         0.19        -0.58          0.9            1        -0.89

         k         0.12        -0.12         0.27        -0.99        -0.89            1


                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha          1.83708          2.19197             -2.4591             6.13327
            rho         0.498362         0.745649           -0.963083             1.95981
      intercept          23.7686          1.71713              20.403             27.1341
              v         -26.4457          39.0446            -102.972             50.0802
              n         0.751729         0.57261           -0.370565             1.87402
              k          988.089          3688.99             -6242.2             8218.37
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	23.4	23.8	3.11	5.52	-0.189
14	8	24.5	22.7	5.66	5.46	0.916
26	8	22.4	22.2	2.83	5.42	0.127
47	8	19.3	21.3	9.33	5.37	-1.07
320	8	16.3	15.8	4.24	4.99	0.263
1024	8	10.3	10.4	4.81	4.49	-0.043

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	-102.145036	7	218.290071
A2	-94.049629	12	212.099258
A3	-102.143023	8	220.286046
fitted	-103.078418	6	218.156836
R	-117.817514	2	239.635028

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	47.5358	10	<.0001
Test 2	16.1908	5	0.00632
Test 3	16.1868	4	0.002778
Test 4	1.87079	2	0.3924

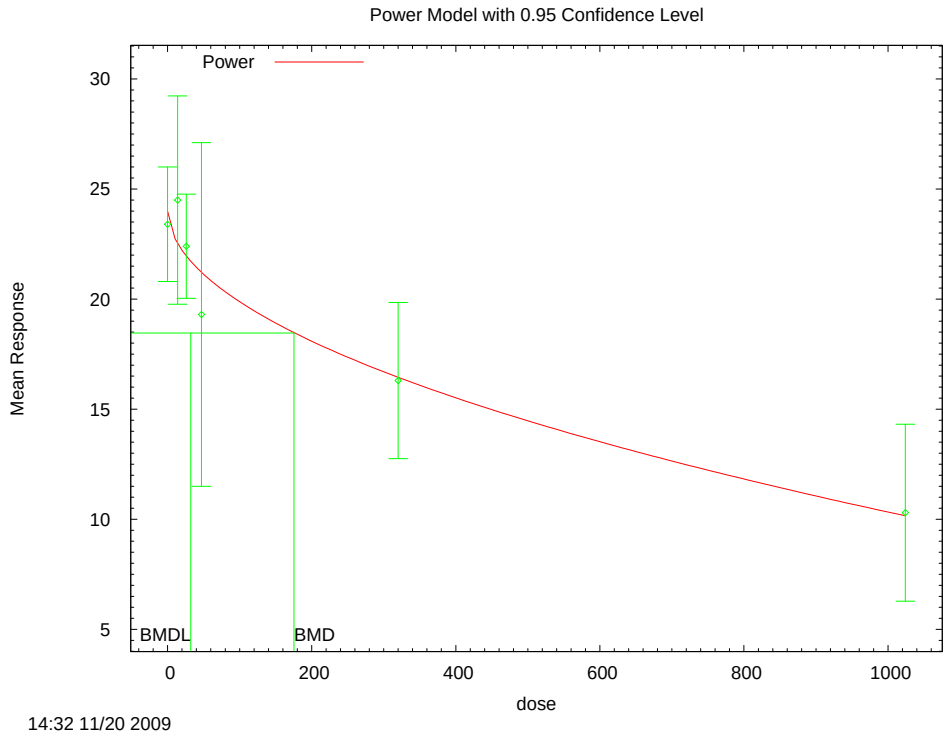
The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

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 =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        167.752

            BMDL =       34.6031
```

E.3.55.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



E.3.55.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
=================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_plasma_FT4.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_plasma_FT4.plt
                                                Fri Nov 20 14:32:04 2009
=================================================================
```

Tbl3, plasma FT4

~~~~~~

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 =	3.38957
rho =	0
control =	24.5
slope =	-0.64474
power =	0.449494

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-1	0.11	-0.098	-0.083
rho	-1	1	-0.12	0.099	0.083
control	0.11	-0.12	1	-0.8	-0.75
slope	-0.098	0.099	-0.8	1	0.99
power	-0.083	0.083	-0.75	0.99	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	1.96489	2.14806	-2.24522	6.175
rho	0.456282	0.730608	-0.975684	1.88825
control	23.9768	1.64641	20.7499	27.2037
slope	-0.373722	0.513355	-1.37988	0.632435
power	0.52088	0.188688	0.151059	0.890701

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	23.4	24	3.11	5.51	-0.296
14	8	24.5	22.5	5.66	5.43	1.04
26	8	22.4	21.9	2.83	5.4	0.242
47	8	19.3	21.2	9.33	5.36	-1
320	8	16.3	16.4	4.24	5.06	-0.0759
1024	8	10.3	10.2	4.81	4.53	0.0903
~~~~~~

```
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         -102.145036           7     218.290071
              A2          -94.049629          12     212.099258
              A3         -102.143023           8     220.286046
          fitted         -103.188719           5     216.377438
               R         -117.817514           2     239.635028


                    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              47.5358         10          <.0001
  Test 2              16.1908          5         0.00632
  Test 3              16.1868          4        0.002778
  Test 4              2.09139          3          0.5537

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 =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 175.43
```

```
BMDL = 32.1986
```

E.3.56. Van Birgelen et al. (1995a): Plasma TT4

E.3.56.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	4	0.94	10.42	0.03	241.86	4.4E+02	2.8E+02	nonconstant variance, power restricted ≥1
exponential (M3)	4	0.94	10.42	0.03	241.86	4.4E+02	2.8E+02	nonconstant variance, power restricted ≥1
exponential (M4)	3	0.94	9.83	0.02	243.27	2.8E+02	2.1E+01	nonconstant variance, power restricted ≥1
exponential (M5)	3	0.94	9.83	0.02	243.27	2.8E+02	2.0E+01	nonconstant variance, power restricted ≥1
exponential (M5)	3	0.94	9.83	0.02	243.27	2.8E+02	2.0E+01	nonconstant variance, power unrestricted
Hill	3	0.94	5.45	0.14	238.89	4.4E+01	error	nonconstant variance, n restricted >1, bound hit
Hill	3	0.94	5.45	0.14	238.89	4.4E+01	error	nonconstant variance, n unrestricted
linear	4	0.94	10.82	0.03	242.26	5.0E+02	3.5E+02	nonconstant variance
polynomial	4	0.94	10.82	0.03	242.26	5.0E+02	3.5E+02	nonconstant variance
power	4	0.94	10.82	0.03	242.26	5.0E+02	3.5E+02	nonconstant variance, power restricted ≥1, bound hit
power	3	0.94	8.70	0.03	242.14	1.6E+02	2.2E+01	nonconstant variance, power unrestricted
exponential (M2) [c]	**4**	**0.94**	**9.83**	**0.04**	**239.86**	**4.4E+02**	**3.0E+02**	**constant variance, power restricted ≥1**
exponential (M3)	4	0.94	9.83	0.04	239.86	4.4E+02	3.0E+02	constant variance, power restricted ≥1
exponential (M4)	3	0.94	9.24	0.03	241.27	2.8E+02	2.6E+01	constant variance, power restricted ≥1
exponential (M5)	3	0.94	9.24	0.03	241.27	2.8E+02	2.3E+01	constant variance, power restricted ≥1
exponential (M5) [d]	3	0.94	9.24	0.03	241.27	2.8E+02	2.3E+01	constant variance, power unrestricted
Hill	3	0.94	6.31	0.10	238.33	4.5E+01	error	constant variance, n restricted >1, bound hit
Hill [d]	3	0.94	6.31	0.10	238.33	4.5E+01	error	constant variance, n unrestricted

Model	Degrees of Freedom	Variance p-Value [a]	χ^2 Test Statistic	χ^2 p-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
linear	4	0.94	10.23	0.04	240.26	5.0E+02	3.7E+02	constant variance
polynomial	4	0.94	10.23	0.04	240.26	5.0E+02	3.7E+02	constant variance
power	4	0.94	10.23	0.04	240.26	5.0E+02	3.7E+02	constant variance, power restricted ≥1, bound hit
power [d]	3	0.94	8.14	0.04	240.16	1.7E+02	2.4E+01	constant variance, power unrestricted

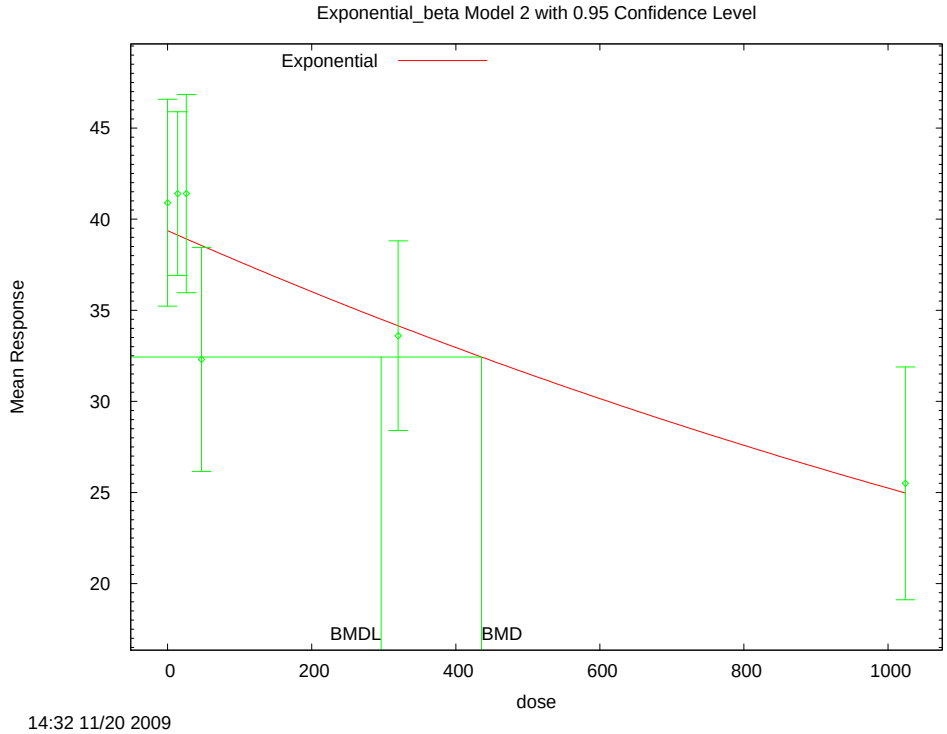
[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d] Alternate model also presented in this appendix

E.3.56.2. *Figure for Selected Model: Exponential (M2), Constant Variance, Power Restricted ≥1*



E.3.56.3. *Output File for Selected Model: Exponential (M2), Constant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_CV_BMR1_plasma_TT4.(d)
         Gnuplot Plotting File:
                                                    Fri Nov 20 14:32:54 2009
 ================================================================

 Tbl3, plasma TT4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 2
                  --------          --------
                    lnalpha           3.66719
                        rho(S)              0
                          a             43.47
                          b         0.00268876
                          c           0.558678
                          d                  1

     (S) = Specified


                     Parameter Estimates

                   Variable          Model 2
                   --------          -------
                    lnalpha           3.85975
                        rho                 0
                          a           39.9223
                          b        0.00192618
```

```
                          c          0.587293
                          d                 1


               Table of Stats From Input Data

     Dose      N         Obs Mean     Obs Std Dev
     -----    ---       ----------   -------------
         0      8         40.9        6.788
        14      8         41.4        5.374
        26      8         41.4        6.505
        47      8         32.3        7.354
       320      8         33.6        6.223
      1024      8         25.5        7.637


                  Estimated Values of Interest

      Dose      Est Mean      Est Std     Scaled Residual
     ------    ----------    ---------    ----------------
         0         39.36        6.931           0.6265
        14         39.12        6.931           0.9302
        26         38.91        6.931            1.015
        47         38.55        6.931           -2.551
       320         34.15        6.931          -0.2227
      1024         24.97        6.931           0.2158


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       -112.0125            7       238.025
                        A2       -111.4015           12      246.8029
                        A3       -112.0125            7       238.025
                         R       -127.4455            2       258.891
                         2        -116.929            3       239.858


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 4:  Does Model 2 fit the data? (A3 vs. 2)


                             Tests of Interest
```

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	32.09	10	0.0003871
Test 2	1.222	5	0.9427
Test 3	1.222	5	0.9427
Test 4	9.833	4	0.04334

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. Model 2 may not adequately describe the data; you may want to consider another model.

Benchmark Dose Computations:

Specified Effect = 1.000000

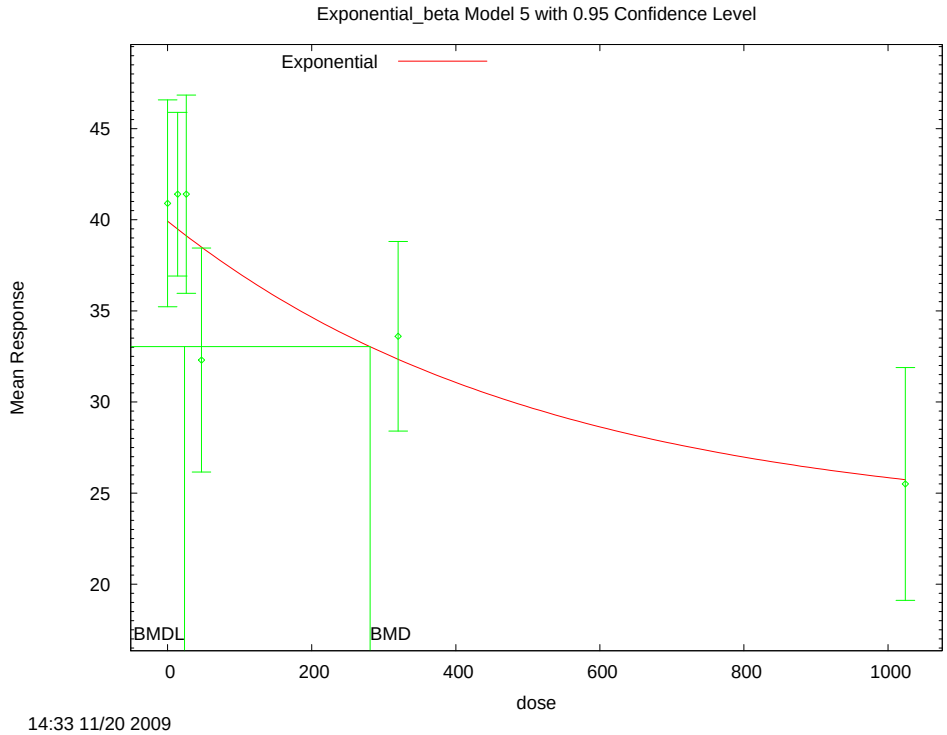
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 435.731

BMDL = 296.489

E.3.56.4. *Figure for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*



E.3.56.5. *Output File for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*

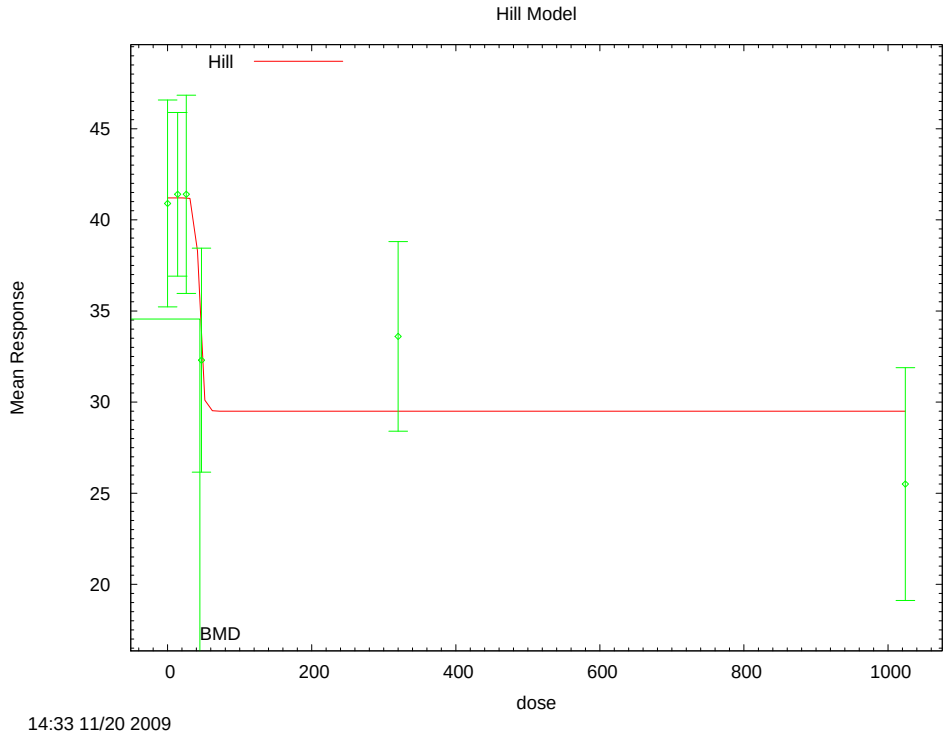
```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_CV_Unrest_BMR1_plasma_TT4.(d)
         Gnuplot Plotting File:
                                                  Fri Nov 20 14:33:03 2009
 ================================================================

 Tbl3, plasma TT4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 5
                --------          --------
                  lnalpha             3.66719
                      rho(S)                0
                        a                43.47
                        b           0.00268876
                        c             0.558678
                        d                    1

  (S) = Specified


                   Parameter Estimates

                 Variable          Model 5
                 --------          -------
                  lnalpha           3.85975
                      rho                 0
                        a           39.9223
                        b        0.00192618
                        c          0.587293
                        d                 1


          Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   ------------
      0      8         40.9        6.788
     14      8         41.4        5.374
     26      8         41.4        6.505
     47      8         32.3        7.354
    320      8         33.6        6.223
   1024      8         25.5        7.637


                Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
  ------    ----------    ---------    ----------------
      0         39.92        6.889           0.4014
     14         39.48        6.889           0.7867
     26         39.12        6.889           0.9372
     47          38.5        6.889           -2.544
    320         32.34        6.889           0.5167
   1024         25.74        6.889         -0.09785


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       -112.0125           7       238.025
                        A2       -111.4015          12      246.8029
                        A3       -112.0125           7       238.025
                         R       -127.4455           2       258.891
                         5        -116.634           4       241.268


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 7a: Does Model 5 fit the data? (A3 vs 5)


                            Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                        32.09          10           0.0003871
  Test 2                        1.222           5              0.9427
  Test 3                        1.222           5              0.9427
 Test 7a                        9.243           3             0.02623


  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 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 =      281.101
```

```
                BMDL =      23.4709
```

E.3.56.6. *Figure for Unrestricted Model: Hill, Constant Variance, n Unrestricted*



E.3.56.7. *Output File for Unrestricted Model: Hill, constant Variance, n Unrestricted*

```
 ========================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Hill_CV_Unrest_BMR1_plasma_TT4.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Hill_CV_Unrest_BMR1_plasma_TT4.plt
                                                 Fri Nov 20 14:33:05 2009
 ========================================================================

 Tbl3, plasma TT4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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

alpha =	44.7333	
rho =	0	Specified
intercept =	40.9	
v =	-15.4	
n =	2.59801	
k =	44.9231	

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	1.6e-009	-1e-009	8.3e-008
intercept	1.6e-009	1	-0.63	-0.12
v	-1e-009	-0.63	1	-0.29
k	8.3e-008	-0.12	-0.29	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	44.637	9.11149	26.7788	62.4952
intercept	41.2336	1.36385	38.5605	43.9067
v	-11.6836	2.15625	-15.9098	-7.45747
n	18	NA		
k	44.0222	3.14538	37.8573	50.187

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	40.9	41.2	6.79	6.68	-0.141
14	8	41.4	41.2	5.37	6.68	0.0704
26	8	41.4	41.2	6.51	6.68	0.0708
47	8	32.3	32.3	7.35	6.68	-3.05e-005
320	8	33.6	29.5	6.22	6.68	1.71
1024	8	25.5	29.5	7.64	6.68	-1.71

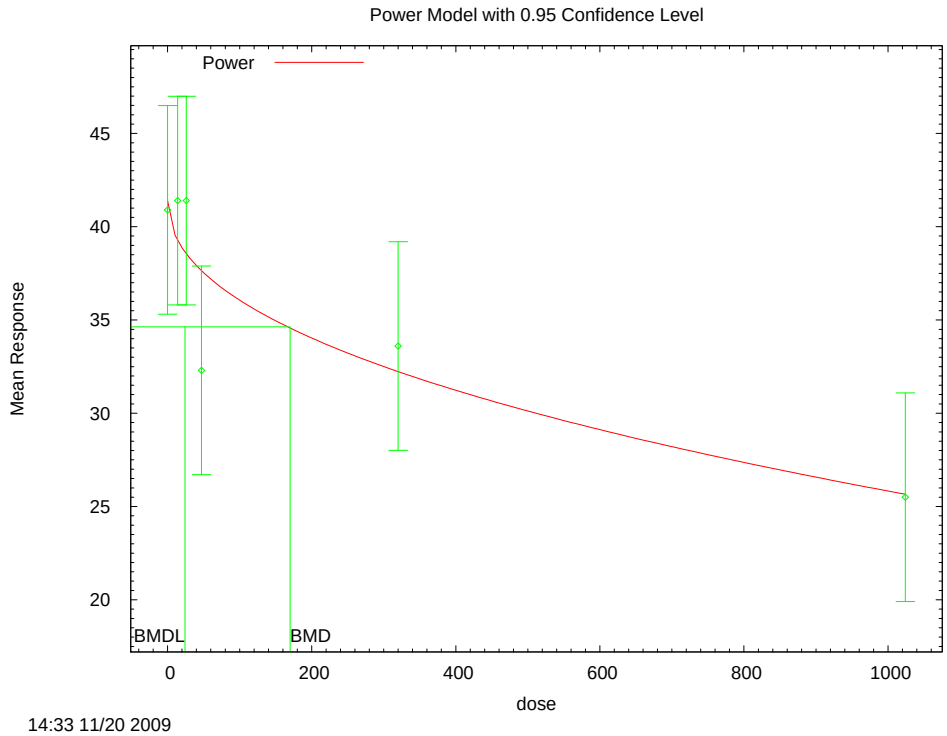
Model Descriptions for likelihoods calculated

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         -112.012501            7     238.025002
             A2         -111.401462           12     246.802924
             A3         -112.012501            7     238.025002
          fitted        -115.165512            4     238.331023
              R         -127.445484            2     258.890968


                    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               32.088         10       0.0003871
  Test 2              1.22208          5          0.9427
  Test 3              1.22208          5          0.9427
  Test 4              6.30602          3         0.09763

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 =        44.7355


BMDL computation failed.
```

E.3.56.8. *Figure for Unrestricted Model: Power, Constant Variance, Power Unrestricted*



E.3.56.9. *Output File for Unrestricted Model: Power, Constant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Pwr_CV_Unrest_BMR1_plasma_TT4.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Pwr_CV_Unrest_BMR1_plasma_TT4.plt
                                                 Fri Nov 20 14:33:06 2009
 ================================================================

 Tbl3, plasma TT4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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
```

```
                          alpha =      44.7333
                            rho =            0   Specified
                        control =         41.4
                          slope =     -4.42652
                          power =     0.155038


            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     5.3e-011     3.5e-010     5.9e-010

     control     5.3e-011            1        -0.81        -0.76

       slope     3.5e-010        -0.81            1         0.99

       power     5.9e-010        -0.76         0.99            1



                                 Parameter Estimates

                                                          95.0% Wald Confidence Interval
         Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
            alpha          46.3718           9.4656             27.8195             64.924
          control           41.441           2.1824             37.1636            45.7184
            slope        -0.626626         0.890104             -2.3712            1.11795
            power         0.464532         0.195802           0.0807676           0.848296


       Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     8       40.9         41.4         6.79         6.81         -0.225
   14     8       41.4         39.3         5.37         6.81           0.87
   26     8       41.4         38.6         6.51         6.81           1.17
   47     8       32.3         37.7         7.35         6.81          -2.24
  320     8       33.6         32.3         6.22         6.81          0.538
 1024     8       25.5         25.8         7.64         6.81         -0.108


 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	-112.012501	7	238.025002
A2	-111.401462	12	246.802924
A3	-112.012501	7	238.025002
fitted	-116.080583	4	240.161165
R	-127.445484	2	258.890968

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	32.088	10	0.0003871
Test 2	1.22208	5	0.9427
Test 3	1.22208	5	0.9427
Test 4	8.13616	3	0.04328

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 = 170.004

BMDL = 24.0807

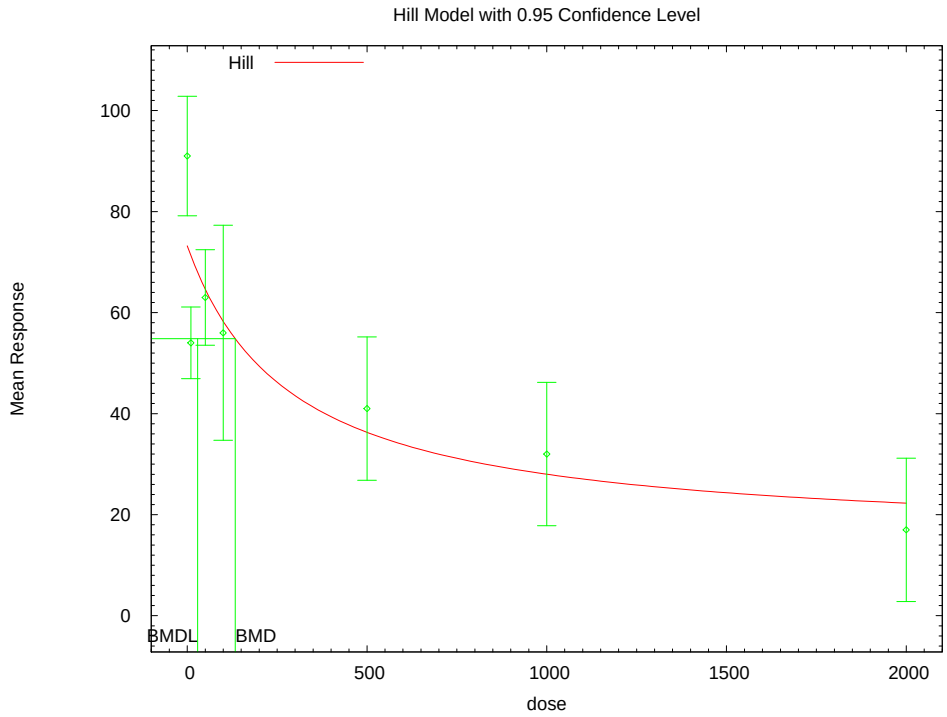
E.3.57. White et al. (1986): CH50

E.3.57.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-d)	BMDL (ng/kg-d)	Model Notes
exponential (M2)	5	0.09	20.99	0.00	391.47	4.5E+02	2.8E+02	nonconstant variance, power restricted ≥1
exponential (M3)	5	0.09	20.99	0.00	391.47	4.5E+02	2.8E+02	nonconstant variance, power restricted ≥1
exponential (M4)	4	0.09	19.65	0.00	392.13	3.1E+02	1.1E+02	nonconstant variance, power restricted ≥1
exponential (M5)	4	0.09	19.65	0.00	392.13	3.1E+02	1.1E+02	nonconstant variance, power restricted ≥1
Hill	4	0.09	18.75	0.00	391.22	2.0E+02	3.6E+01	nonconstant variance, n restricted >1, bound hit
linear	5	0.09	25.95	<.0001	396.43	8.1E+02	5.9E+02	nonconstant variance
polynomial	5	0.09	25.95	<.0001	396.43	8.1E+02	5.9E+02	nonconstant variance
power	5	0.09	25.95	<.0001	396.43	8.1E+02	5.9E+02	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	5	0.09	21.77	0.00	390.45	4.0E+02	2.6E+02	constant variance, power restricted ≥1
exponential (M3)	5	0.09	21.77	0.00	390.45	4.0E+02	2.6E+02	constant variance, power restricted ≥1
exponential (M4)	4	0.09	20.51	0.00	391.19	2.7E+02	7.2E+01	constant variance, power restricted ≥1
exponential (M5)	4	0.09	20.51	0.00	391.19	2.7E+02	7.2E+01	constant variance, power restricted ≥1
Hill [c]	**4**	**0.09**	**19.30**	**0.00**	**389.98**	**1.3E+02**	**2.9E+01**	**constant variance, n restricted >1, bound hit**
linear	5	0.09	26.50	<.0001	395.18	7.3E+02	5.7E+02	constant variance
polynomial	5	0.09	26.50	<.0001	395.18	7.3E+02	5.7E+02	constant variance
power	5	0.09	26.50	<.0001	395.18	7.3E+02	5.7E+02	constant variance, power restricted ≥1, bound hit

[a] Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected
[b] Values <0.1 fail to meet BMDS goodness-of-fit criteria
[c] Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

E.3.57.2. *Figure for Selected Model: Hill, Constant Variance, n Restricted >1, Bound Hit*



E.3.57.3. *Output File for Selected Model: Hill, Constant Variance, n Restricted >1, Bound Hit*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AniDose\HillConstVar_BMR1_CH50.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AniDose\HillConstVar_BMR1_CH50.plt
                                                Tue Oct 06 19:52:50 2009
 ================================================================

 [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
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   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
                          alpha =      273.143
                            rho =            0   Specified
                      intercept =           91
                              v =          -74
                              n =    0.0969998
                              k =           10


           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    -1.4e-008    -3.3e-008     6.7e-009

 intercept    -1.4e-008            1         0.38         -0.8

         v    -3.3e-008         0.38            1        -0.81

         k     6.7e-009         -0.8        -0.81            1



                                 Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha          337.326          63.7486             212.381             462.271
      intercept          73.1945          6.21329             61.0167             85.3723
              v         -58.2543           12.308            -82.3776             -34.131
              n                1               NA
              k          289.939          354.891            -405.635             985.512

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         73.2         14.1         18.4           2.74
   10     8         54         71.3         8.49         18.4          -2.66
   50     8         63         64.6         11.3         18.4          -0.25
  100     8         56         58.3         25.5         18.4         -0.347
  500     8         41         36.3           17         18.4           0.72
 1000     8         32           28           17         18.4          0.611
 2000     8         17         22.3           17         18.4         -0.819



 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         -181.340979            8     378.681959
             A2         -175.820265           14     379.640529
             A3         -181.340979            8     378.681959
          fitted        -190.989397            4     389.978794
              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              11.0414          6          0.0871
   Test 4              19.2968          4       0.0006871

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 =        133.503

            BMDL =        28.903
```

E.4. REFERENCES

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APPENDIX F

Cancer Benchmark Dose Modeling

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 F. CANCER BENCHMARK DOSE MODELING

F.1. BLOOD SERUM BMDS RESULTS

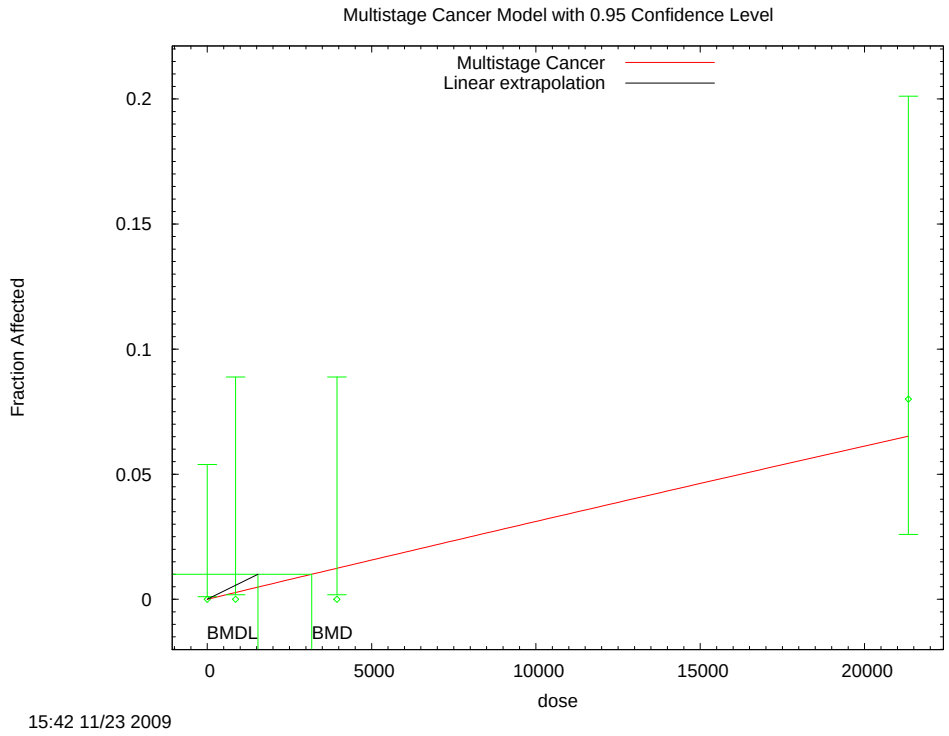
F.1.1. Kociba et al. (1978): Female, Stratified Squamous Cell Carcinoma of Hard Palate or Nasal Turbinates

F.1.1.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**3**	**0.94**	**0.82**	**31.56**	**3.2E+03**	**1.5E+03**	**betas restricted ≥0**
Multistage cancer, 2-degree	3	0.15	0.99	30.17	7.5E+03	1.9E+03	betas restricted ≥0
Multistage cancer, 3-degree	3	0.03	1.00	29.93	1.1E+04	2.0E+03	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.1.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.1.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ========================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_palate_nasal.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_palate_nasal.plt
                                                 Mon Nov 23 15:42:08 2009
 ========================================================================

 Source - Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   Independent variable = Dose

 Total number of observations = 5
 Total number of records with missing values = 1
 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) =  4.1047e-006


           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)     3.16499e-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         -13.9385         4
    Fitted model          -14.782         1       1.68697      3          0.6398
   Reduced model         -20.2589         1       12.6409      3        0.005481

           AIC:          31.5639


                                 Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          85        0.000
   860.4590     0.0027         0.136     0.000          50       -0.369
  3944.9299     0.0124         0.620     0.000          50       -0.793
 21334.0000     0.0653         3.265     4.000          50        0.421

 Chi^2 = 0.94      d.f. = 3        P-value = 0.8153


    Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        3175.47

             BMDL =        1539.87

             BMDU =        8231.22

Taken together, (1539.87, 8231.22) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =  6.49406e-006
```

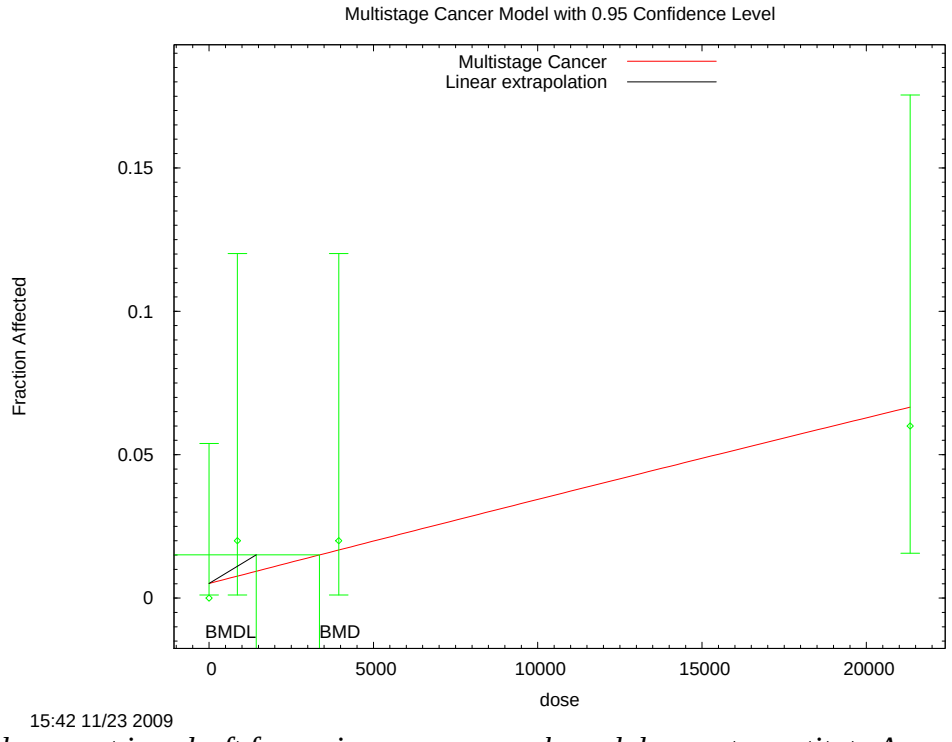
F.1.2. Kociba et al. (1978): Female, Stratified Squamous Cell Carcinoma of Tongue

F.1.2.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**1.50**	**0.47**	**47.93**	**3.4E+03**	**1.4E+03**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	1.50	0.47	47.93	3.4E+03	1.4E+03	betas restricted ≥0
Multistage cancer, 3-degree	2	1.50	0.47	47.93	3.4E+03	1.4E+03	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.2.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.2.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_tongue.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_tongue.plt
                                              Mon Nov 23 15:42:27 2009
 ================================================================

 Source - Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   Independent variable = Dose

 Total number of observations = 5
 Total number of records with missing values = 1
 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 =   0.00925136
                       Beta(1) = 2.49061e-006


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.58

   Beta(1)        -0.58            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background       0.00510493            *                *                   *
        Beta(1)     2.99496e-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        -21.1523         4
   Fitted model        -21.9667         2        1.6288      2          0.4429
  Reduced model        -24.1972         1       6.08976      3          0.1073
```

```
            AIC:         47.9334


                                  Goodness  of  Fit
                                                                        Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0051         0.434     0.000          85       -0.660
   860.4590     0.0077         0.383     1.000          50        1.000
  3944.9299     0.0168         0.840     1.000          50        0.177
 21334.0000     0.0667         3.334     3.000          50       -0.189

 Chi^2 = 1.50      d.f. = 2        P-value = 0.4716


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        3355.75

            BMDL =        1432.78

            BMDU =        19112.8

Taken together, (1432.78, 19112.8) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =  6.97946e-006
```

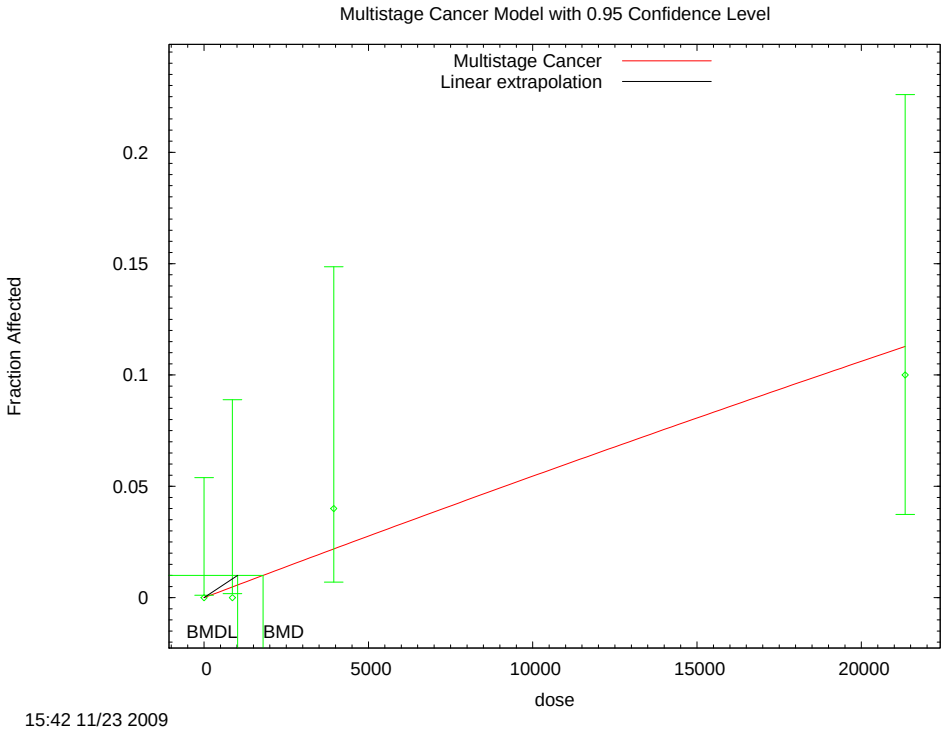
F.1.3. Kociba et al. (1978): Female, Adenoma of Adrenal Cortex

F.1.3.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**3**	**1.09**	**0.78**	**52.49**	**1.8E+03**	**1.0E+03**	**betas restricted ≥0**
Multistage cancer, 2-degree	3	1.09	0.78	52.49	1.8E+03	1.0E+03	betas restricted ≥0
Multistage cancer, 3-degree	3	1.09	0.78	52.49	1.8E+03	1.0E+03	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.3.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.3.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_adre_adenoma.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_adre_adenoma.plt
                                                 Mon Nov 23 15:42:49 2009
 ======================================================================

 Source - Table 5
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   Independent variable = Dose

 Total number of observations = 5
 Total number of records with missing values = 1
 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 =   0.00493749
                        Beta(1) = 4.83499e-006


           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)     5.60622e-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        -24.6514         4
   Fitted model        -25.2438         1       1.18487      3          0.7566
  Reduced model        -31.4904         1       13.6781      3        0.003378

           AIC:         52.4876


                                Goodness  of  Fit
                                                                    Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          85        0.000
   860.4590     0.0048         0.241     0.000          50       -0.492
  3944.9299     0.0219         1.094     2.000          50        0.876
 21334.0000     0.1127         5.636     5.000          50       -0.285

 Chi^2 = 1.09      d.f. = 3        P-value = 0.7793


   Benchmark Dose Computation

Specified effect =          0.01

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =        1792.71

            BMDL =        1020.18

            BMDU =        3628.63
```

```
Taken together, (1020.18, 3628.63) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =   9.8022e-006
```

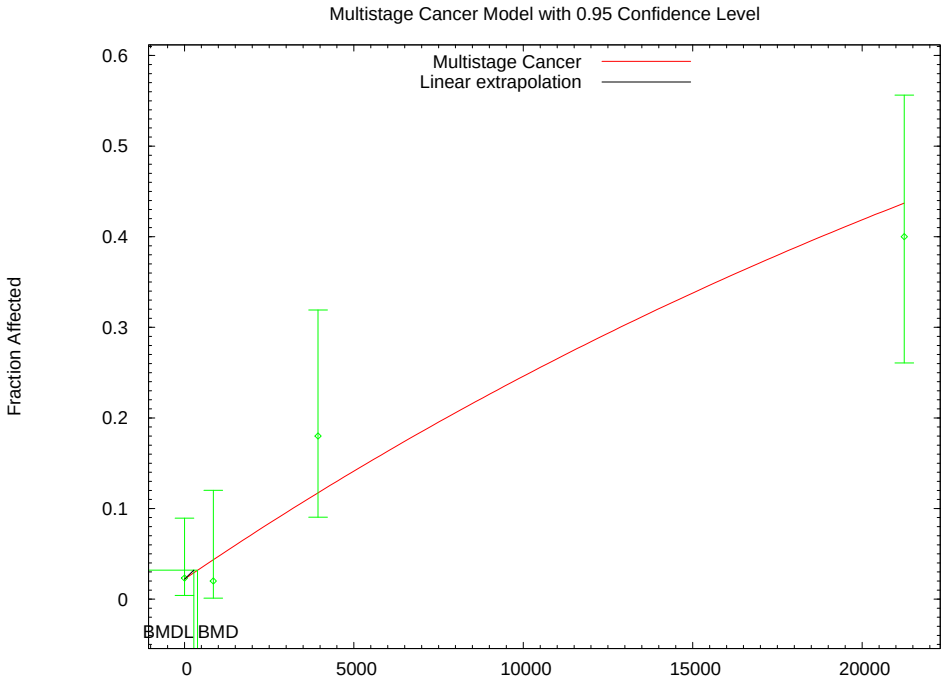
F.1.4. Kociba et al. (1978): Female, Hepatocellular Adenoma(s) or Carcinoma(s)

F.1.4.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**2.81**	**0.24**	**143.26**	**3.9E+02**	**2.8E+02**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	2.81	0.24	143.26	3.9E+02	2.8E+02	betas restricted ≥0
Multistage cancer, 3-degree	2	2.81	0.24	143.26	3.9E+02	2.8E+02	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.4.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.4.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_liver_ad_carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_liver_ad_carc.plt
                                                Mon Nov 23 15:43:10 2009
 ================================================================

 Source - Table 1 in Goodman and Sauer 1992
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =    0.0400267
                        Beta(1) = 2.26421e-005


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.51

   Beta(1)        -0.51            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background         0.022147            *                *                   *
        Beta(1)     2.60216e-005            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -68.2561         4
   Fitted model        -69.6304         2       2.74863      2           0.253
  Reduced model        -89.1983         1       41.8843      3         <.0001
```

```
            AIC:         143.261


                                  Goodness  of  Fit
                                                                        Scaled
      Dose      Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
    0.0000     0.0221         1.905     2.000          86        0.070
  852.5169     0.0436         2.180     1.000          50       -0.817
 3941.9464     0.1175         5.874     9.000          50        1.373
21246.0000     0.4374        19.685    18.000          45       -0.506

 Chi^2 = 2.81      d.f. = 2        P-value = 0.2449


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         386.23

            BMDL =        276.228

            BMDU =        577.635

Taken together, (276.228, 577.635) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =   3.6202e-005
```

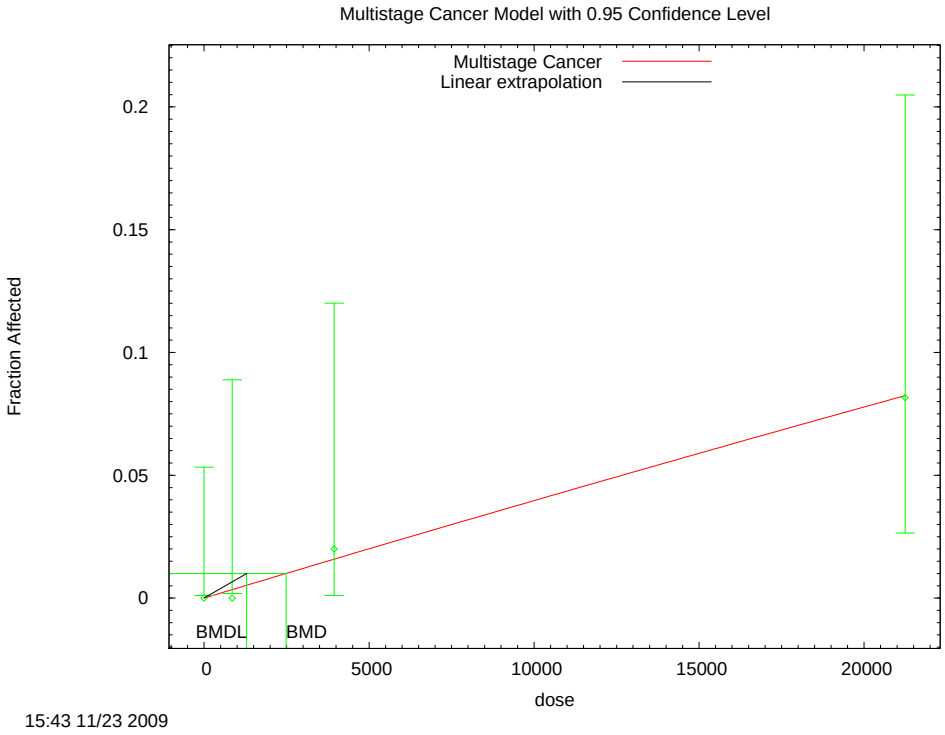
F.1.5. Kociba et al. (1978): Female, Stratified Squamous Cell Carcinoma of Hard Palate or Nasal Turbinates

F.1.5.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**3**	**0.94**	**0.82**	**31.56**	**3.2E+03**	**1.5E+03**	**betas restricted ≥0**
Multistage cancer, 2-degree	3	0.15	0.99	30.17	7.5E+03	1.9E+03	betas restricted ≥0
Multistage cancer, 3-degree	3	0.03	1.00	29.93	1.1E+04	2.0E+03	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.5.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.5.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_nasal.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_nasal.plt
                                                Mon Nov 23 15:43:31 2009
 ======================================================================

 Source - Table 5
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 = 7.11589e-005
                        Beta(1) =  4.0351e-006


           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)      4.0463e-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        -18.7562         4
    Fitted model       -18.9547         1      0.397016      3          0.9409
   Reduced model       -24.1972         1        10.882      3         0.01238

           AIC:         39.9093


                                 Goodness  of  Fit
                                                                      Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          86        0.000
   852.5169     0.0034         0.172     0.000          50       -0.416
  3941.9464     0.0158         0.791     1.000          50        0.237
 21246.0000     0.0824         4.036     4.000          49       -0.019

 Chi^2 = 0.23      d.f. = 3        P-value = 0.9728


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        2483.84

            BMDL =        1289.34

            BMDU =        5762.51
```

```
Taken together, (1289.34, 5762.51) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =   7.7559e-006
```

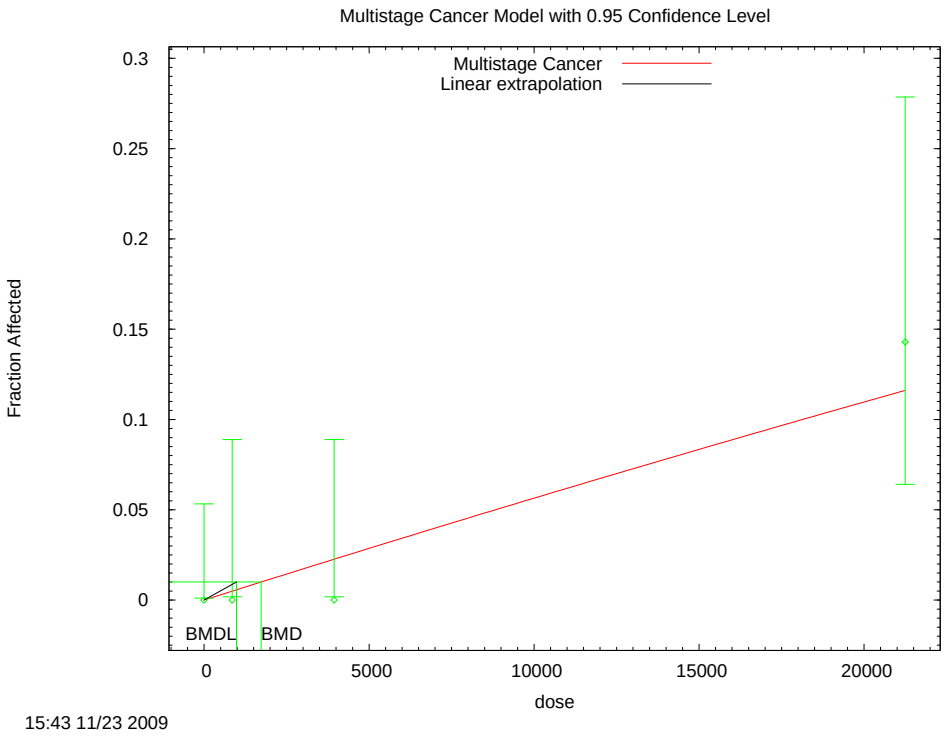
F.1.6. Kociba et al. (1978): Female, Keratinizing Squamous Cell Carcinoma of Lung

F.1.6.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**3**	**1.75**	**0.63**	**45.30**	**1.7E+03**	**9.8E+02**	**betas restricted ≥0**
Multistage cancer, 2-degree	3	0.28	0.96	42.74	5.5E+03	1.5E+03	betas restricted ≥0
Multistage cancer, 3-degree	3	0.05	1.00	42.29	8.6E+03	1.7E+03	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.6.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.6.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_kera_carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_kera_carc.plt
                                                Mon Nov 23 15:43:52 2009
 ================================================================

 Source - Table 5
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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) = 7.61927e-006


          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)     5.80969e-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        -20.0957         4
  Fitted model        -21.6489         1       3.10635      3          0.3755
 Reduced model        -31.4904         1       22.7894      3         <.0001

          AIC:         45.2978


                                 Goodness  of  Fit
                                                                  Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
   0.0000     0.0000         0.000     0.000          86        0.000
 852.5169     0.0049         0.247     0.000          50       -0.498
3941.9464     0.0226         1.132     0.000          50       -1.076
21246.0000    0.1161         5.690     7.000          49        0.584

Chi^2 = 1.75      d.f. = 3        P-value = 0.6263


  Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        1729.93

            BMDL =        984.302

            BMDU =        3461.69
```

```
Taken together, (984.302, 3461.69) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =  1.01595e-005
```

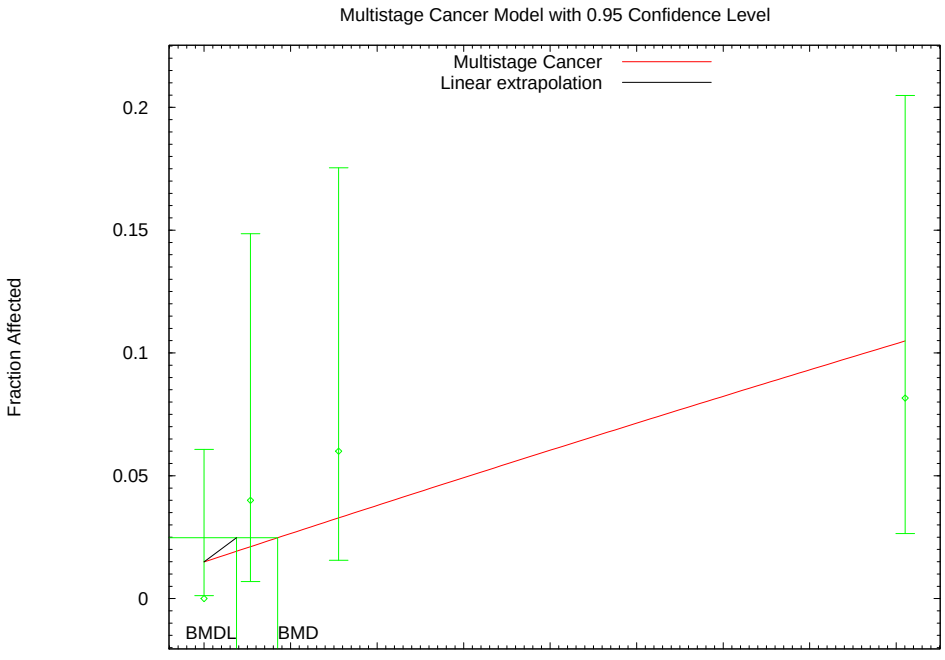
F.1.7. National Toxicology Program (1982): Female Rat, Subcutaneous Tissue. Fibrosarcoma

F.1.7.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**3.44**	**0.18**	**75.38**	**1.7E+03**	**7.5E+02**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	3.44	0.18	75.38	1.7E+03	7.5E+02	betas restricted ≥0
Multistage cancer, 3-degree	2	3.44	0.18	75.38	1.7E+03	7.5E+02	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.7.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.7.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_sub_fibro.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_sub_fibro.plt
                                                Mon Nov 23 15:44:12 2009
 ================================================================

 Source - Table 10
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =     0.026791
                        Beta(1) = 3.88561e-006


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.63

   Beta(1)        -0.63            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0149169            *                *                   *
        Beta(1)     5.91146e-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        -33.5998         4
   Fitted model        -35.6885         2       4.17734      2          0.1239
  Reduced model        -37.7465         1       8.29346      3         0.04032
```

```
            AIC:         75.3769


                                  Goodness  of  Fit
                                                                        Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0149         1.119     0.000          75       -1.066
  1072.2652     0.0211         1.057     2.000          50        0.927
  3111.2349     0.0329         1.643     3.000          50        1.076
 16207.0000     0.1049         5.141     4.000          49       -0.532

 Chi^2 = 3.44      d.f. = 2        P-value = 0.1795


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        1700.14

            BMDL =        751.001

            BMDU =   1.77581e+009

Taken together, (751.001, 1.77581e+009) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =  1.33156e-005
```

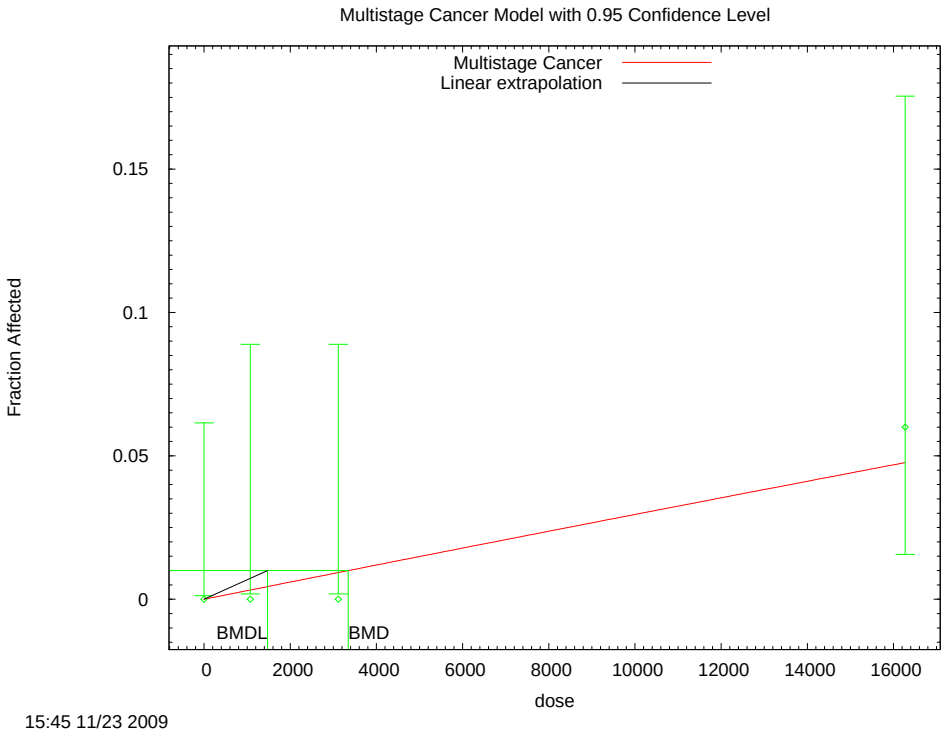
F.1.8. National Toxicology Program (1982): Female Rat, Liver, Neoplastic Nodule or Hepatocellular Carcinoma

F.1.8.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**3**	**0.80**	**0.22**	**135.20**	**6.4E+02**	**4.0E+02**	**betas restricted ≥0**
Multistage cancer, 2-degree	3	0.13	0.49	133.45	3.0E+03	4.8E+02	betas restricted ≥0
Multistage cancer, 3-degree	3	0.02	0.24	135.44	3.9E+03	4.8E+02	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.8.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.8.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_liver_nod.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_liver_nod.plt
                                                 Mon Nov 23 15:45:38 2009
 ======================================================================

 Source - Table 9
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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) = 4.03747e-006


           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)     3.00492e-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        -11.3484         4
    Fitted model       -12.0545         1       1.41226      3          0.7027
   Reduced model       -15.9189         1       9.14109      3         0.02747

           AIC:          26.109


                                 Goodness  of  Fit
                                                                    Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          74        0.000
  1071.8576     0.0032         0.161     0.000          50       -0.402
  3115.7313     0.0093         0.466     0.000          50       -0.686
 16272.0000     0.0477         2.386     3.000          50        0.407

 Chi^2 = 0.80      d.f. = 3        P-value = 0.8501


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        3344.63

            BMDL =        1472.42

            BMDU =        10322.4
```

```
Taken together, (1472.42, 10322.4) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =  6.79156e-006
```

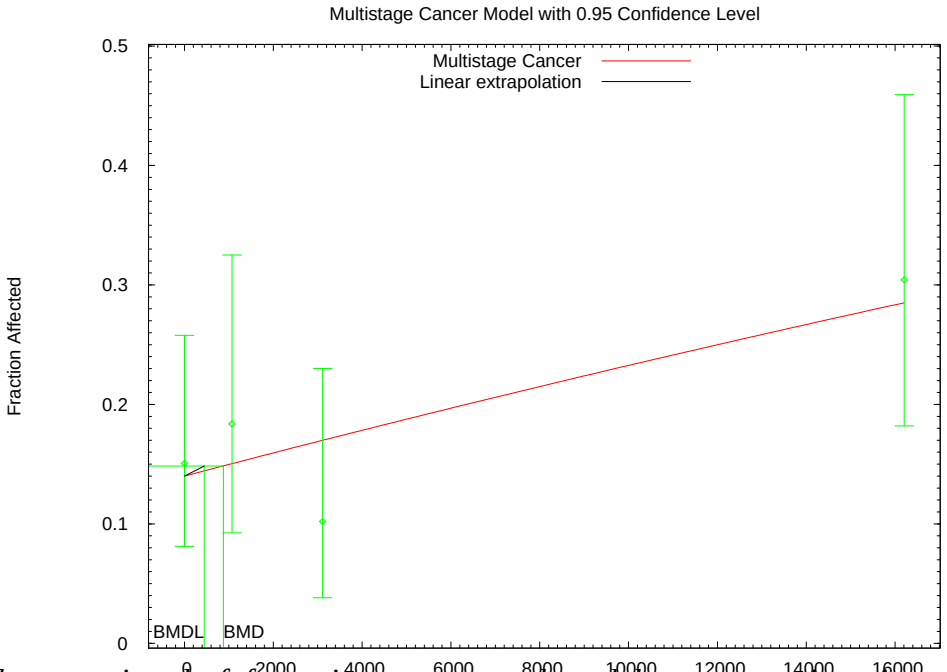
F.1.9. National Toxicology Program (1982): Female Rat, Adrenal, Cortical Adenoma, or Carcinoma or Adenoma, NOS

F.1.9.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**2.18**	**0.34**	**203.83**	**8.8E+02**	**4.4E+02**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	1.51	0.47	203.03	3.6E+03	4.9E+02	betas restricted ≥0
Multistage cancer, 3-degree	2	1.37	0.51	202.87	5.9E+03	5.0E+02	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.9.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.9.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_adre_cort_ad_carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_adre_cort_ad_carc.plt
                                                Mon Nov 23 15:44:55 2009
 ================================================================

 Source - Table 10
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =     0.134119
                        Beta(1) = 1.27888e-005


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.54

   Beta(1)        -0.54            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background         0.139831            *                *                   *
        Beta(1)     1.14475e-005            *                *                   *

* - Indicates that this value is not calculated.


                         Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -98.7282         4
   Fitted model        -99.9133         2       2.37035      2          0.3057
  Reduced model        -102.201         1       6.94636      3         0.07363
```

```
            AIC:         203.827


                                  Goodness  of  Fit
                                                                        Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.1398        10.208    11.000          73        0.267
  1072.2652     0.1503         7.366     9.000          49        0.653
  3111.2349     0.1699         8.326     5.000          49       -1.265
 16207.0000     0.2855        13.132    14.000          46        0.283

  Chi^2 = 2.18      d.f. = 2        P-value = 0.3363


    Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        877.947

             BMDL =        443.554

             BMDU =   6.93624e+008

Taken together, (443.554, 6.93624e+008) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =  2.25452e-005
```

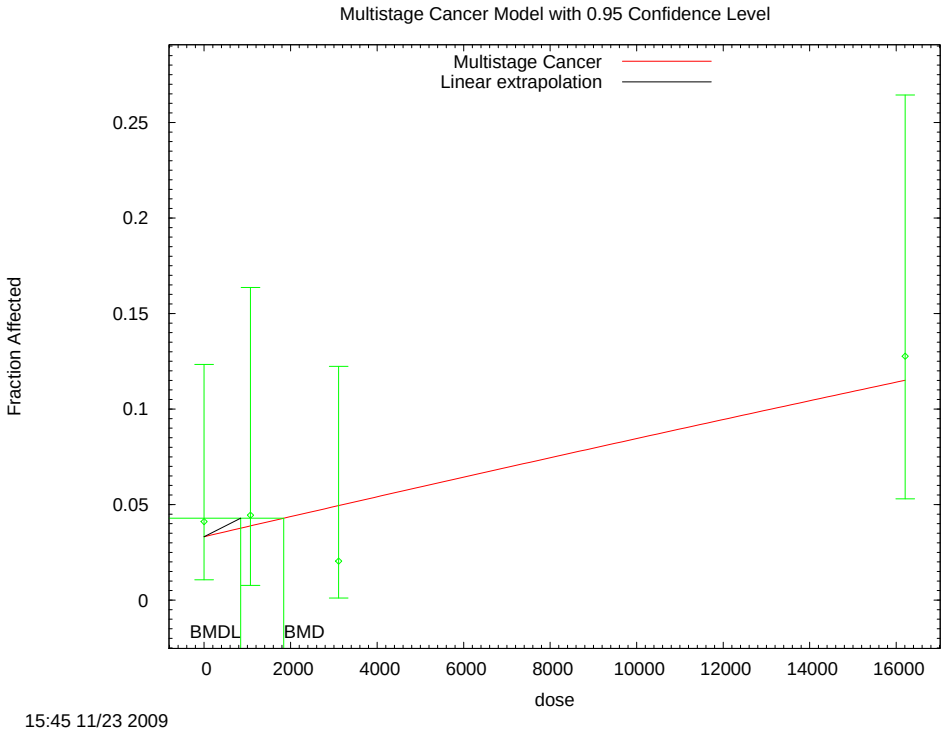
F.1.10. National Toxicology Program (1982): Female Rat, Thyroid, Follicular-Cell Adenoma

F.1.10.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**1.13**	**0.57**	**92.41**	**1.8E+03**	**8.5E+02**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	0.62	0.74	91.75	5.2E+03	9.2E+02	betas restricted ≥0
Multistage cancer, 3-degree	2	0.52	0.77	91.63	7.5E+03	9.4E+02	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.10.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.10.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ========================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_thy_ad.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_thy_ad.plt
                                                 Mon Nov 23 15:45:17 2009
 ========================================================================

 Source - Table 10
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =    0.0282954
                        Beta(1) = 6.36609e-006


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.54

   Beta(1)        -0.54            1



                                 Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0332349            *                *                   *
        Beta(1)     5.46313e-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        -43.5264         4
    Fitted model       -44.2066         2       1.36031      2          0.5065
  Reduced model        -46.2299         1       5.40699      3          0.1443

            AIC:         92.4132


                                  Goodness  of  Fit
                                                                      Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0332         2.426     3.000          73        0.375
  1072.2652     0.0389         1.750     2.000          45        0.193
  3111.2349     0.0495         2.427     1.000          49       -0.939
 16207.0000     0.1152         5.412     6.000          47        0.269

 Chi^2 = 1.13      d.f. = 2        P-value = 0.5677


    Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        1839.67

             BMDL =        846.279

             BMDU =        11586.6

Taken together, (846.279, 11586.6) is a 90     % two-sided confidence
```

```
interval for the BMD

Multistage Cancer Slope Factor =  1.18164e-005
```

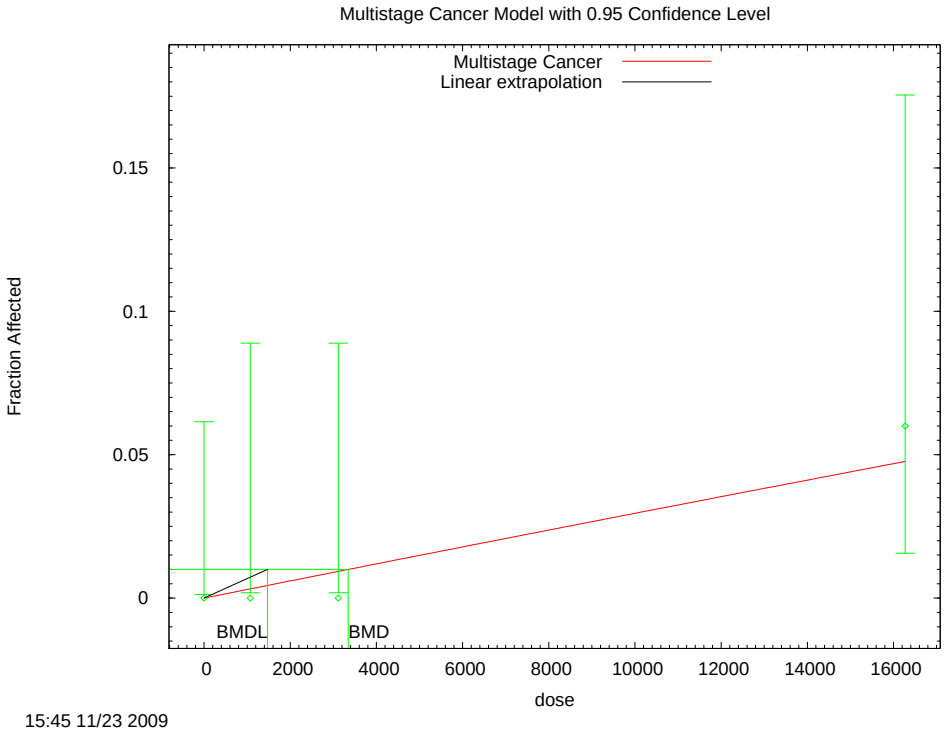
F.1.11. National Toxicology Program (1982): Male Rat, Liver, Neoplastic Nodule or Hepatocellular Carcinoma

F.1.11.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**3**	**0.80**	**0.22**	**135.20**	**6.4E+02**	**4.0E+02**	**betas restricted ≥0**
Multistage cancer, 2-degree	3	0.13	0.49	133.45	3.0E+03	4.8E+02	betas restricted ≥0
<ultistage cancer, 3-degree	3	0.02	0.24	135.44	3.9E+03	4.8E+02	betas restricted ≥0

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria
[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

F.1.11.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.11.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 =================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_liver_nod.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_liver_nod.plt
                                                  Mon Nov 23 15:45:38 2009
 =================================================================

 Source - Table 9
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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) = 4.03747e-006


           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)     3.00492e-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        -11.3484         4
    Fitted model       -12.0545         1       1.41226      3          0.7027
   Reduced model       -15.9189         1       9.14109      3         0.02747

           AIC:          26.109


                                 Goodness  of  Fit
                                                                      Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          74        0.000
  1071.8576     0.0032         0.161     0.000          50       -0.402
  3115.7313     0.0093         0.466     0.000          50       -0.686
 16272.0000     0.0477         2.386     3.000          50        0.407

 Chi^2 = 0.80      d.f. = 3        P-value = 0.8501


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        3344.63

            BMDL =        1472.42

            BMDU =        10322.4
```

```
Taken together, (1472.42, 10322.4) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =  6.79156e-006
```

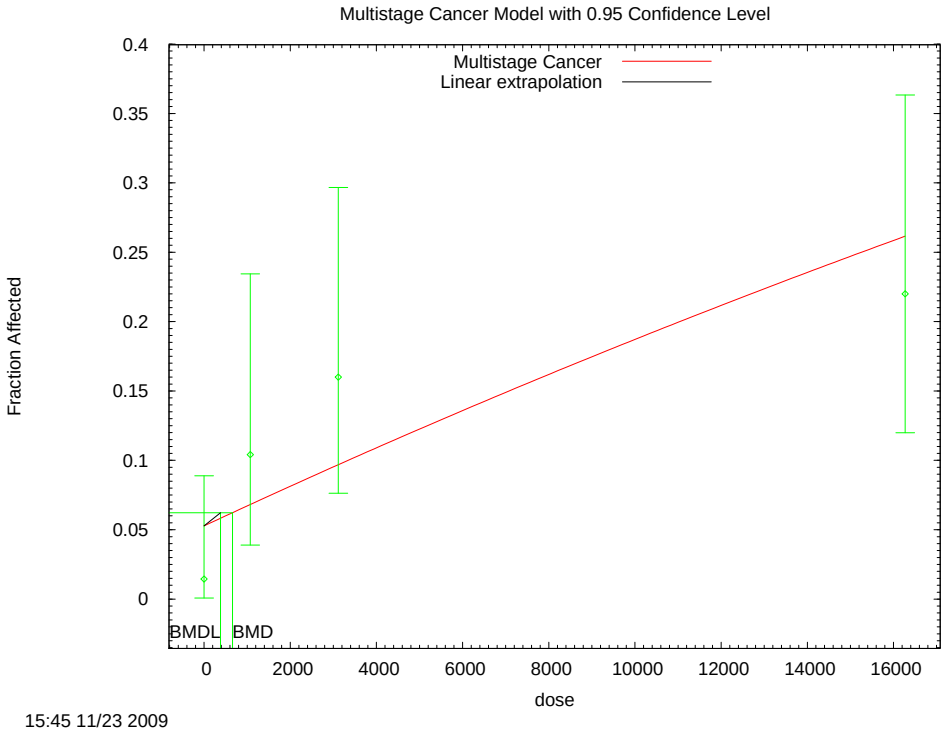
F.1.12. National Toxicology Program (1982): Male Ra, Thyroid, Follicular-Cell Adenoma or Carcinoma

F.1.12.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**5.73**	**0.06**	**149.25**	**6.6E+02**	**3.8E+02**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	5.73	0.06	149.25	6.6E+02	3.8E+02	betas restricted ≥0
Multistage cancer, 3-degree	2	5.73	0.06	149.25	6.6E+02	3.8E+02	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.12.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.12.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ========================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_thyroid.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_thyroid.plt
                                                 Mon Nov 23 15:45:59 2009
 ========================================================================

 Source - Table 9
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =    0.0767848
                        Beta(1) = 1.11362e-005


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.62

   Beta(1)        -0.62            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0527729            *                *                   *
        Beta(1)     1.52871e-005            *                *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -69.5946         4
    Fitted model       -72.6245         2       6.05993      2         0.04832
  Reduced model        -77.5267         1       15.8643      3        0.001209

            AIC:         149.249


                                 Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------------
     0.0000     0.0528         3.641     1.000          69       -1.422
  1071.8576     0.0682         3.272     5.000          48        0.990
  3115.7313     0.0968         4.842     8.000          50        1.510
 16272.0000     0.2614        13.069    11.000          50       -0.666

 Chi^2 = 5.73      d.f. = 2        P-value = 0.0571


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        657.439

             BMDL =        380.166

             BMDU =        1571.51

Taken together, (380.166, 1571.51) is a 90     % two-sided confidence
```

```
interval for the BMD

Multistage Cancer Slope Factor =  2.63043e-005
```

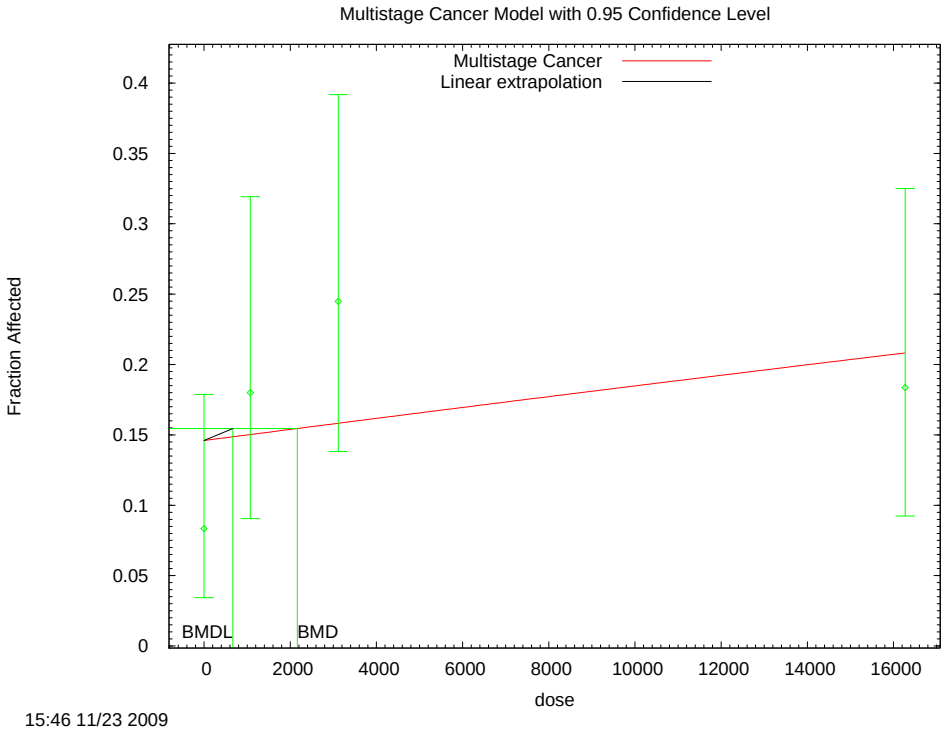
F.1.13. National Toxicology Program (1982): Male Rat, Adrenal Cortex, Adenoma

F.1.13.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**5.55**	**0.06**	**199.31**	**2.2E+03**	**6.7E+02**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	5.55	0.06	199.31	2.2E+03	6.7E+02	betas restricted ≥0
Multistage cancer, 3-degree	2	5.55	0.06	199.31	2.2E+03	6.7E+02	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.13.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.13.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_adre_cort.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_adre_cort.plt
                                                Mon Nov 23 15:46:20 2009
 ================================================================

 Source - Table 9
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =      0.16365
                        Beta(1) = 2.66257e-006


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.61

   Beta(1)        -0.61            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background         0.146024            *               *                   *
        Beta(1)      4.6499e-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        -94.8672         4
    Fitted model       -97.6531         2       5.57181      2         0.06167
   Reduced model       -98.0432         1       6.35197      3         0.09569

            AIC:         199.306


                                 Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.1460        10.514     6.000          72       -1.506
  1071.8576     0.1503         7.513     9.000          50        0.588
  3115.7313     0.1583         7.757    12.000          49        1.661
 16272.0000     0.2083        10.204     9.000          49       -0.424

 Chi^2 = 5.55      d.f. = 2        P-value = 0.0623


    Benchmark Dose Computation

Specified effect =          0.01

Risk Type        =      Extra risk

Confidence level =          0.95

              BMD =       2161.41

             BMDL =       665.411


BMDU did not converge for BMR = 0.010000
BMDU calculation failed
             BMDU = Inf
```

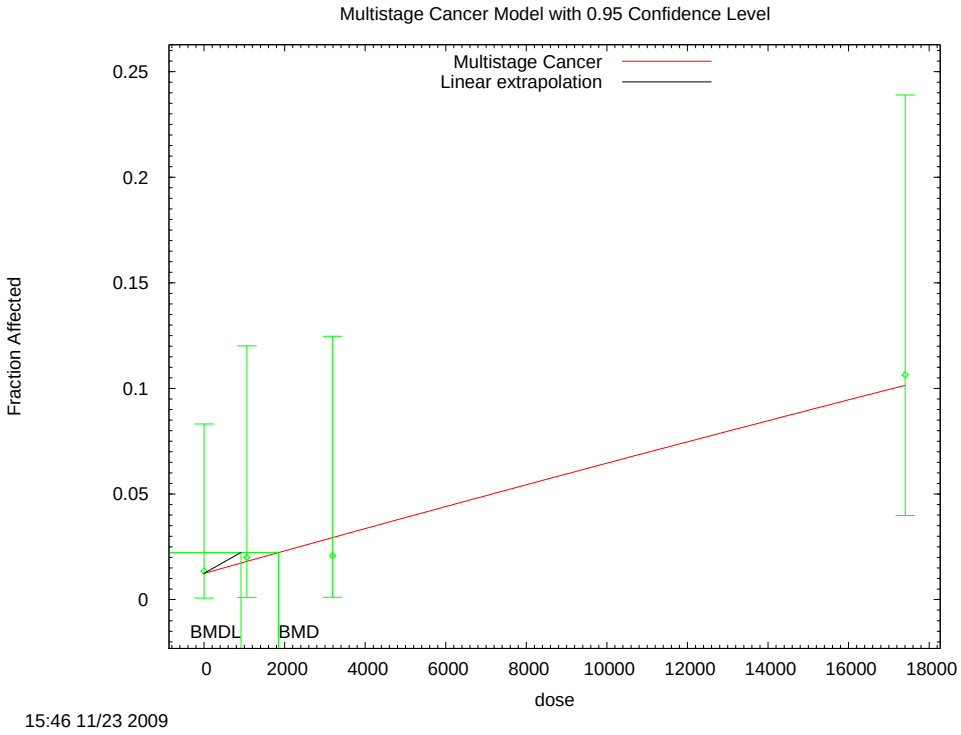
F.1.14. National Toxicology Program (1982): Female Mice, Subcutaneous Tissue, Fibrosarcoma

F.1.14.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**3.44**	**0.18**	**75.38**	**1.7E+03**	**7.5E+02**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	3.44	0.18	75.38	1.7E+03	7.5E+02	betas restricted ≥0
Multistage cancer, 3-degree	2	3.44	0.18	75.38	1.7E+03	7.5E+02	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.14.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.14.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_subcu_fibro.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_subcu_fibro.plt
                                                 Mon Nov 23 15:46:40 2009
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =    0.0104441
                        Beta(1) = 5.78849e-006


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.55

   Beta(1)        -0.55            1



                                 Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0124215            *                *                   *
        Beta(1)     5.43453e-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        -30.9876         4
    Fitted model       -31.0699         2       0.16463      2           0.921
  Reduced model        -34.3291         1       6.68308      3         0.08272

            AIC:         66.1398


                                  Goodness  of  Fit
                                                                    Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0124         0.919     1.000          74        0.085
  1063.6377     0.0181         0.906     1.000          50        0.100
  3184.3353     0.0294         1.410     1.000          48       -0.350
 17406.0000     0.1016         4.773     5.000          47        0.110

 Chi^2 = 0.15      d.f. = 2        P-value = 0.9269


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        1849.35

             BMDL =        916.028

             BMDU =        6164.32

Taken together, (916.028, 6164.32) is a 90     % two-sided confidence
```

```
interval for the BMD

Multistage Cancer Slope Factor =  1.09167e-005
```

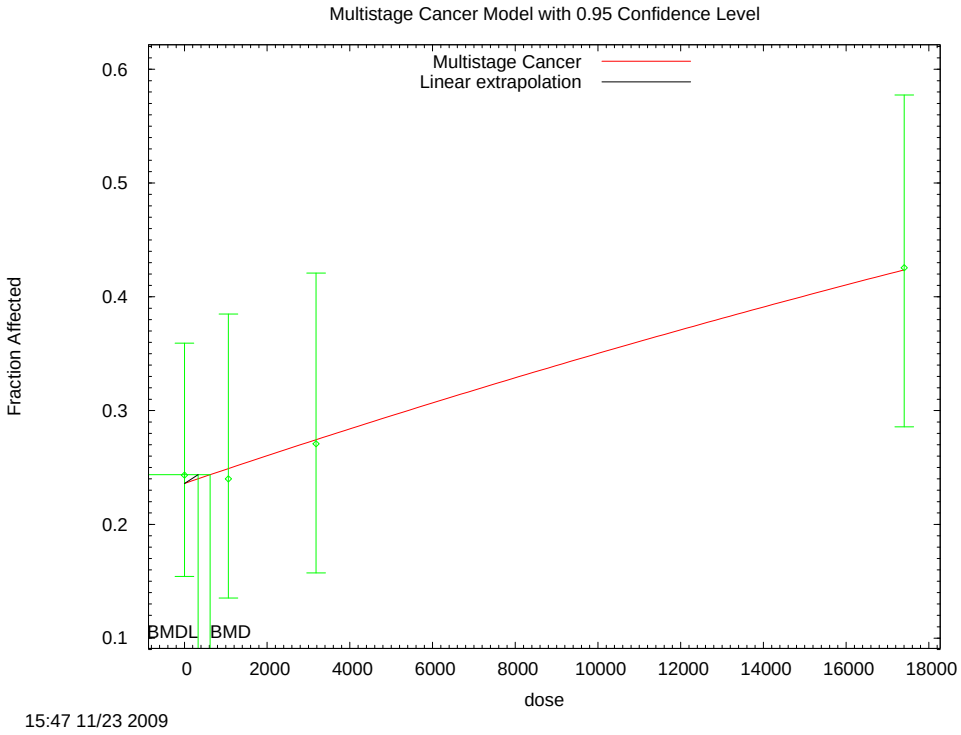
F.1.15. National Toxicology Program (1982): Female Mice, Hematopoietic System, Lymphoma

F.1.15.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**0.05**	**0.98**	**261.45**	**6.2E+02**	**3.3E+02**	**betas restricted ≥0**
Multistage cancer, 2-degree	1	0.03	0.87	263.43	9.3E+02	3.3E+02	betas restricted ≥0
Multistage cancer, 3-degree	1	0.03	0.87	263.43	9.3E+02	3.3E+02	betas restricted ≥0

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b] Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.15.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.15.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_mice_f_lymphoma.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_mice_f_lymphoma.plt
                                                  Mon Nov 23 15:47:00 2009
 ================================================================

 Table 15 page 64 Hematopoietic System Lymphoma or Leukemia
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =     0.234156
                        Beta(1) =   1.645e-005


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.54

   Beta(1)        -0.54            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
      Background         0.236108            *                 *                   *
         Beta(1)     1.61681e-005            *                 *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

         Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -128.699         4
     Fitted model       -128.723         2     0.0471776      2          0.9767
   Reduced model        -131.412         1       5.42487      3          0.1432

            AIC:         261.446


                                Goodness  of  Fit
                                                                      Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.2361        17.472    18.000          74        0.145
  1063.6377     0.2491        12.457    12.000          50       -0.149
  3184.3353     0.2744        13.173    13.000          48       -0.056
 17406.0000     0.4235        19.904    20.000          47        0.028

 Chi^2 = 0.05      d.f. = 2        P-value = 0.9767


    Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        621.617

             BMDL =        330.742

             BMDU =         2332.7

Taken together, (330.742, 2332.7 ) is a 90     % two-sided confidence
```

```
interval for the BMD

Multistage Cancer Slope Factor =   3.0235e-005
```

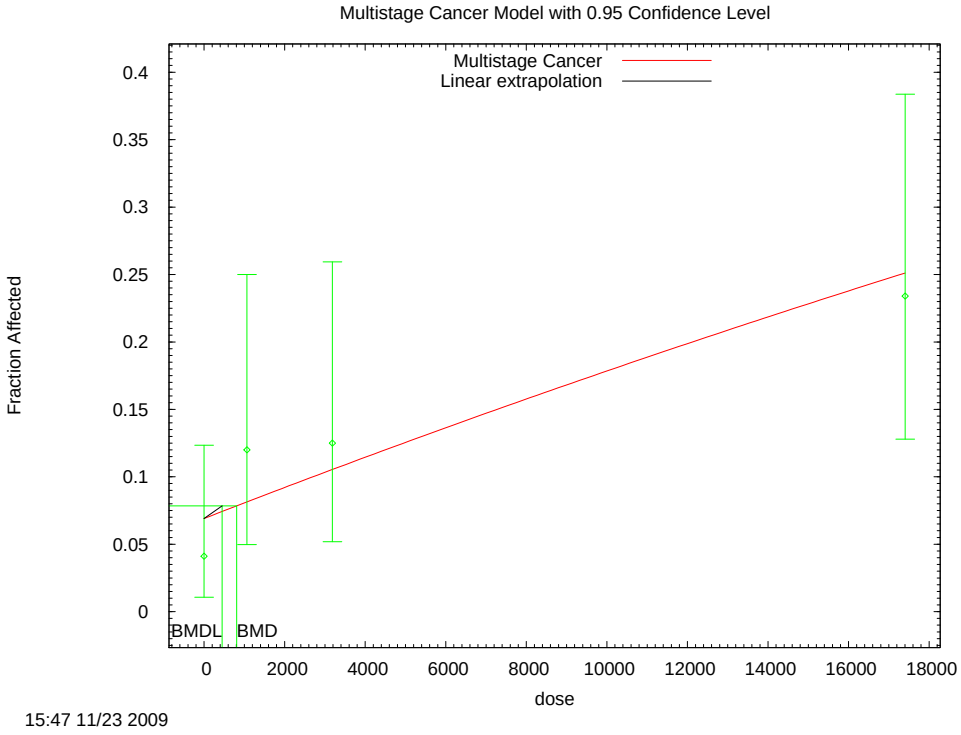
F.1.16. National Toxicology Program (1982): Female Mice, Liver, Hepatocellular Adenoma or Carcinoma

F.1.16.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**2.15**	**0.34**	**155.21**	**8.1E+02**	**4.5E+02**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	2.15	0.34	155.21	8.1E+02	4.5E+02	betas restricted ≥0
Multistage cancer, 3-degree	2	2.15	0.34	155.21	8.1E+02	4.5E+02	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.16.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.16.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_mice_f_liv_aden_carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_mice_f_liv_aden_carc.plt
                                                  Mon Nov 23 15:47:20 2009
 ================================================================

 0
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   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 = Mean
   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 =    0.0808715
                        Beta(1) = 1.07435e-005


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.57

   Beta(1)        -0.57            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0691337            *               *                   *
        Beta(1)     1.24516e-005            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -74.5177         4
    Fitted model         -75.603         2       2.17074      2          0.3378
   Reduced model        -79.6703         1       10.3053      3         0.01614

           AIC:         155.206


                                  Goodness  of  Fit
                                                                 Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0691         5.047     3.000          73       -0.944
  1063.6377     0.0814         4.069     6.000          50        0.999
  3184.3353     0.1053         5.055     6.000          48        0.444
 17406.0000     0.2505        11.774    11.000          47       -0.261

 Chi^2 = 2.15      d.f. = 2        P-value = 0.3405


    Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        807.155

             BMDL =        448.599

             BMDU =        2161.58

Taken together, (448.599, 2161.58) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =  2.22916e-005
```

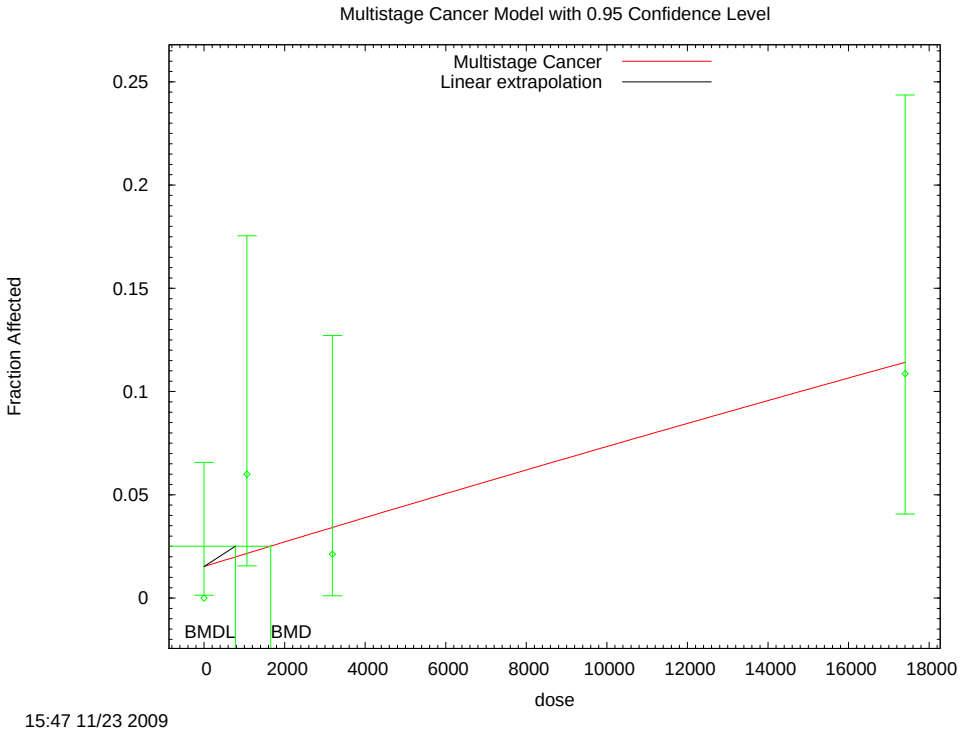
F.1.17. National Toxicology Program (1982): Female Mice, Thyroid, Follicular-Cell Adenoma

F.1.17.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**3.44**	**0.18**	**75.38**	**1.7E+03**	**7.5E+02**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	3.44	0.18	75.38	1.7E+03	7.5E+02	betas restricted ≥0
Multistage cancer, 3-degree	2	3.44	0.18	75.38	1.7E+03	7.5E+02	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.17.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.17.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_mice_f_thyroid_aden.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_mice_f_thyroid_aden.plt
                                                  Mon Nov 23 15:47:40 2009
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =    0.0202008
                        Beta(1) = 5.39488e-006


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.58

   Beta(1)        -0.58            1



                                 Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0152512            *                *                   *
        Beta(1)     6.07986e-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        -32.0017         4
    Fitted model       -34.3878         2       4.77223      2         0.09199
  Reduced model        -37.2405         1       10.4776      3         0.01491

            AIC:         72.7756


                                  Goodness  of  Fit
                                                                      Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0153         1.052     0.000          69       -1.034
  1063.6377     0.0216         1.080     3.000          50        1.868
  3184.3353     0.0341         1.604     1.000          47       -0.485
 17406.0000     0.1141         5.250     5.000          46       -0.116

 Chi^2 = 4.81      d.f. = 2        P-value = 0.0904


    Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        1653.05

             BMDL =        778.784

             BMDU =        6460.82

Taken together, (778.784, 6460.82) is a 90     % two-sided confidence
```

```
interval for the BMD

Multistage Cancer Slope Factor =  1.28405e-005
```

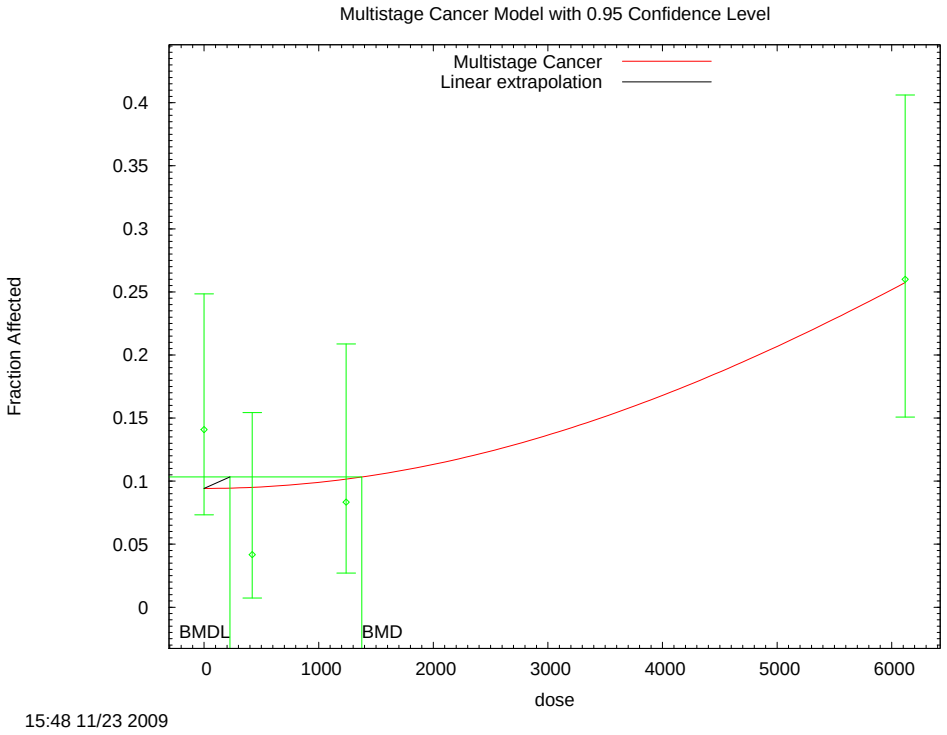
F.1.18. National Toxicology Program (1982): Male Mice, Lung, Alveolar/Bronchiolar Adenoma or Carcinoma

F.1.18.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree	2	4.87	0.09	168.35	3.5E+02	1.9E+02	betas restricted ≥0
Multistage cancer, 2-degree[b]	**2**	**3.58**	**0.17**	**166.95**	**1.4E+03**	**2.3E+02**	**betas restricted ≥0**
Multistage cancer, 3-degree	2	3.41	0.18	166.80	2.3E+03	2.3E+02	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.18.2. *Figure for Selected Model: Multistage Cancer, 2-Degree, Betas Restricted ≥0*



F.1.18.3. *Output File for Selected Model: Multistage Cancer, 2-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc2_ngkgd_lung_aden_carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc2_ngkgd_lung_aden_carc.plt
                                                  Mon Nov 23 15:48:02 2009
 ======================================================================

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   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 = Mean
   Independent variable = Dose

 Total number of observations = 4
 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 =     0.086839
                        Beta(1) =            0
                        Beta(2) = 5.59843e-009


            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        -0.46

   Beta(2)        -0.46            1


                                 Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0942375            *                *                   *
        Beta(1)                0            *                *                   *
        Beta(2)     5.31152e-009            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -79.5959         4
   Fitted model        -81.4737         2       3.75561      2          0.1529
  Reduced model        -85.3351         1       11.4782      3        0.009402

            AIC:         166.947


                                  Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
    0.0000     0.0942         6.691    10.000          71        1.344
  420.0366     0.0951         4.564     2.000          48       -1.262
 1239.6134     0.1016         4.877     4.000          48       -0.419
 6117.5662     0.2575        12.876    13.000          50        0.040

 Chi^2 = 3.58      d.f. = 2        P-value = 0.1673


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        1375.56
```

```
             BMDL =        225.385

             BMDU =        2284.92

Taken together, (225.385, 2284.92) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =  4.43686e-005
```

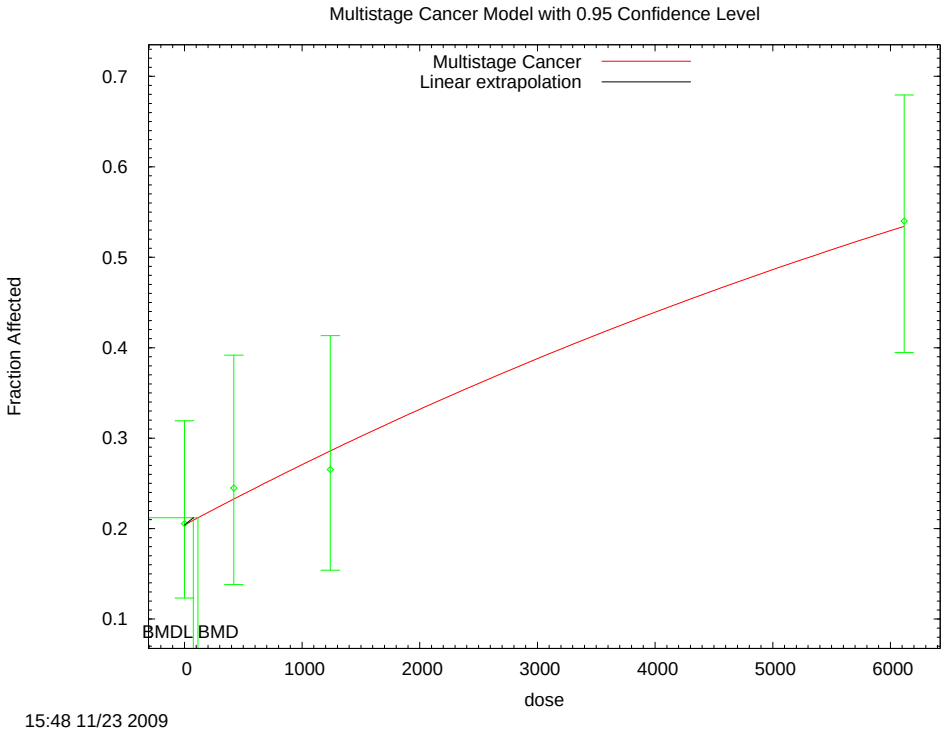
F.1.19. National Toxicology Program (1982): Male Mice, Liver, Hepatocellular Adenoma or Carcinoma

F.1.19.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**0.15**	**0.93**	**258.55**	**1.1E+02**	**7.5E+01**	**betas restricted ≥0**
Multistage cancer, 2-degree	1	0.08	0.78	260.48	1.7E+02	7.5E+01	betas restricted ≥0
Multistage cancer, 3-degree	1	0.07	0.79	260.47	1.6E+02	7.5E+01	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.19.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.19.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_mice_m_liver_aden_carc.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_mice_m_liver_aden_carc.plt
                                                  Mon Nov 23 15:48:23 2009
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   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 = Mean
   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 =     0.201516
                        Beta(1) = 8.94392e-005


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.53

   Beta(1)        -0.53            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
      Background         0.204153            *                *                   *
         Beta(1)     8.75513e-005            *                *                   *

* - Indicates that this value is not calculated.



                         Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -127.199         4
    Fitted model       -127.274         2      0.151061      2          0.9273
   Reduced model       -135.589         1       16.7801      3       0.0007843

            AIC:         258.549



                                Goodness  of  Fit
                                                                    Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.2042        14.903    15.000          73        0.028
   420.0366     0.2329        11.412    12.000          49        0.199
  1239.6134     0.2860        14.014    13.000          49       -0.321
  6117.5662     0.5342        26.709    27.000          50        0.083

 Chi^2 = 0.15      d.f. = 2        P-value = 0.9278


    Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        114.794

             BMDL =        74.9717

             BMDU =        208.915
```

```
Taken together, (74.9717, 208.915) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =   0.000133384
```

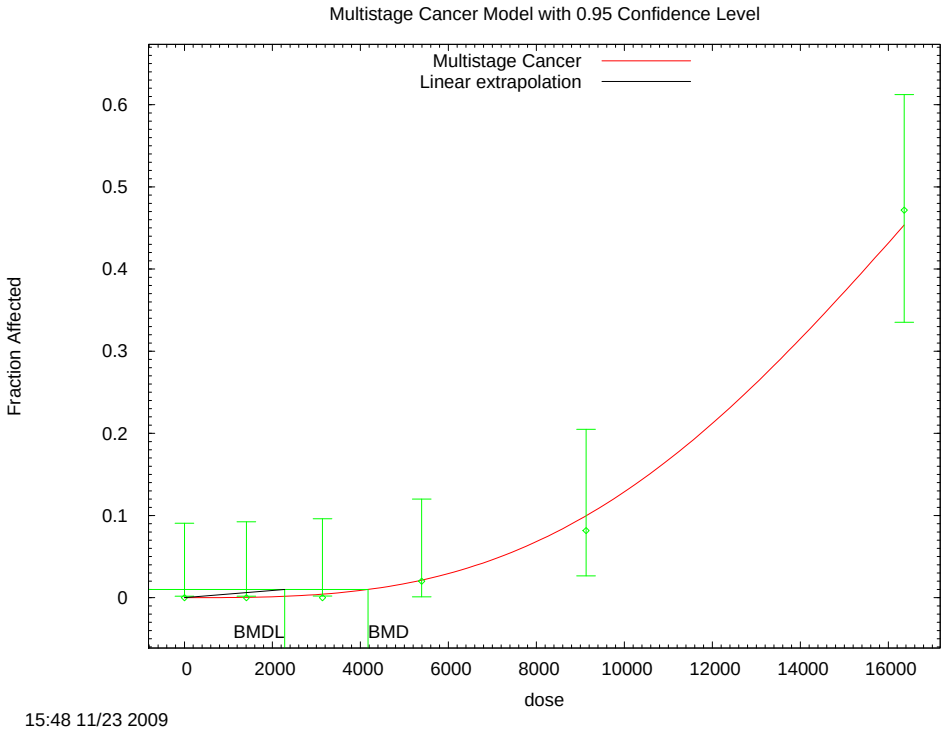
F.1.20. National Toxicology Program (2006): Liver, Cholangiocarcinoma

F.1.20.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree	5	20.87	0.00	138.46	5.2E+02	3.9E+02	betas restricted ≥0
Multistage cancer, 2-degree	5	5.09	0.40	119.37	2.3E+03	1.6E+03	betas restricted ≥0
Multistage cancer, 3-degree[b]	**5**	**0.47**	**0.99**	**113.51**	**4.2E+03**	**2.3E+03**	**betas restricted ≥0**

[a] Values <0.1 fail to meet BMDS goodness-of-fit criteria
[b] Best-fitting model as assessed by lowest-AIC criterion, bolded

F.1.20.2. *Figure for Selected Model: Multistage Cancer, 3-Degree, Betas Restricted ≥0*



F.1.20.3. *Output File for Selected Model: Multistage Cancer, 3-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc3_ngkgd_liv_cho-carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc3_ngkgd_liv_cho-carc.plt
                                                  Mon Nov 23 15:48:43 2009
 ================================================================

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   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 = Mean
   Independent variable = Dose

 Total number of observations = 6
 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
                        Beta(1) =           0
                        Beta(2) =           0
                        Beta(3) = 1.46324e-013


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                Beta(3)

  Beta(3)           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           *               *                   *
        Beta(3)     1.38296e-013           *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -55.408         6
    Fitted model        -55.7539        1      0.691685      5          0.9834
   Reduced model        -96.9934        1       83.1708      5         <.0001

           AIC:         113.508


                                 Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          49        0.000
 1408.4504     0.0004         0.019     0.000          48       -0.136
 3137.0446     0.0043         0.196     0.000          46       -0.444
 5392.9593     0.0215         1.073     1.000          50       -0.071
 9128.8027     0.0999         4.893     4.000          49       -0.426
16361.0000     0.4543        24.078    25.000          53        0.254

 Chi^2 = 0.47      d.f. = 5        P-value = 0.9933


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95
```

```
                BMD =        4173.08

               BMDL =        2277.15

               BMDU =        4642.18

Taken together, (2277.15, 4642.18) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =  4.39145e-006
```

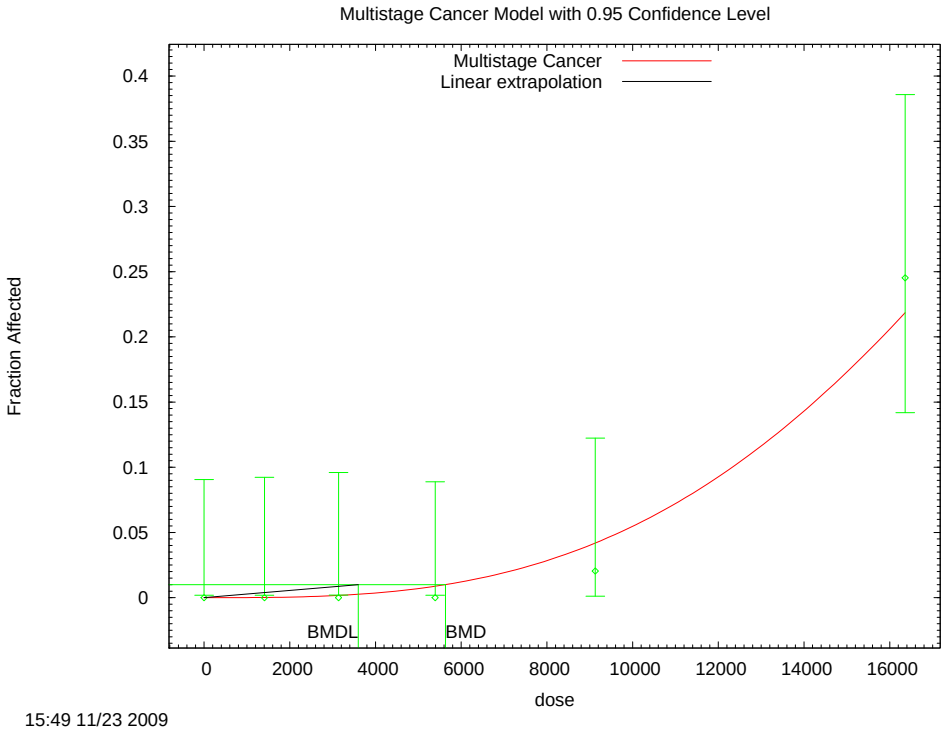
F.1.21. National Toxicology Program (2006): Liver, Hepatocellular Adenoma

F.1.21.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree	5	12.73	0.03	87.02	1.2E+03	8.0E+02	betas restricted ≥0
Multistage cancer, 2-degree	5	4.29	0.51	76.98	3.6E+03	2.4E+03	betas restricted ≥0
Multistage cancer, 3-degree[b]	**5**	**1.32**	**0.93**	**72.78**	**5.6E+03**	**3.6E+03**	**betas restricted ≥0**

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.21.2. *Figure for Selected Model: Multistage Cancer, 3-Degree, Betas Restricted ≥0*



F.1.21.3. *Output File for Selected Model: Multistage Cancer, 3-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc3_ngkgd_liv_hepat_ad.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc3_ngkgd_liv_hepat_ad.plt
                                                 Mon Nov 23 15:49:03 2009
 ================================================================

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   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 = Mean
   Independent variable = Dose

 Total number of observations = 6
 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
                        Beta(1) =           0
                        Beta(2) =           0
                        Beta(3) = 6.51095e-014


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                Beta(3)

  Beta(3)           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           *               *                   *
        Beta(3)     5.62766e-014           *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -34.4075         6
    Fitted model       -35.3908         1       1.96651      5          0.8538
   Reduced model       -56.3333         1       43.8515      5         <.0001

           AIC:         72.7815


                                 Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          49        0.000
 1408.4504     0.0002         0.008     0.000          48       -0.087
 3137.0446     0.0017         0.080     0.000          46       -0.283
 5392.9593     0.0088         0.439     0.000          50       -0.666
 9128.8027     0.0419         2.054     1.000          49       -0.751
16361.0000     0.2184        11.577    13.000          53        0.473

 Chi^2 = 1.32      d.f. = 5        P-value = 0.9330


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95
```

```
                BMD =        5631.42

               BMDL =        3596.03

               BMDU =        6597.97

Taken together, (3596.03, 6597.97) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =  2.78084e-006
```

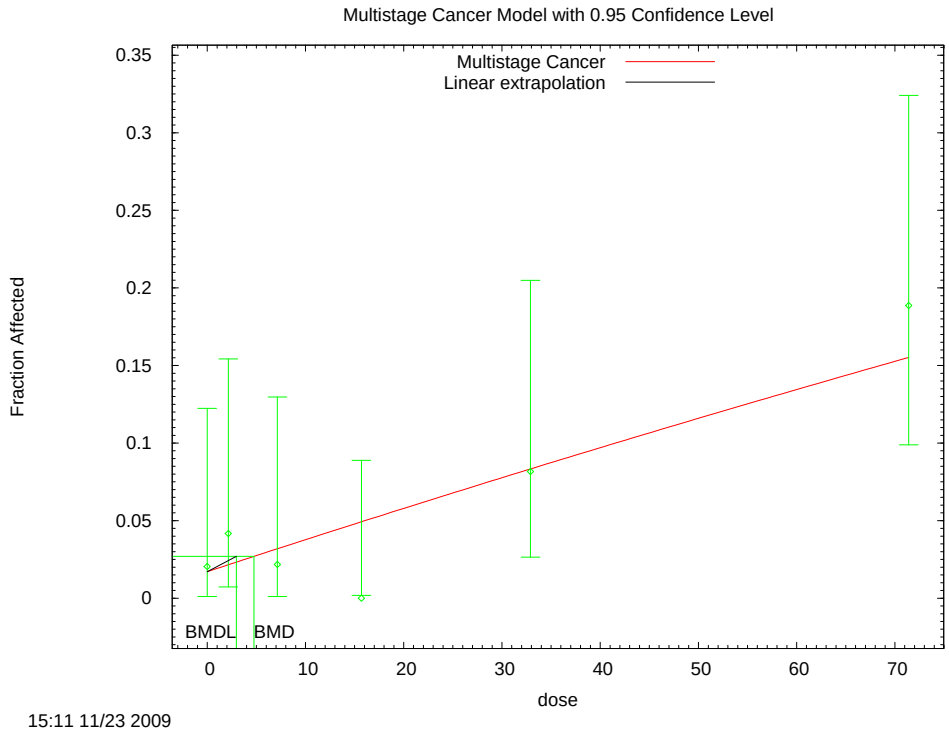
F.1.22. National Toxicology Program (2006): Oral mucosa, Squamous Cell Carcinoma

F.1.22.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree	**4**	**4.15**	**0.39**	**125.48**	**4.8E+00**	**3.0E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree[b]	4	2.83	0.59	123.25	1.6E+01	3.8E+00	betas restricted ≥0, bound hit
Multistage cancer, 3-degree	4	2.83	0.59	123.25	1.6E+01	3.8E+00	betas restricted ≥0, bound hit

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.22.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0, Bound Hit*



F.1.22.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0, Bound Hit*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_oral_carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_oral_carc.plt
                                                 Mon Nov 23 15:11:37 2009
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   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 = Mean
   Independent variable = Dose

 Total number of observations = 6
 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 =   0.00607545
                        Beta(1) =   0.00265195


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1         -0.6

   Beta(1)         -0.6            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
      Background        0.0171416            *                *                   *
         Beta(1)       0.00211536            *                *                   *

* - Indicates that this value is not calculated.



                         Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -57.5353         6
    Fitted model       -60.7418         2       6.41293      4          0.1704
   Reduced model       -67.7782         1       20.4858      5        0.001013

           AIC:         125.484


                                  Goodness  of  Fit
                                                                    Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0171         0.840     1.000          49        0.176
     2.1400     0.0216         1.036     2.000          48        0.958
     7.1400     0.0319         1.466     1.000          46       -0.391
    15.7000     0.0492         2.462     0.000          50       -1.609
    32.9000     0.0832         4.078     4.000          49       -0.040
    71.4000     0.1549         8.211    10.000          53        0.679

 Chi^2 = 4.15      d.f. = 4        P-value = 0.3855


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        4.75111

            BMDL =         2.9556
```

```
            BMDU =        9.19454

Taken together, (2.9556 , 9.19454) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =     0.0033834
```

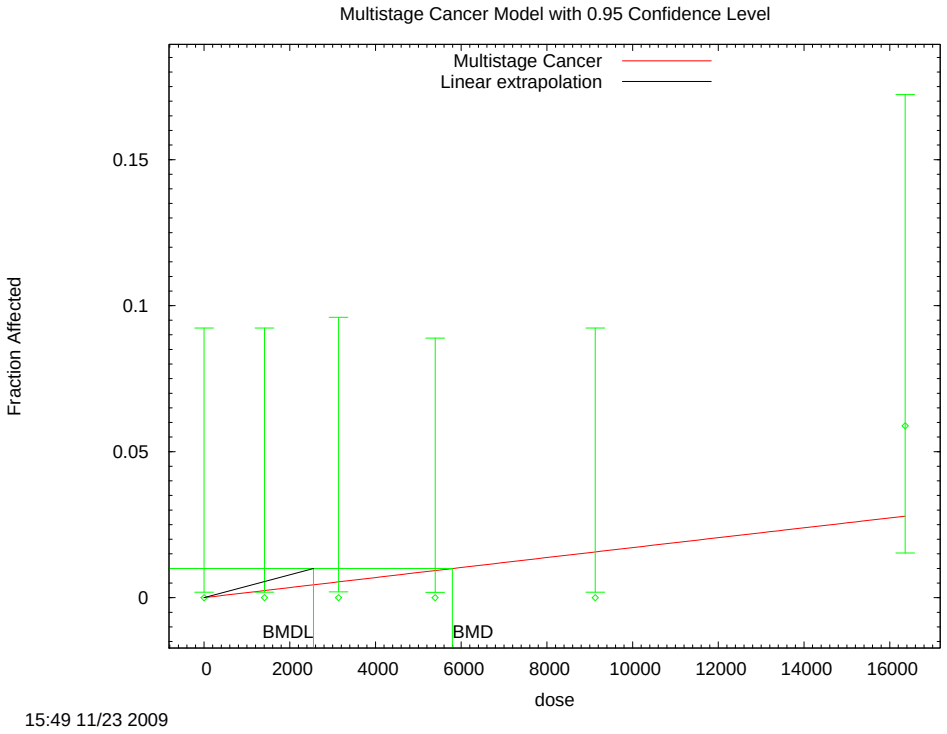
F.1.23. National Toxicology Program (2006): Pancreas, Adenoma or Carcinoma

F.1.23.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**5**	**3.39**	**0.64**	**29.37**	**5.8E+03**	**2.6E+03**	**betas restricted ≥0**
Multistage cancer, 2-degree	5	1.36	0.93	27.06	8.0E+03	4.0E+03	betas restricted ≥0
Multistage cancer, 3-degree	5	0.64	0.99	25.97	9.6E+03	5.2E+03	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.23.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.23.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_panc_ad_carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_panc_ad_carc.plt
                                                 Mon Nov 23 15:49:45 2009
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   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 = Mean
   Independent variable = Dose

 Total number of observations = 6
 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) = 3.46905e-006


           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)     1.73461e-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        -11.4096         6
    Fitted model       -13.6863         1       4.55338      5          0.4728
   Reduced model       -16.7086         1        10.598      5         0.05996

           AIC:         29.3726


                                Goodness  of  Fit
                                                                    Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          48        0.000
  1408.4504     0.0024         0.117     0.000          48       -0.343
  3137.0446     0.0054         0.250     0.000          46       -0.501
  5392.9593     0.0093         0.466     0.000          50       -0.686
  9128.8027     0.0157         0.754     0.000          48       -0.875
 16361.0000     0.0280         1.427     3.000          51        1.336

 Chi^2 = 3.39      d.f. = 5        P-value = 0.6404


   Benchmark Dose Computation

Specified effect =          0.01

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =          5794

            BMDL =        2550.9
```

```
             BMDU =        18101.1

Taken together, (2550.9 , 18101.1) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =  3.92019e-006
```

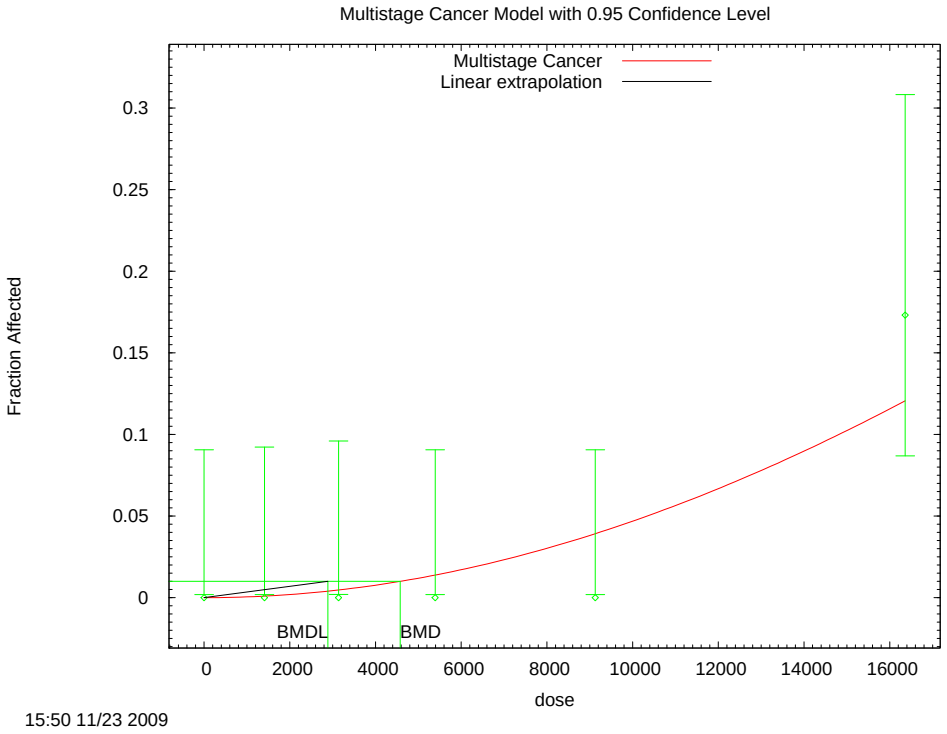
F.1.24. National Toxicology Program (2006): Lung, Cystic Keratinizing Epithelioma

F.1.24.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree	5	10.52	0.06	64.03	1.9E+03	1.1E+03	betas restricted ≥0
Multistage cancer, 2-degree[b]	**5**	**4.30**	**0.51**	**56.94**	**4.6E+03**	**2.9E+03**	**betas restricted ≥0**
Multistage cancer, 3-degree	5	2.03	0.84	53.56	6.6E+03	4.3E+03	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.24.2. *Figure for Selected Model: Multistage Cancer, 2-Degree, Betas Restricted ≥0*



F.1.24.3. *Output File for Selected Model: Multistage Cancer, 2-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc2_ngkgd_lung_epith.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc2_ngkgd_lung_epith.plt
                                                 Mon Nov 23 15:50:07 2009
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   Independent variable = Dose

 Total number of observations = 6
 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
                        Beta(1) =           0
                        Beta(2) = 7.12912e-010


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)
                 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(2)            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)     4.80115e-010            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -23.958         6
    Fitted model        -27.4714         1       7.02665      5          0.2187
   Reduced model        -40.2069         1       32.4976      5         <.0001

           AIC:         56.9427


                                 Goodness  of  Fit
                                                                      Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          49        0.000
  1408.4504     0.0010         0.046     0.000          48       -0.214
  3137.0446     0.0047         0.217     0.000          46       -0.467
  5392.9593     0.0139         0.679     0.000          49       -0.830
  9128.8027     0.0392         1.922     0.000          49       -1.414
 16361.0000     0.1206         6.271     9.000          52        1.162

 Chi^2 = 4.30      d.f. = 5        P-value = 0.5067


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        4575.28
```

```
              BMDL =        2889.79

              BMDU =        6187.18

Taken together, (2889.79, 6187.18) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =  3.46046e-006
```

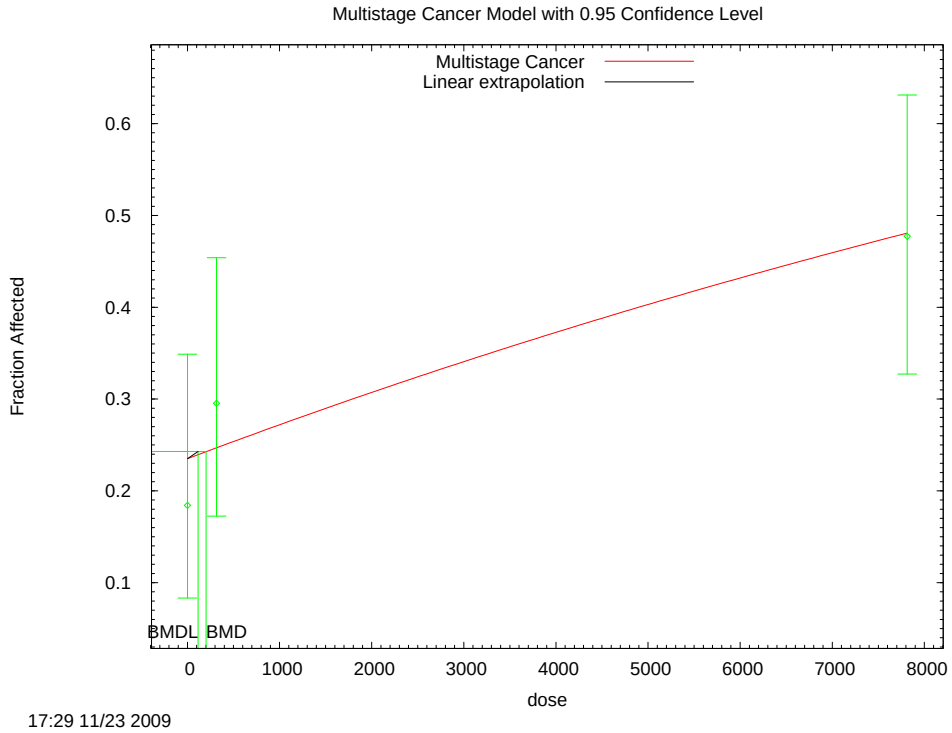
F.1.25. Toth et al. (1978): 1YR, Liver, Tumors

F.1.25.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**1**	**1.10**	**0.29**	**155.74**	**2.0E+02**	**1.2E+02**	**betas restricted ≥0**
Multistage cancer, 2-degree	1	1.10	0.29	155.74	2.0E+02	1.2E+02	betas restricted ≥0
Multistage cancer, 0-degree			0.29	-999.00	error	error	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.1.25.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.1.25.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_adr_cor_1yr.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\msc1_ngkgd_adr_cor_1yr.plt
                                                 Mon Nov 23 17:29:16 2009
 ======================================================================

 Table 1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   Independent variable = Dose

 Total number of observations = 3
 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 =     0.234944
                        Beta(1) = 4.90901e-005


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.55

   Beta(1)        -0.55            1



                                 Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background         0.235288            *                *                   *
        Beta(1)     4.96192e-005            *                *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -75.3127         3
    Fitted model       -75.8701         2       1.11477      1           0.291
  Reduced model        -79.4897         1       8.35401      2         0.01534

            AIC:          155.74


                                 Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
     0.0000     0.2353         8.941     7.000          38       -0.742
   315.4949     0.2472        10.875    13.000          44        0.743
  7814.0188     0.4811        21.167    21.000          44       -0.050

 Chi^2 = 1.10      d.f. = 1        P-value = 0.2932


    Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        202.549

             BMDL =        115.257

             BMDU =        555.609

Taken together, (115.257, 555.609) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =  8.67623e-005
```

F.2. ADMINISTERED DOSE BMDS RESULTS

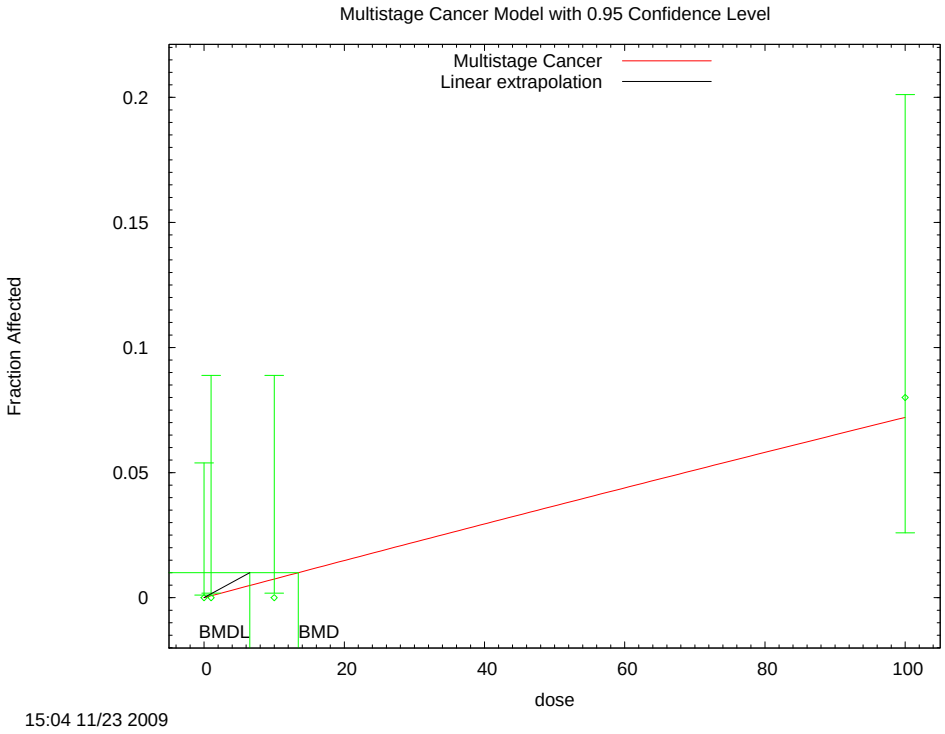
F.2.1. Kociba et al. (1978): Female, Stratified Squamous Cell Carcinoma of Hard Palate or Nasal Turbinates

F.2.1.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**3**	**0.46**	**0.93**	**30.75**	**1.3E+01**	**6.5E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	3	0.04	1.00	29.96	3.5E+01	7.2E+00	betas restricted ≥0
Multistage cancer, 3-degree	3	0.00	1.00	29.89	4.9E+01	7.3E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.1.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.1.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ========================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_palate_nasal.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_palate_nasal.plt
                                                 Mon Nov 23 15:04:28 2009
 ========================================================================

 Source - Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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) =  0.000858074


           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)       0.00074801            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -13.9385         4
    Fitted model       -14.3726         1      0.868297      3          0.8331
   Reduced model       -20.2589         1       12.6409      3        0.005481

           AIC:         30.7452


                                 Goodness  of  Fit
                                                                      Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          85        0.000
     1.0000     0.0007         0.037     0.000          50       -0.193
    10.0000     0.0075         0.373     0.000          50       -0.613
   100.0000     0.0721         3.604     4.000          50        0.217

 Chi^2 = 0.46      d.f. = 3        P-value = 0.9276


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        13.4361

            BMDL =        6.51522

            BMDU =         34.829
```

```
Taken together, (6.51522, 34.829 ) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =    0.00153487
```

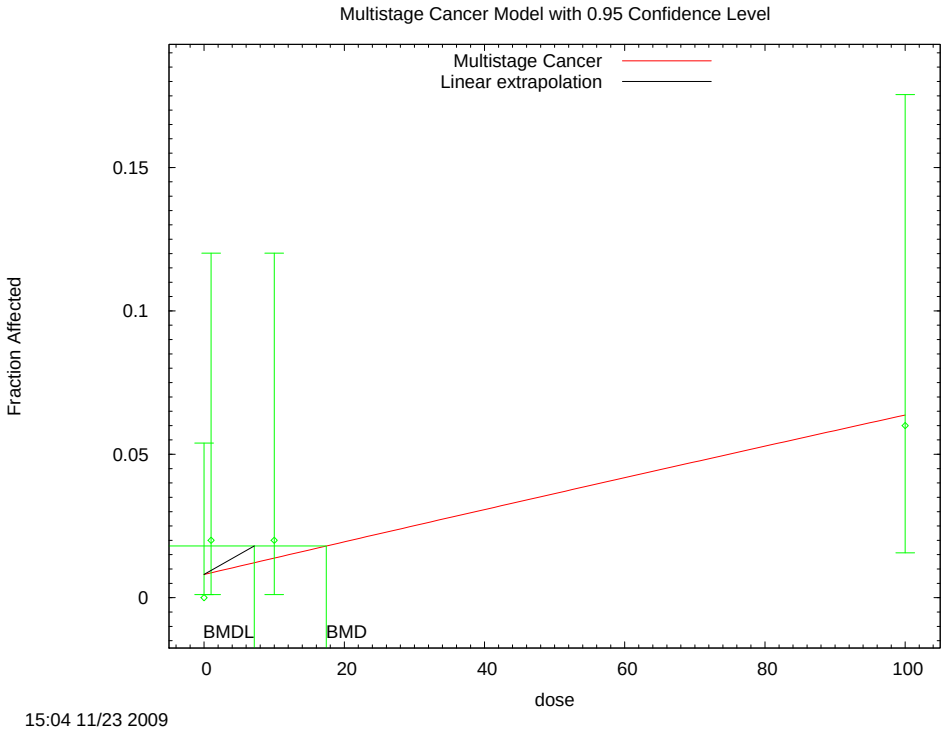
F.2.2. Kociba et al. (1978): Female, Stratified Squamous Cell Carcinoma of Tongue

F.2.2.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**1.59**	**0.45**	**48.37**	**1.7E+01**	**7.1E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	1.59	0.45	48.37	1.7E+01	7.1E+00	betas restricted ≥0
Multistage cancer, 3-degree	2	1.59	0.45	48.37	1.7E+01	7.1E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.2.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.2.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_tongue.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_tongue.plt
                                                Mon Nov 23 15:04:49 2009
 ================================================================

 Source - Table 4
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =    0.0113883
                        Beta(1) =  0.000508703


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.52

   Beta(1)        -0.52            1


                                 Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background       0.00809154            *                *                   *
        Beta(1)      0.000576915            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -21.1523         4
    Fitted model       -22.1838         2       2.06309      2          0.3565
   Reduced model       -24.1972         1       6.08976      3          0.1073

            AIC:         48.3677


                                  Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0081         0.688     0.000          85       -0.833
     1.0000     0.0087         0.433     1.000          50        0.865
    10.0000     0.0138         0.690     1.000          50        0.376
   100.0000     0.0637         3.185     3.000          50       -0.107

 Chi^2 = 1.59      d.f. = 2        P-value = 0.4506


    Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        17.4208

             BMDL =        7.14637

             BMDU =   3.20359e+006

Taken together, (7.14637, 3.20359e+006) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =    0.00139931
```

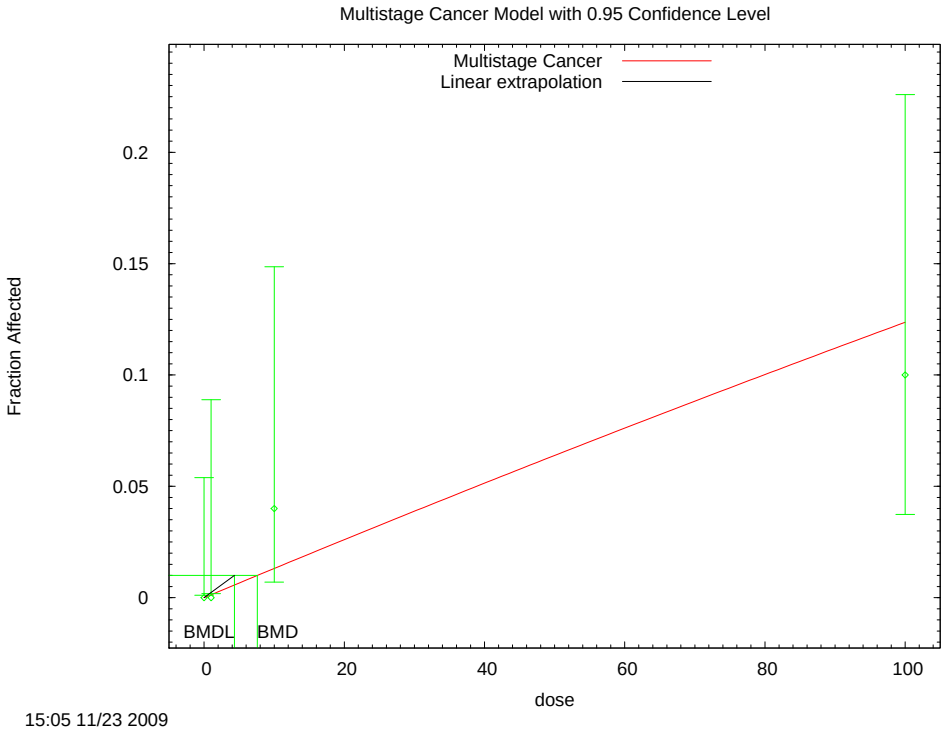
F.2.3. Kociba et al. (1978): Female. Adenoma of Adrenal Cortex

F.2.3.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**3**	**3.11**	**0.38**	**53.52**	**7.6E+00**	**4.3E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	3	3.11	0.38	53.52	7.6E+00	4.3E+00	betas restricted ≥0
Multistage cancer, 3-degree	3	3.11	0.38	53.52	7.6E+00	4.3E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.3.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.3.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_adre_adenoma.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_adre_adenoma.plt
                                                Mon Nov 23 15:05:10 2009
 ================================================================

 Source - Table 5
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =   0.00927818
                        Beta(1) =   0.00098105


           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)       0.00132464            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -24.6514         4
   Fitted model         -25.759         1        2.2152      3           0.529
  Reduced model        -31.4904         1       13.6781      3        0.003378

           AIC:         53.5179


                                 Goodness  of  Fit
                                                                      Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          85        0.000
     1.0000     0.0013         0.066     0.000          50       -0.257
    10.0000     0.0132         0.658     2.000          50        1.666
   100.0000     0.1241         6.203     5.000          50       -0.516

 Chi^2 = 3.11      d.f. = 3        P-value = 0.3755


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        7.58722

            BMDL =        4.31737

            BMDU =         17.638
```

```
Taken together, (4.31737, 17.638 ) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =    0.00231623
```

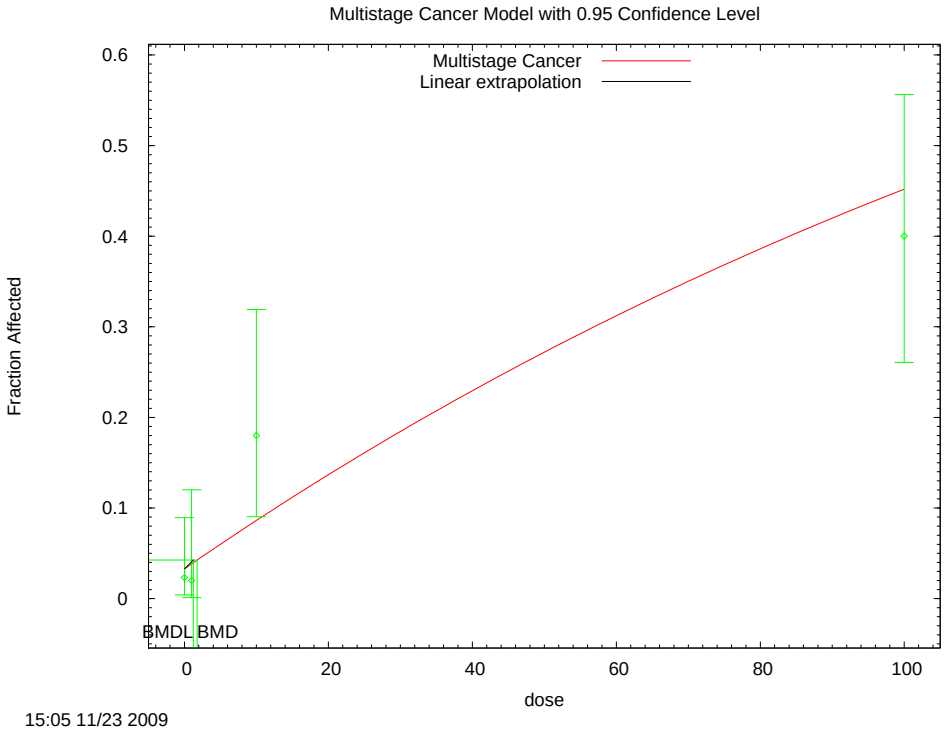
F.2.4. Kociba et al. (1978): Female, Hepatocellular Adenoma(S) or Carcinoma(s)

F.2.4.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**6.77**	**0.03**	**146.20**	**1.8E+00**	**1.2E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	6.77	0.03	146.20	1.8E+00	1.2E+00	betas restricted ≥0
Multistage cancer, 3-degree	2	6.77	0.03	146.20	1.8E+00	1.2E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.4.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.4.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ========================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_liver_ad_carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_liver_ad_carc.plt
                                                  Mon Nov 23 15:05:31 2009
 ========================================================================

 Source - Table 1 in Goodman and Sauer 1992
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =    0.0591902
                        Beta(1) =   0.00458516


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.47

   Beta(1)        -0.47            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0328755            *               *                   *
        Beta(1)       0.00568299            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -68.2561         4
    Fitted model       -71.0993         2       5.68634      2         0.05824
   Reduced model       -89.1983         1       41.8843      3         <.0001

           AIC:         146.199


                                 Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
    0.0000     0.0329         2.827     2.000          86       -0.500
    1.0000     0.0384         1.918     1.000          50       -0.676
   10.0000     0.0863         4.315     9.000          50        2.359
  100.0000     0.4521        20.346    18.000          45       -0.703

 Chi^2 = 6.77      d.f. = 2        P-value = 0.0339


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         1.7685

            BMDL =        1.22517

            BMDU =        2.77641

Taken together, (1.22517, 2.77641) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =    0.00816214
```

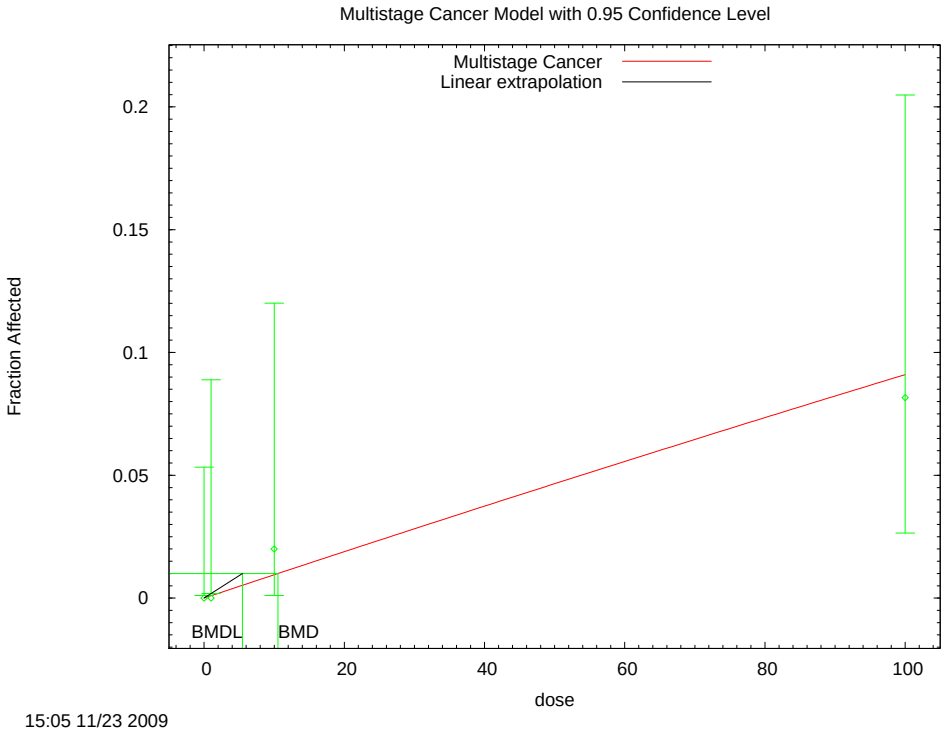
F.2.5. Kociba et al. (1978): Female, Stratified Squamous Cell Carcinoma of Hard Palate or Nasal Turbinates

F.2.5.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**3**	**0.46**	**0.93**	**30.75**	**1.3E+01**	**6.5E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	3	0.04	1.00	29.96	3.5E+01	7.2E+00	betas restricted ≥0
Multistage cancer, 3-degree	3	0.00	1.00	29.89	4.9E+01	7.3E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.5.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.5.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_nasal.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_nasal.plt
                                                 Mon Nov 23 15:05:50 2009
 ======================================================================

 Source - Table 5
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =   0.00343283
                        Beta(1) =  0.000825276


           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)      0.000953868            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -18.7562         4
    Fitted model       -19.0532         1      0.594034      3          0.8978
   Reduced model       -24.1972         1        10.882      3         0.01238

           AIC:         40.1064


                                 Goodness  of  Fit
                                                                      Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          86        0.000
     1.0000     0.0010         0.048     0.000          50       -0.218
    10.0000     0.0095         0.475     1.000          50        0.766
   100.0000     0.0910         4.458     4.000          49       -0.227

 Chi^2 = 0.69      d.f. = 3        P-value = 0.8764


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        10.5364

            BMDL =        5.46907

            BMDU =         25.864
```

```
Taken together, (5.46907, 25.864 ) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =    0.00182846
```

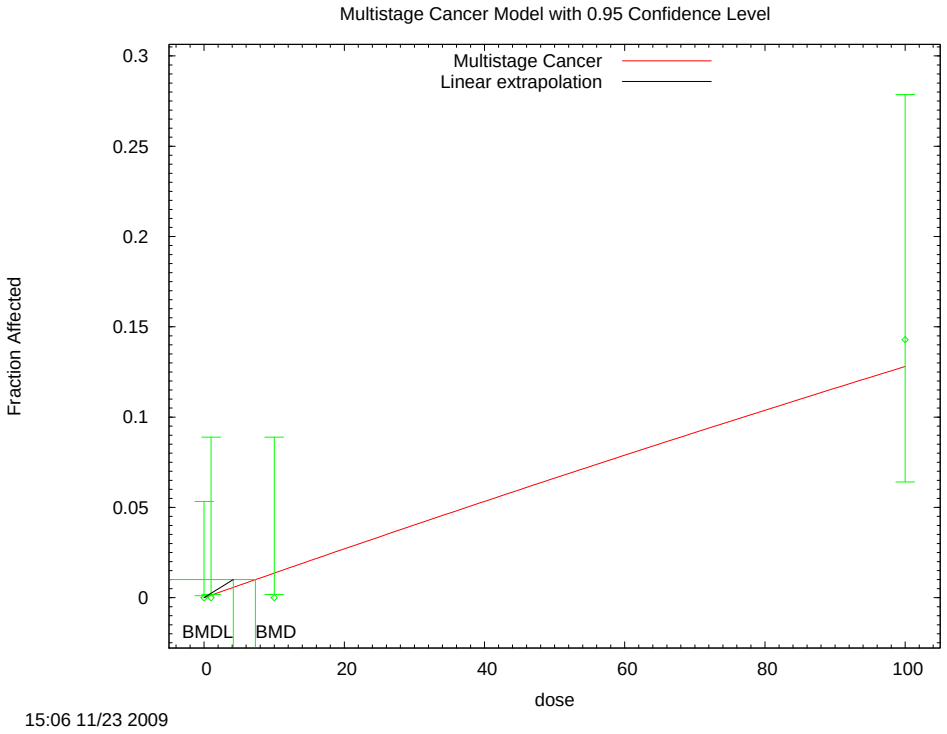
F.2.6. Kociba et al. (1978): Female, Keratinizing Squamous Cell Carcinoma of Lung

F.2.6.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**3**	**0.85**	**0.84**	**43.79**	**7.3E+00**	**4.2E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	3	0.08	0.99	42.35	2.6E+01	4.9E+00	betas restricted ≥0
Multistage cancer, 3-degree	3	0.01	1.00	42.21	4.0E+01	5.0E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.6.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.6.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_kera_carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_kera_carc.plt
                                                Mon Nov 23 15:06:12 2009
 ================================================================

 Source - Table 5
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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) =   0.00158635


           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)        0.0013747            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -20.0957         4
    Fitted model       -20.8959         1       1.60041      3          0.6593
   Reduced model       -31.4904         1       22.7894      3         <.0001

           AIC:         43.7918


                                Goodness  of  Fit
                                                                    Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          86        0.000
     1.0000     0.0014         0.069     0.000          50       -0.262
    10.0000     0.0137         0.683     0.000          50       -0.832
   100.0000     0.1284         6.294     7.000          49        0.302

 Chi^2 = 0.85      d.f. = 3        P-value = 0.8370


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        7.31091

            BMDL =        4.15929

            BMDU =        14.6306
```

```
Taken together, (4.15929, 14.6306) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =    0.00240426
```

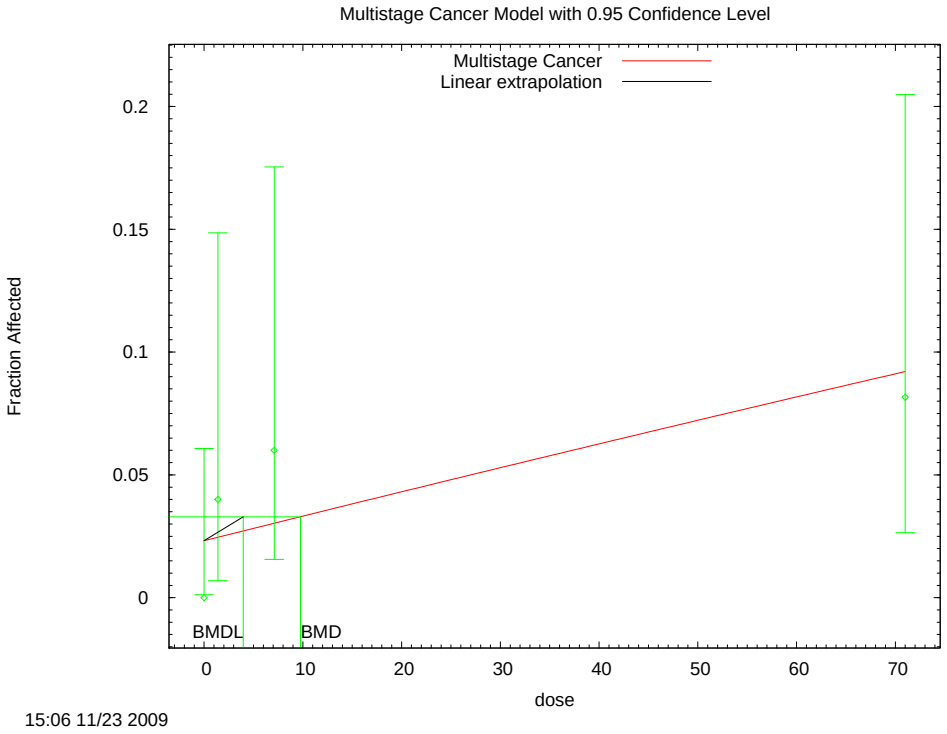
F.2.7. National Toxicology Program (1982): Female Rats, Subcutaneous Tissue, Fibrosarcoma

F.2.7.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**3.84**	**0.15**	**76.38**	**9.8E+00**	**4.0E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	3.84	0.15	76.38	9.8E+00	4.0E+00	betas restricted ≥0
Multistage cancer, 3-degree	2	3.84	0.15	76.38	9.8E+00	4.0E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.7.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.7.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_sub_fibro.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_sub_fibro.plt
                                                 Mon Nov 23 15:06:33 2009
 ======================================================================

 Source - Table 10
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =     0.030595
                        Beta(1) =  0.000799545


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.54

   Beta(1)        -0.54            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0231556            *               *                   *
        Beta(1)       0.00102962            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -33.5998         4
    Fitted model       -36.1883         2       5.17698      2         0.07513
   Reduced model       -37.7465         1       8.29346      3         0.04032

           AIC:         76.3766


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------------
    0.0000     0.0232         1.737     0.000          75       -1.333
    1.4000     0.0246         1.228     2.000          50        0.705
    7.1000     0.0303         1.514     3.000          50        1.227
   71.0000     0.0920         4.509     4.000          49       -0.252

 Chi^2 = 3.84      d.f. = 2        P-value = 0.1463


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        9.76124

            BMDL =        3.96354

            BMDU =   1.03301e+006

Taken together, (3.96354, 1.03301e+006) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =      0.002523
```

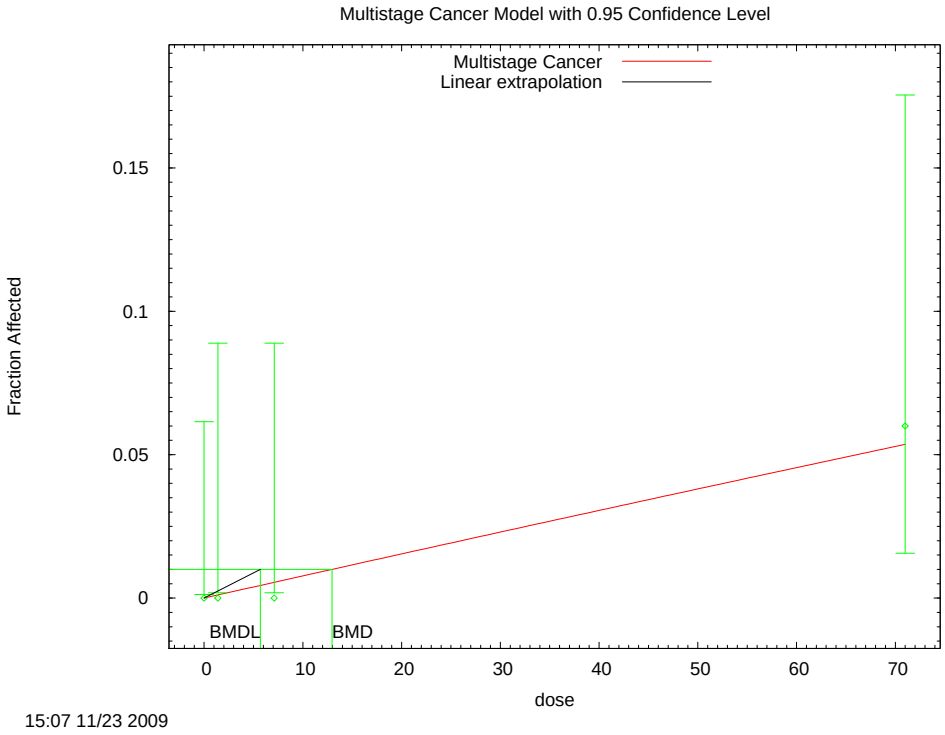
F.2.8. National Toxicology Program (1982): Female Rats, Liver, Neoplastic Nodule or Hepatocellular Carcinoma

F.2.8.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**3**	**0.37**	**0.40**	**133.83**	**2.6E+00**	**1.6E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	3	0.03	0.50	133.44	1.3E+01	1.7E+00	betas restricted ≥0
Multistage cancer, 3-degree	3	0.00	0.50	133.44	1.3E+01	1.7E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.8.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.8.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_liver_nod.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_liver_nod.plt
                                                Mon Nov 23 15:07:55 2009
 ======================================================================

 Source - Table 9
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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) =  0.000900399


           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)      0.000775683            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -11.3484         4
    Fitted model       -11.6976         1      0.698469      3          0.8736
   Reduced model       -15.9189         1       9.14109      3         0.02747

           AIC:         25.3952


                                  Goodness  of  Fit
                                                                    Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          74        0.000
     1.4000     0.0011         0.054     0.000          50       -0.233
     7.1000     0.0055         0.275     0.000          50       -0.525
    71.0000     0.0536         2.679     3.000          50        0.201

 Chi^2 = 0.37      d.f. = 3        P-value = 0.9462


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        12.9568

            BMDL =        5.70369

            BMDU =        39.9878
```

```
Taken together, (5.70369, 39.9878) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =    0.00175325
```

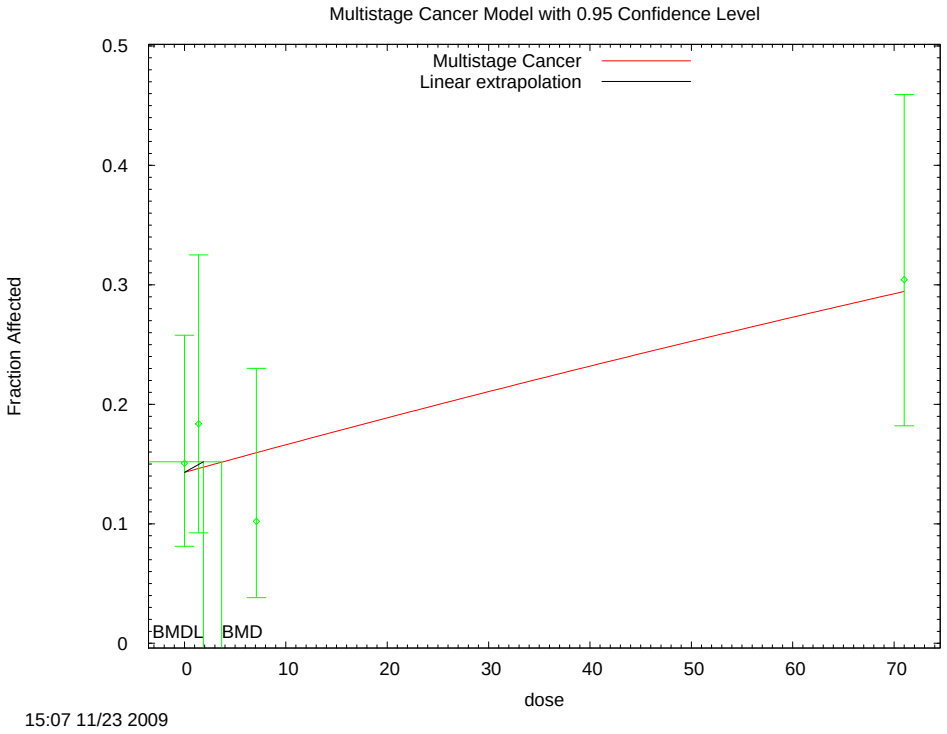
F.2.9. National Toxicology Program (1982): Female Rats, Adrenal, Cortical Adenoma, or Carcinoma or Adenoma, NOS

F.2.9.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**1.81**	**0.40**	**203.38**	**3.7E+00**	**1.9E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	1.38	0.50	202.89	1.6E+01	2.0E+00	betas restricted ≥0
Multistage cancer, 3-degree	2	1.33	0.51	202.83	2.6E+01	2.0E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.9.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.9.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ========================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_adre_cort_ad_carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_adre_cort_ad_carc.plt
                                                  Mon Nov 23 15:07:15 2009
 ========================================================================

 Source - Table 10
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =     0.140663
                        Beta(1) =   0.00289845


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.48

   Beta(1)        -0.48            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background         0.143284            *               *                   *
        Beta(1)       0.00273674            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -98.7282         4
    Fitted model       -99.6898         2       1.92318      2          0.3823
   Reduced model       -102.201         1       6.94636      3         0.07363

            AIC:          203.38


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
    0.0000     0.1433        10.460    11.000          73        0.180
    1.4000     0.1466         7.181     9.000          49        0.735
    7.1000     0.1598         7.829     5.000          49       -1.103
   71.0000     0.2946        13.551    14.000          46        0.145

 Chi^2 = 1.81      d.f. = 2        P-value = 0.4046


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        3.67237

            BMDL =        1.87133

            BMDU =        15.4002

Taken together, (1.87133, 15.4002) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =    0.00534381
```

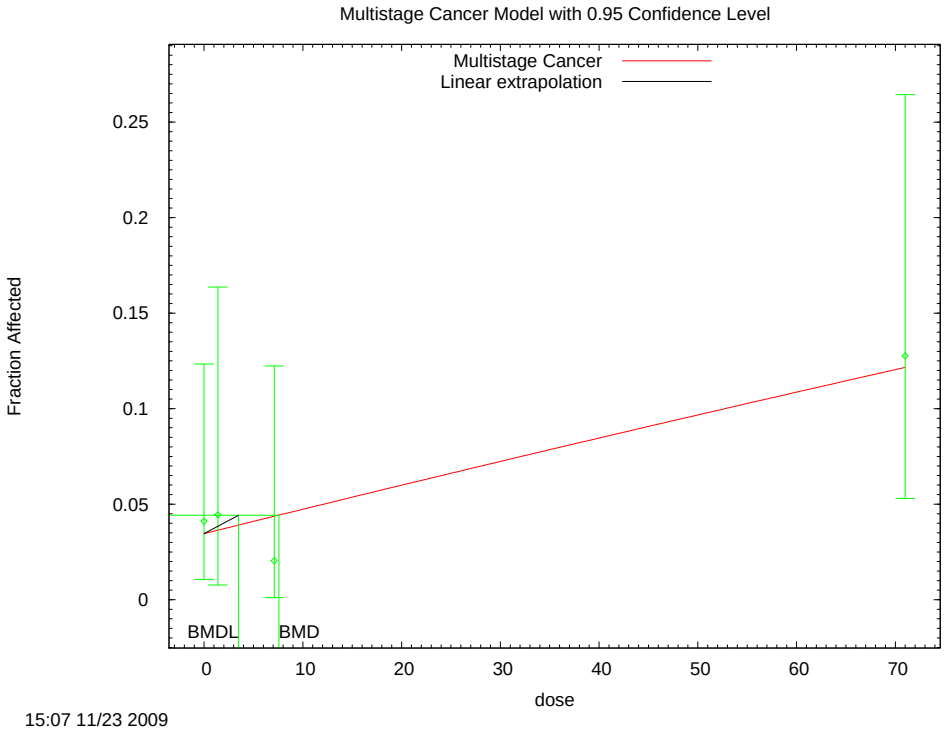
F.2.10. National Toxicology Program (1982): Female Rats, Thyroid, Follicular-Cell Adenoma

F.2.10.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**0.83**	**0.66**	**92.02**	**7.6E+00**	**3.5E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	0.53	0.77	91.64	2.3E+01	3.7E+00	betas restricted ≥0
Multistage cancer, 3-degree	2	0.49	0.78	91.60	3.3E+01	3.7E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.10.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.10.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_thy_ad.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_thy_ad.plt
                                                 Mon Nov 23 15:07:34 2009
 ======================================================================

 Source - Table 10
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =     0.032089
                        Beta(1) =   0.00143599


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1         -0.5

   Beta(1)         -0.5            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0345958            *                *                   *
        Beta(1)       0.00132742            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -43.5264         4
    Fitted model       -44.0098         2      0.966786      2          0.6167
   Reduced model       -46.2299         1       5.40699      3          0.1443

           AIC:         92.0196


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
    0.0000     0.0346         2.525     3.000          73        0.304
    1.4000     0.0364         1.637     2.000          45        0.289
    7.1000     0.0437         2.139     1.000          49       -0.796
   71.0000     0.1214         5.707     6.000          47        0.131

 Chi^2 = 0.83      d.f. = 2        P-value = 0.6614


   Benchmark Dose Computation

Specified effect =          0.01

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =       7.57131

            BMDL =       3.48815

            BMDU =        964541

Taken together, (3.48815, 964541 ) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =    0.00286685
```

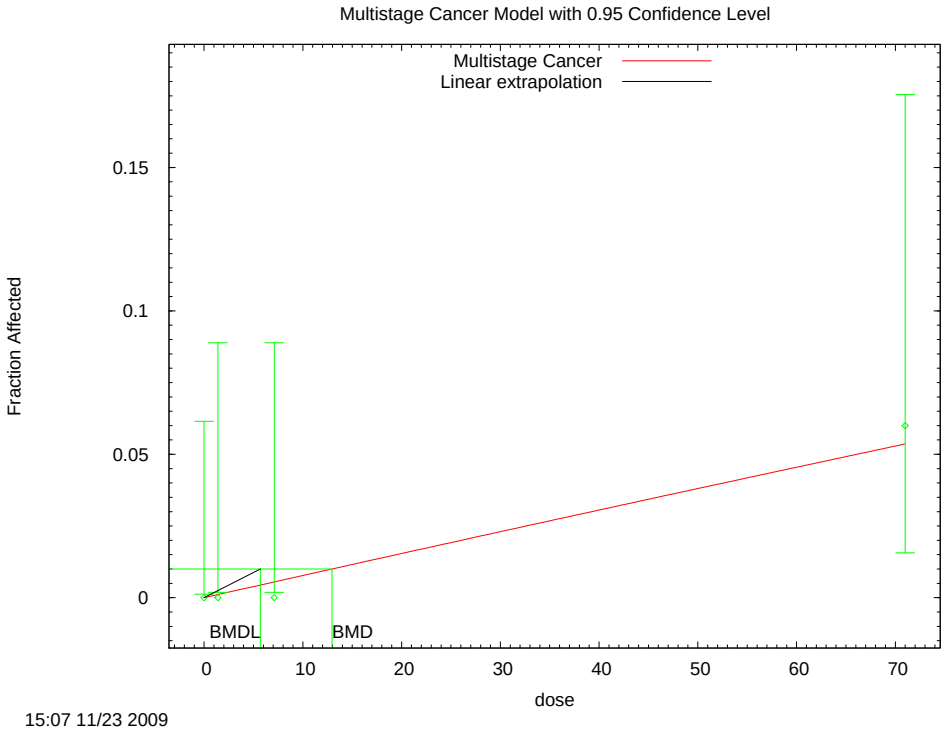
F.2.11. National Toxicology Program (1982): Male Rats, Liver, Neoplastic Nodule or Hepatocellular Carcinoma

F.2.11.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**3**	**0.37**	**0.40**	**133.83**	**2.6E+00**	**1.6E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	3	0.03	0.50	133.44	1.3E+01	1.7E+00	betas restricted ≥0
Multistage cancer, 3-degree	3	0.00	0.50	133.44	1.3E+01	1.7E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.11.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.11.3. *Output File for selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_liver_nod.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_liver_nod.plt
                                                Mon Nov 23 15:07:55 2009
 ================================================================

 Source - Table 9
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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) =  0.000900399


           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)      0.000775683            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -11.3484         4
    Fitted model       -11.6976         1      0.698469      3          0.8736
   Reduced model       -15.9189         1       9.14109      3         0.02747

           AIC:         25.3952


                                 Goodness  of  Fit
                                                                    Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          74        0.000
     1.4000     0.0011         0.054     0.000          50       -0.233
     7.1000     0.0055         0.275     0.000          50       -0.525
    71.0000     0.0536         2.679     3.000          50        0.201

 Chi^2 = 0.37      d.f. = 3        P-value = 0.9462


   Benchmark Dose Computation

Specified effect =          0.01

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =        12.9568

            BMDL =        5.70369

            BMDU =        39.9878
```

```
Taken together, (5.70369, 39.9878) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =    0.00175325
```

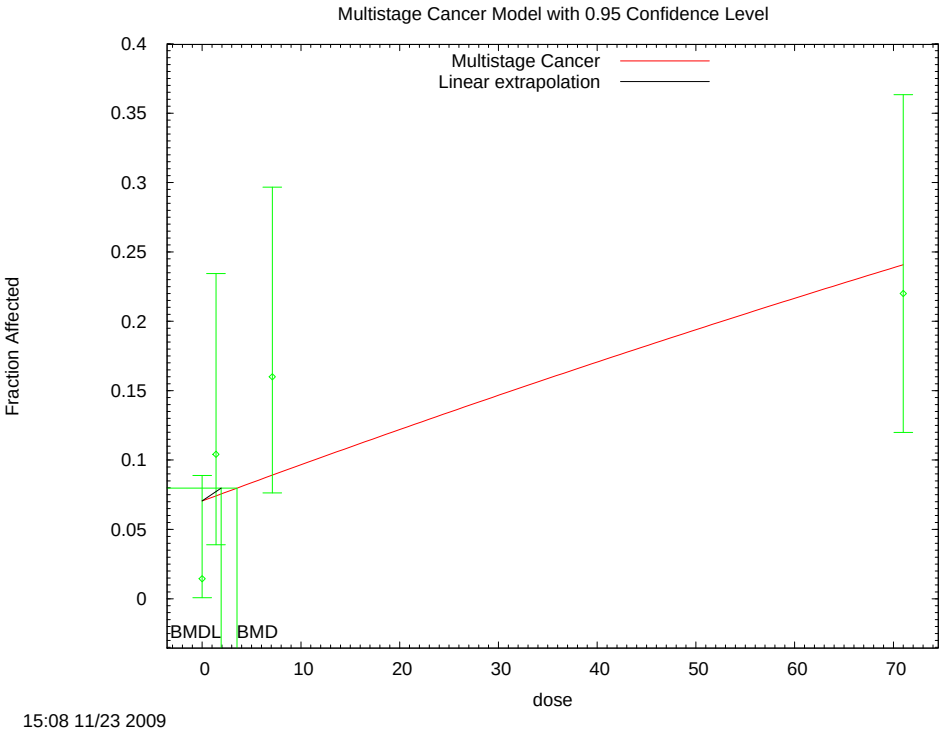
F.2.12. National Toxicology Program (1982): Male Rats, Thyroid, Follicular-Cell Adenoma or Carcinoma

F.2.12.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**7.14**	**0.03**	**151.22**	**3.5E+00**	**1.9E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	7.14	0.03	151.22	3.5E+00	1.9E+00	betas restricted ≥0
Multistage cancer, 3-degree	2	7.14	0.03	151.22	3.5E+00	1.9E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.12.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.12.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_thyroid.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_thyroid.plt
                                                Mon Nov 23 15:08:16 2009
 ================================================================

 Source - Table 9
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =    0.0867382
                        Beta(1) =   0.00232055


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.53

   Beta(1)        -0.53            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0704713            *                *                   *
        Beta(1)       0.00285481            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -69.5946         4
    Fitted model       -73.6119         2       8.03468      2          0.018
   Reduced model       -77.5267         1       15.8643      3        0.001209

            AIC:         151.224


                                 Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
     0.0000     0.0705         4.863     1.000          69       -1.817
     1.4000     0.0742         3.561     5.000          48        0.793
     7.1000     0.0891         4.456     8.000          50        1.759
    71.0000     0.2410        12.051    11.000          50       -0.347

 Chi^2 = 7.14      d.f. = 2        P-value = 0.0281


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =         3.5205

             BMDL =        1.91558

             BMDU =        9.76663

Taken together, (1.91558, 9.76663) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =    0.00522034
```

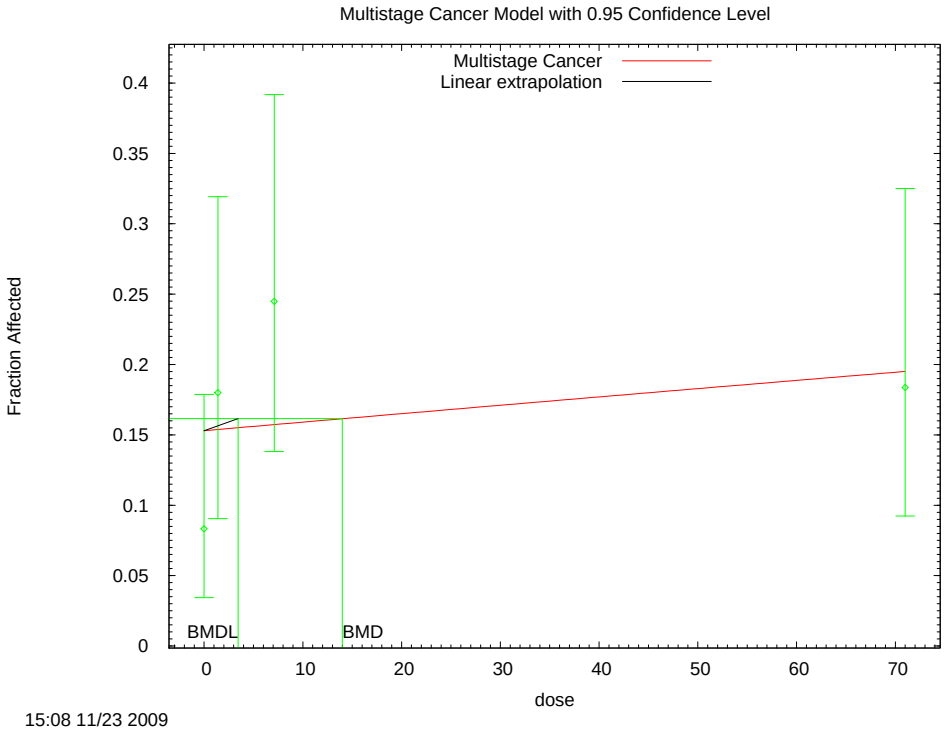
F.2.13. National Toxicology Program (1982): Male Rats, Adrenal cortex, Adenoma

F.2.13.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**5.83**	**0.05**	**199.67**	**1.4E+01**	**3.4E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	5.83	0.05	199.67	1.4E+01	3.4E+00	betas restricted ≥0
Multistage cancer, 3-degree	2	5.83	0.05	199.67	1.4E+01	3.4E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.13.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.13.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_adre_cort.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_adre_cort.plt
                                                 Mon Nov 23 15:08:35 2009
 ======================================================================

 Source - Table 9
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =     0.168444
                        Beta(1) =  0.000395949


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.53

   Beta(1)        -0.53            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background         0.153096            *               *                   *
        Beta(1)      0.000718012            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -94.8672         4
    Fitted model       -97.8359         2       5.93732      2         0.05137
   Reduced model       -98.0432         1       6.35197      3         0.09569

            AIC:         199.672


                                  Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.1531        11.023     6.000          72       -1.644
     1.4000     0.1539         7.697     9.000          50        0.510
     7.1000     0.1574         7.713    12.000          49        1.682
    71.0000     0.1952         9.564     9.000          49       -0.203

 Chi^2 = 5.83      d.f. = 2        P-value = 0.0541


    Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        13.9974

             BMDL =         3.4443


BMDU did not converge for BMR = 0.010000
BMDU calculation failed
             BMDU = Inf
```

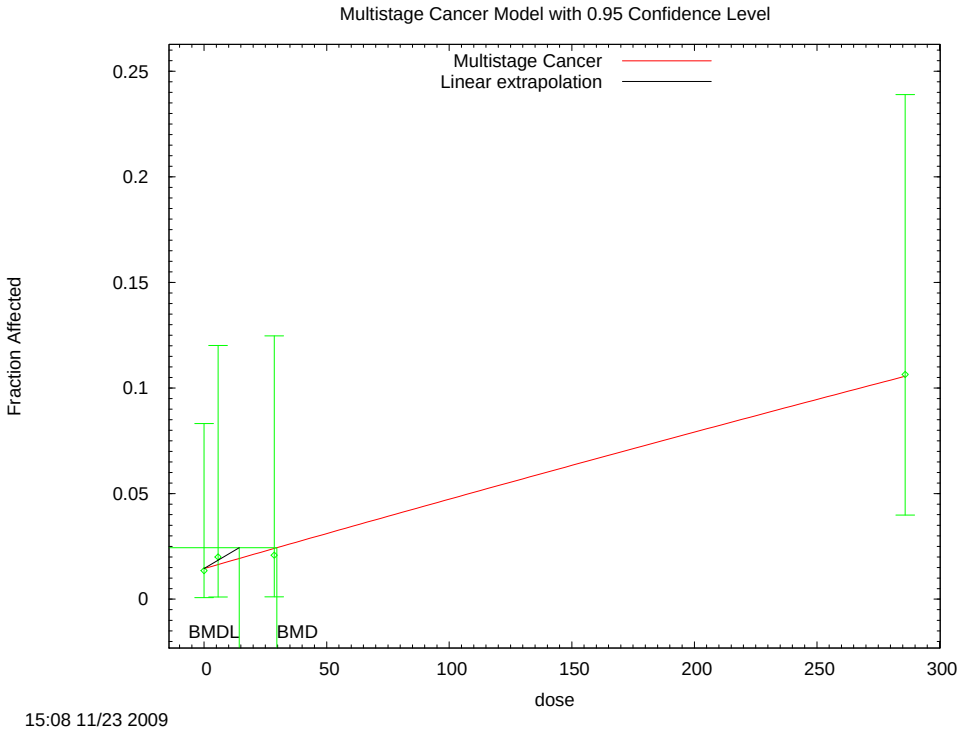
F.2.14. National Toxicology Program (1982): Female Mice, Subcutaneous Tissue, Fibrosarcoma

F.2.14.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**3.84**	**0.15**	**76.38**	**9.8E+00**	**4.0E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	3.84	0.15	76.38	9.8E+00	4.0E+00	betas restricted ≥0
Multistage cancer, 3-degree	2	3.84	0.15	76.38	9.8E+00	4.0E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.14.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.14.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_subcu_fibro.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_subcu_fibro.plt
                                                Mon Nov 23 15:08:56 2009
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   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 =    0.0143554
                        Beta(1) =  0.000341874


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1         -0.5

   Beta(1)         -0.5            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0145028            *                *                   *
        Beta(1)      0.000338561            *                *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -30.9876         4
    Fitted model        -31.0199         2     0.0645971      2          0.9682
   Reduced model        -34.3291         1       6.68308      3         0.08272

           AIN:         66.0397


                                  Goodness  of  Fit
                                                                 Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0145         1.073     1.000          74       -0.071
     5.7000     0.0164         0.820     1.000          50        0.200
    28.6000     0.0240         1.152     1.000          48       -0.143
   286.0000     0.1055         4.956     5.000          47        0.021

 Chi^2 = 0.07      d.f. = 2        P-value = 0.9675


    Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        29.6855

             BMDL =        14.3524

             BMDU =        100.382

Taken together, (14.3524, 100.382) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =   0.000696747
```

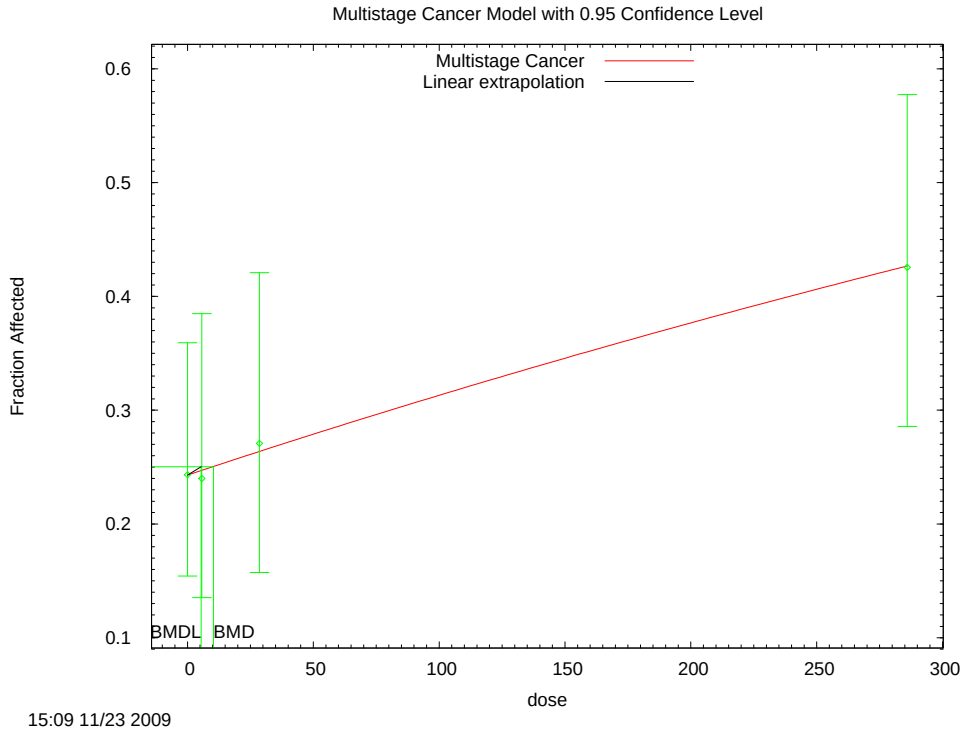
F.2.15. National Toxicology Program (1982): Female Mice, Hematopoietic System, Lymphoma

F.2.15.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**0.03**	**0.99**	**261.43**	**1.0E+01**	**5.5E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	0.03	0.99	261.43	1.0E+01	5.5E+00	betas restricted ≥0
Multistage cancer, 3-degree	2	0.03	0.99	261.43	1.0E+01	5.5E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.15.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.15.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_mice_f_lymphoma.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_mice_f_lymphoma.plt
                                                 Mon Nov 23 15:09:17 2009
 ================================================================

 Table 15 page 64 Hematopoietic System Lymphoma or Leukemia
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   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 = Mean
   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 =     0.242959
                        Beta(1) =  0.000967723


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.48

   Beta(1)        -0.48            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background         0.242712            *               *                   *
        Beta(1)      0.000971954            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -128.699         4
    Fitted model       -128.712         2     0.0264819      2          0.9868
   Reduced model       -131.412         1       5.42487      3          0.1432

            AIC:         261.425


                                 Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.2427        17.961    18.000          74        0.011
     5.7000     0.2469        12.345    12.000          50       -0.113
    28.6000     0.2635        12.647    13.000          48        0.116
   286.0000     0.4265        20.045    20.000          47       -0.013

 Chi^2 = 0.03      d.f. = 2        P-value = 0.9868


    Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        10.3403

             BMDL =        5.45599

             BMDU =        38.9139

Taken together, (5.45599, 38.9139) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =    0.00183285
```

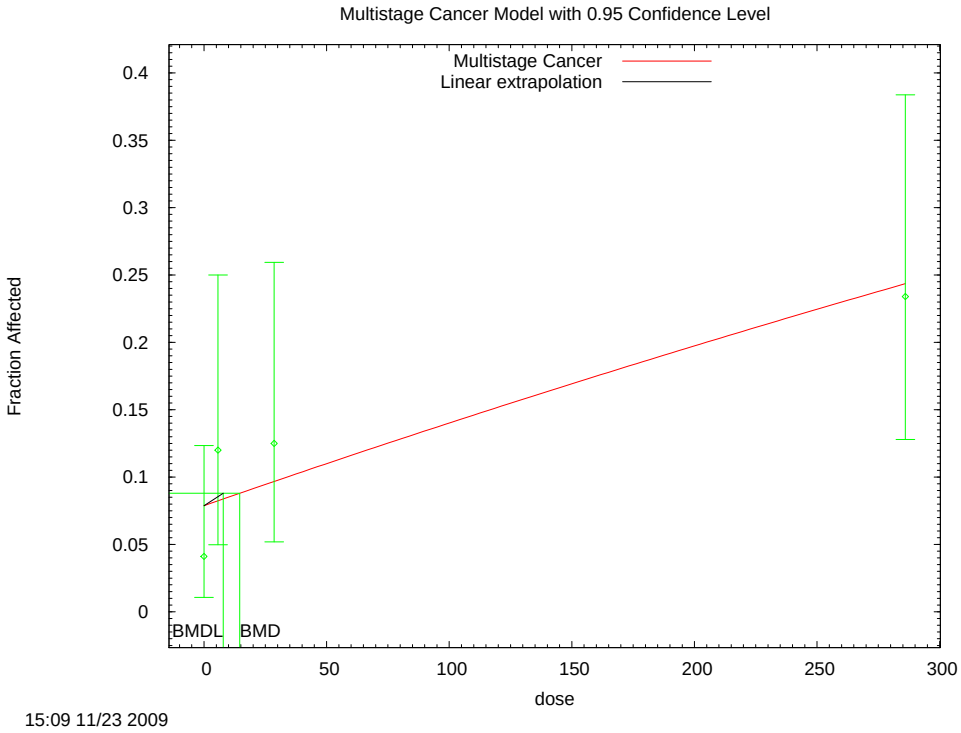
F.2.16. National Toxicology Program (1982): Female Mice, Liver, Hepatocellular Adenoma or Carcinoma

F.2.16.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**2.82**	**0.24**	**156.00**	**1.5E+01**	**7.8E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	2.82	0.24	156.00	1.5E+01	7.8E+00	betas restricted ≥0
Multistage cancer, 3-degree	2	2.82	0.24	156.00	1.5E+01	7.8E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.16.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.16.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_mice_f_liv_aden_carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_mice_f_liv_aden_carc.plt
                                                 Mon Nov 23 15:09:36 2009
 ======================================================================

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   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 = Mean
   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 =    0.0888873
                        Beta(1) =  0.000616931


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1         -0.5

   Beta(1)         -0.5            1



                                 Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0788077            *                *                   *
        Beta(1)      0.000689385            *                *                   *

* - Indicates that this value is not calculated.



                         Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -74.5177         4
    Fitted model       -76.0006         2       2.96597      2           0.227
  Reduced model        -79.6703         1       10.3053      3         0.01614

            AIC:         156.001


                                  Goodness  of  Fit
                                                                    Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0788         5.753     3.000          73       -1.196
     5.7000     0.0824         4.121     6.000          50        0.966
    28.6000     0.0968         4.646     6.000          48        0.661
   286.0000     0.2436        11.452    11.000          47       -0.153

 Chi^2 = 2.82      d.f. = 2        P-value = 0.2436


    Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        14.5787

             BMDL =        7.82902

             BMDU =        42.4536

Taken together, (7.82902, 42.4536) is a 90     % two-sided confidence
```

```
interval for the BMD

Multistage Cancer Slope Factor =     0.0012773
```

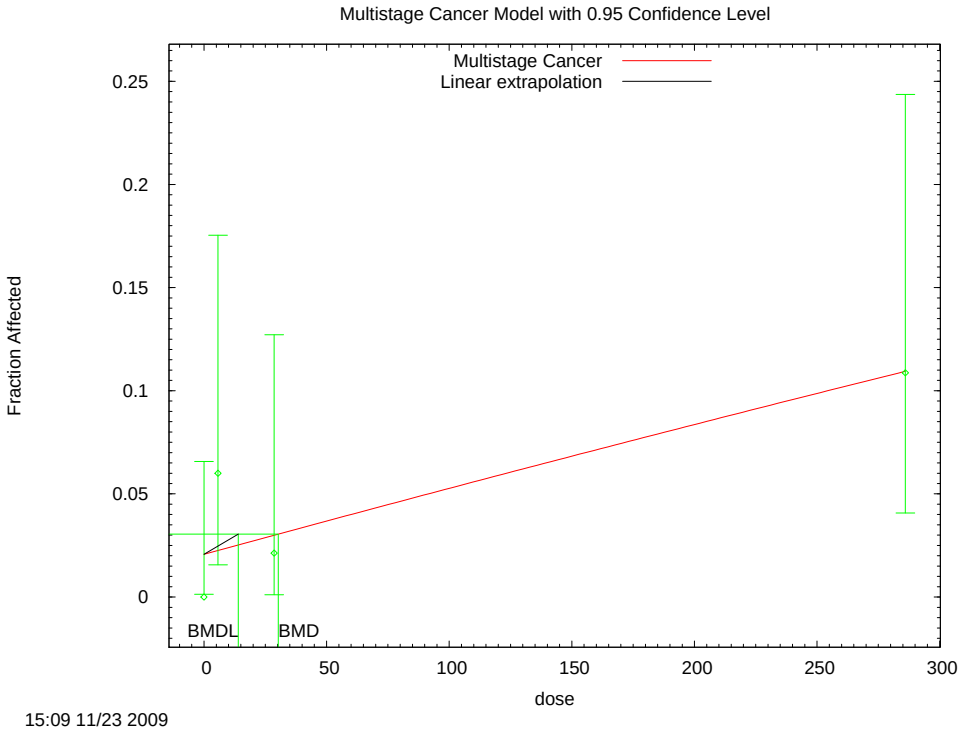
F.2.17. National Toxicology Program (1982): Female Mice, Thyroid Follicular Cell Adenoma

F.2.17.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**3.84**	**0.15**	**76.38**	**9.8E+00**	**4.0E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	3.84	0.15	76.38	9.8E+00	4.0E+00	betas restricted ≥0
Multistage cancer, 3-degree	2	3.84	0.15	76.38	9.8E+00	4.0E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.17.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.17.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_mice_f_thyroid_aden.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_mice_f_thyroid_aden.plt
                                                  Mon Nov 23 15:09:56 2009
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   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 = Mean
   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 =      0.02405
                        Beta(1) =  0.000315564


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.51

   Beta(1)        -0.51            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0207192            *               *                   *
        Beta(1)     0.000331835            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -32.0017         4
    Fitted model       -34.6122         2       5.22112      2         0.07349
   Reduced model       -37.2405         1       10.4776      3         0.01491

           AIC:         73.2245


                                 Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
    0.0000     0.0207         1.430     0.000          69       -1.208
    5.7000     0.0226         1.128     3.000          50        1.782
   28.6000     0.0300         1.409     1.000          47       -0.350
  286.0000     0.1094         5.032     5.000          46       -0.015

 Chi^2 = 4.76      d.f. = 2        P-value = 0.0927


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        30.2871

            BMDL =         13.993

            BMDU =        130.014

Taken together, (13.993 , 130.014) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =   0.000714641
```

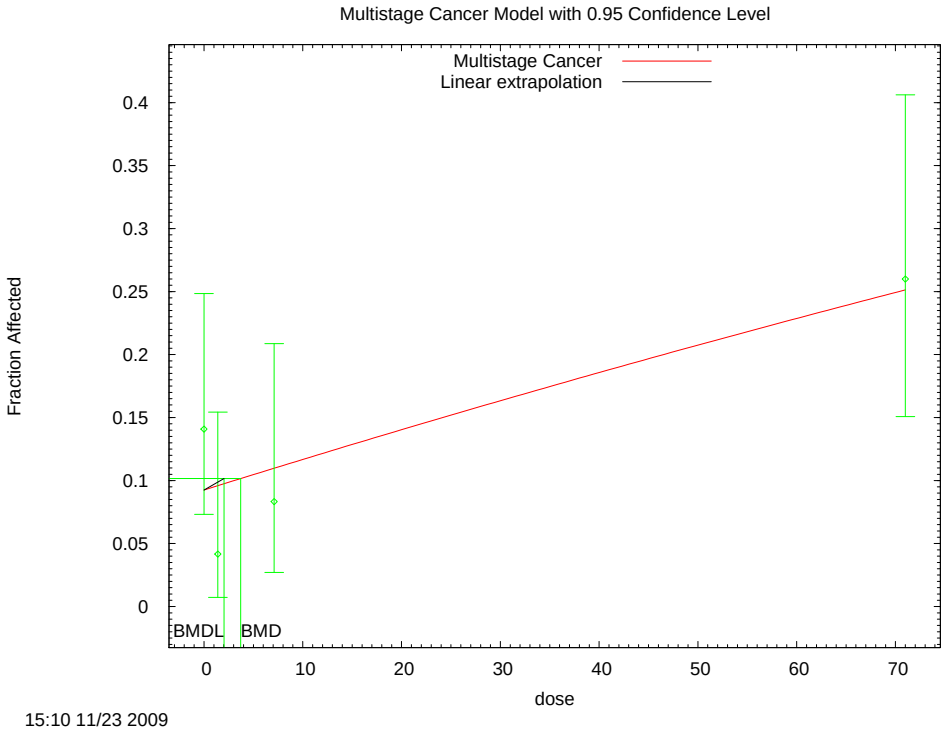
F.2.18. National Toxicology Program (1982): Male Mice, Lung, Alveolar/Bronchiolar Adenoma or Carcinoma

F.2.18.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**3.97**	**0.14**	**167.34**	**3.7E+00**	**2.0E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	3.41	0.18	166.81	1.6E+01	2.1E+00	betas restricted ≥0
Multistage cancer, 3-degree	2	3.38	0.18	166.78	2.6E+01	2.1E+00	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.18.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.18.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_lung_aden_carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_lung_aden_carc.plt
                                                 Mon Nov 23 15:10:17 2009
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   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 = Mean
   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 =    0.0827179
                        Beta(1) =   0.00298266


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.49

   Beta(1)        -0.49            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0925449            *                *                   *
        Beta(1)       0.00271189            *                *                   *

* - Indicates that this value is not calculated.



                         Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -79.5959         4
    Fitted model       -81.6704         2       4.14885      2          0.1256
  Reduced model        -85.3351         1       11.4782      3        0.009402

           AIC:         167.341


                                 Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------------
    0.0000     0.0925         6.571    10.000          71        1.404
    1.4000     0.0960         4.607     2.000          48       -1.278
    7.1000     0.1099         5.273     4.000          48       -0.588
   71.0000     0.2515        12.574    13.000          50        0.139

 Chi^2 = 3.97      d.f. = 2        P-value = 0.1375


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        3.70603

             BMDL =         2.0263

             BMDU =         10.562

Taken together, (2.0263 , 10.562 ) is a 90     % two-sided confidence
```

```
interval for the BMD

Multistage Cancer Slope Factor =     0.0049351
```

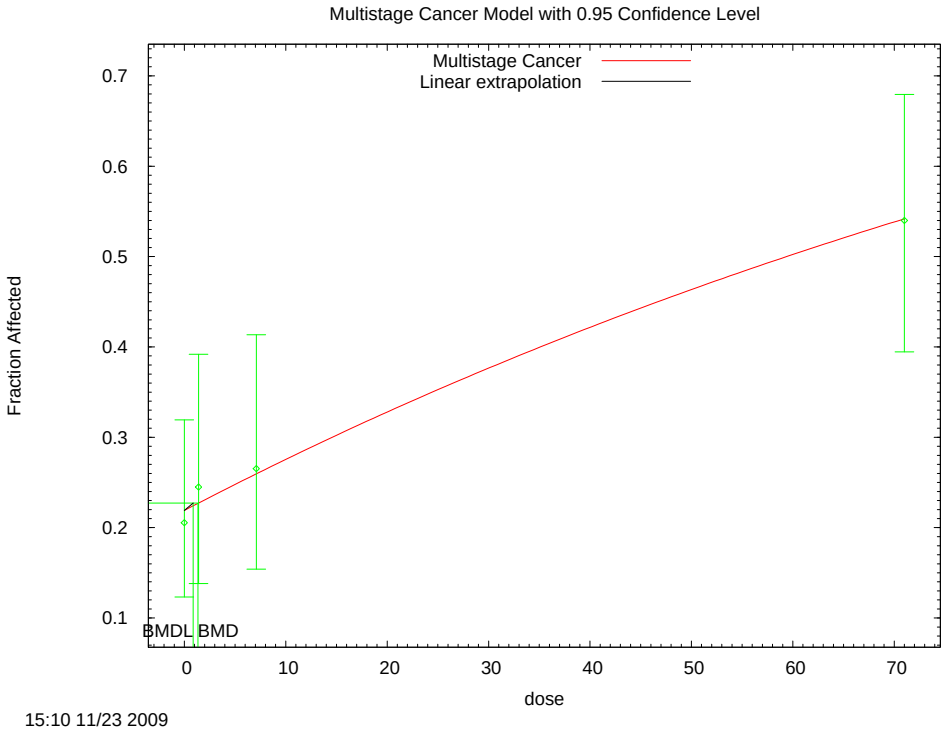
F.2.19. National Toxicology Program (1982): Male Mice, Liver, Hepatocellular Adenoma or Carcinoma

F.2.19.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**2**	**0.17**	**0.92**	**258.57**	**1.3E+00**	**8.6E-01**	**betas restricted ≥0**
Multistage cancer, 2-degree	2	0.17	0.92	258.57	1.3E+00	8.6E-01	betas restricted ≥0
Multistage cancer, 3-degree	2	0.17	0.92	258.57	1.3E+00	8.6E-01	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.19.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.19.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_mice_m_liver_aden_carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_mice_m_liver_aden_carc.plt
                                                  Mon Nov 23 15:10:37 2009
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   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 = Mean
   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 =      0.22264
                        Beta(1) =    0.0074005


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.46

   Beta(1)        -0.46            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background         0.219315            *               *                   *
        Beta(1)       0.00750879            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -127.199         4
    Fitted model       -127.286         2      0.174343      2          0.9165
   Reduced model       -135.589         1       16.7801      3       0.0007843

           AIC:         258.572


                                 Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
    0.0000     0.2193        16.010    15.000          73       -0.286
    1.4000     0.2275        11.146    12.000          49        0.291
    7.1000     0.2598        12.732    13.000          49        0.087
   71.0000     0.5419        27.096    27.000          50       -0.027

 Chi^2 = 0.17      d.f. = 2        P-value = 0.9164


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        1.33848

            BMDL =       0.861975

            BMDU =         2.4671

Taken together, (0.861975, 2.4671 ) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =     0.0116013
```

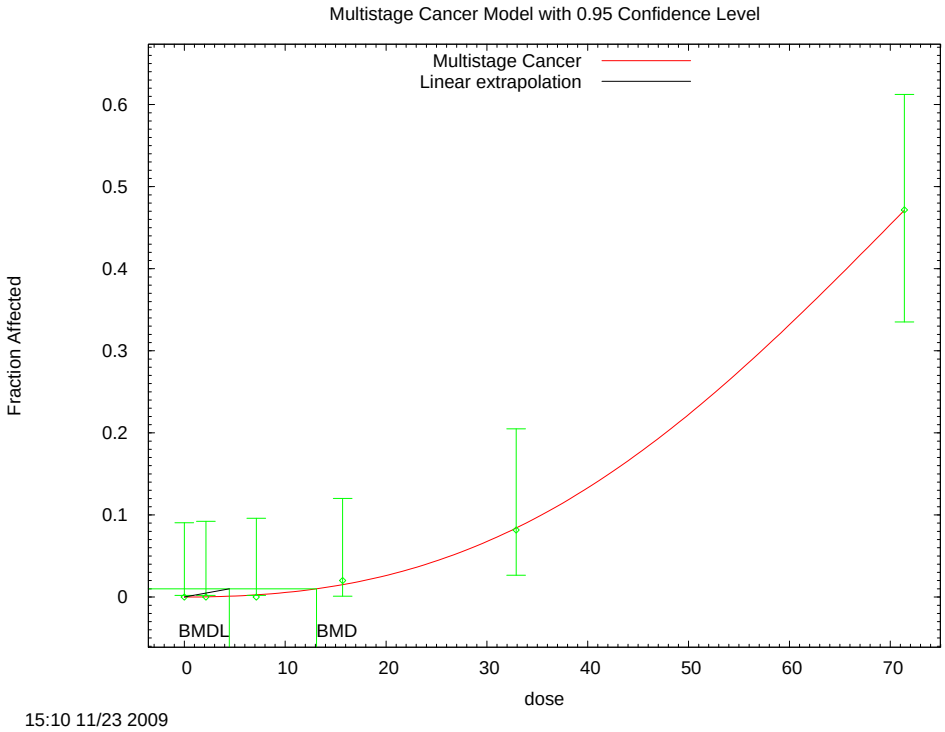
F.2.20. National Toxicology Program (2006): Liver, Cholangiocarcinoma

F.2.20.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree	5	12.91	0.02	129.07	1.9E+00	1.4E+00	betas restricted ≥0
Multistage cancer, 2-degree	5	1.18	0.95	114.35	9.4E+00	5.3E+00	betas restricted ≥0
Multistage cancer, 3-degree[b]	**4**	**0.22**	**0.99**	**115.16**	**1.3E+01**	**4.5E+00**	**betas restricted ≥0**

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.20.2. *Figure for Selected Model: Multistage Cancer, 3-Degree, Betas Restricted ≥0*



F.2.20.3. *Output File for Selected Model: Multistage Cancer, 3-Degree, Betas Restricted ≥0*

```
 ========================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc3_ngkgd_liv_cho-carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc3_ngkgd_liv_cho-carc.plt
                                                 Mon Nov 23 15:10:57 2009
 ========================================================================

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   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 = Mean
   Independent variable = Dose

 Total number of observations = 6
 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
                        Beta(1) =  0.000561481
                        Beta(2) = 1.74365e-005
                        Beta(3) = 1.40248e-006


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)
                 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        -0.99

  Beta(3)        -0.99            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)     4.35927e-005            *               *                   *
        Beta(3)     1.14186e-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         -55.408         6
    Fitted model       -55.5789         2       0.34181      4          0.987
   Reduced model       -96.9934         1       83.1708      5         <.0001

           AIC:         115.158


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          49        0.000
     2.1400     0.0002         0.010     0.000          48       -0.101
     7.1400     0.0026         0.121     0.000          46       -0.349
    15.7000     0.0150         0.752     1.000          50        0.288
    32.9000     0.0841         4.121     4.000          49       -0.062
    71.4000     0.4716        24.994    25.000          53        0.002

 Chi^2 = 0.22      d.f. = 4        P-value = 0.9945


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk
```

```
Confidence level =           0.95

              BMD =        13.1014

             BMDL =        4.46755

             BMDU =        19.1783

Taken together, (4.46755, 19.1783) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =    0.00223836
```

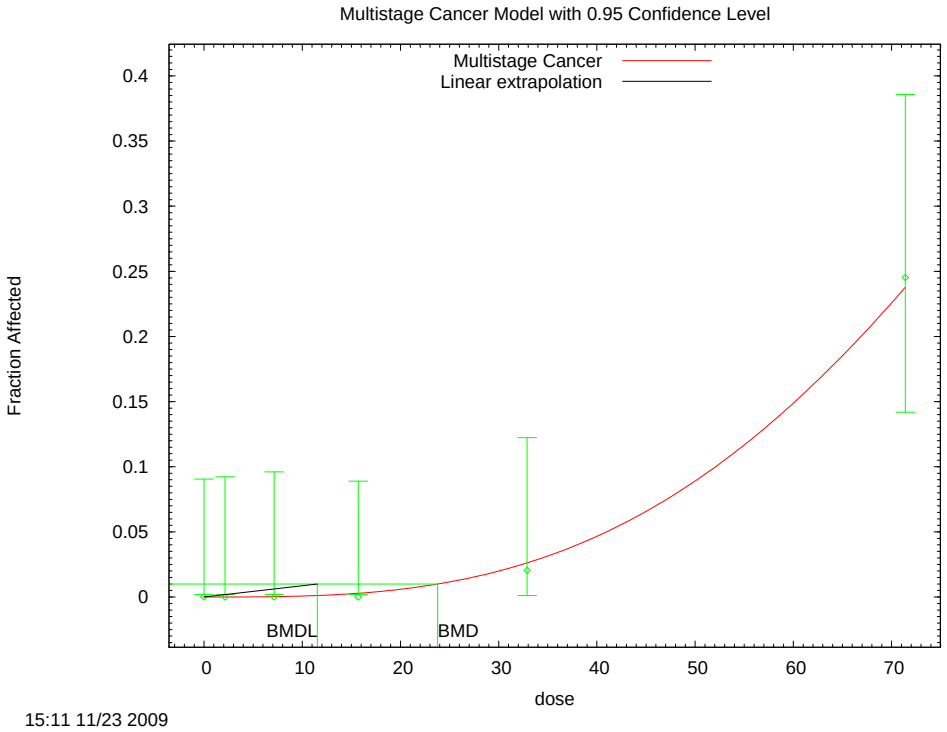
F.2.21. National Toxicology Program (2006): Liver, Hepatocellular Adenoma

F.2.21.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree	5	8.50	0.13	82.31	4.4E+00	2.9E+00	betas restricted ≥0
Multistage cancer, 2-degree	5	1.94	0.86	73.66	1.5E+01	8.6E+00	betas restricted ≥0
Multistage cancer, 3-degree[b]	**5**	**0.24**	**1.00**	**71.22**	**2.4E+01**	**1.2E+01**	**betas restricted ≥0**

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded

F.2.21.2. *Figure for Selected Model: Multistage Cancer, 3-Degree, Betas Restricted ≥0*



F.2.21.3. *Output File for Selected Model: Multistage Cancer, 3-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc3_ngkgd_liv_hepat_ad.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc3_ngkgd_liv_hepat_ad.plt
                                                  Mon Nov 23 15:11:17 2009
 ======================================================================

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   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 = Mean
   Independent variable = Dose

 Total number of observations = 6
 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
                        Beta(1) =           0
                        Beta(2) =           0
                        Beta(3) = 7.77141e-007


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

                Beta(3)

  Beta(3)           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            *               *                   *
        Beta(3)     7.46408e-007            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -34.4075         6
    Fitted model       -34.6078         1       0.40065      5          0.9953
   Reduced model       -56.3333         1       43.8515      5         <.0001

           AIC:         71.2156


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          49        0.000
    2.1400     0.0000         0.000     0.000          48       -0.019
    7.1400     0.0003         0.012     0.000          46       -0.112
   15.7000     0.0029         0.144     0.000          50       -0.380
   32.9000     0.0262         1.285     1.000          49       -0.255
   71.4000     0.2379        12.609    13.000          53        0.126

 Chi^2 = 0.24      d.f. = 5        P-value = 0.9986


  Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95
```

```
              BMD =        23.7904

             BMDL =        11.5343

             BMDU =        27.8755

Taken together, (11.5343, 27.8755) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =   0.000866978
```

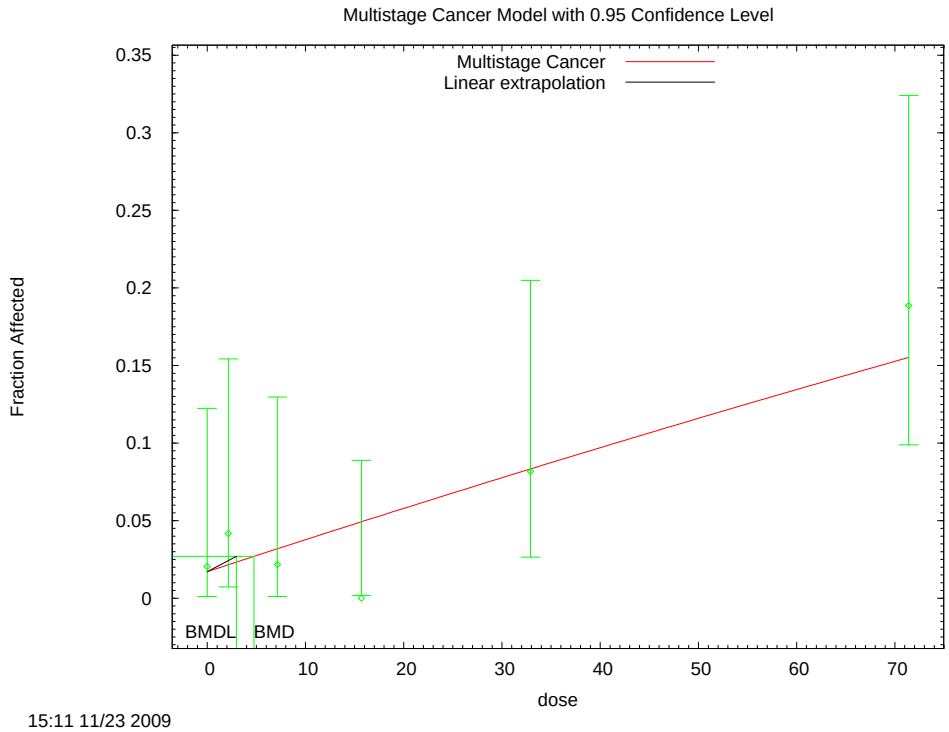
F.2.22. National Toxicology Program (2006): Oral Mucosa, Squamous Cell Carcinoma

F.2.22.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
multistage cancer, 1-degree	**4**	**4.15**	**0.39**	**125.48**	**4.8E+00**	**3.0E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree[b]	4	2.83	0.59	123.25	1.6E+01	3.8E+00	betas restricted ≥0, bound hit
Multistage cancer, 3-degree	4	2.83	0.59	123.25	1.6E+01	3.8E+00	betas restricted ≥0, bound hit

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b] Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.22.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0, Bound Hit*



F.2.22.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0, Bound Hit*

```
 ================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_oral_carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_oral_carc.plt
                                                Mon Nov 23 15:11:37 2009
 ================================================================

 0
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   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 = Mean
   Independent variable = Dose

 Total number of observations = 6
 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 =   0.00607545
                        Beta(1) =   0.00265195


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1         -0.6

   Beta(1)         -0.6            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
        Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
      Background        0.0171416            *                *                   *
         Beta(1)       0.00211536            *                *                   *

* - Indicates that this value is not calculated.



                         Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -57.5353         6
    Fitted model       -60.7418         2       6.41293      4          0.1704
   Reduced model       -67.7782         1       20.4858      5        0.001013

           AIC:         125.484


                                  Goodness  of  Fit
                                                                    Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
     0.0000     0.0171         0.840     1.000          49        0.176
     2.1400     0.0216         1.036     2.000          48        0.958
     7.1400     0.0319         1.466     1.000          46       -0.391
    15.7000     0.0492         2.462     0.000          50       -1.609
    32.9000     0.0832         4.078     4.000          49       -0.040
    71.4000     0.1549         8.211    10.000          53        0.679

 Chi^2 = 4.15      d.f. = 4        P-value = 0.3855


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        4.75111

            BMDL =         2.9556
```

```
            BMDU =        9.19454

Taken together, (2.9556 , 9.19454) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =     0.0033834
```

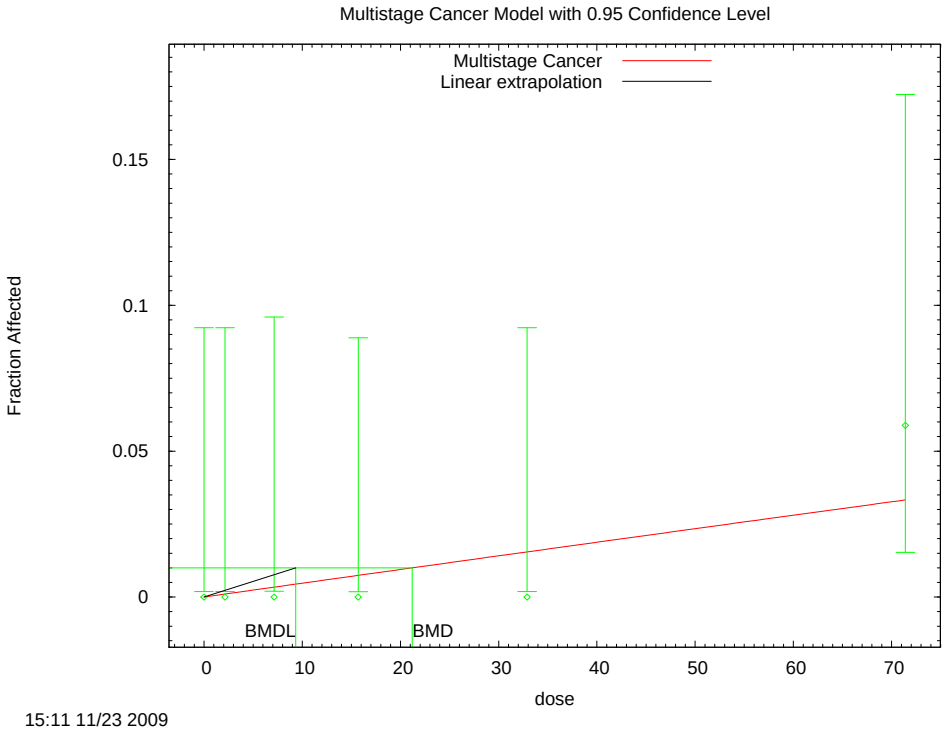
F.2.23. National Toxicology Program (2006): Pancreas, Adenoma or Carcinoma

F.2.23.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree[b]	**5**	**2.37**	**0.80**	**28.32**	**2.1E+01**	**9.3E+00**	**betas restricted ≥0**
Multistage cancer, 2-degree	5	0.80	0.98	26.23	3.3E+01	1.4E+01	betas restricted ≥0
Multistage cancer, 3-degree	5	0.32	1.00	25.43	4.1E+01	1.8E+01	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.23.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.23.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_panc_ad_carc.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_panc_ad_carc.plt
                                                 Mon Nov 23 15:11:58 2009
 ======================================================================

 0
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   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 = Mean
   Independent variable = Dose

 Total number of observations = 6
 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) =  0.000817541


           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)      0.000474004            *                *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -11.4096         6
   Fitted model        -13.1581         1       3.49702      5          0.6238
  Reduced model        -16.7086         1        10.598      5         0.05996

           AIC:         28.3163


                                 Goodness  of  Fit
                                                                      Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          48        0.000
     2.1400     0.0010         0.049     0.000          48       -0.221
     7.1400     0.0034         0.155     0.000          46       -0.395
    15.7000     0.0074         0.371     0.000          50       -0.611
    32.9000     0.0155         0.743     0.000          48       -0.869
    71.4000     0.0333         1.697     3.000          51        1.017

 Chi^2 = 2.37      d.f. = 5        P-value = 0.7964


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        21.2031

            BMDL =        9.33481
```

```
            BMDU =        65.4351

Taken together, (9.33481, 65.4351) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =    0.00107126
```

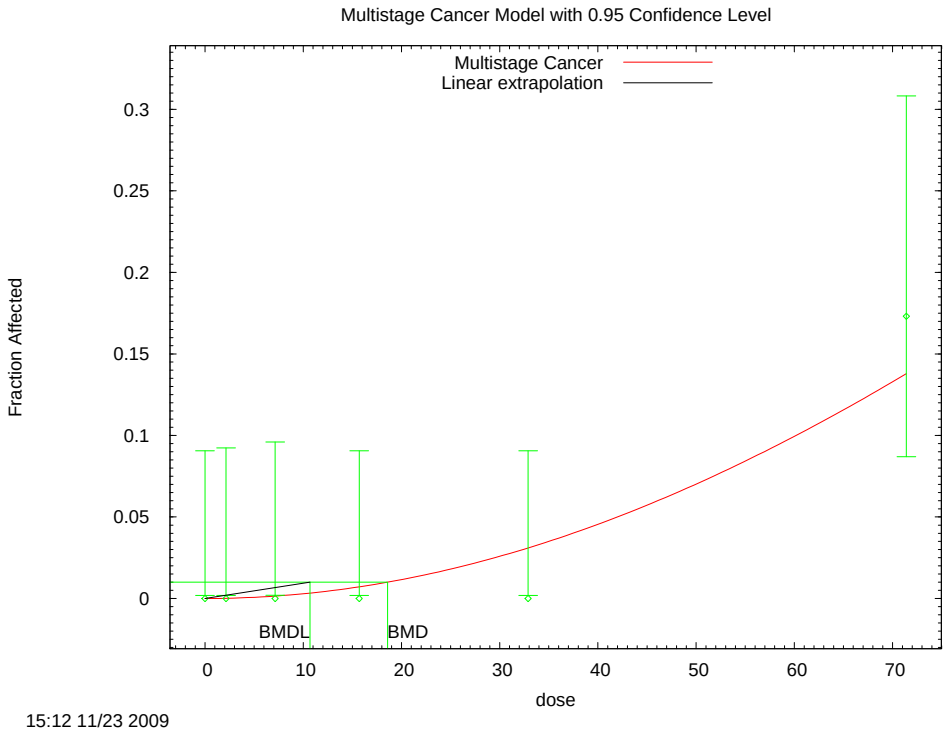
F.2.24. National Toxicology Program (2006): Lung, Cystic Keratinizing Epithelioma

F.2.24.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Multistage cancer, 1-degree	5	7.42	0.19	60.81	6.9E+00	4.2E+00	betas restricted ≥0
Multistage cancer, 2-degree[b]	**5**	**2.54**	**0.77**	**54.36**	**1.9E+01**	**1.1E+01**	**betas restricted ≥0**
Multistage cancer, 3-degree	5	1.02	0.96	51.85	2.8E+01	1.6E+01	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.24.2. *Figure for Selected Model: Multistage Cancer, 2-Degree, Betas Restricted ≥0*



F.2.24.3. *Output File for Selected Model: Multistage Cancer, 2-Degree, Betas Restricted ≥0*

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc2_ngkgd_lung_epith.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc2_ngkgd_lung_epith.plt
                                                Mon Nov 23 15:12:20 2009
 ======================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   Independent variable = Dose

 Total number of observations = 6
 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
                       Beta(1) =            0
                       Beta(2) = 3.77591e-005


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -Background    -Beta(1)
                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(2)            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)     2.91011e-005            *                *                  *

* - Indicates that this value is not calculated.



                       Analysis of Deviance Table

      Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
    Full model         -23.958         6
  Fitted model        -26.1815         1       4.44693      5           0.487
 Reduced model        -40.2069         1       32.4976      5         <.0001

          AIC:          54.363


                                 Goodness  of  Fit
                                                                  Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
   0.0000     0.0000         0.000     0.000          49        0.000
   2.1400     0.0001         0.006     0.000          48       -0.080
   7.1400     0.0015         0.068     0.000          46       -0.261
  15.7000     0.0071         0.350     0.000          49       -0.594
  32.9000     0.0310         1.519     0.000          49       -1.252
  71.4000     0.1379         7.170     9.000          52        0.736

 Chi^2 = 2.54      d.f. = 5        P-value = 0.7708


  Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        18.5839
```

```
              BMDL =        10.6878

              BMDU =        25.1324

Taken together, (10.6878, 25.1324) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =   0.000935646
```

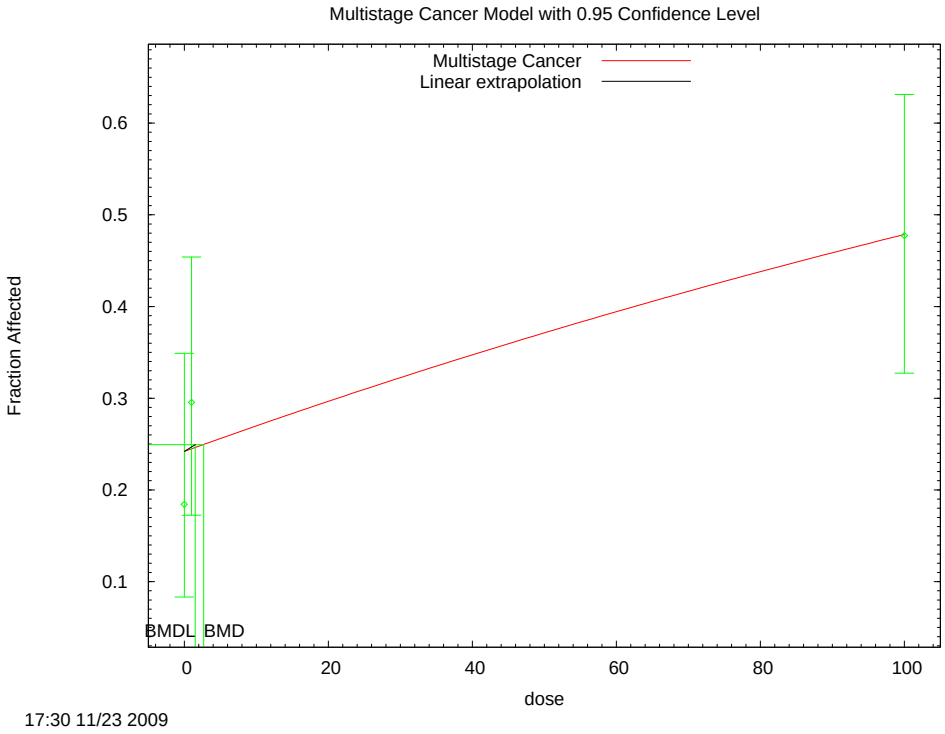
F.2.25. Toth et al. (1978): 1YR, Liver, Tumors

F.2.25.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	χ^2 Test Statistic	χ^2 p-Value[a]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
multistage cancer, 1-degree[b]	**1**	**1.30**	**0.25**	**155.95**	**2.7E+00**	**1.5E+00**	**betas restricted ≥0**
multistage cancer, 2-degree	1	1.30	0.25	155.95	2.7E+00	1.5E+00	betas restricted ≥0
multistage cancer, 0-degree			0.25	-999.00	error	error	betas restricted ≥0

[a]Values <0.1 fail to meet BMDS goodness-of-fit criteria.
[b]Best-fitting model as assessed by lowest-AIC criterion, bolded.

F.2.25.2. *Figure for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*



F.2.25.3. *Output File for Selected Model: Multistage Cancer, 1-Degree, Betas Restricted ≥0*

```
 ========================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\msc1_ngkgd_adr_cor_1yr.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\msc1_ngkgd_adr_cor_1yr.plt
                                                 Mon Nov 23 17:30:17 2009
 ========================================================================

 Table 1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = Mean
   Independent variable = Dose

 Total number of observations = 3
 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 =     0.240176
                        Beta(1) =   0.00374745


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.53

   Beta(1)        -0.53            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background           0.2418            *               *                   *
        Beta(1)       0.00373791            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -75.3127         3
    Fitted model       -75.9728         2        1.3201      1          0.2506
   Reduced model       -79.4897         1       8.35401      2         0.01534

           AIC:         155.946


                                 Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
     0.0000     0.2418         9.188     7.000          38       -0.829
     1.0000     0.2446        10.764    13.000          44        0.784
   100.0000     0.4783        21.044    21.000          44       -0.013

 Chi^2 = 1.30      d.f. = 1        P-value = 0.2537


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        2.68876

            BMDL =        1.52183

            BMDU =        7.54263

Taken together, (1.52183, 7.54263) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =    0.00657103
```

F.3. HUMAN EQUIVALENT DOSES FOR 1, 5, AND 10% EXTRA RISK

Comparison of Human Equivalent Doses from Benchmark Dose Modeling Assuming 1%, 5%, and 10% Extra Risk

Study	Species	Sex	Morphology: topography	BMD_{01} HED (ng/kg-day)	$BMDL_{01}$ HED (ng/kg-day)	BMD_{05} HED (ng/kg-day)	$BMDL_{05}$ HED (ng/kg-day)	BMD_{10} HED (ng/kg-day)	$BMDL_{10}$ HED (ng/kg-day)
Kociba, 1978	Rat	Male	Stratified squamous cell carcinoma of hard palate or nasal turbinates	4.7E-01	1.6E-01	4.6E+00	1.7E+00	1.1E+01	4.6E+00
			Stratified squamous cell carcinoma of tongue	5.1E-01	1.4E-01	4.9E+00	1.6E+00	1.2E+01	4.1E+00
			Adenoma of adrenal cortex	2.0E-01	8.5E-02	2.1E+00	9.7E-01	5.5E+00	2.6E+00
		Female	Hepatocellular adenoma(s) or carcinoma(s)	1.9E-02	1.2E-02	2.3E-01	1.4E-01	6.7E-01	4.1E-01
			Stratified squamous cell carcinoma of hard palate or nasal turbinates	3.3E-01	1.2E-01	3.3E+00	1.3E+00	8.3E+00	3.6E+00
			Keratinizing squamous cell carcinoma of lung	1.9E-01	8.0E-02	2.0E+00	9.2E-01	5.3E+00	2.5E+00
NTP, 1982	Rat	Female	Subcutaneous tissue: fibrosarcoma	1.8E-01	5.3E-02	2.0E+00	6.2E-01	5.2E+00	1.7E+00
			Liver: neoplastic nodule or hepatocellular carcinoma	4.2E-02	2.1E-02	4.9E-01	2.4E-01	1.4E+00	7.1E-01
			Adrenal: cortical adenoma, or carcinoma or adenoma, NOS	6.8E-02	2.4E-02	7.8E-01	2.8E-01	2.2E+00	8.2E-01
			Thyroid: follicular-cell adenoma	2.1E-01	6.4E-02	2.2E+00	7.4E-01	5.7E+00	2.0E+00
		Male	Liver: neoplastic nodule or hepatocellular carcinoma	5.1E-01	1.5E-01	4.9E+00	1.6E+00	1.2E+01	4.3E+00
			Thyroid: follicular-cell adenoma or carcinoma	4.3E-02	1.9E-02	5.1E-01	2.3E-01	1.4E+00	6.6E-01
			Adrenal cortex: adenoma	2.6E-01	4.4E-02	2.8E+00	5.2E-01	7.0E+00	1.5E+00
	Mouse	Female	Subcutaneous tissue: fibrosarcoma	2.1E-01	7.2E-02	2.2E+00	8.3E-01	5.8E+00	2.3E+00
			Hematopoietic system: lymphoma or leukemia	4.0E-02	1.5E-02	4.7E-01	1.8E-01	1.3E+00	5.3E-01
			Liver: hepatocellular adenoma or carcinoma	5.9E-02	2.4E-02	6.9E-01	2.9E-01	1.9E+00	8.3E-01
			Thyroid: follicular-cell adenoma	1.8E-01	5.6E-02	1.9E+00	6.5E-01	5.0E+00	1.8E+00
		Male	Lung: alveolar/bronchiolar adenoma or carcinoma	1.3E-01	8.6E-03	4.6E-01	1.0E-01	7.7E-01	3.0E-01
			Liver: hepatocellular adenoma or carcinoma	3.1E-03	1.7E-03	3.7E-02	1.9E-02	1.1E-01	5.7E-02
NTP, 2006	Rat	Female	Liver: cholangiocarcinoma	7.0E-01	2.9E-01	1.5E+00	1.2E+00	2.1E+00	1.8E+00
			Liver: hepatocellular adenoma	1.1E+00	5.6E-01	2.3E+00	1.8E+00	3.2E+00	2.7E+00
			Oral mucosa: squamous cell carcinoma	1.1E-01	5.5E-02	1.2E+00	6.4E-01	3.3E+00	1.8E+00
			Pancreas: adenoma or carcinoma	1.1E+00	3.4E-01	5.3E+00	3.1E+00	8.3E+00	5.0E+00
			Lung: cystic keratinizing epithelioma	8.0E-01	4.1E-01	2.5E+00	1.8E+00	4.1E+00	2.9E+00
Toth, 1979	Mouse	Male	Liver: tumors	5.1E-03	1.9E-03	6.7E-02	2.7E-02	2.0E-01	8.5E-02

F.4. REFERENCES

Goodman, DG; Sauer, RM. (1992) Hepatotoxicity and carcinogenicity in female Sprague-Dawley rats treated with 2,3,7,8-tetrachlorordibenzo-p-dioxin (TCDD): a Pathology Working Group reevaluation. Regul Toxicol Pharmacol 15:245–252.

Kociba, RJ; Keyes, DG; Beyer, JE; et al. (1978) Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Toxicol Appl Pharmacol 46(2):279–303.

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APPENDIX G

Endpoints Excluded From Reference Dose Derivation Based on Toxicological Relevance

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
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APPENDIX G. ENDPOINTS EXCLUDED FROM REFERENCE DOSE DERIVATION BASED ON TOXICOLOGICAL RELEVANCE

The National Academy of Sciences (NAS) 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 (IRIS) 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.

Kitchin and Woods (1979) administered female Sprague-Dawley rats a single gavage dose of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and measured cytochrome P450 levels and benzo(a)pyrene hydroxylase (BPH) activity as a marker of hepatic microsomal cytochrome P448-mediated enzyme activity. They found a statistically significant increase in BPH at doses ≥2 ng/kg and a significant increase in cytochrome P450 levels at doses ≥600 ng/kg. Aryl hydrocarbon hydrolase and EROD were both significantly increased 3 months after exposure; however the elevation did not maintain statistical significance at 6 months. No other indicators of hepatic effects were analyzed. 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 hepatotoxicity and carcinogenicity of TCDD is unknown, and CYP induction is not considered a relevant POD without obvious pathological significance.

In multiple studies by Hassoun et al. (1998, 2000, 2002, 2003), various indicators of oxidative stress were measured in hepatic and brain tissue of female B6C3F1 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 (Hassoun et al., 1998). In this study, all oxidative stress markers were significantly effected, 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.

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 B6C3F1 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.

To examine the central nervous system response to TCDD, Kuchiiwa et al (2002) analyzed the effect of in utero and lactational TCDD exposure on the serotonergic system in the brainstem of male ddY mice. Female mice were administered TCDD by oral gavage once a week for 8 weeks prior to pregnancy and, using an immunocytochemical detection method, the raphe nuclei in the brainstem of male offspring was monitored for serotogergic neurons. TCDD at 0.7 ng/kg-day caused a 25−50% reduction in the immunostaining of serotonin, however there were no differences in external morphology, birth or postnatal body weights between TCDD-exposed and control offspring. The authors suggest that these findings may indicate that TCDD acts as a neuroteratogen by mediating long-term alterations in neuronal serotonin synthesis and serotonergic function. However, no other relevant neurotoxicity endpoints were examined or reported. Thus, reduced serotonin is not an adverse endpoint of toxicological significance in and of itself, and this study is deemed unsuitable as a POD candidate.

Mally and Chipman (2002) evaluated the effect of TCDD on gap junctions, hypothesizing that as a nongenotoxic carcinogen, TCDD may induce tumor formation by disturbing tissue homeostasis. Female F344 rats were dosed with TCDD by oral gavage for either 3 consecutive days or 2 days a week for 28 days. Gap junction connexin (Cx) plaque expression and hepatocyte proliferation was measured. The study authors report a decrease in Cx32 plaque number and area in the liver of rats exposed to 0.7 ng/kg-day and higher, however they did not find an associated increase in hepatocyte proliferation. No clinical signs of toxicity were observed, and histological examination of the liver revealed no abnormalities. In the absence of additional indicators of hepatotoxicity, a decrease in Cx32 plaque formation is not clearly linked to TCDD-mediated hepatotoxicity or hepatocarcinogenicty, nor is it considered an adverse effect. This endpoint is not considered a toxicologically relevant POD.

Vanden Heuvel et al. (1994) analyzed changes in hepatic 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 (RT-PCR) on hepatic RNA, they compared levels of "dioxin responsive" mRNA's (CYP1A1, 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 (3-fold) 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.

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 B6C3F1 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.

Because TCDD had been detected in the soil of contaminated locations, determining the bioavailability of TCDD from ingested soil may be important to the calculation of safe exposure levels. Lucier et al. (1986) fed adult female Sprague-Dawley rats TCDD contaminated soil or gave them TCDD in corn oil at various doses and compared the effects of TCDD on biochemical parameters from liver tissue. They found that equivalent doses of TCDD in corn oil and soil produced similar increases in hepatic aryl hydrocarbon hydroxylase activity (AHH) and UDP glucuronyltransferase activity. They determined that AHH was statistically induced 1.8-fold at 15 ng/kg in corn oil and 40 ng/kg in soil. Cytochrome P450 was significantly increased at higher doses. No clinical signs of acute toxicity or changes in body weight were observed. The association between AHH activity and TCDD-mediated hepatotoxicity is unknown and no adverse endpoints were measured. Thus, this endpoint is not suitable as a POD candidate.

Sugita-Konishi et al. (2003) investigated the change in host resistance of mice offspring lactationally exposed to TCDD. Pregnant C57BL/6NCji mice were administered TCDD via drinking water from parturition to weaning of the offspring (17 days). One group of offspring was then infected with *Listeria monocytogenes* and blood and spleen samples were collected various time points post infection. Uninfected, TCDD exposed offspring were weighed and their spleens and thymuses removed for assay of cellular content and protein expression. TCDD exposure caused a statistically-significant decrease in relative spleen weight and a statistically-significant increase in thymic CD4+ cells in the high-dose group (11.3 ng/kg-day). Offspring infected with *Listeria* following TCDD exposure exhibited a statistically significant increase in serum tumor necrosis factor alpha (TNF-α) 2 days after infection in both sexes in the low- (1.14 ng/kg-day) and high-dose groups. The authors conclude that exposure to TCDD disrupted the host resistance of the offspring at the lowest dose tested, despite the primary immune parameters being unaffected. Without an obvious association between TCDD and immune function, however, this endpoint is not suitable for identification of a LOAEL. Thus, the LOAEL for this study is 11.3 ng/kg-day, and the NOAEL is 1.14 ng/kg-day.

Sewall et al. (1993) investigated alterations in the epidermal growth factor receptor (EGFR) pathway in a two-stage initiation promotion model of TCDD hepatic cancer. EGFR signaling has been implicated in the altered cell growth induction by tumor promoters. Female Sprague-Dawley rats were administered TCDD biweekly by oral gavage for 30 weeks following initiation by a single dose of diethylnitrosamine (DEN). A group also received TCDD without prior DEN initiation. Livers were harvested and fixed from sacrificed animals and sections tested for EGFR binding, autophosphorylation, immunolocalization, and hepatic cell proliferation. The authors report a significant dose-dependent decrease in plasma membrane EGFR maximum binding capacity in TCDD-exposed rats beginning at 3.5 ng/kg-day. However, at this same dose, the authors note a statistically significant decrease in cell proliferation (as measured by DNA replication labeling), with increases in proliferation only occurring at higher doses (125 ng/kg-day). No other indicators of hepatic toxicity or tumorigenicity were assessed. The role of EGFR in TCDD-mediated hepatotoxicity and hepatocarcinogenicity is unknown, and as such, this endpoint cannot be unequivocally linked to TCDD-induced hepatic effects nor labeled as adverse. Thus, it is not suitable as a POD candidate.

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APPENDIX H

Cancer Precursor Benchmark Dose Modeling

NOTICE

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APPENDIX H. CANCER PRECURSOR BENCHMARK DOSE MODELING

H.1. BMDS INPUT TABLES

H.1.1. Hassoun et al. (2000)

	Administered Dose (ng/kg-day)					
	0	3	10	22	46	100
	Internal Dose (ng/kg blood) [a]					
	0	1,068	2,542	4,489	7,718	13,960
Endpoint	n = 6	n = 6	n = 6	n = 6	n = 6	n = 6
CytC liver	0.15 ± 0.07	0.18 ± 0.05 [b]	0.19 ± 0.06	0.27 ± 0.06 [c]	0.39 ± 0.06 [c]	0.44 ± 0.11 [c]
DNA SSB	7.41 ± 1.54	10.78 ± 1.25 [b,c]	13.6 ± 1.69 [c]	15.3 ± 1.71 [c]	20.4 ± 2.25 [c]	23.5 ± 1.37 [c]
TBARs liver	1.47 ± 0.29	1.55 ± 0.54 [b]	2.15 ± 0.36 [c]	2.28 ± 0.25 [c]	2.62 ± 0.52 [c]	2.29 ± 0.49 [c]

[a]From the Emond PRPK model described in 3.3.
[b]LOEL for selected endpoint.
[c]Statistically significant as compared to control ($p < 0.05$).

H.1.2. Kitchin et al. (1979)

	Administered Dose (ng/kg-day)					
	0	0.2	0.667	1.33	6.67	20
	Internal Dose (ng/kg blood) [a]					
	0	70	232	463	2,318	6,949
Endpoint	n = 9	n = 4	n = 4	n = 4	n = 4	n = 4
BaP hydrolase activity (continued on next line)	4.9 ± 1.11	4.9 ± 1.18 [b]	6.7 ± 1.4 [c,d]	7.2 ± 1.8 [d]	8.3 ± 0.26 [e]	14 ± 5 [e]
	Administered Dose (ng/kg-day)					
	66.7	200	667	1,670	6,670	
	Internal Dose (ng/kg blood) [a]					
	23,185	69,657	232,550	581,930	2,332,100	
Endpoint	n = 4	n = 4	n = 4	n = 4	n = 4	
BaP hydrolase activity (continued)	59 ± 6.8 [e]	96 ± 46 [e]	155 ± 16.4 [e]	182 ± 26 [e]	189 ± 26 [e]	

[a]From the Emond PRPK model described in 3.3.
[b]NOEL for selected endpoint.
[c]LOEL for selected endpoint.
[d]Statistically significant as compared to control ($p < 0.05$).
[e]Statistically significant as compared to control ($p < 0.001$).

H.1.3. National Toxicology Program. (2006), 31 Week Exposure

Endpoint	Administered Dose (ng/kg-day)					
	0	2.14	7.14	15.7	32.9	71.4
	Internal Dose (ng/kg blood) [a]					
	0	1,284	2,932	5,075	8,629	15,503
	n = 9	n = 10	n = 10	n = 10	n = 10	n = 10
Tbl11 Index ,week 31	0.33 ± 0.19	0.85 ± 0.65 [b]	0.96 ± 0.74 [b]	0.79 ± 0.46 [b]	1.33 ± 1.12 [b]	3.85 ± 3.08 [b]
Lung EROD, week 31	2.07 ± 0.97	25.34 ± 2.55 [c]	30.39 ± 5.83 [c]	50.19 ± 8.68 [c]	49.07 ± 13.91 [c]	48.42 ± 8.93 [c]

[a]From the Emond PRPK model described in 3.3.
[b]Statistically significant as compared to control ($p < 0.05$).
[c]Statistically significant as compared to control ($p < 0.01$).

H.1.4. National Toxicology Program (2006), 53 Week Exposure

Endpoint	Administered Dose (ng/kg-day)					
	0	2.14	7.14	15.7	32.9	71.4
	Internal Dose (ng/kg blood) [a]					
	0	1,354	3,056	5,259	8,918	16,001
	n = 8	n = 8	n = 8	n = 8	n = 8	n = 8
Liver EROD, week 53	3.61 ± 0.49	7.27 ± 0.56 [b]	14.76 ± 1.61 [b]	17.28 ± 1.59 [b]	20.58 ± 3.05 [b]	21.21 ± 3.82 [b]
Lung EROD, week 53	3.01 ± 1.58	27.15 ± 5.27 [b]	42.85 ± 11.15 [b]	36.57 ± 12.99 [b]	43.75 ± 18.55 [b]	43.71 ± 6.32 [b]

[a]From the Emond PRPK model described in 3.3.
[b]Statistically significant as compared to control ($p < 0.01$).

H.1.5. National Toxicology Program (2006), 2 Year Exposure

Endpoint	Administered Dose (ng/kg-day)					
	0	2.14	7.14	15.7	32.9	71.4
	Internal Dose (ng/kg blood) [a]					
	0	1,408	3,137	5,393	9,129	16,361
	n = 53	n = 54	n = 53	n = 53	n = 53	n = 53
Toxic Hepatopathy	0/53 (0%)	2/54 (0%)	8/53 (20%) [b]	30/53 (60%) [b]	45/53 (80%) [b]	53/53 (100%) [b]

[a]From the Emond PRPK model described in 3.3.
[b]Statistically significant as compared to control ($p < 0.01$).

H.1.6. Van Birgelen et al. (1995a, b)

Endpoint	Administered Dose (ng/kg-day)					
	0	14	26	47	320	1,024
	Internal Dose (ng/kg blood) [a]					
	0	3,969	6,479	9,968	47,606	137,820
	n = 8	n = 8	n = 8	n = 8	n = 8	n = 8
T4 UGT	0.33 ± 0.2	0.6 ± 0.42	0.64 ± 0.45 [b]	0.87 ± 0.91 [b]	2.08 ± 1.33 [b]	2.59 ± 0.88 [b]
UGT 1A1	101 ± 15.59	194 ± 36.37 [b]	Not reported.	304 ± 17.32 [b]	452 ± 48.5 [b]	296 ± 148.96 [b]

[a]From the Emond PRPK model described in 3.3.
[b]Statistically significant as compared to control ($p < 0.05$).

H.1.7. Vanden Heuvel et al. (1994)

Endpoint	Administered Dose (ng/kg-day)						
	0	0.1	1	10	100	1,000	10,000
	Internal Dose (ng/kg blood) [a]						
	0	4	36	302	2,149	14,301	114,690
	n = 13	n = 5	n = 12	n = 7	n = 7	n = 11	n = 5
Hepatic CYP1A1 mRNA Expression	5.4 ± 3.61	7.2 ± 5.59	14.8 ± 14.9 [b]	12.8 ± 4.5 [b]	536 ± 320.14 [b]	18000 ± 15223.31 [b]	36700 ± 22137.07 [b]

[a]From the Emond PRPK model described in 3.3.
[b]Statistically significant as compared to control ($p < 0.05$).

H.2. ALTERNATE DOSE: BLOOD SERUM BMDS RESULTS

H.2.1. Hassoun et al. (2000): CytC liver

H.2.1.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	4	0.39	10.22	0.04	-145.92	3.5E+03	2.5E+03	nonconstant variance, power restricted ≥1
exponential (M3)	4	0.39	10.22	0.04	-145.92	3.5E+03	2.5E+03	nonconstant variance, power restricted ≥1
exponential (M4)	3	0.39	3.38	0.34	-150.76	1.6E+03	9.7E+02	nonconstant variance, power restricted ≥1
exponential (M5)	2	0.39	0.56	0.76	-151.58	3.0E+03	1.4E+03	nonconstant variance, power restricted ≥1
exponential (M5)	2	0.39	0.56	0.76	-151.58	3.0E+03	1.4E+03	nonconstant variance, power unrestricted

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
Hill	2	0.39	0.66	0.72	-151.47	3.1E+03	error	nonconstant variance, n restricted >1
Hill	2	0.39	0.66	0.72	-151.47	3.1E+03	error	nonconstant variance, n unrestricted
linear	4	0.39	4.68	0.32	-151.45	2.1E+03	1.4E+03	nonconstant variance
polynomial	4	0.39	4.68	0.32	-151.45	2.1E+03	1.4E+03	nonconstant variance
power	4	0.39	4.68	0.32	-151.45	2.1E+03	1.4E+03	nonconstant variance, power restricted ≥1, bound hit
power	3	0.39	4.26	0.23	-149.87	1.6E+03	6.8E+02	nonconstant variance, power unrestricted
exponential (M2)	4	0.39	12.17	0.02	-143.33	5.1E+03	4.3E+03	constant variance, power restricted ≥1
exponential (M3)	4	0.39	12.17	0.02	-143.33	5.1E+03	4.3E+03	constant variance, power restricted ≥1
exponential (M4)	3	0.39	3.37	0.34	-150.14	1.9E+03	1.2E+03	constant variance, power restricted ≥1
exponential (M5) [c]	**2**	**0.39**	**0.48**	**0.79**	**-151.03**	**3.3E+03**	**1.7E+03**	**constant variance, power restricted ≥1**
exponential (M5) [d]	2	0.39	0.48	0.79	-151.03	3.3E+03	1.7E+03	constant variance, power unrestricted
Hill	2	0.39	0.59	0.74	-150.91	3.4E+03	1.8E+03	constant variance, n restricted >1
Hill [d]	2	0.39	0.59	0.74	-150.91	3.4E+03	1.8E+03	constant variance, n unrestricted
linear	4	0.39	6.42	0.17	-149.09	3.1E+03	2.4E+03	constant variance
polynomial	4	0.39	6.42	0.17	-149.09	3.1E+03	2.4E+03	constant variance
power	4	0.39	6.42	0.17	-149.09	3.1E+03	2.4E+03	constant variance, power restricted ≥1, bound hit
power [d]	3	0.39	4.84	0.18	-148.66	1.8E+03	7.4E+02	constant variance, power unrestricted

[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

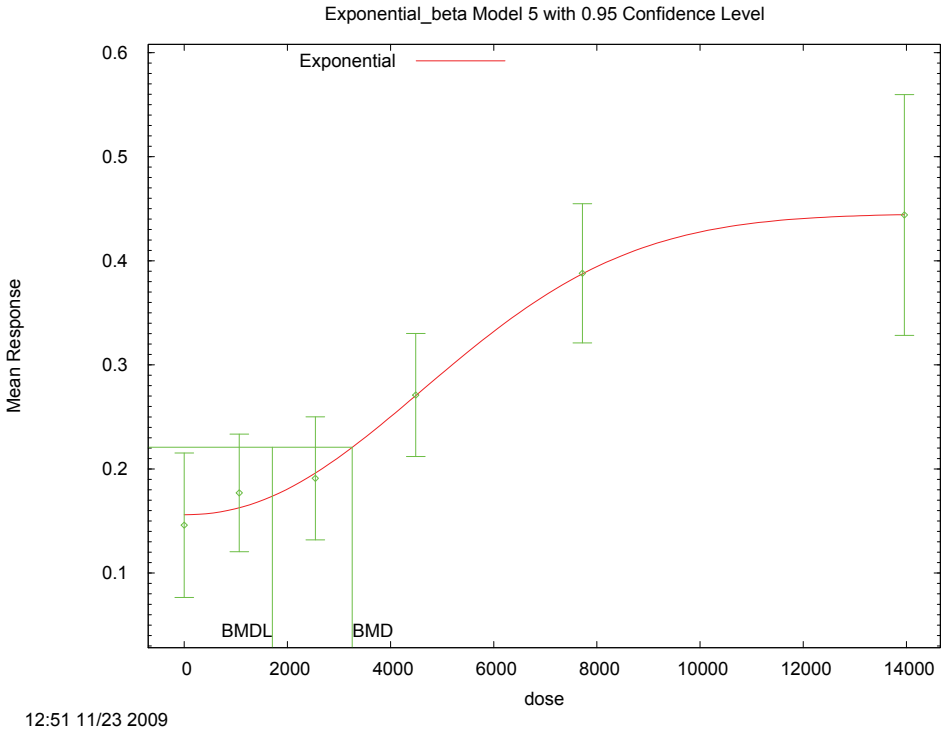
[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

1

H.2.1.2. *Figure for Selected Model: Exponential (M5), Constant Variance, Power Restricted ≥1*



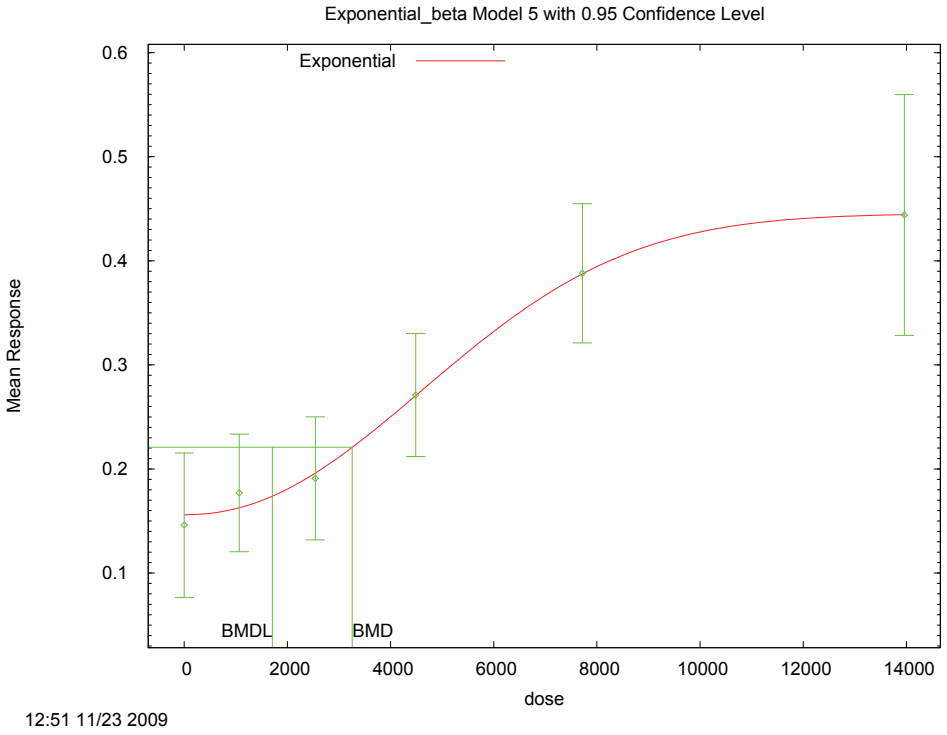
H.2.1.3. *Output File for Selected Model: Exponential (M5), Constant Variance, Power Restricted ≥1*

```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\Exp_CV_BMR1_CytC_Liver.(d)
         Gnuplot Plotting File:
                                                  Mon Nov 23 12:51:43 2009
 ========================================================================

 TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 5
                --------          --------
                  lnalpha            -5.48625
                      rho(S)                0
                        a              0.1387
                        b         4.08913e-005
                        c              6.40231
                        d                    1

  (S) = Specified



                  Parameter Estimates

                 Variable          Model 5
                 --------          -------
                  lnalpha          -5.47298
                      rho                 0
                        a          0.156024
                        b        0.00016181
                        c           2.85354
                        d           2.14237


          Table of Stats From Input Data

    Dose      N         Obs Mean     Obs Std Dev
    -----    ---       ----------   -------------
        0      6        0.146      0.06614
     1068      6        0.177      0.05389
     2542      6        0.191      0.05634
     4489      6        0.271      0.05634
     7718      6        0.388      0.06369
 1.396e+004      6        0.444       0.1102


                Estimated Values of Interest

     Dose      Est Mean      Est Std     Scaled Residual
    ------    ----------    ---------    ----------------
        0         0.156       0.0648          -0.3789
     1068        0.1627       0.0648           0.5416
     2542        0.1961       0.0648          -0.1919
     4489        0.2705       0.0648          0.01767
     7718        0.3874       0.0648          0.02225
1.396e+004        0.4443       0.0648          -0.0107


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        80.75258           7     -147.5052
                   A2        83.37355          12     -142.7471
                   A3        80.75258           7     -147.5052
                    R        55.82002           2       -107.64
                    5        80.51365           5     -151.0273


Additive constant for all log-likelihoods =     -33.08.  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                        55.11           10           < 0.0001
  Test 2                        5.242            5             0.3871
  Test 3                        5.242            5             0.3871
 Test 7a                       0.4779            2             0.7875


  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 7a is greater than .1.  Model 5 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 =      3257.85

              BMDL =      1709.28
```

H.2.1.4. *Figure for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*



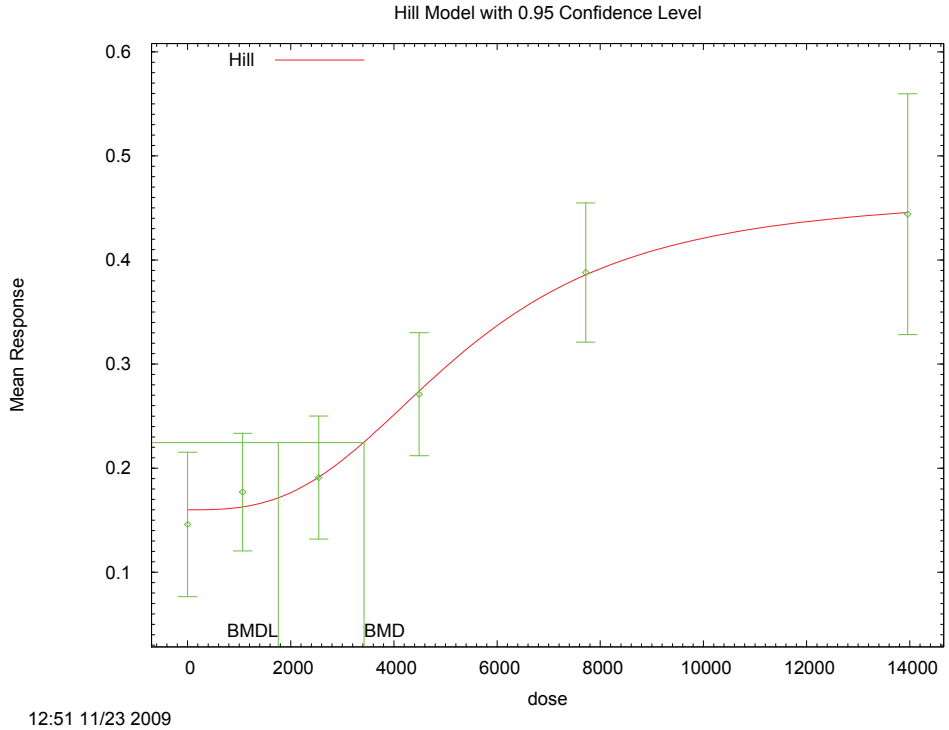
H.2.1.5. *Output file for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*

```
 ======================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\Exp_CV_Unrest_BMR1_CytC_Liver.(d)
         Gnuplot Plotting File:
                                                  Mon Nov 23 12:51:49 2009
 ======================================================================

 TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 5
                --------          --------
                  lnalpha            -5.48625
                      rho(S)                0
                        a               0.1387
                        b         4.08913e-005
                        c              6.40231
                        d                    1

  (S) = Specified



                  Parameter Estimates

                 Variable          Model 5
                 --------          -------
                  lnalpha          -5.47298
                      rho                 0
                        a          0.156024
                        b        0.00016181
                        c           2.85354
                        d           2.14237


          Table of Stats From Input Data

      Dose      N         Obs Mean     Obs Std Dev
      -----    ---       ----------   -------------
         0      6        0.146      0.06614
      1068      6        0.177      0.05389
      2542      6        0.191      0.05634
      4489      6        0.271      0.05634
      7718      6        0.388      0.06369
  1.396e+004      6        0.444       0.1102


                Estimated Values of Interest

       Dose      Est Mean      Est Std     Scaled Residual
      ------    ----------    ---------    ----------------
         0         0.156       0.0648          -0.3789
      1068        0.1627       0.0648           0.5416
      2542        0.1961       0.0648          -0.1919
      4489        0.2705       0.0648          0.01767
      7718        0.3874       0.0648          0.02225
1.396e+004        0.4443       0.0648          -0.0107


   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        80.75258           7     -147.5052
                      A2        83.37355          12     -142.7471
                      A3        80.75258           7     -147.5052
                       R        55.82002           2       -107.64
                       5        80.51365           5     -151.0273


Additive constant for all log-likelihoods =     -33.08.  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                        55.11           10            < 0.0001
  Test 2                        5.242            5              0.3871
  Test 3                        5.242            5              0.3871
 Test 7a                       0.4779            2              0.7875


  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 7a is greater than .1.  Model 5 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 =      3257.85

              BMDL =      1709.28
```

H.2.1.6. *Figure for Unrestricted Model: Hill, Constant Variance, n Unrestricted*



H.2.1.7. *Output File for Unrestricted Model: Hill, Constant Variance, n Unrestricted*

```
 ======================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\Hill_CV_Unrest_BMR1_CytC_Liver.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\Hill_CV_Unrest_BMR1_CytC_Liver.plt
                                                 Mon Nov 23 12:51:51 2009
 ======================================================================

 TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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
                          alpha =     0.004972
```

```
                          rho =            0   Specified
                    intercept =        0.146
                            v =        0.298
                            n =           18
                            k =      10285.5


          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    -2.4e-008     4.5e-008    -5.6e-008     2.4e-008

 intercept    -2.4e-008            1        -0.61         0.52        0.098

         v     4.5e-008        -0.61            1        -0.83          0.6

         n    -5.6e-008         0.52        -0.83            1        -0.48

         k     2.4e-008        0.098          0.6        -0.48            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha       0.00421237      0.000992864          0.00226639          0.00615834
      intercept         0.159647        0.0202575            0.119943            0.199351
              v         0.303055        0.0583218            0.188746            0.417363
              n          2.91267           1.3832            0.201656             5.62369
              k          5344.44          923.736             3533.95             7154.93


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   -----------

    0     6      0.146         0.16       0.0661       0.0649         -0.515
 1068     6      0.177        0.162       0.0539       0.0649          0.551
 2542     6      0.191        0.191       0.0563       0.0649        0.00541
 4489     6      0.271        0.273       0.0563       0.0649        -0.0938
 7718     6      0.388        0.385       0.0637       0.0649          0.101
1.396e+004     6      0.444        0.445         0.11       0.0649        -0.0481


 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	80.752584	7	-147.505168
A2	83.373547	12	-142.747094
A3	80.752584	7	-147.505168
fitted	80.455153	5	-150.910305
R	55.820023	2	-107.640047

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	55.107	10	<.0001
Test 2	5.24193	5	0.3871
Test 3	5.24193	5	0.3871
Test 4	0.594862	2	0.7427

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

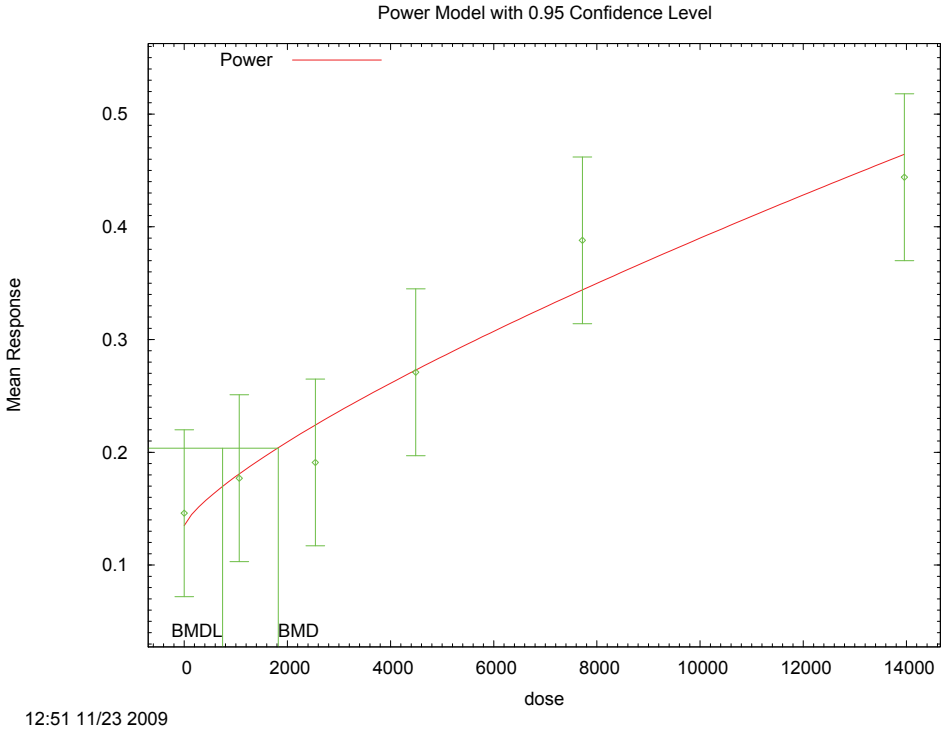
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 3420.29

BMDL = 1757.33

H.2.1.8. *Figure for Unrestricted Model: Power, Constant Variance, Power Unrestricted*



H.2.1.9. *Output File for Unrestricted Model: Power, Constant Variance, Power Unrestricted*

```
 ========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\Pwr_CV_Unrest_BMR1_CytC_Liver.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\Pwr_CV_Unrest_BMR1_CytC_Liver.plt
                                                 Mon Nov 23 12:51:51 2009
 ========================================================================

 TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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
                          alpha =     0.004972
```

```
                          rho =            0   Specified
                      control =        0.146
                        slope = 2.56594e-005
                        power =     0.980719


          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     4.5e-009    -1.5e-009     1.3e-009

   control     4.5e-009            1        -0.71         0.68

     slope    -1.5e-009        -0.71            1           -1

     power     1.3e-009         0.68           -1            1


                                Parameter Estimates

                                                                  95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha       0.00474021       0.00111728          0.00255039          0.00693004
        control          0.13485        0.0248098           0.0862235            0.183476
          slope      0.000217707      0.000332694        -0.000434363         0.000869776
          power         0.766684         0.157896            0.457213             1.07615


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     6      0.146        0.135       0.0661       0.0688          0.397
 1068     6      0.177        0.181       0.0539       0.0688         -0.126
 2542     6      0.191        0.224       0.0563       0.0688          -1.16
 4489     6      0.271        0.272       0.0563       0.0688        -0.0436
 7718     6      0.388        0.343       0.0637       0.0688           1.6
1.396e+004     6      0.444        0.463         0.11       0.0688         -0.666


 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           80.752584            7    -147.505168
              A2           83.373547           12    -142.747094
              A3           80.752584            7    -147.505168
          fitted           78.330124            4    -148.660249
               R           55.820023            2    -107.640047


                    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               55.107         10          <.0001
   Test 2              5.24193          5          0.3871
   Test 3              5.24193          5          0.3871
   Test 4              4.84492          3          0.1835

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 = 1823.19


            BMDL = 743.833
```

H.2.2. Hassoun et al. (2000): DNA SSB

H.2.2.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	4	0.75	39.08	<0.0001	112.91	4.1E+03	2.5E+03	nonconstant variance, power restricted ≥1
exponential (M3)	4	0.75	39.08	<0.0001	112.91	4.1E+03	2.5E+03	nonconstant variance, power restricted ≥1
exponential (M4)	3	0.75	4.29	0.23	80.12	5.6E+02	3.6E+02	nonconstant variance, power restricted ≥1
exponential (M5)	3	0.75	4.29	0.23	80.12	5.6E+02	3.6E+02	nonconstant variance, power restricted ≥1
exponential (M5)	3	0.75	4.29	0.23	80.12	5.6E+02	3.6E+02	nonconstant variance, power unrestricted
Hill	3	0.75	4.16	0.25	79.99	5.0E+02	3.9E+02	nonconstant variance, n restricted >1, bound hit
Hill	2	0.75	3.82	0.15	81.65	3.7E+02	1.3E+02	nonconstant variance, n unrestricted
linear	4	0.75	25.42	<.0001	99.26	1.6E+03	9.6E+02	nonconstant variance
polynomial	4	0.75	25.42	<.0001	99.26	1.6E+03	9.6E+02	nonconstant variance
power	4	0.75	25.42	<.0001	99.26	1.6E+03	9.6E+02	nonconstant variance, power restricted ≥1, bound hit
power	3	0.75	5.14	0.16	80.98	1.9E+02	7.4E+01	nonconstant variance, power unrestricted
exponential (M2)	4	0.75	38.85	<0.0001	111.13	3.6E+03	3.0E+03	constant variance, power restricted ≥1
exponential (M3)	4	0.75	38.85	<0.0001	111.13	3.6E+03	3.0E+03	constant variance, power restricted ≥1
exponential (M4) [c]	**3**	**0.75**	**4.30**	**0.23**	**78.59**	**6.6E+02**	**5.0E+02**	**constant variance, power restricted ≥1**
exponential (M5)	3	0.75	4.30	0.23	78.59	6.6E+02	5.0E+02	constant variance, power restricted ≥1
exponential (M5) [d]	3	0.75	4.30	0.23	78.59	6.6E+02	5.0E+02	constant variance, power unrestricted
Hill	3	0.75	4.31	0.23	78.59	6.0E+02	4.4E+02	constant variance, n restricted >1, bound hit
Hill [d]	2	0.75	4.09	0.13	80.38	4.8E+02	1.5E+02	constant variance, n unrestricted
linear	4	0.75	25.33	<.0001	97.62	2.0E+03	1.6E+03	constant variance
polynomial	4	0.75	25.33	<.0001	97.62	2.0E+03	1.6E+03	constant variance
power	4	0.75	25.33	<.0001	97.62	2.0E+03	1.6E+03	constant variance, power restricted ≥1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
power [d]	3	0.75	5.61	0.13	79.89	2.5E+02	1.1E+02	constant variance, power unrestricted

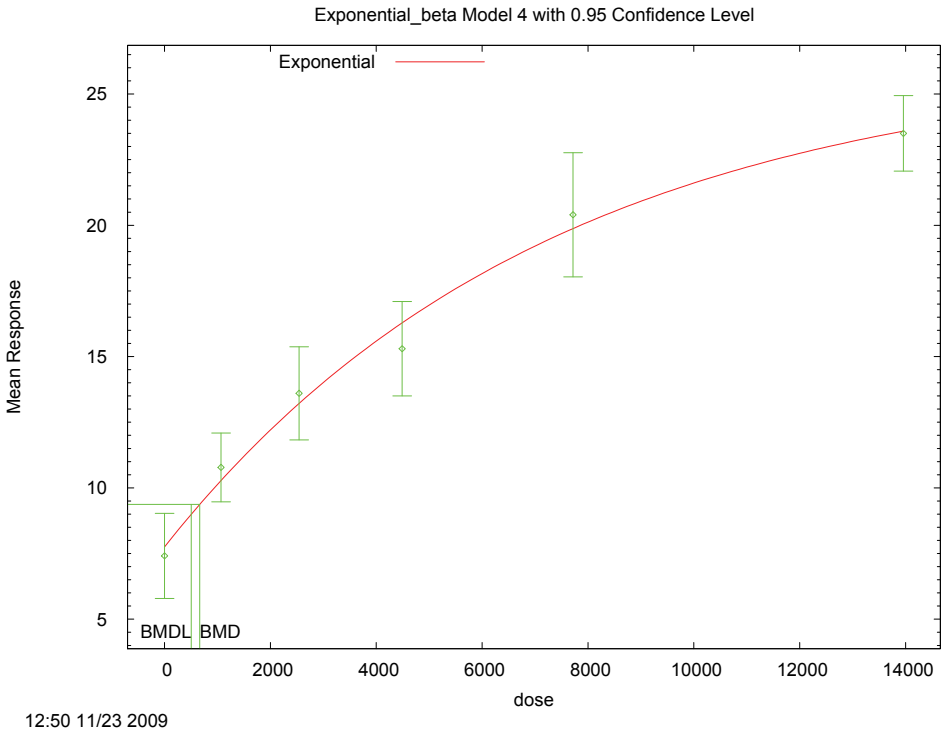
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.2.2.2. *Figure for Selected Model: Exponential (M4), Constant Variance, Power Restricted ≥1*



H.2.2.3. *Output File For Selected Model: Exponential (M4), Constant Variance, Power Restricted ≥1*

```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\Exp_CV_BMR1_DNA_SSB.(d)
         Gnuplot Plotting File:
                                                 Mon Nov 23 12:50:08 2009
 ========================================================================

 DNA single-strand breaks, liver only (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 = 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            0.841244
                    rho(S)                0
                      a              7.0395
                      b          0.000187891
                      c              3.50522
                      d                     1

  (S) = Specified


                Parameter Estimates

               Variable          Model 4
               --------          -------
                lnalpha          0.960792
                    rho                 0
                      a           7.75279
                      b       0.000136903
                      c           3.39666
                      d                  1


       Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      6         7.41        1.543
   1068      6        10.78        1.249
   2542      6         13.6         1.69
   4489      6         15.3        1.715
   7718      6         20.4        2.254
  1.396e+004      6         23.5        1.372


              Estimated Values of Interest
```

Dose	Est Mean	Est Std	Scaled Residual
0	7.753	1.617	-0.5194
1068	10.28	1.617	0.7575
2542	13.21	1.617	0.5853
4489	16.28	1.617	-1.49
7718	19.87	1.617	0.7958
1.396e+004	23.59	1.617	-0.1293

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	-33.14239	7	80.28478
A2	-31.81197	12	87.62394
A3	-33.14239	7	80.28478
R	-80.44209	2	164.8842
4	-35.29426	4	78.58852

Additive constant for all log-likelihoods = -33.08. 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	97.26	10	< 0.0001
Test 2	2.661	5	0.7521
Test 3	2.661	5	0.7521
Test 6a	4.304	3	0.2305

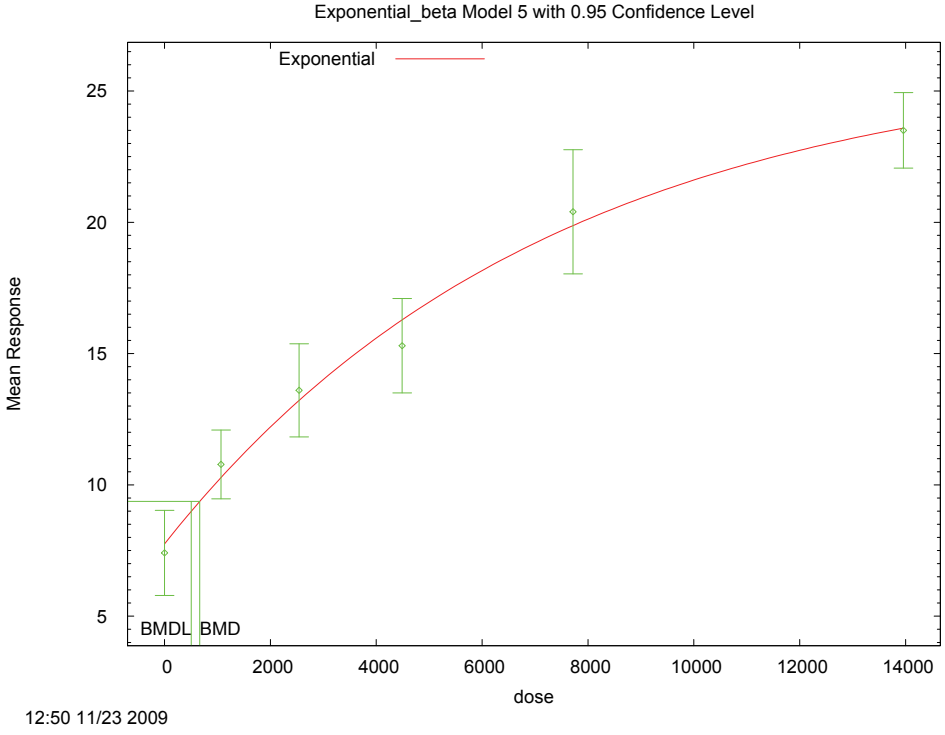
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

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 =      664.925

               BMDL =      504.974
```

H.2.2.4. *Figure for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*



H.2.2.5. *Output File for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*

```
=============================================================================
        Exponential Model. (Version: 1.5;  Date: 4/23/2009)
        Input Data File: C:\USEPA\BMDS21\Nov23\Blood\Exp_CV_Unrest_BMR1_DNA_SSB.(d)
        Gnuplot Plotting File:
                                                  Mon Nov 23 12:50:16 2009
=============================================================================
```

DNA single-strand breaks, liver only (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 = 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 5
lnalpha	0.841244
rho(S)	0
a	7.0395
b	0.000187891
c	3.50522
d	1

(S) = Specified

Parameter Estimates

Variable	Model 5
lnalpha	0.960792
rho	0
a	7.75279
b	0.000136903
c	3.39666
d	1

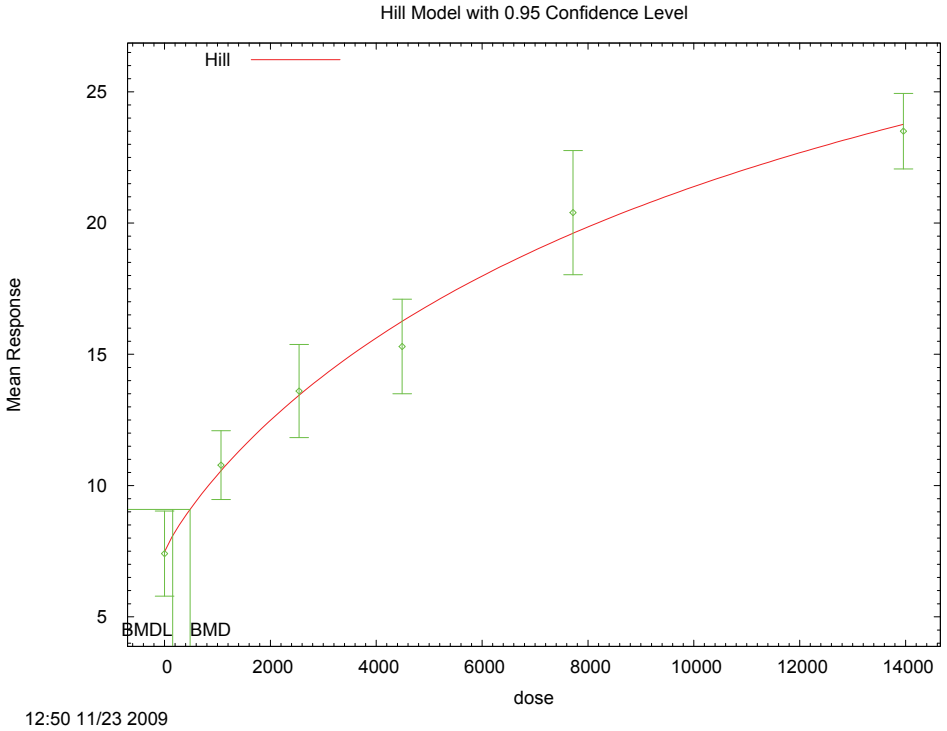
Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	6	7.41	1.543
1068	6	10.78	1.249
2542	6	13.6	1.69
4489	6	15.3	1.715
7718	6	20.4	2.254
~~~~~~

```
      1.396e+004      6         23.5        1.372


                  Estimated Values of Interest

       Dose      Est Mean      Est Std     Scaled Residual
     ------    ----------    ---------    ----------------
          0         7.753        1.617           -0.5194
       1068         10.28        1.617            0.7575
       2542         13.21        1.617            0.5853
       4489         16.28        1.617             -1.49
       7718         19.87        1.617            0.7958
1.396e+004         23.59        1.617           -0.1293


   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       -33.14239           7      80.28478
                       A2       -31.81197          12      87.62394
                       A3       -33.14239           7      80.28478
                        R       -80.44209           2      164.8842
                        5       -35.29426           4      78.58852


   Additive constant for all log-likelihoods =     -33.08.  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                      97.26            10           < 0.0001
     Test 2                      2.661             5             0.7521
     Test 3                      2.661             5             0.7521
    Test 7a                      4.304             3             0.2305


     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 7a is greater than .1.  Model 5 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 =      664.925

               BMDL =      504.974
```

H.2.2.6. *Figure for Unrestricted Model: Hill, Constant Variance, n Unrestricted*



H.2.2.7. *Output File For Unrestricted Model: Hill, Constant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\Hill_CV_Unrest_BMR1_DNA_SSB.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\Hill_CV_Unrest_BMR1_DNA_SSB.plt
                                              Mon Nov 23 12:50:18 2009
 ================================================================
```

DNA single-strand breaks, liver only (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 is not restricted
A constant variance model is fit

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

alpha =	2.7831	
rho =	0	Specified
intercept =	7.41	
v =	16.09	
n =	0.235041	
k =	10849.8	

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	-2.8e-008	7.4e-008	-6.3e-008	7.2e-008
intercept	-2.8e-008	1	-0.34	0.47	-0.28
v	7.4e-008	-0.34	1	-0.95	1
n	-6.3e-008	0.47	-0.95	1	-0.95
k	7.2e-008	-0.28	1	-0.95	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	2.59837	0.612441	1.398	3.79873
intercept	7.4823	0.666037	6.17689	8.78771
v	32.65	17.9338	-2.49963	67.7997
n	0.876148	0.260495	0.365588	1.38671
k	14136.3	16730.5	-18654.9	46927.4

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	7.41	7.48	1.54	1.61	-0.11

1068	6	10.8	10.6	1.25	1.61	0.336
2542	6	13.6	13.4	1.69	1.61	0.27
4489	6	15.3	16.2	1.71	1.61	-1.41
7718	6	20.4	19.6	2.25	1.61	1.25
1.396e+004	6	23.5	23.7	1.37	1.61	-0.331

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	-33.142389	7	80.284779
A2	-31.811970	12	87.623940
A3	-33.142389	7	80.284779
fitted	-35.187895	5	80.375790
R	-80.442086	2	164.884172

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	97.2602	10	<.0001
Test 2	2.66084	5	0.7521
Test 3	2.66084	5	0.7521
Test 4	4.09101	2	0.1293

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

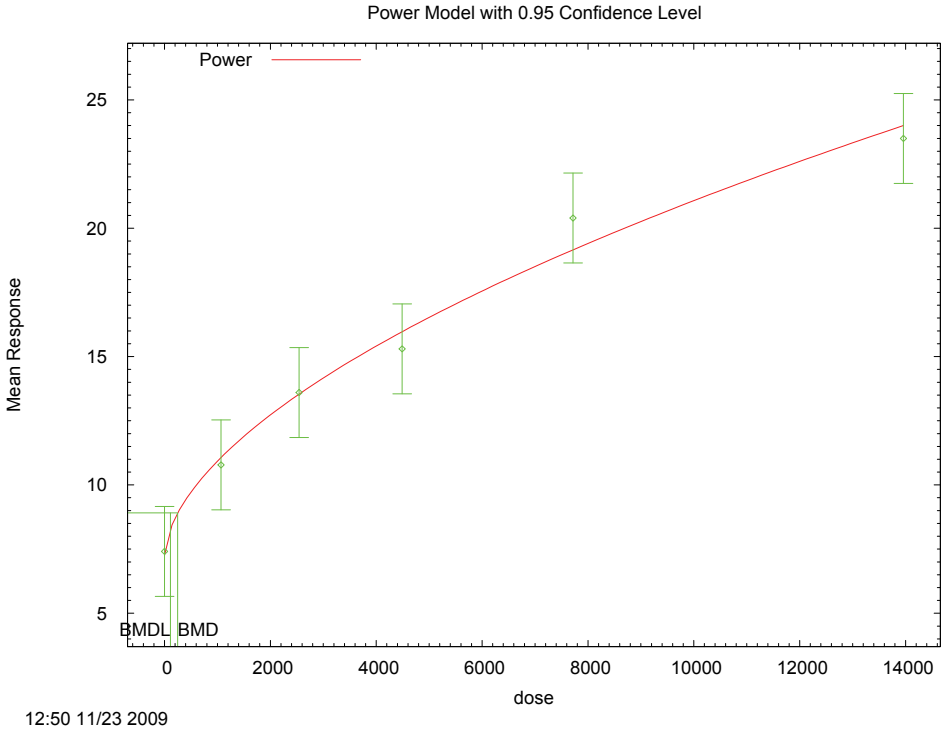
The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

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 =        483.289

            BMDL =       153.678
```

H.2.2.8. *Figure for Unrestricted Model: Power, Constant Variance, Power Unrestricted*



H.2.2.9. *Output File for Unrestricted Model: Power, Constant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\Pwr_CV_Unrest_BMR1_DNA_SSB.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\Pwr_CV_Unrest_BMR1_DNA_SSB.plt
                                          Mon Nov 23 12:50:18 2009
 ================================================================

 DNA single-strand breaks, liver only (Table 3)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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
                        alpha =       2.7831
                          rho =            0   Specified
                      control =         7.41
                        slope =    0.0433022
                        power =     0.620052


          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     2.5e-009    -5.4e-009     5.7e-009

  control     2.5e-009            1        -0.71         0.66

    slope    -5.4e-009        -0.71            1           -1

    power     5.7e-009         0.66           -1            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         alpha          2.71023         0.638807             1.45819             3.96226
       control          7.26415          0.64416             6.00162             8.52668
         slope        0.0685886        0.0392449            -0.00833            0.145507
         power         0.575949        0.0589672            0.460375            0.691523


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     6       7.41         7.26         1.54         1.65          0.217
 1068     6       10.8         11.1         1.25         1.65         -0.433
 2542     6       13.6         13.5         1.69         1.65          0.094
 4489     6       15.3           16         1.71         1.65         -0.993
 7718     6       20.4         19.2         2.25         1.65           1.85
1.396e+004     6       23.5           24         1.37         1.65         -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          -33.142389            7      80.284779
              A2          -31.811970           12      87.623940
              A3          -33.142389            7      80.284779
           fitted         -35.946581            4      79.893162
               R          -80.442086            2     164.884172


                    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              97.2602         10          <.0001
   Test 2              2.66084          5          0.7521
   Test 3              2.66084          5          0.7521
   Test 4              5.60838          3          0.1323

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 = 249.162


             BMDL = 111.676
```

H.2.3. Hassoun et al. (2000): TBARs Liver

H.2.3.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	4	0.33	17.56	0.00	-7.04	7.4E+03	3.9E+03	nonconstant variance, power restricted ≥1
exponential (M3)	4	0.33	17.56	0.00	-7.04	7.4E+03	3.9E+03	nonconstant variance, power restricted ≥1
exponential (M4)	3	0.33	4.35	0.23	-18.26	1.0E+03	5.1E+02	nonconstant variance, power restricted ≥1
exponential (M5)	2	0.33	2.78	0.25	-17.82	1.6E+03	6.5E+02	nonconstant variance, power restricted ≥1
exponential (M5)	2	0.33	2.78	0.25	-17.82	1.6E+03	6.5E+02	nonconstant variance, power unrestricted
Hill	2	0.33	2.52	0.28	-18.09	1.7E+03	8.1E+02	nonconstant variance, n restricted >1
Hill	2	0.33	2.52	0.28	-18.09	1.7E+03	8.1E+02	nonconstant variance, n unrestricted
linear	4	0.33	15.72	0.00	-8.88	5.1E+03	2.4E+03	nonconstant variance
polynomial	4	0.33	15.72	0.00	-8.88	5.1E+03	2.4E+03	nonconstant variance
power	4	0.33	15.72	0.00	-8.88	5.1E+03	2.4E+03	nonconstant variance, power restricted ≥1, bound hit
power	3	0.33	8.40	0.04	-14.21	5.3E+02	8.3E+00	nonconstant variance, power unrestricted
exponential (M2)	4	0.33	18.02	0.00	-8.52	9.6E+03	6.7E+03	constant variance, power restricted ≥1
exponential (M3)	4	0.33	18.02	0.00	-8.52	9.6E+03	6.7E+03	constant variance, power restricted ≥1
exponential (M4)	3	0.33	4.79	0.19	-19.75	1.2E+03	6.3E+02	constant variance, power restricted ≥1
exponential (M5)	2	0.33	2.86	0.24	-19.68	1.9E+03	8.4E+02	constant variance, power restricted ≥1
exponential (M5) [d]	2	0.33	2.86	0.24	-19.68	1.9E+03	8.4E+02	constant variance, power unrestricted
Hill [c]	**2**	**0.33**	**2.60**	**0.27**	**-19.93**	**1.8E+03**	**9.6E+02**	**constant variance, n restricted >1**
Hill [d]	2	0.33	2.60	0.27	-19.93	1.8E+03	9.6E+02	constant variance, n unrestricted
linear	4	0.33	16.75	0.00	-9.79	8.0E+03	5.3E+03	constant variance
polynomial	4	0.33	16.75	0.00	-9.79	8.0E+03	5.3E+03	constant variance
power	4	0.33	16.75	0.00	-9.79	8.0E+03	5.3E+03	constant variance, power restricted ≥1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
power [d]	3	0.33	9.75	0.02	-14.79	1.0E+03	5.7E+01	constant variance, power unrestricted

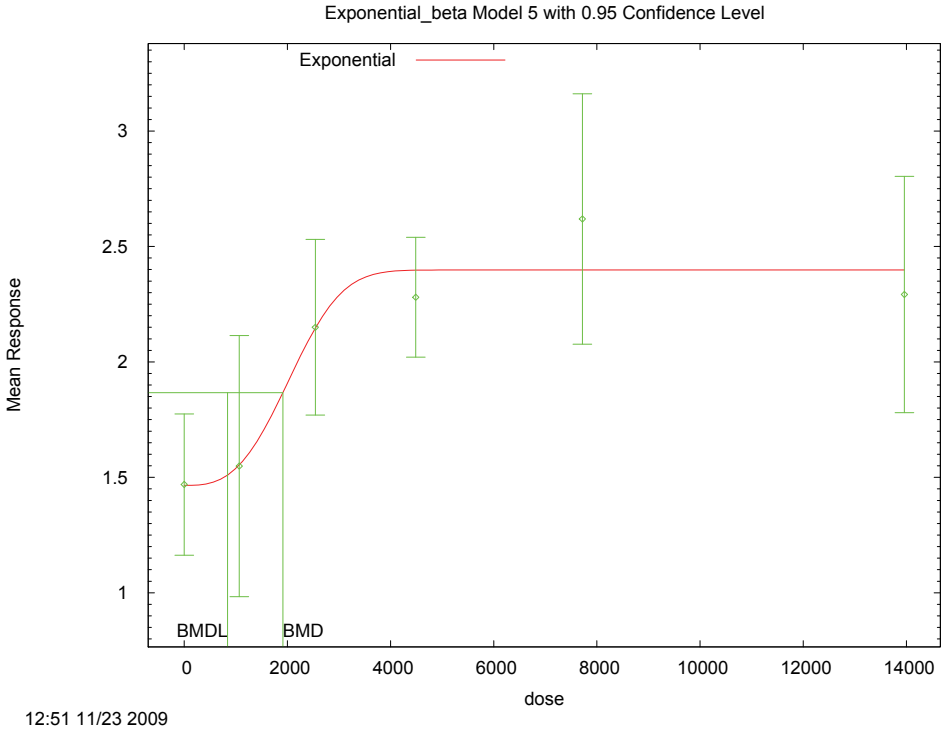
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.2.3.2. *Figure for Selected Model: Exponential (M5), Constant Variance, Power Unrestricted*



H.2.3.3. *Output File for Selected Model: Exponential (M5), Constant Variance, Power Unrestricted*

```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\Exp_CV_Unrest_BMR1_TBARs_Liver.(d)
         Gnuplot Plotting File:
                                                Mon Nov 23 12:51:02 2009
 ========================================================================

 TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 5
              --------          --------
                lnalpha            -1.90388
                    rho(S)                0
                      a             1.39555
                      b          0.000142164
                      c             1.97051
                      d                   1

  (S) = Specified



                Parameter Estimates

               Variable          Model 5
               --------          -------
                lnalpha          -1.82448
                    rho                0
                      a           1.46526
                      b       0.000431089
                      c           1.63651
                      d           2.96871


       Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      6        1.469       0.2915
   1068      6        1.549       0.5389
   2542      6         2.15       0.3625
   4489      6         2.28       0.2474
   7718      6        2.619       0.5168
  1.396e+004      6        2.292       0.4874


              Estimated Values of Interest
```

Dose	Est Mean	Est Std	Scaled Residual
0	1.465	0.4016	0.0228
1068	1.554	0.4016	-0.03039
2542	2.147	0.4016	0.01965
4489	2.397	0.4016	-0.7145
7718	2.398	0.4016	1.348
1.396e+004	2.398	0.4016	-0.646

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	16.26977	7	-18.53954
A2	19.12783	12	-14.25565
A3	16.26977	7	-18.53954
R	2.44294	2	-0.8858799
5	14.84065	5	-19.6813

Additive constant for all log-likelihoods = -33.08. 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	33.37	10	0.000236
Test 2	5.716	5	0.3348
Test 3	5.716	5	0.3348
Test 7a	2.858	2	0.2395

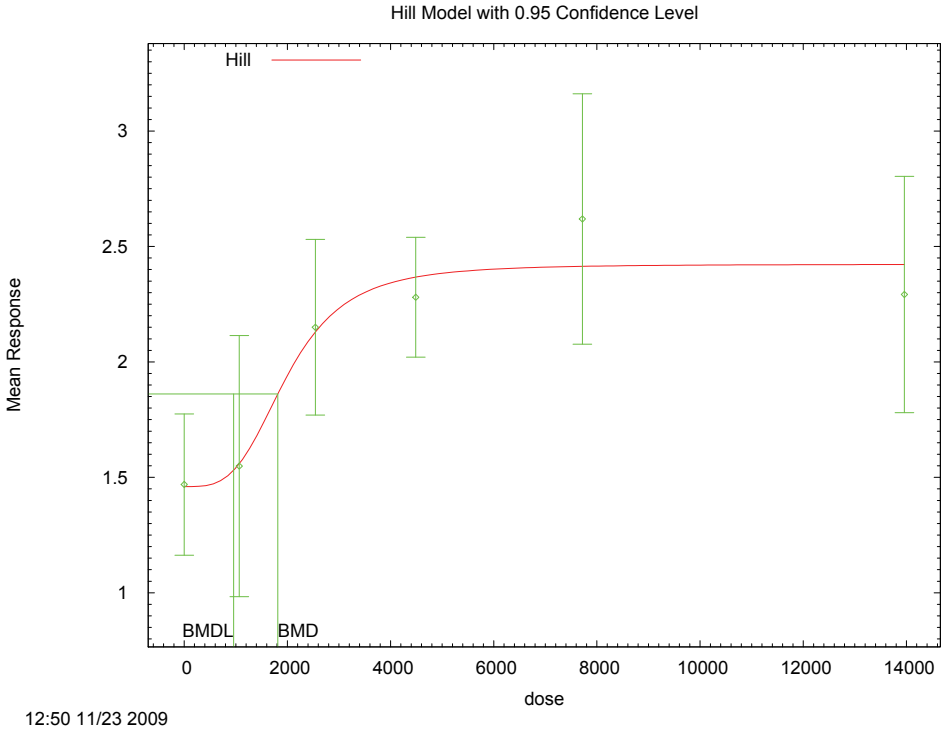
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

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 7a is greater than .1.  Model 5 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 =      1911.82

                BMDL =      840.487
```

H.2.3.4. *Figure for Unrestricted Model: Hill, Constant Variance, n Restricted >1*



H.2.3.5. *Output File for Unrestricted Model: Hill, Constant Variance, n Restricted >1*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\Hill_CV_BMR1_TBARs_Liver.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\Hill_CV_BMR1_TBARs_Liver.plt
                                          Mon Nov 23 12:50:58 2009
 ================================================================

 TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
```

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 = 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

alpha =	0.178788	
rho =	0	Specified
intercept =	1.469	
v =	1.15	
n =	1.27851	
k =	2801.9	

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	1.1e-007	-1.4e-007	1.2e-007	-7.6e-009
intercept	1.1e-007	1	-0.82	0.48	0.52
v	-1.4e-007	-0.82	1	-0.61	-0.22
n	1.2e-007	0.48	-0.61	1	0.29
k	-7.6e-009	0.52	-0.22	0.29	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.16017	0.0377524	0.0861764	0.234163
intercept	1.46138	0.152797	1.1619	1.76086
v	0.963032	0.20228	0.56657	1.35949
n	3.44649	2.43475	-1.32553	8.21851
k	2002.3	562.074	900.655	3103.95

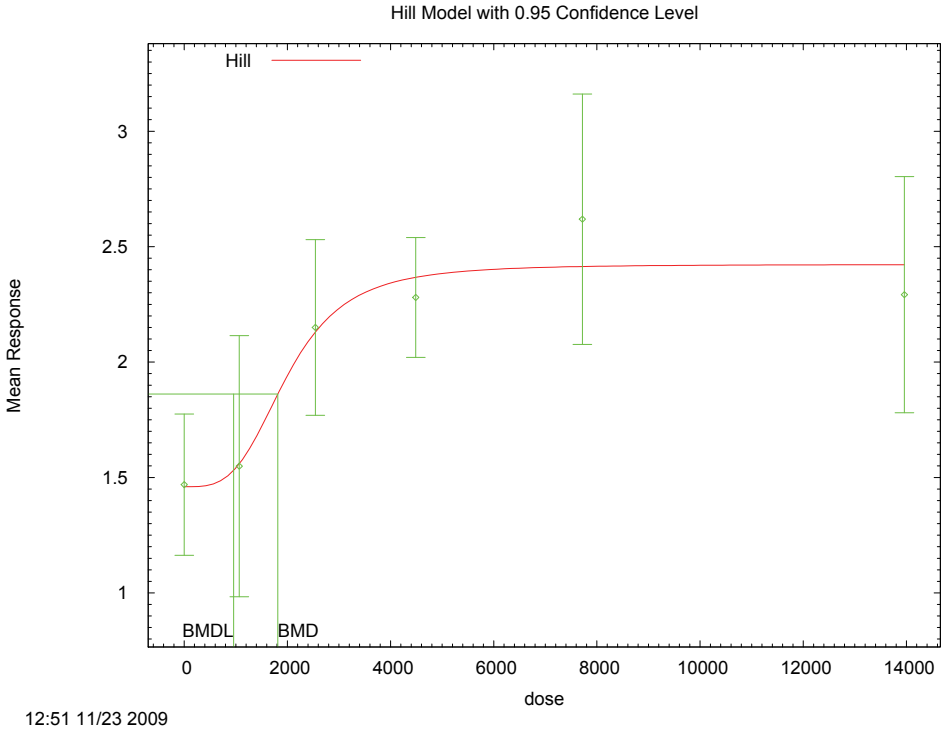
Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	1.47	1.46	0.291	0.4	0.0466
1068	6	1.55	1.56	0.539	0.4	-0.0697
2542	6	2.15	2.13	0.363	0.4	0.12
4489	6	2.28	2.37	0.247	0.4	-0.54
7718	6	2.62	2.42	0.517	0.4	1.25

```
1.396e+004     6       2.29         2.42        0.487          0.4         -0.803


 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           16.269770           7     -18.539539
             A2           19.127827          12     -14.255654
             A3           16.269770           7     -18.539539
          fitted          14.967385           5     -19.934770
              R            2.442940           2      -0.885880


                   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              33.3698         10        0.000236
   Test 2              5.71611          5          0.3348
   Test 3              5.71611          5          0.3348
   Test 4              2.60477          2          0.2719

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 =        1813.69

            BMDL =       957.252
```

H.2.3.6. *Figure for Unrestricted Model: Hill, Constant Variance, n Unrestricted*



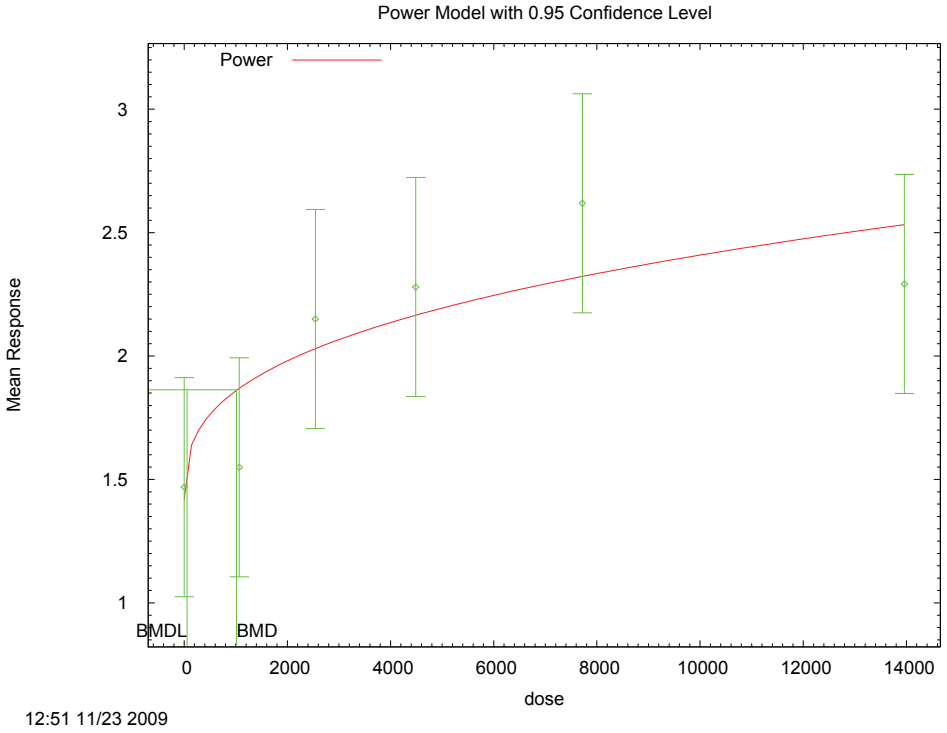
H.2.3.7. *Output File for Unrestricted Model: Hill, Constant Variance, n Unrestricted*

```
 ========================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\Hill_CV_Unrest_BMR1_TBARs_Liver.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\Hill_CV_Unrest_BMR1_TBARs_Liver.plt
                                                Mon Nov 23 12:51:04 2009
 ========================================================================

 TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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
                         alpha =     0.178788
                           rho =            0   Specified
                     intercept =        1.469
                             v =         1.15
                             n =      1.27851
                             k =       2801.9


          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     1.1e-007    -1.4e-007     1.2e-007    -7.6e-009

 intercept     1.1e-007            1        -0.82         0.48         0.52

         v    -1.4e-007        -0.82            1        -0.61        -0.22

         n     1.2e-007         0.48        -0.61            1         0.29

         k    -7.6e-009         0.52        -0.22         0.29            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha          0.16017        0.0377524           0.0861764            0.234163
      intercept          1.46138         0.152797              1.1619             1.76086
              v         0.963032          0.20228            0.56657             1.35949
              n          3.44649          2.43475           -1.32553             8.21851
              k           2002.3          562.074             900.655             3103.95


      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     6       1.47         1.46        0.291          0.4         0.0466
 1068     6       1.55         1.56        0.539          0.4        -0.0697
 2542     6       2.15         2.13        0.363          0.4           0.12
 4489     6       2.28         2.37        0.247          0.4          -0.54
 7718     6       2.62         2.42        0.517          0.4           1.25
1.396e+004     6       2.29         2.42        0.487          0.4         -0.803


 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           16.269770            7     -18.539539
              A2           19.127827           12     -14.255654
              A3           16.269770            7     -18.539539
           fitted          14.967385            5     -19.934770
               R           2.442940             2      -0.885880


                    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              33.3698         10        0.000236
   Test 2              5.71611          5          0.3348
   Test 3              5.71611          5          0.3348
   Test 4              2.60477          2          0.2719

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 =        1813.69

            BMDL =       957.252
```

H.2.3.8. *Figure for Unrestricted Model: Power, Constant Variance, Power Unrestricted*



H.2.3.9. *Output File for Unrestricted Model: Power, Constant Variance, Power Unrestricted*

```
 ========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Blood\Pwr_CV_Unrest_BMR1_TBARs_Liver.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Blood\Pwr_CV_Unrest_BMR1_TBARs_Liver.plt
                                                 Mon Nov 23 12:51:05 2009
 ========================================================================

 TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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
                          alpha =     0.178788
```

```
                          rho =            0   Specified
                      control =        1.469
                        slope =  0.000328724
                        power =     0.885141


          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     3.9e-011    -2.9e-010     3.6e-010

   control     3.9e-011            1        -0.59         0.47

     slope    -2.9e-010        -0.59            1        -0.99

     power     3.6e-010         0.47        -0.99            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha         0.195332        0.0460403            0.105095             0.28557
        control          1.42145          0.17171              1.0849             1.75799
          slope        0.0382805        0.0492936         -0.0583331            0.134894
          power         0.353387         0.132966           0.0927779            0.613996


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     6       1.47         1.42        0.291        0.442          0.264
 1068     6       1.55         1.87        0.539        0.442          -1.79
 2542     6       2.15         2.03        0.363        0.442          0.649
 4489     6       2.28         2.17        0.247        0.442          0.616
 7718     6       2.62         2.33        0.517        0.442           1.62
1.396e+004     6       2.29         2.54        0.487        0.442          -1.36


 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           16.269770            7     -18.539539
              A2           19.127827           12     -14.255654
              A3           16.269770            7     -18.539539
          fitted           11.394946            4     -14.789892
               R            2.442940            2      -0.885880


                    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              33.3698         10        0.000236
   Test 2              5.71611          5          0.3348
   Test 3              5.71611          5          0.3348
   Test 4              9.74965          3         0.02082

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 = 1014.75


            BMDL = 56.7719
```

H.2.4. Kitchin et al. (1979): BaP Hydrolase Activity

H.2.4.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	9	<0.0001	247.10	<0.0001	452.74	9.3E+05	4.3E+05	nonconstant variance, power restricted ≥1
exponential (M3)	9	<0.0001	247.10	<0.0001	452.74	9.3E+05	4.3E+05	nonconstant variance, power restricted ≥1
exponential (M4)	8	<0.0001	18.95	0.02	226.59	6.3E+02	4.8E+02	nonconstant variance, power restricted ≥1
exponential (M5) [c]	**7**	**<0.0001**	**16.76**	**0.02**	**226.41**	**1.2E+03**	**5.6E+02**	**nonconstant variance, power restricted ≥1**
exponential (M5) [d]	7	<0.0001	16.76	0.02	226.41	1.2E+03	5.6E+02	nonconstant variance, power unrestricted
Hill	7	<.0001	296.88	<.0001	506.53	error	error	nonconstant variance, n restricted >1
Hill [d]	7	<.0001	296.88	<.0001	506.53	error	error	nonconstant variance, n unrestricted
linear	9	<.0001	94.23	<.0001	299.87	9.6E+02	6.9E+02	nonconstant variance
polynomial	9	<.0001	-197.64	<.0001	8.00	error	error	nonconstant variance
power	9	<.0001	94.23	<.0001	299.87	9.6E+02	6.9E+02	nonconstant variance, power restricted ≥1, bound hit
power [d]	8	<.0001	63.63	<.0001	271.27	1.0E+02	4.4E+01	nonconstant variance, power unrestricted
exponential (M2)	9	<0.0001	129.40	<0.0001	451.64	1.3E+06	1.1E+06	constant variance, power restricted ≥1
exponential (M3)	9	<0.0001	129.40	<0.0001	451.64	1.3E+06	1.1E+06	constant variance, power restricted ≥1
exponential (M4)	8	<0.0001	6.96	0.54	331.23	9.5E+03	7.3E+03	constant variance, power restricted ≥1
exponential (M5)	8	<0.0001	6.96	0.54	331.23	9.5E+03	7.3E+03	constant variance, power restricted ≥1
exponential (M5)	8	<0.0001	6.96	0.54	331.23	9.5E+03	7.3E+03	constant variance, power unrestricted
Hill	7	<.0001	35.69	<.0001	361.95	6.3E+04	2.6E+03	constant variance, n restricted >1
Hill	7	<.0001	35.69	<.0001	361.95	6.3E+04	3.0E+02	constant variance, n unrestricted
linear	9	<.0001	120.38	<.0001	442.64	6.6E+05	5.1E+05	constant variance
polynomial	9	<.0001	120.38	<.0001	442.64	6.6E+05	5.1E+05	constant variance
power	9	<.0001	120.38	<.0001	442.64	6.6E+05	5.1E+05	constant variance, power restricted ≥1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
power	8	<.0001	51.09	<.0001	375.35	4.1E+02	8.6E+01	constant variance, power unrestricted

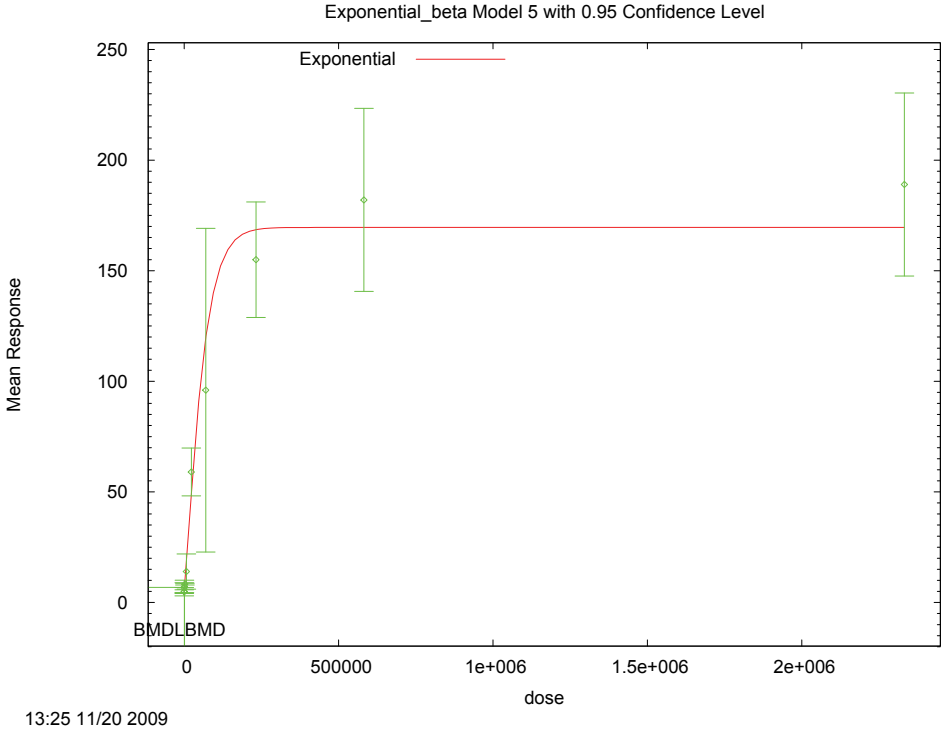
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.2.4.2. *Figure for Selected Model: Exponential (M5), Nonconstant Variance, Power Restricted ≥1*



H.2.4.3. *Output File for Selected Model: Exponential (M5), Nonconstant Variance, Power Restricted ≥1*

```
 ======================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_BMR1_BaP_hydro_act.(d)
         Gnuplot Plotting File:
                                                  Fri Nov 20 13:25:02 2009
 ======================================================================

 Kitchin 1979, Tbl3, BaP hydrolase activity
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 11
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 5
               --------          --------
                 lnalpha            -3.27793
                     rho             1.92227
                       a               4.655
                       b         1.52141e-006
                       c              42.6316
                       d                    1


                  Parameter Estimates

                Variable          Model 5
                --------          -------
                 lnalpha          -2.64351
                     rho           1.93772
                       a           5.43367
                       b      1.65224e-005
                       c            31.204
                       d           1.21424


        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
     0      9          4.9         1.11
  69.5      4          4.9         1.18
   232      4          6.7          1.4
   463      4          7.2          1.8
  2318      4          8.3         0.26
  6949      4           14            5
2.319e+004      4           59          6.8
6.966e+004      4           96           46
2.326e+005      4          155         16.4
5.819e+005      4          182           26
2.332e+006      4          189           26
```

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	5.434	1.375	-1.165
69.5	5.478	1.385	-0.8342
232	5.625	1.421	1.513
463	5.875	1.483	1.787
2318	8.529	2.127	-0.2151
6949	16.87	4.119	-1.392
2.319e+004	49.41	11.67	1.644
6.966e+004	119.4	27.44	-1.708
2.326e+005	168.6	38.32	-0.7087
5.819e+005	169.6	38.53	0.6461
2.332e+006	169.6	38.53	1.009

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	-158.1306	12	340.2613
A2	-84.80028	22	213.6006
A3	-98.82189	13	223.6438
R	-234.6252	2	473.2504
5	-107.2031	6	226.4062

Additive constant for all log-likelihoods = -45.03. 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)

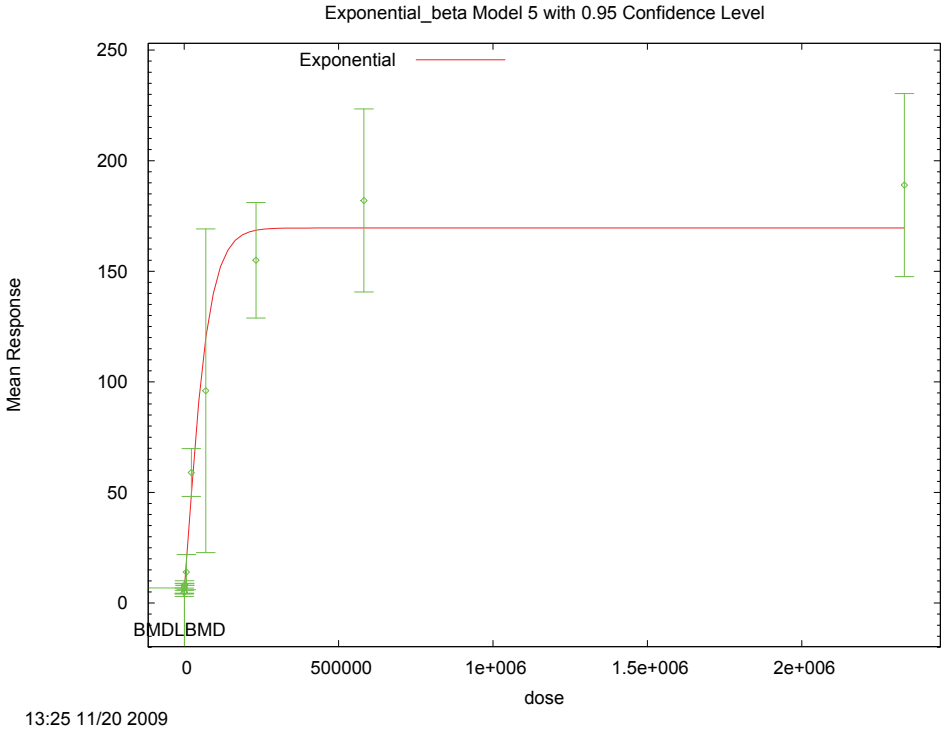
Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	299.6	20	< 0.0001
Test 2	146.7	10	< 0.0001
Test 3	28.04	9	0.0009381
Test 7a	16.76	7	0.01899

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 =      1182.79

               BMDL =      556.132
```

H.2.4.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



H.2.4.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
==========================================================================
```

```
          Exponential Model. (Version: 1.5;  Date: 4/23/2009)
          Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_Unrest_BMR1_BaP_hydro_act.(d)
          Gnuplot Plotting File:
                                                    Fri Nov 20 13:25:17 2009
 ========================================================================

 Kitchin 1979, Tbl3, BaP hydrolase activity
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 11
   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 5
                --------          --------
                  lnalpha            -3.27793
                      rho             1.92227
                        a               4.655
                        b         1.52141e-006
                        c             42.6316
                        d                    1



                  Parameter Estimates

                 Variable          Model 5
                 --------          -------
                  lnalpha          -2.64351
                      rho           1.93772
                        a           5.43367
                        b      1.65224e-005
                        c             31.204
                        d           1.21424


          Table of Stats From Input Data

     Dose      N         Obs Mean     Obs Std Dev
     -----    ---       ----------   -------------
        0      9          4.9          1.11
     69.5      4          4.9          1.18
```

```
         232      4          6.7          1.4
         463      4          7.2          1.8
        2318      4          8.3         0.26
        6949      4           14            5
       2.319e+004      4           59          6.8
       6.966e+004      4           96           46
       2.326e+005      4          155         16.4
       5.819e+005      4          182           26
       2.332e+006      4          189           26


                    Estimated Values of Interest

       Dose      Est Mean      Est Std     Scaled Residual
      ------    ----------    ---------    ----------------
          0         5.434        1.375           -1.165
       69.5         5.478        1.385          -0.8342
        232         5.625        1.421            1.513
        463         5.875        1.483            1.787
       2318         8.529        2.127          -0.2151
       6949         16.87        4.119           -1.392
  2.319e+004         49.41        11.67            1.644
  6.966e+004         119.4        27.44           -1.708
  2.326e+005         168.6        38.32          -0.7087
  5.819e+005         169.6        38.53           0.6461
  2.332e+006         169.6        38.53            1.009


   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       -158.1306           12      340.2613
                       A2       -84.80028           22      213.6006
                       A3       -98.82189           13      223.6438
                        R       -234.6252            2      473.2504
                        5       -107.2031            6      226.4062


   Additive constant for all log-likelihoods =     -45.03.  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	299.6	20	< 0.0001
Test 2	146.7	10	< 0.0001
Test 3	28.04	9	0.0009381
Test 7a	16.76	7	0.01899

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

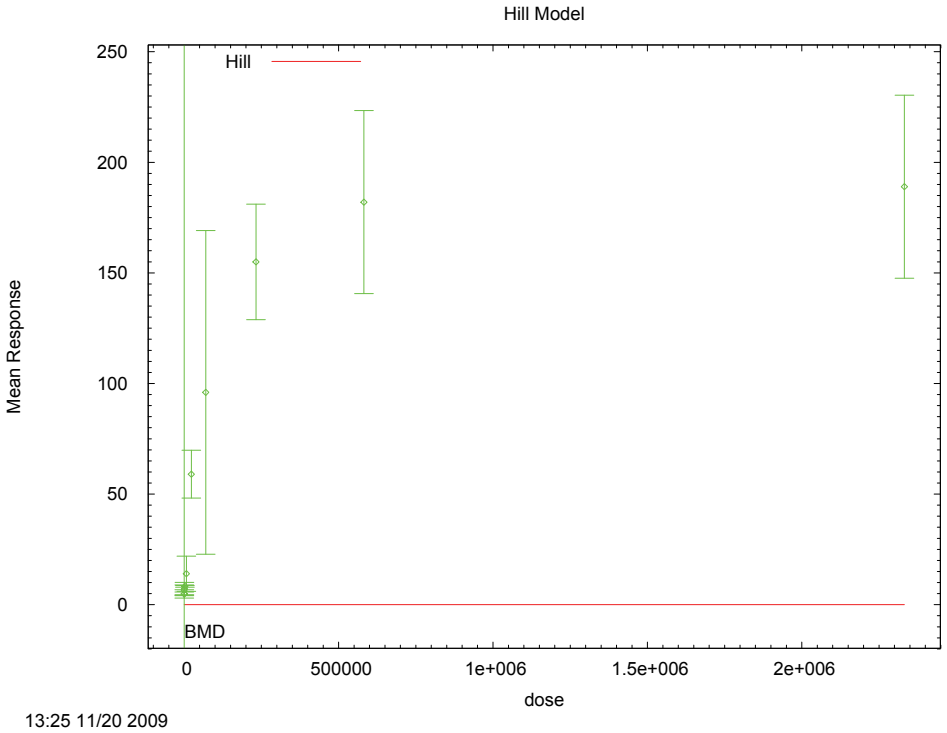
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 1182.79

BMDL = 556.132

H.2.4.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



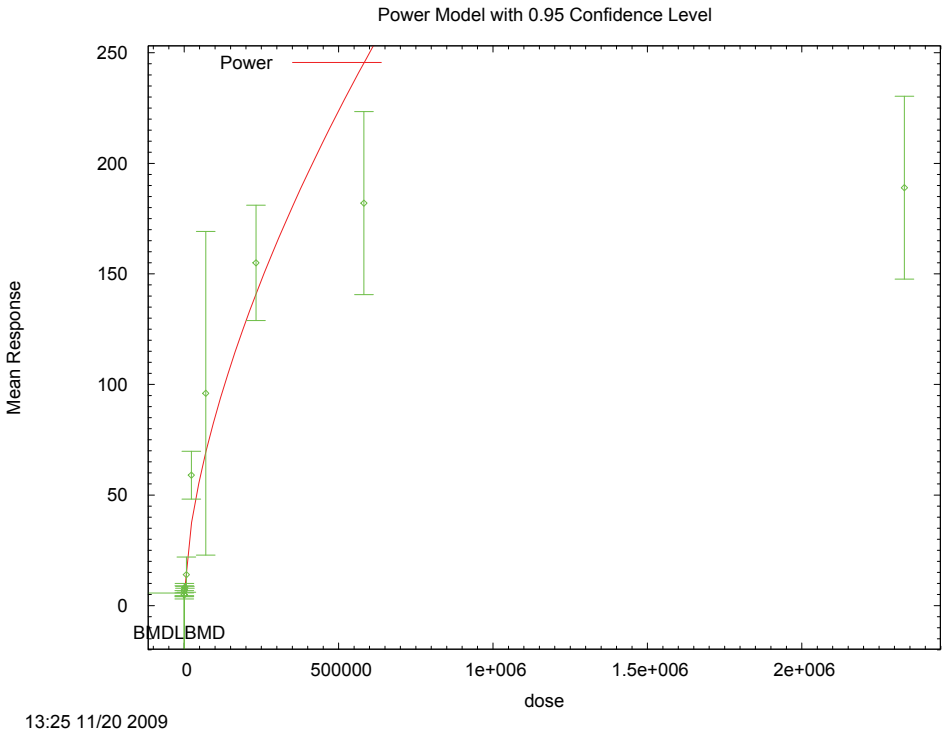
H.2.4.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_BaP_hydro_act.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_BaP_hydro_act.plt
                                              Fri Nov 20 13:25:18 2009
 ================================================================

 Kitchin 1979, Tbl3, BaP hydrolase activity
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 11
   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 =      5.70855
                           rho =            0
                     intercept =          4.9
                             v =        184.1
                             n =           18
                             k =       392820


          Asymptotic Correlation Matrix of Parameter Estimates

                lalpha          rho    intercept            v            n            k

   lalpha       NA             NA             NA             NA             NA             NA

      rho       NA             NA             NA             NA             NA             NA

intercept       NA             NA                  1       NA              0.28          0.1

        v       NA             NA             NA             NA             NA             NA

        n       NA             NA                0.28       NA                  1        -0.98

        k       NA             NA                0.1        NA             -0.98            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        lalpha          10.1833              NA                    NA                   NA
           rho        0.0839751              NA                    NA                   NA
     intercept    -2.28069e-006              NA                    NA                   NA
             v          184.001              NA                    NA                   NA
             n          17.9976              NA                    NA                   NA
             k     1.41183e+007              NA                    NA                   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     9        4.9   -2.28e-006         1.11         94.3          0.156
 69.5     4        4.9   -2.28e-006         1.18         94.3          0.104
  232     4        6.7   -2.28e-006          1.4         94.3          0.142
  463     4        7.2   -2.28e-006          1.8         94.3          0.153
 2318     4        8.3   -2.28e-006         0.26         94.3          0.176
 6949     4         14   -2.28e-006            5         94.3          0.297
2.319e+004     4          59   -2.28e-006          6.8         94.3           1.25
6.966e+004     4          96   -2.28e-006           46         94.3           2.04
2.326e+005     4         155   -2.28e-006         16.4         94.3           3.29
5.819e+005     4         182   -2.28e-006           26         94.3           3.86
2.332e+006     4         189   -2.28e-006           26         94.3           4.01



 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         -158.130647          12     340.261294
              A2          -84.800279          22     213.600558
              A3          -98.821893          13     223.643786
          fitted         -247.263464           6     506.526929
               R         -234.625213           2     473.250426


                    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               299.65         20          <.0001
   Test 2              146.661         10          <.0001
   Test 3              28.0432          9       0.0009381
```

```
   Test 4              296.883          7          <.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 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 =        1.#QNAN


BMDL computation failed.
```

H.2.4.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



H.2.4.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_BaP_hydro_act.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_BaP_hydro_act.plt
                                                Fri Nov 20 13:25:19 2009
 ================================================================

 Kitchin 1979, Tbl3, BaP hydrolase activity
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 11
   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 =      5.70855
                           rho =            0
                       control =          4.9
                         slope =    0.0304965
                         power =     0.593743


          Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho      control        slope        power

  lalpha            1         -0.9        -0.45         0.25        -0.23

     rho         -0.9            1         0.35        -0.18         0.12

 control        -0.45         0.35            1        -0.44         0.42

   slope         0.25        -0.18        -0.44            1        -0.98

   power        -0.23         0.12         0.42        -0.98            1


                              Parameter Estimates

                                                      95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        lalpha         -3.42042         0.570798           -4.53917            -2.30168
           rho          2.42941         0.164247            2.10749             2.75133
       control          4.52558         0.315791            3.90665             5.14452
         slope        0.0642178        0.0318952         0.00170434            0.126731
         power         0.619697        0.0482017           0.525223             0.71417


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

   0        9        4.9         4.53         1.11         1.13          0.993
```

```
 69.5     4        4.9         5.42         1.18         1.41         -0.732
  232     4        6.7          6.4          1.4         1.72          0.344
  463     4        7.2         7.41          1.8         2.06           -0.2
 2318     4        8.3         12.3         0.26         3.83          -2.11
 6949     4         14           20            5         6.86          -1.74
2.319e+004     4         59         37.1          6.8         14.6           3.01
6.966e+004     4         96         68.9           46         30.9           1.75
2.326e+005     4        155          140         16.4         73.4          0.397
5.819e+005     4        182          244           26          144         -0.868
2.332e+006     4        189          572           26          404          -1.89



 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         -158.130647          12     340.261294
              A2          -84.800279          22     213.600558
              A3          -98.821893          13     223.643786
          fitted         -130.634662           5     271.269325
               R         -234.625213           2     473.250426


                    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               299.65         20          <.0001
   Test 2              146.661         10          <.0001
   Test 3              28.0432          9       0.0009381
   Test 4              63.6255          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 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 = 102.508


             BMDL = 44.1703
```

H.2.5. National Toxicology Program. (2006): EROD Liver Week 53

H.2.5.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	4	<0.0001	113.40	<0.0001	203.18	7.6E+03	5.1E+03	nonconstant variance, power restricted ≥1
exponential (M3)	4	<0.0001	113.40	<0.0001	203.18	7.6E+03	5.1E+03	nonconstant variance, power restricted ≥1
exponential (M4)	3	<0.0001	20.95	0.00	112.76	1.2E+02	8.2E+01	nonconstant variance, power restricted ≥1
exponential (M5)	2	<0.0001	6.69	0.04	100.50	3.1E+02	2.0E+02	nonconstant variance, power restricted ≥1
Hill [c]	**2**	**<.0001**	**3.09**	**0.21**	**96.90**	**4.2E+02**	**3.0E+02**	**nonconstant variance, n restricted >1**
Hill [d]	2	<.0001	3.09	0.21	96.90	4.2E+02	3.0E+02	nonconstant variance, n unrestricted
linear	4	<.0001	73.05	<.0001	162.86	1.5E+02	1.1E+02	nonconstant variance
polynomial	4	<.0001	-81.81	<.0001	8.00	6.0E-08	error	nonconstant variance
power	4	<.0001	73.05	<.0001	162.86	1.5E+02	1.1E+02	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	4	<0.0001	77.17	<0.0001	201.35	7.0E+03	5.9E+03	constant variance, power restricted ≥1
exponential (M3)	4	<0.0001	77.17	<0.0001	201.35	7.0E+03	5.9E+03	constant variance, power restricted ≥1
exponential (M4)	3	<0.0001	7.36	0.06	133.54	4.6E+02	3.6E+02	constant variance, power restricted ≥1
exponential (M5)	2	<0.0001	4.20	0.12	132.37	7.3E+02	4.5E+02	constant variance, power restricted ≥1
Hill	2	<.0001	2.31	0.31	130.49	9.1E+02	6.1E+02	constant variance, n restricted >1
Hill	2	<.0001	2.31	0.31	130.49	9.1E+02	6.1E+02	constant variance, n unrestricted
linear	4	<.0001	64.69	<.0001	188.86	4.0E+03	3.2E+03	constant variance
polynomial	4	<.0001	64.69	<.0001	188.86	4.0E+03	3.2E+03	constant variance
power	4	<.0001	64.69	<.0001	188.86	4.0E+03	3.2E+03	constant variance, power restricted ≥1, bound hit

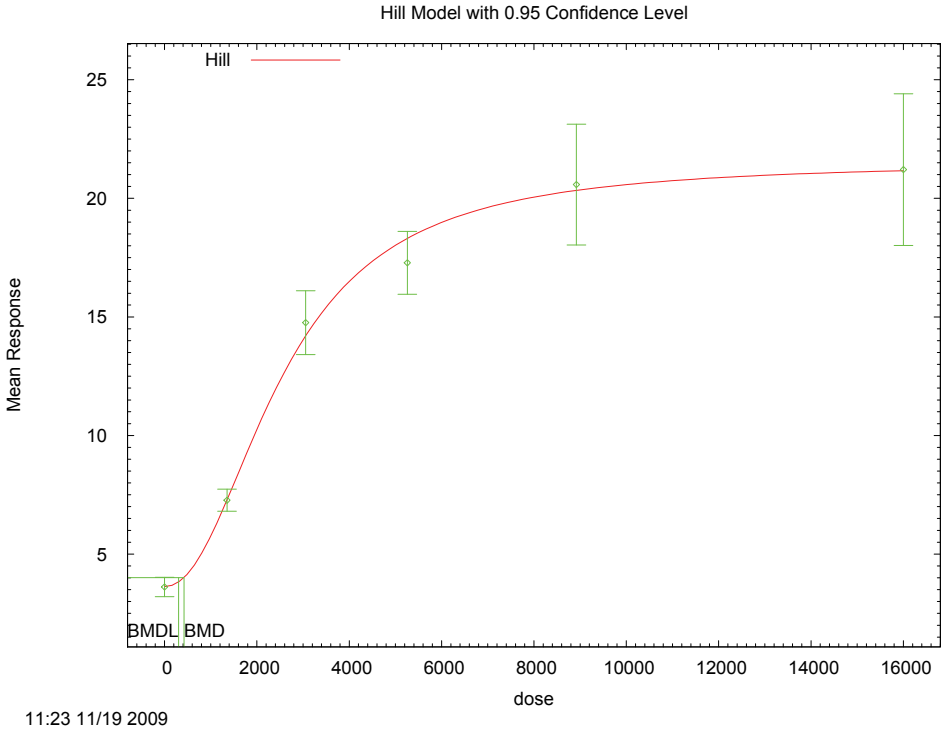
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.2.5.2. *Figure for Selected Model: Hill, Nonconstant Variance, n Restricted >1*



H.2.5.3. *Output file for Selected Model: Hill, Nonconstant Variance, n Restricted >1*

```
 ========================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Hill_BMR1_Tbl12_wk53_EROD_liv.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\AD\Blood\Hill_BMR1_Tbl12_wk53_EROD_liv.plt
                                                 Thu Nov 19 11:23:04 2009
 ========================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 =      1.59547
                           rho =            0
```

```
                      intercept =        3.614
                              v =       17.599
                              n =      2.06282
                              k =      3589.94


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho    intercept            v            n            k

    lalpha            1        -0.96        -0.16        0.088        -0.06        0.042

       rho        -0.96            1         0.15        -0.12        0.062       -0.045

 intercept        -0.16         0.15            1        -0.18         0.13        0.073

         v        0.088        -0.12        -0.18            1         -0.7         0.82

         n        -0.06        0.062         0.13         -0.7            1        -0.78

         k        0.042       -0.045        0.073         0.82        -0.78            1


                                Parameter Estimates

                                                                 95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -4.86517         0.742003            -6.31947            -3.41087
            rho          2.26994         0.287404             1.70664             2.83324
      intercept          3.62886         0.133846             3.36652             3.89119
              v          17.8693         0.946035             16.0151             19.7235
              n          2.12332         0.238762             1.65535             2.59128
              k          2573.21          216.955             2147.99             2998.43


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     8       3.61         3.63        0.486        0.379         -0.111
 1354     8       7.27         7.27        0.557        0.834          0.013
 3056     8       14.8         14.2         1.61         1.78          0.925
 5259     8       17.3         18.3         1.59         2.38          -1.19
 8918     8       20.6         20.3         3.05         2.68           0.29
1.6e+004     8       21.2         21.1         3.82          2.8          0.077


 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	-59.086537	7	132.173073
A2	-37.515858	12	99.031716
A3	-40.906180	8	97.812359
fitted	-42.452016	6	96.904031
R	-116.710291	2	237.420582

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	158.389	10	<.0001
Test 2	43.1414	5	<.0001
Test 3	6.78064	4	0.1479
Test 4	3.09167	2	0.2131

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

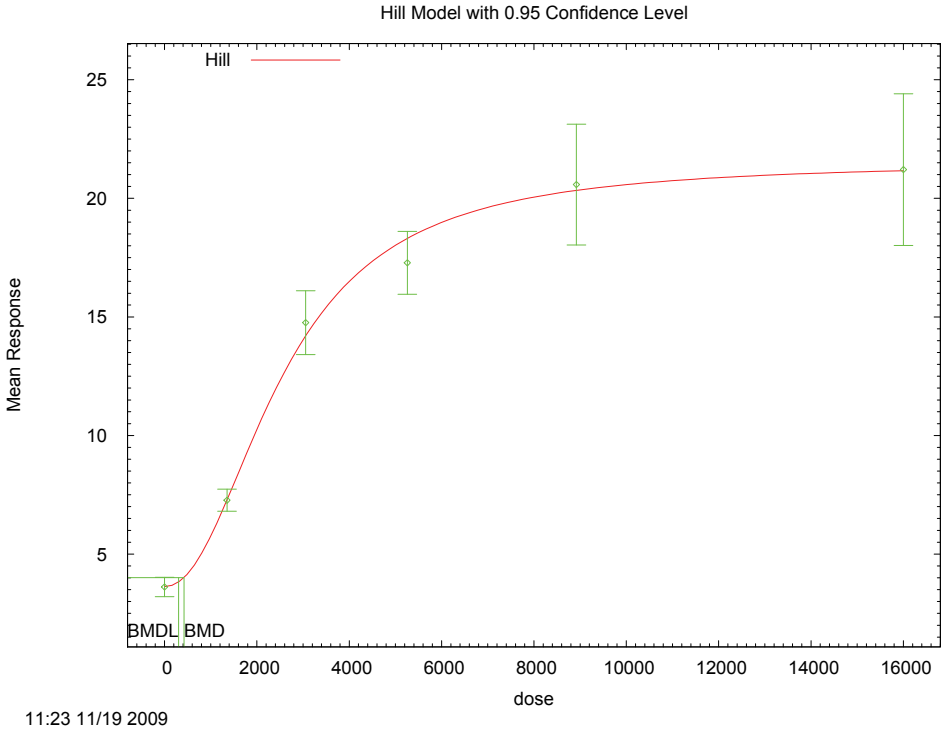
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 423.477

BMDL = 304.577

H.2.5.4. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



H.2.5.5. *Output file for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_Tbl12_wk53_EROD_liv.(d)
         Gnuplot Plotting File:
C:\USEPA\BMDS21\AD\Blood\Hill_Unrest_BMR1_Tbl12_wk53_EROD_liv.plt
                                                Thu Nov 19 11:23:13 2009
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 =      1.59547
```

```
                          rho =           0
                    intercept =       3.614
                            v =      17.599
                            n =     2.06282
                            k =     3589.94
```

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	intercept	v	n	k
lalpha	1	-0.96	-0.16	0.088	-0.06	0.042
rho	-0.96	1	0.15	-0.12	0.062	-0.045
intercept	-0.16	0.15	1	-0.18	0.13	0.073
v	0.088	-0.12	-0.18	1	-0.7	0.82
n	-0.06	0.062	0.13	-0.7	1	-0.78
k	0.042	-0.045	0.073	0.82	-0.78	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	-4.86517	0.742003	-6.31947	-3.41087
rho	2.26994	0.287404	1.70664	2.83324
intercept	3.62886	0.133846	3.36652	3.89119
v	17.8693	0.946034	16.0151	19.7235
n	2.12332	0.238762	1.65535	2.59128
k	2573.21	216.955	2147.99	2998.43

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	3.61	3.63	0.486	0.379	-0.111
1354	8	7.27	7.27	0.557	0.834	0.013
3056	8	14.8	14.2	1.61	1.78	0.925
5259	8	17.3	18.3	1.59	2.38	-1.19
8918	8	20.6	20.3	3.05	2.68	0.29
1.6e+004	8	21.2	21.1	3.82	2.8	0.077

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	-59.086537	7	132.173073
A2	-37.515858	12	99.031716
A3	-40.906180	8	97.812359
fitted	-42.452016	6	96.904032
R	-116.710291	2	237.420582

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	158.389	10	<.0001
Test 2	43.1414	5	<.0001
Test 3	6.78064	4	0.1479
Test 4	3.09167	2	0.2131

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 = 423.477

BMDL = 304.577

H.2.6. National Toxicology Program. (2006): Lung EROD Week 31

H.2.6.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	4	<0.0001	123.80	<0.0001	390.99	1.2E+04	8.1E+03	nonconstant variance, power restricted ≥1
exponential (M3)	4	<0.0001	123.80	<0.0001	390.99	1.2E+04	8.1E+03	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**3**	**<0.0001**	**13.01**	**0.00**	**282.20**	**4.1E+01**	**2.9E+01**	**nonconstant variance, power restricted ≥1**
exponential (M5)	3	<0.0001	13.01	0.00	282.20	4.1E+01	2.9E+01	nonconstant variance, power restricted ≥1
exponential (M5) [d]	3	<0.0001	13.01	0.00	282.20	4.1E+01	2.9E+01	nonconstant variance, power unrestricted
Hill	4	<.0001	59.49	<.0001	326.67	1.3E-11	1.3E-11	nonconstant variance, n restricted >1, bound hit
Hill [d]	4	<.0001	59.49	<.0001	326.67	1.3E-11	1.3E-11	nonconstant variance, n unrestricted
linear	4	<.0001	116.14	<.0001	383.32	4.1E+03	1.5E+03	nonconstant variance
polynomial	4	<.0001	123.25	<.0001	390.43	1.3E+04	7.5E+01	nonconstant variance
power	4	<.0001	116.14	<.0001	383.32	4.1E+03	1.5E+03	nonconstant variance, power restricted ≥1, bound hit
power [d]	3	<.0001	23.64	<.0001	292.82	4.5E-02	4.5E-02	nonconstant variance, power unrestricted
exponential (M2)	4	<0.0001	80.66	<0.0001	390.82	9.0E+03	7.5E+03	constant variance, power restricted ≥1
exponential (M3)	4	<0.0001	80.66	<0.0001	390.82	9.0E+03	7.5E+03	constant variance, power restricted ≥1
exponential (M4)	3	<0.0001	12.08	0.01	324.24	4.6E+02	3.4E+02	constant variance, power restricted ≥1
exponential (M5)	2	<0.0001	12.08	0.00	326.24	4.6E+02	3.4E+02	constant variance, power restricted ≥1
exponential (M5)	2	<0.0001	12.08	0.00	326.24	4.6E+02	3.4E+02	constant variance, power unrestricted
Hill	2	<.0001	14.17	0.00	328.33	5.1E+02	2.4E+02	constant variance, n restricted >1
Hill	2	<.0001	14.17	0.00	328.33	5.1E+02	1.9E+02	constant variance, n unrestricted
linear	4	<.0001	71.44	<.0001	381.60	5.6E+03	4.4E+03	constant variance
polynomial	4	<.0001	71.44	<.0001	381.60	5.6E+03	4.4E+03	constant variance
power	4	<.0001	71.44	<.0001	381.60	5.6E+03	4.4E+03	constant variance, power restricted ≥1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
power	3	<.0001	23.14	<.0001	335.30	2.0E+01	2.0E+00	constant variance, power unrestricted

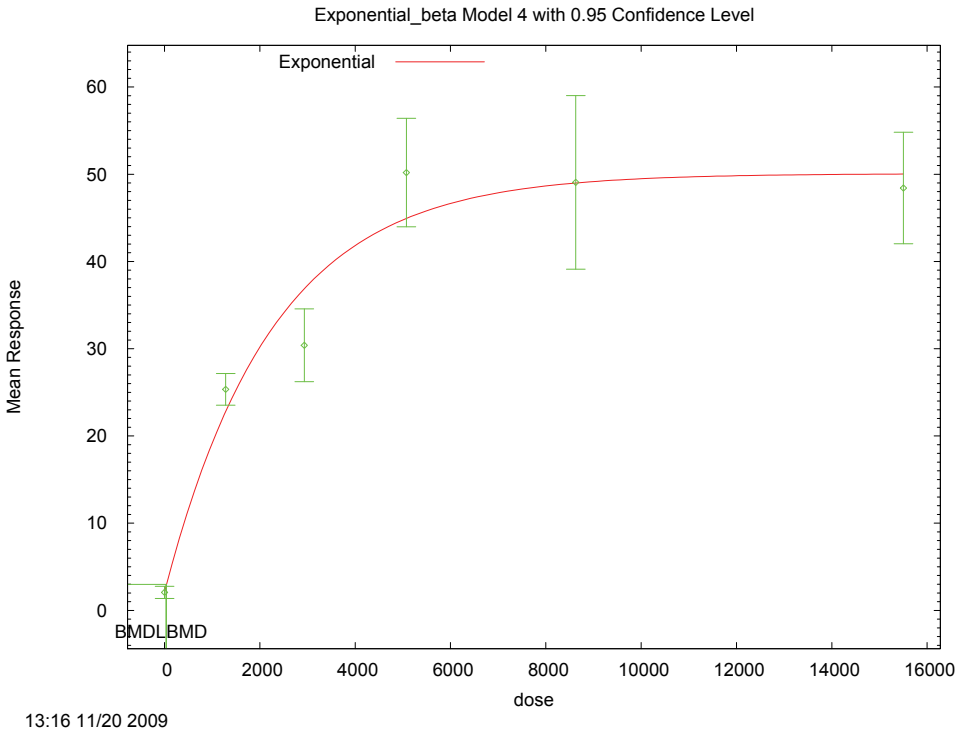
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.2.6.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



H.2.6.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
 ======================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_BMR1_Lung_EROD_wk31.(d)
         Gnuplot Plotting File:
                                                Fri Nov 20 13:16:38 2009
 ======================================================================

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   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 = 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             -1.42653
                    rho              1.46168
                      a              1.96745
                      b          0.000226755
                      c              26.7857
                      d                    1


                Parameter Estimates

               Variable          Model 4
               --------          -------
                lnalpha          -1.47384
                    rho           1.57432
                      a           2.11972
                      b       0.000440068
                      c           23.6215
                      d                 1


        Table of Stats From Input Data

 Dose      N         Obs Mean     Obs Std Dev
 -----    ---       ----------   -------------
     0     10        2.071       0.9708
  1284     10        25.34        2.549
  2932     10        30.39        5.831
  5075     10        50.19         8.68
  8629     10        49.07        13.91
 1.55e+004     10        48.42        8.933


              Estimated Values of Interest

  Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
```

0	2.12	0.8646	-0.1782
1284	22.82	5.612	1.423
2932	36.88	8.189	-2.506
5075	44.93	9.567	1.738
8629	49	10.24	0.02179
1.55e+004	50.02	10.41	-0.4854

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	-152.0793	7	318.1586
A2	-123.367	12	270.734
A3	-129.5911	8	275.1823
R	-206.5175	2	417.0349
4	-136.0978	5	282.1956

Additive constant for all log-likelihoods = -55.14. 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	166.3	10	< 0.0001
Test 2	57.42	5	< 0.0001
Test 3	12.45	4	0.01431
Test 6a	13.01	3	0.004608

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.

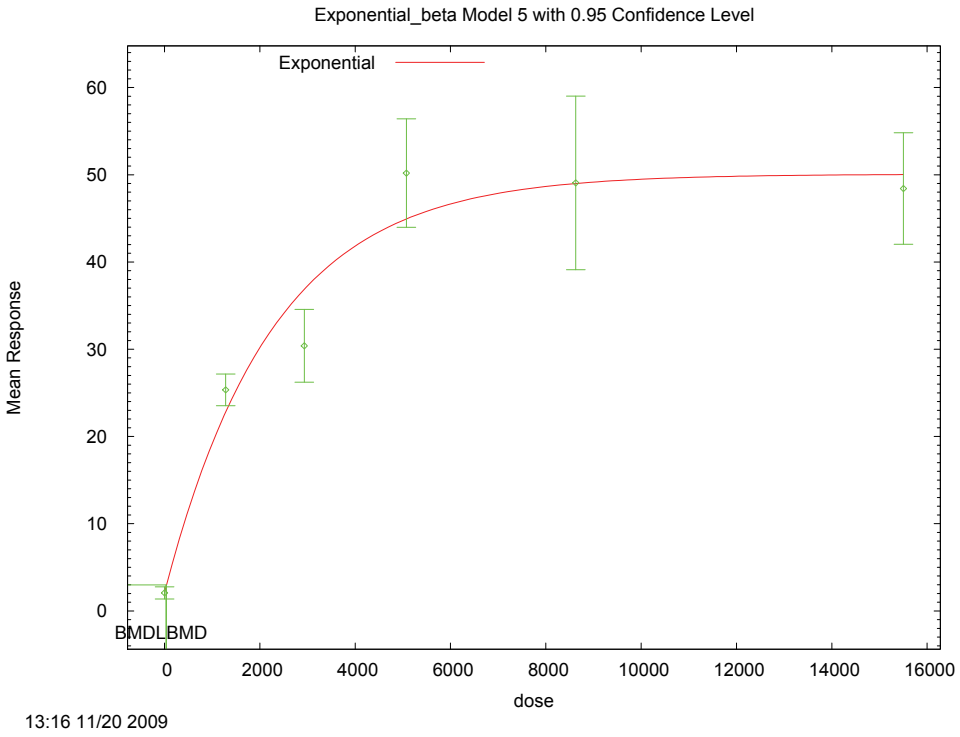
The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

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 =      41.3446

               BMDL =      28.8946
```

H.2.6.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



H.2.6.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_Unrest_BMR1_Lung_EROD_wk31.(d)
         Gnuplot Plotting File:
                                                 Fri Nov 20 13:16:45 2009
 ========================================================================

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```

```
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 = 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 5
               --------          --------
                 lnalpha            -1.42653
                     rho             1.46168
                       a             1.96745
                       b          0.000226755
                       c             26.7857
                       d                    1


                  Parameter Estimates

                Variable          Model 5
                --------          -------
                 lnalpha          -1.47384
                     rho           1.57432
                       a           2.11972
                       b       0.000440068
                       c           23.6215
                       d                  1


        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0     10        2.071        0.9708
   1284     10        25.34         2.549
   2932     10        30.39         5.831
   5075     10        50.19          8.68
   8629     10        49.07         13.91
 1.55e+004     10        48.42         8.933


               Estimated Values of Interest

  Dose      Est Mean      Est Std     Scaled Residual
```

0	2.12	0.8646	-0.1782
1284	22.82	5.612	1.423
2932	36.88	8.189	-2.506
5075	44.93	9.567	1.738
8629	49	10.24	0.02179
1.55e+004	50.02	10.41	-0.4854

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	-152.0793	7	318.1586
A2	-123.367	12	270.734
A3	-129.5911	8	275.1823
R	-206.5175	2	417.0349
5	-136.0978	5	282.1956

Additive constant for all log-likelihoods = -55.14. 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	166.3	10	< 0.0001
Test 2	57.42	5	< 0.0001
Test 3	12.45	4	0.01431
Test 7a	13.01	3	0.004608

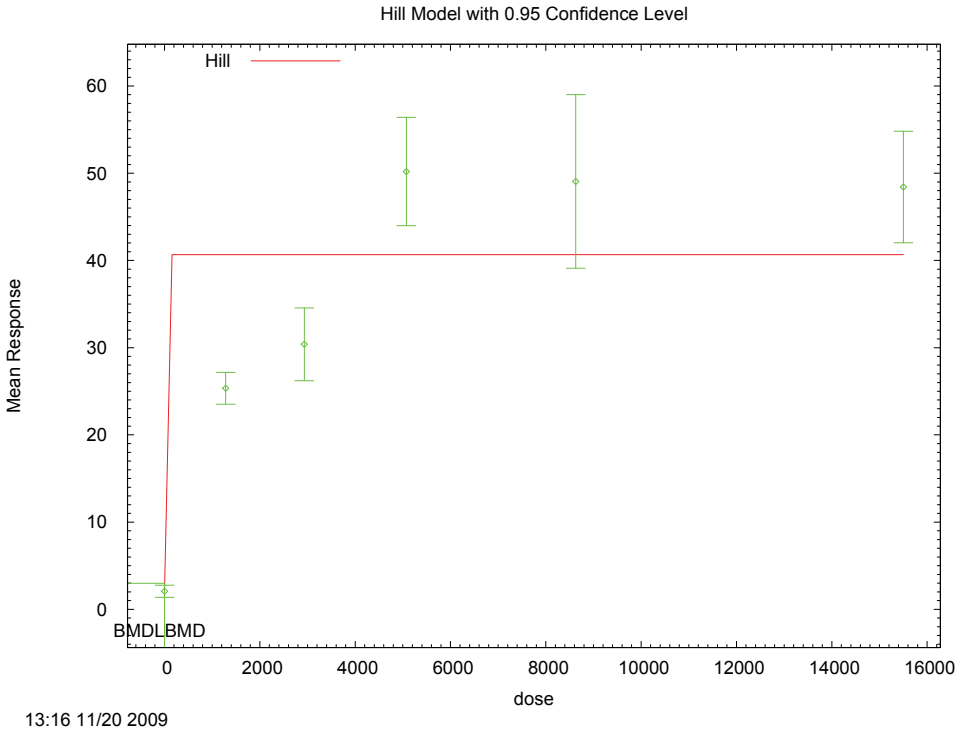
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

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 =      41.3446

                BMDL =      28.8946
```

H.2.6.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



H.2.6.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ========================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_Lung_EROD_wk31.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_Lung_EROD_wk31.plt
                                                 Fri Nov 20 13:16:47 2009
 ========================================================================

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   The form of the response function is:
```
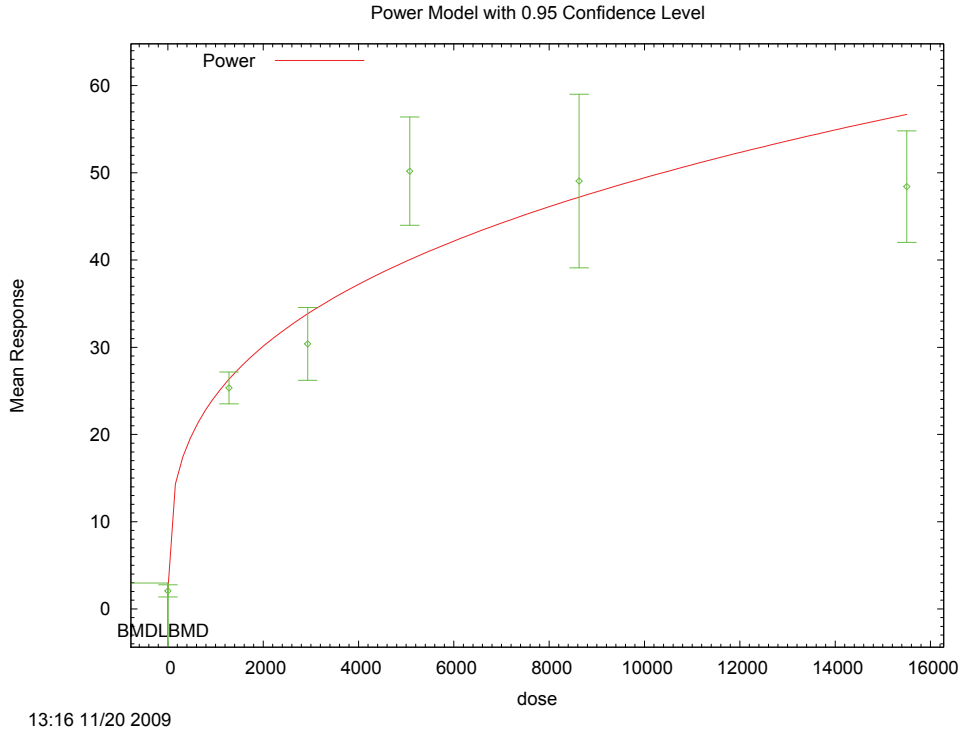

```
Y[dose] = intercept + v*dose^n/(k^n + dose^n)


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 = 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 =      4.17467
                           rho =            0
                     intercept =        2.071
                             v =       48.119
                             n =           18
                             k =      4322.89


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -n    -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

   lalpha            1        -0.95        -0.49         0.11

      rho        -0.95            1         0.45        -0.22

intercept        -0.49         0.45            1        -0.15

        v         0.11        -0.22        -0.15            1


                                 Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        lalpha         -1.47774         0.642044          -2.73613           -0.219359
           rho           1.8037         0.187436           1.43633             2.17107
     intercept            2.071         0.291246           1.50017             2.64183
             v          38.6102           1.9322           34.8232             42.3972
             n               18               NA
             k      1.5503e-011               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        2.07         2.07        0.971        0.921     -2.27e-007
 1284    10        25.3         40.7         2.55         13.5          -3.59
 2932    10        30.4         40.7         5.83         13.5          -2.41
 5075    10        50.2         40.7         8.68         13.5           2.23
 8629    10        49.1         40.7         13.9         13.5           1.96
```

```
1.55e+004    10       48.4         40.7         8.93         13.5           1.81


 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         -152.079318           7     318.158637
              A2         -123.366985          12     270.733969
              A3         -129.591134           8     275.182269
          fitted         -159.335928           4     326.671856
               R         -206.517459           2     417.034919


                    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              166.301         10          <.0001
   Test 2              57.4247          5          <.0001
   Test 3              12.4483          4         0.01431
   Test 4              59.4896          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 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 =   1.26143e-011

BMDL =  1.26143e-011
```

H.2.6.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



H.2.6.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ======================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_Lung_EROD_wk31.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_Lung_EROD_wk31.plt
                                                 Fri Nov 20 13:16:48 2009
 ======================================================================

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   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 =	4.17467
rho =	0
control =	2.071
slope =	2.58483
power =	0.313845

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.94	-0.42	0.14	-0.14
rho	-0.94	1	0.38	-0.17	0.15
control	-0.42	0.38	1	-0.11	0.094
slope	0.14	-0.17	-0.11	1	-1
power	-0.14	0.15	0.094	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-1.53087	0.573913	-2.65572	-0.406018
rho	1.64612	0.167167	1.31848	1.97376
control	2.1082	0.270802	1.57744	2.63896
slope	2.35281	0.945551	0.499559	4.20605
power	0.325737	0.0465627	0.234476	0.416998

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	2.07	2.11	0.971	0.859	-0.137
1284	10	25.3	26.3	2.55	6.86	-0.453
2932	10	30.4	33.8	5.83	8.43	-1.28
5075	10	50.2	40	8.68	9.69	3.33
8629	10	49.1	47.2	13.9	11.1	0.545
1.55e+004	10	48.4	56.6	8.93	12.9	-2.01

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	-152.079318	7	318.158637
A2	-123.366985	12	270.733969
A3	-129.591134	8	275.182269
fitted	-141.409222	5	292.818443
R	-206.517459	2	417.034919

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	166.301	10	<.0001
Test 2	57.4247	5	<.0001
Test 3	12.4483	4	0.01431
Test 4	23.6362	3	<.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 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 = 0.0454117

BMDL = 0.0454112

H.2.7. National Toxicology Program. (2006): Lung EROD Week 53

H.2.7.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	4	<0.0001	64.02	<0.0001	314.33	1.8E+04	1.1E+04	nonconstant variance, power restricted ≥1
exponential (M3)	4	<0.0001	64.02	<0.0001	314.33	1.8E+04	1.1E+04	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**3**	**<0.0001**	**3.63**	**0.30**	**255.94**	**5.3E+01**	**3.3E+01**	**nonconstant variance, power restricted ≥1**
exponential (M5)	2	<0.0001	2.58	0.28	256.88	5.8E+02	3.6E+01	nonconstant variance, power restricted ≥1
exponential (M5) [d]	2	<0.0001	2.58	0.28	256.88	5.8E+02	3.6E+01	nonconstant variance, power unrestricted
Hill	3	<.0001	16.10	0.00	268.40	1.7E-05	1.7E-05	nonconstant variance, n restricted >1
Hill [d]	3	<.0001	16.10	0.00	268.40	1.7E-05	1.7E-05	nonconstant variance, n unrestricted
linear	4	<.0001	62.93	<.0001	313.23	1.5E+04	6.9E+03	nonconstant variance
polynomial	5	<.0001	81.88	<.0001	330.18	error	2.0E+03	nonconstant variance
power	4	<.0001	62.93	<.0001	313.23	1.5E+04	6.9E+03	nonconstant variance, power restricted ≥1, bound hit
power [d]	3	<.0001	8.76	0.03	261.07	1.1E-04	1.1E-04	nonconstant variance, power unrestricted
exponential (M2)	4	<0.0001	39.91	<0.0001	316.45	1.1E+04	8.8E+03	constant variance, power restricted ≥1
exponential (M3)	4	<0.0001	39.91	<0.0001	316.45	1.1E+04	8.8E+03	constant variance, power restricted ≥1
exponential (M4)	3	<0.0001	3.69	0.30	282.22	4.0E+02	2.4E+02	constant variance, power restricted ≥1
exponential (M5)	2	<0.0001	2.71	0.26	283.24	1.1E+03	2.7E+02	constant variance, power restricted ≥1
exponential (M5)	2	<0.0001	2.71	0.26	283.24	1.1E+03	2.7E+02	constant variance, power unrestricted
Hill	3	<.0001	2.71	0.44	281.24	1.2E+03	1.6E+02	constant variance, n restricted >1, bound hit
Hill	3	<.0001	2.71	0.44	281.24	1.2E+03	3.8E+01	constant variance, n unrestricted
linear	4	<.0001	36.71	<.0001	313.25	8.3E+03	5.9E+03	constant variance
polynomial	4	<.0001	36.71	<.0001	313.25	8.3E+03	5.9E+03	constant variance
power	4	<.0001	36.71	<.0001	313.25	8.3E+03	5.9E+03	constant variance, power restricted ≥1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
power	3	<.0001	6.08	0.11	284.61	2.8E+00	9.6E-05	constant variance, power unrestricted

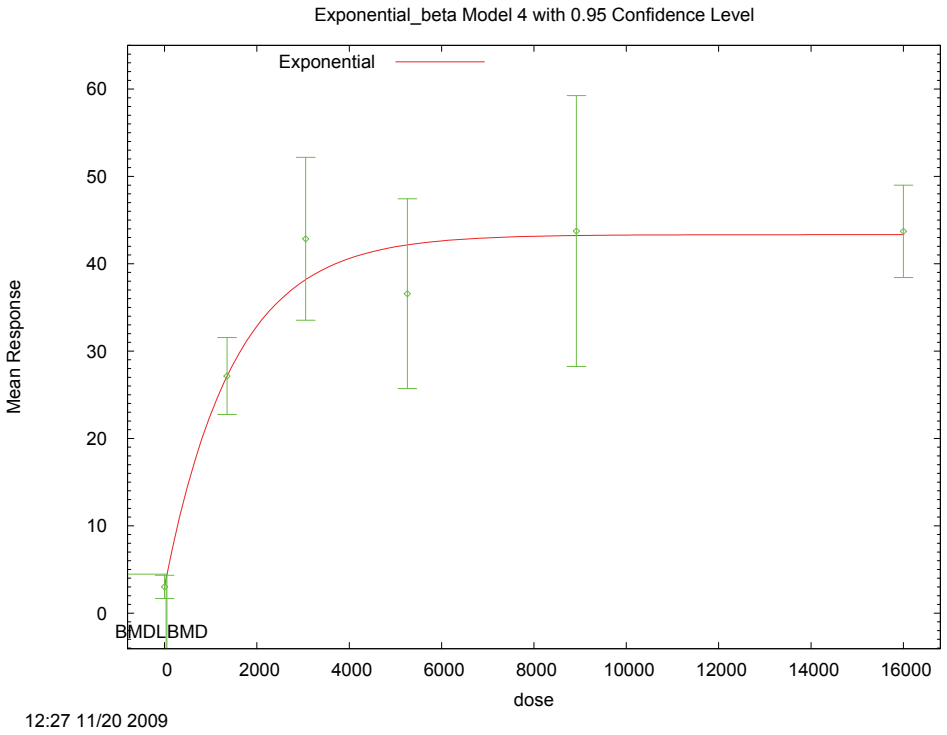
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.2.7.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



H.2.7.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
 ======================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_BMR1_Lung_EROD_wk53.(d)
         Gnuplot Plotting File:
                                                 Fri Nov 20 12:27:08 2009
 ======================================================================

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   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 = 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             -0.80064
                    rho              1.47683
                      a              2.86045
                      b         0.000243673
                      c              16.0581
                      d                    1


                Parameter Estimates

               Variable          Model 4
               --------          -------
                lnalpha          -1.14118
                    rho           1.62714
                      a           3.06882
                      b       0.000715169
                      c            13.702
                      d           3.78652


        Table of Stats From Input Data

 Dose      N         Obs Mean     Obs Std Dev
 -----    ---       ----------   -------------
     0      8        3.011        1.584
  1354      8        27.15        5.269
  3056      8        42.85        11.15
  5259      8        36.57        12.99
  8918      8        43.75        18.55
 1.6e+004      8        43.71        6.322


              Estimated Values of Interest

  Dose      Est Mean      Est Std     Scaled Residual
------    ----------    ---------    ----------------
```

0	3.061	1.408	-0.1008
1354	27.14	8.377	0.001867
3056	38.19	11.07	1.191
5259	42.16	12.01	-1.317
8918	43.23	12.25	0.1192
1.6e+004	43.33	12.28	0.08869

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	-135.2677	7	284.5353
A2	-115.6885	12	255.3771
A3	-121.1517	8	258.3034
R	-162.0902	2	328.1805
4	-122.9684	5	255.9369

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	92.8	10	< 0.0001
Test 2	39.16	5	< 0.0001
Test 3	10.93	4	0.0274
Test 6a	3.633	3	0.3039

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.

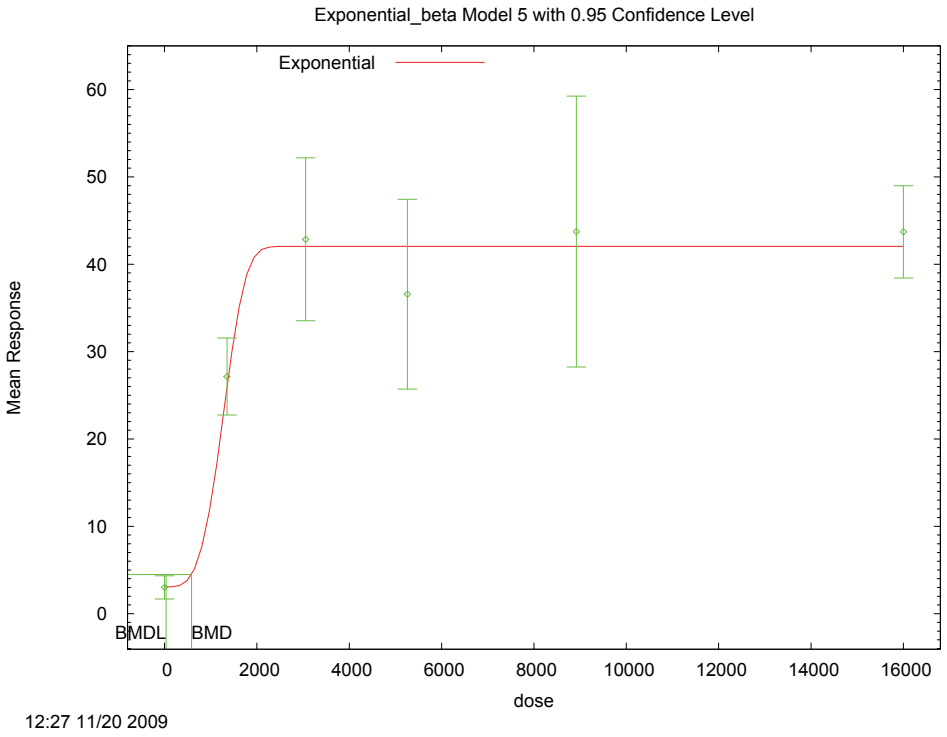
The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

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 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 =      52.8515

               BMDL =      32.5706
```

H.2.7.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



H.2.7.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_Unrest_BMR1_Lung_EROD_wk53.(d)
         Gnuplot Plotting File:
                                                Fri Nov 20 12:27:17 2009
 ========================================================================

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```

```
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 = 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 5
               --------          --------
                 lnalpha            -0.80064
                     rho             1.47683
                       a             2.86045
                       b          0.000243673
                       c             16.0581
                       d                    1


                  Parameter Estimates

                Variable          Model 5
                --------          -------
                 lnalpha          -1.14118
                     rho           1.62714
                       a           3.06882
                       b       0.000715169
                       c            13.702
                       d           3.78652


        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      8        3.011        1.584
   1354      8        27.15        5.269
   3056      8        42.85        11.15
   5259      8        36.57        12.99
   8918      8        43.75        18.55
  1.6e+004      8        43.71        6.322


              Estimated Values of Interest

  Dose      Est Mean      Est Std     Scaled Residual
```

0	3.069	1.407	-0.1162
1354	25.95	7.993	0.4234
3056	42.05	11.84	0.1907
5259	42.05	11.84	-1.309
8918	42.05	11.84	0.4055
1.6e+004	42.05	11.84	0.3976

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	-135.2677	7	284.5353
A2	-115.6885	12	255.3771
A3	-121.1517	8	258.3034
R	-162.0902	2	328.1805
5	-122.4411	6	256.8821

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 7a: Does Model 5 fit the data? (A3 vs 5)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	92.8	10	< 0.0001
Test 2	39.16	5	< 0.0001
Test 3	10.93	4	0.0274
Test 7a	2.579	2	0.2755

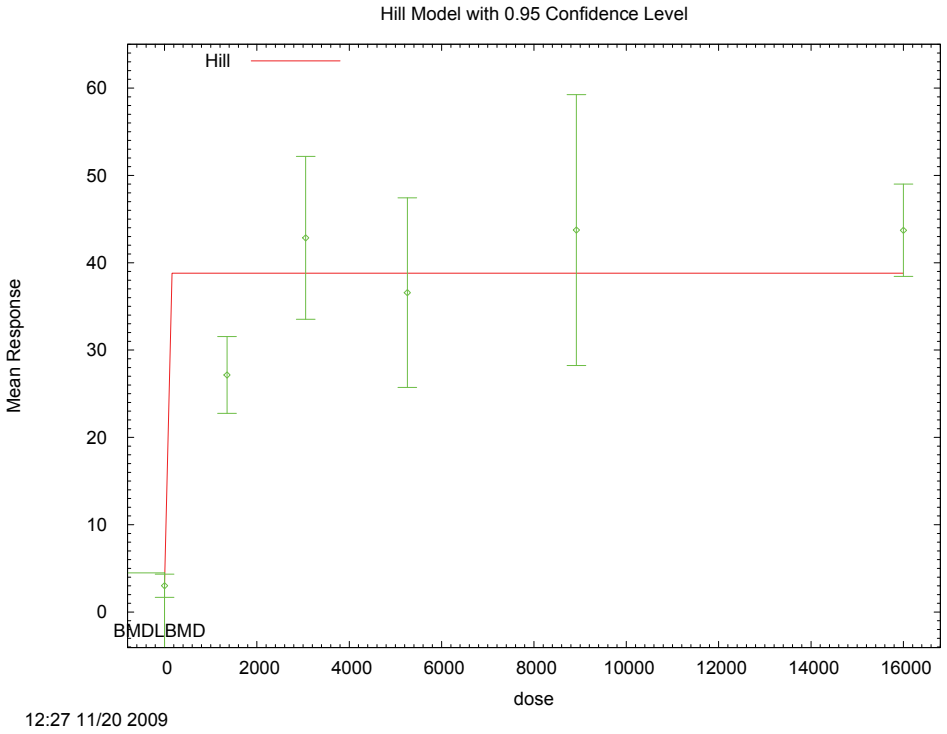
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

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 greater than .1.  Model 5 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 =      584.449

               BMDL =      36.2497
```

H.2.7.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



H.2.7.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ========================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_Lung_EROD_wk53.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_Lung_EROD_wk53.plt
                                                 Fri Nov 20 12:27:19 2009
 ========================================================================

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    The form of the response function is:
```
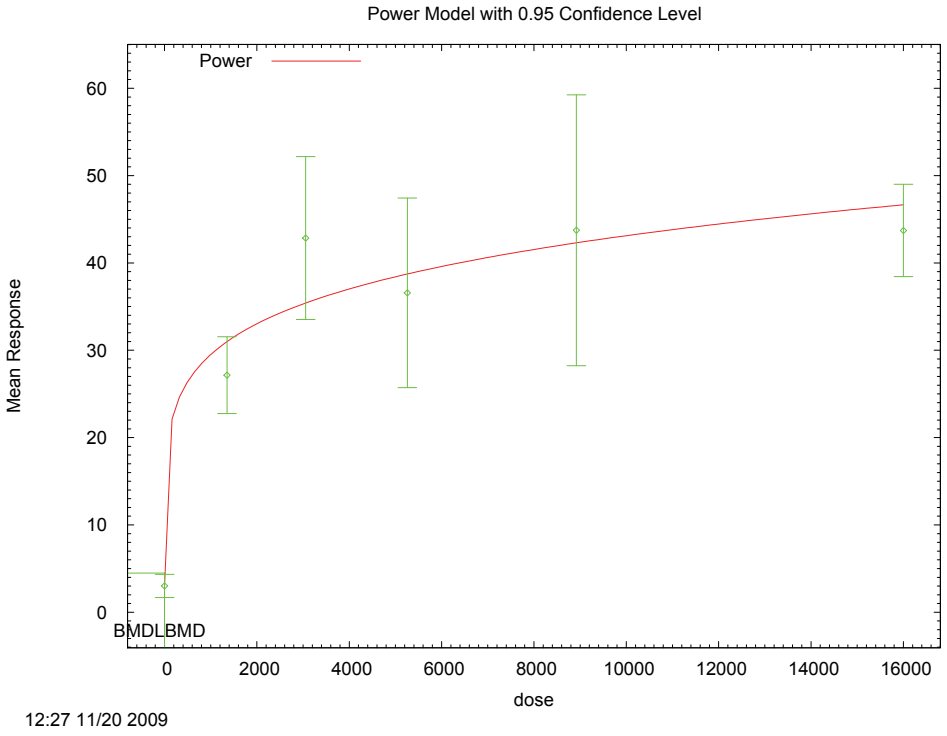

```
   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   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 = 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 =      4.76968
                          rho =            0
                    intercept =        3.011
                            v =       40.735
                            n =      2.49974
                            k =      1565.11


           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        -0.96         -0.5         0.17      NA

       rho         -0.96            1         0.47        -0.25      NA

 intercept          -0.5         0.47            1        -0.25      NA

         v          0.17        -0.25        -0.25            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         -1.07501              NA                    NA                  NA
           rho          1.68859              NA                    NA                  NA
     intercept            3.011              NA                    NA                  NA
             v          35.7938              NA                    NA                  NA
             n          5.85653              NA                    NA                  NA
             k     2.91999e-005              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     8       3.01         3.01         1.58         1.48     -2.78e-009
 1354     8       27.1         38.8         5.27         12.8          -2.57
 3056     8       42.8         38.8         11.2         12.8          0.891
 5259     8       36.6         38.8           13         12.8         -0.493
 8918     8       43.7         38.8         18.5         12.8           1.09
1.6e+004     8       43.7         38.8         6.32         12.8           1.08


 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         -135.267662            7     284.535325
             A2         -115.688533           12     255.377067
             A3         -121.151707            8     258.303413
         fitted         -129.200555            5     268.401110
              R         -162.090242            2     328.180484


                    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              92.8034         10          <.0001
   Test 2              39.1583          5          <.0001
   Test 3              10.9263          4          0.0274
   Test 4              16.0977          3        0.001083

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 =   1.70749e-005

            BMDL =  1.70749e-005
```

H.2.7.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



H.2.7.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ======================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_Lung_EROD_wk53.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_Lung_EROD_wk53.plt
                                                Fri Nov 20 12:27:20 2009
 ======================================================================

 Tbl 12, Week 53, Lung Microsomes EROD
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =      4.76968
                          rho =            0
                      control =        3.011
                        slope =      7.10636
                        power =     0.187655


          Asymptotic Correlation Matrix of Parameter Estimates

                lalpha          rho      control        slope        power

 lalpha              1        -0.96        -0.49        0.062       -0.046

    rho          -0.96            1         0.45       -0.074        0.051

control          -0.49         0.45            1       -0.075        0.049

  slope          0.062       -0.074       -0.075            1           -1

  power         -0.046        0.051        0.049           -1            1


                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
     Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
       lalpha         -1.02691         0.818371           -2.63089            0.577065
          rho           1.6303         0.240525            1.15888             2.10172
      control          3.01554         0.519298            1.99773             4.03334
        slope          7.64061          4.22038           -0.631172             15.9124
        power          0.18001        0.0639858           0.0546001             0.30542


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0       8       3.01         3.02         1.58         1.47       -0.00872
 1354       8       27.1           31         5.27         9.83          -1.11
 3056       8       42.8         35.4         11.2           11           1.92
 5259       8       36.6         38.7           13         11.8          -0.52
 8918       8       43.7         42.3         18.5         12.7          0.323
1.6e+004      8        43.7         46.7         6.32         13.7         -0.607


 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         -135.267662            7     284.535325
             A2         -115.688533           12     255.377067
             A3         -121.151707            8     258.303413
          fitted        -125.533162            5     261.066325
              R         -162.090242            2     328.180484


                    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              92.8034         10          <.0001
   Test 2              39.1583          5          <.0001
   Test 3              10.9263          4          0.0274
   Test 4              8.76291          3         0.03261

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 = 0.000106161


             BMDL = 0.000106161
```

H.2.8. National Toxicology Program. (2006): Tbl11 Index Week 31

H.2.8.1. *Summary Table of BMDS Modeling Results*

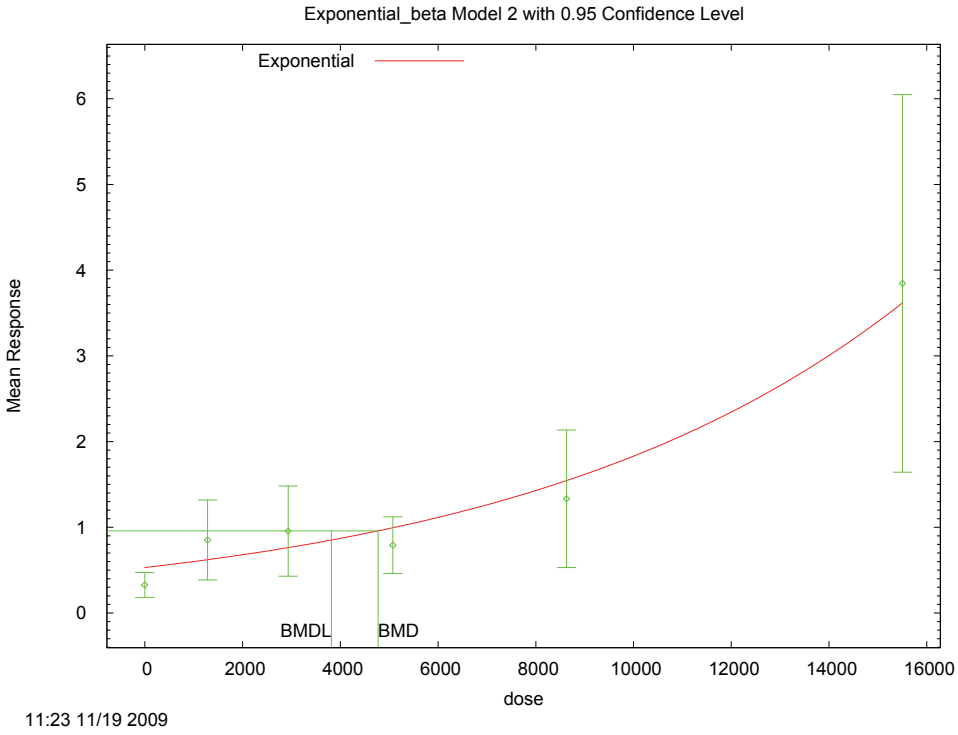
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2) [c]	**4**	**<0.0001**	**20.59**	**0.00**	**46.55**	**4.8E+03**	**3.8E+03**	**nonconstant variance, power restricted ≥1**
exponential (M3)	4	<0.0001	20.59	0.00	46.55	4.8E+03	3.8E+03	nonconstant variance, power restricted ≥1
exponential (M4)	3	<0.0001	23.01	<0.0001	50.97	1.7E+03	1.0E+03	nonconstant variance, power restricted ≥1
exponential (M5)	3	<0.0001	23.01	<0.0001	50.97	1.7E+03	1.0E+03	nonconstant variance, power restricted ≥1
Hill	3	<0.0001	23.01	<0.0001	50.97	1.7E+03	error	nonconstant variance, n restricted >1, bound hit
linear	4	<0.0001	23.01	0.00	48.97	1.7E+03	1.0E+03	nonconstant variance
polynomial	3	<0.0001	22.24	<.0001	50.20	3.4E+03	1.1E+03	nonconstant variance
power	4	<0.0001	23.01	0.00	48.97	1.7E+03	1.0E+03	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	4	<0.0001	1.20	0.88	101.67	1.0E+04	9.0E+03	constant variance, power restricted ≥1
exponential (M3)	3	<0.0001	0.97	0.81	103.44	1.1E+04	9.0E+03	constant variance, power restricted ≥1
exponential (M4)	3	<0.0001	5.31	0.15	107.78	6.8E+03	5.2E+03	constant variance, power restricted ≥1
exponential (M5)	2	<0.0001	1.08	0.58	105.55	1.1E+04	7.5E+03	constant variance, power restricted ≥1
Hill	2	<0.0001	1.08	0.58	105.55	1.1E+04	7.5E+03	constant variance, n restricted >1
linear	4	<0.0001	5.31	0.26	105.78	6.8E+03	5.2E+03	constant variance
polynomial	4	<0.0001	1.44	0.84	101.91	1.0E+04	8.9E+03	constant variance
power	3	<0.0001	1.08	0.78	103.55	1.1E+04	7.5E+03	constant variance, power restricted ≥1

[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]**Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix**

H.2.8.2. *Figure for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*



H.2.8.3. *Output File for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Exp_BMR1_Tbl11_31wk.(d)
         Gnuplot Plotting File:
                                                  Thu Nov 19 11:23:48 2009
 ================================================================

 Tbl 11, 31wk, Hep Cell Proliferation Labeling Index
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 2
lnalpha	-0.674004
rho	2.29189
a	0.31065
b	3.44963e-005
c	24.761
d	1

Parameter Estimates

Variable	Model 2
lnalpha	-0.467457
rho	2.1664
a	0.394038
b	5.38146e-009
c	78344.1
d	1

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	9	0.327	0.189
1284	10	0.852	0.6514
2932	10	0.956	0.7368
5075	10	0.792	0.4617
8629	10	1.333	1.123
1.55e+004	10	3.846	3.08

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.5305	0.4275	-1.428
1284	0.6219	0.4983	1.46
2932	0.7627	0.6067	1.007
5075	0.9946	0.7837	-0.8176
8629	1.545	1.198	-0.5587
1.55e+004	3.619	2.722	0.2635

```
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       -47.23498           7        108.47
                     A2       -8.679256          12       41.35851
                     A3       -8.980651           8        33.9613
                      R       -63.44829           2       130.8966
                      2       -19.27346           4       46.54692


Additive constant for all log-likelihoods =     -54.22.  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                        109.5           10           < 0.0001
  Test 2                        77.11            5           < 0.0001
  Test 3                       0.6028            4             0.9628
  Test 4                        20.59            4          0.0003826


  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 =      4772.05

             BMDL =      3816.47
```

H.2.9. Van Birgelen et al. (1995b): T4 UGT

H.2.9.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	4	<0.0001	33.51	<0.0001	36.92	6.3E+04	4.4E+04	nonconstant variance, power restricted ≥1
exponential (M3)	4	<0.0001	33.51	<0.0001	36.92	6.3E+04	4.4E+04	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**3**	**<0.0001**	**1.50**	**0.68**	**6.90**	**2.7E+03**	**1.5E+03**	**nonconstant variance, power restricted ≥1**
exponential (M5)	2	<0.0001	1.14	0.57	8.55	3.5E+03	1.6E+03	nonconstant variance, power restricted ≥1
exponential (M5) [d]	2	<0.0001	1.14	0.57	8.55	3.5E+03	1.6E+03	nonconstant variance, power unrestricted
Hill	2	<.0001	1.22	0.54	8.63	3.7E+03	1.7E+03	nonconstant variance, n restricted >1
Hill [d]	2	<.0001	1.22	0.54	8.63	3.7E+03	1.5E+03	nonconstant variance, n unrestricted
linear	4	<.0001	19.72	0.00	23.13	1.8E+04	9.1E+03	nonconstant variance
polynomial	4	<.0001	19.72	0.00	23.13	1.8E+04	9.1E+03	nonconstant variance
power	4	<.0001	19.72	0.00	23.13	1.8E+04	9.1E+03	nonconstant variance, power restricted ≥1, bound hit
power [d]	3	<.0001	6.02	0.11	11.42	1.3E+03	2.1E+02	nonconstant variance, power unrestricted
exponential (M2)	4	<0.0001	13.46	0.01	38.87	8.2E+04	6.9E+04	constant variance, power restricted ≥1
exponential (M3)	4	<0.0001	13.46	0.01	38.87	8.2E+04	6.9E+04	constant variance, power restricted ≥1
exponential (M4)	3	<0.0001	0.11	0.99	27.51	1.3E+04	6.7E+03	constant variance, power restricted ≥1
exponential (M5)	2	<0.0001	0.07	0.97	29.47	1.5E+04	6.8E+03	constant variance, power restricted ≥1
exponential (M5)	2	<0.0001	0.07	0.97	29.47	1.5E+04	6.8E+03	constant variance, power unrestricted
Hill	2	<.0001	0.10	0.95	29.50	1.4E+04	5.6E+03	constant variance, n restricted >1
Hill	2	<.0001	0.10	0.95	29.50	1.4E+04	5.1E+03	constant variance, n unrestricted
linear	4	<.0001	8.58	0.07	33.98	5.1E+04	3.9E+04	constant variance
polynomial	4	<.0001	8.58	0.07	33.98	5.1E+04	3.9E+04	constant variance
power	4	<.0001	8.58	0.07	33.98	5.1E+04	3.9E+04	constant variance, power restricted ≥1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
power	3	<.0001	2.70	0.44	30.10	1.1E+04	2.6E+03	constant variance, power unrestricted

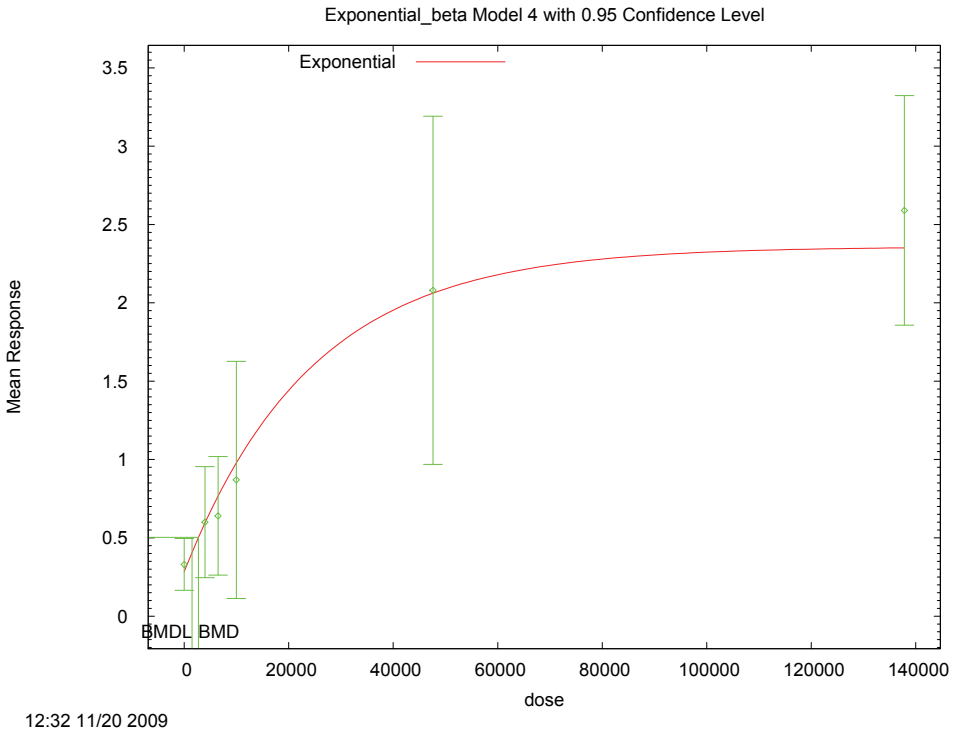
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.2.9.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



H.2.9.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_BMR1_T4_UGT.(d)
         Gnuplot Plotting File:
                                                 Fri Nov 20 12:32:06 2009
 ================================================================

 Tbl2, T4 UGT
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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           -0.937573
                    rho             1.54913
                      a              0.3135
                      b         2.19381e-005
                      c              8.67464
                      d                    1


                Parameter Estimates

               Variable          Model 4
               --------          -------
                lnalpha         -0.934825
                    rho           1.69365
                      a          0.293644
                      b      5.48685e-005
                      c           7.66316
                      d           1.27403


        Table of Stats From Input Data

 Dose      N         Obs Mean     Obs Std Dev
 -----    ---       ----------   -------------
     0      8         0.33        0.198
  3969      8          0.6       0.4243
  6479      8         0.64       0.4525
  9968      8         0.87       0.9051
4.761e+004      8         2.08        1.329
1.378e+005      8         2.59       0.8768


              Estimated Values of Interest

  Dose      Est Mean      Est Std     Scaled Residual
------    ----------    ---------    ----------------
```

0	0.2841	0.2186	0.594
3969	0.5945	0.4063	0.03836
6479	0.7663	0.5029	-0.7106
9968	0.9778	0.6171	-0.4939
4.761e+004	2.062	1.155	0.04516
1.378e+005	2.351	1.289	0.5245

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	-9.701316	7	33.40263
A2	4.934967	12	14.13007
A3	2.296438	8	11.40712
R	-29.51921	2	63.03841
4	1.548351	5	6.903297

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	68.91	10	< 0.0001
Test 2	29.27	5	< 0.0001
Test 3	5.277	4	0.26
Test 6a	1.496	3	0.6832

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.

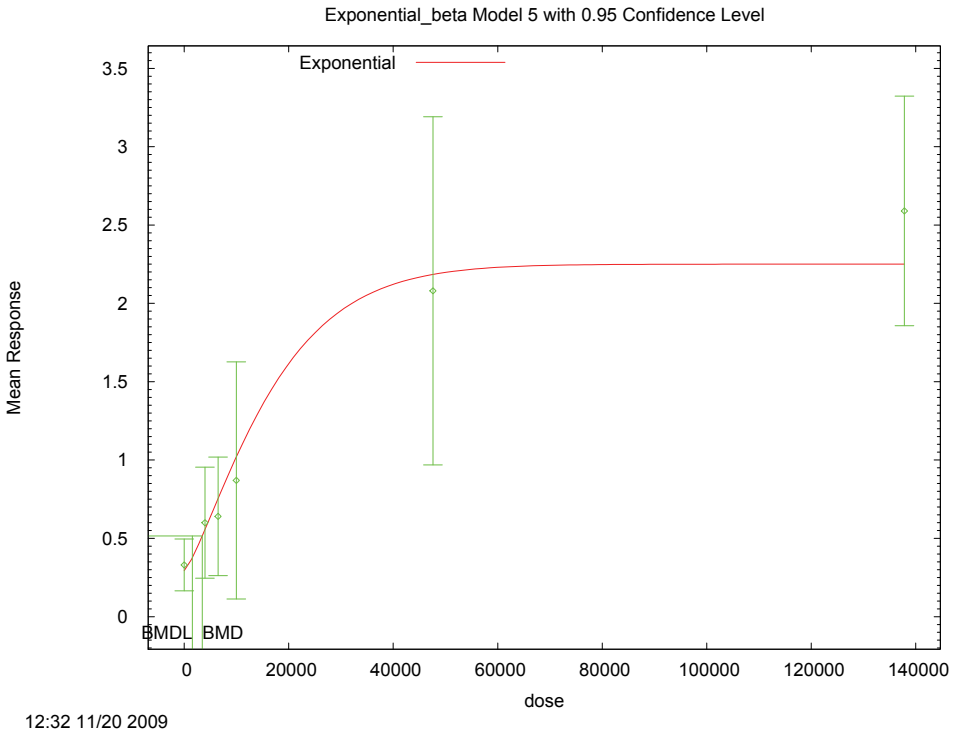
The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

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 =       2726.3

               BMDL =      1491.73
```

H.2.9.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



H.2.9.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_Unrest_BMR1_T4_UGT.(d)
         Gnuplot Plotting File:
                                                Fri Nov 20 12:32:13 2009
 ========================================================================

 Tbl2, T4 UGT
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
```

```
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 = 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 5
              --------          --------
                lnalpha           -0.937573
                    rho             1.54913
                      a              0.3135
                      b         2.19381e-005
                      c              8.67464
                      d                    1


                Parameter Estimates

               Variable          Model 5
               --------          -------
                lnalpha         -0.934825
                    rho           1.69365
                      a          0.293644
                      b      5.48685e-005
                      c           7.66316
                      d           1.27403


        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      8         0.33        0.198
   3969      8          0.6       0.4243
   6479      8         0.64       0.4525
   9968      8         0.87       0.9051
  4.761e+004      8         2.08        1.329
  1.378e+005      8         2.59       0.8768


              Estimated Values of Interest

  Dose      Est Mean      Est Std     Scaled Residual
```

0	0.2936	0.222	0.4632
3969	0.555	0.3806	0.334
6479	0.7533	0.4929	-0.6498
9968	1.019	0.6369	-0.6636
4.761e+004	2.185	1.215	-0.2441
1.378e+005	2.25	1.245	0.7717

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	-9.701316	7	33.40263
A2	4.934967	12	14.13007
A3	2.296438	8	11.40712
R	-29.51921	2	63.03841
5	1.725713	6	8.548574

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 7a: Does Model 5 fit the data? (A3 vs 5)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	68.91	10	< 0.0001
Test 2	29.27	5	< 0.0001
Test 3	5.277	4	0.26
Test 7a	1.141	2	0.5651

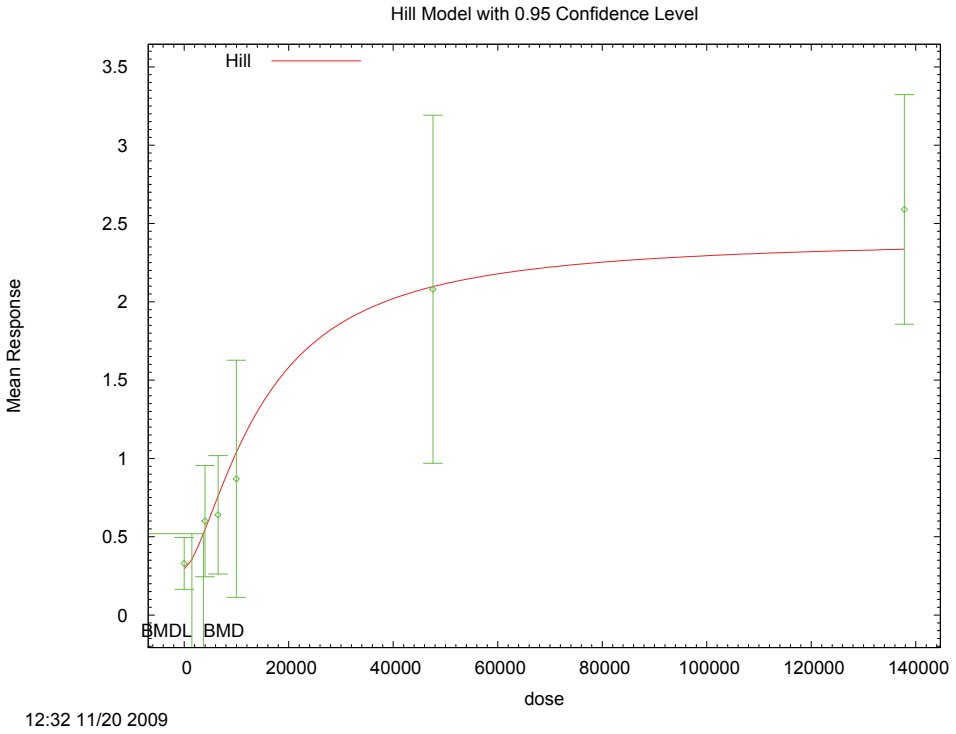
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

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 7a is greater than .1.  Model 5 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 =      3460.45

               BMDL =      1550.03
```

H.2.9.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



H.2.9.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

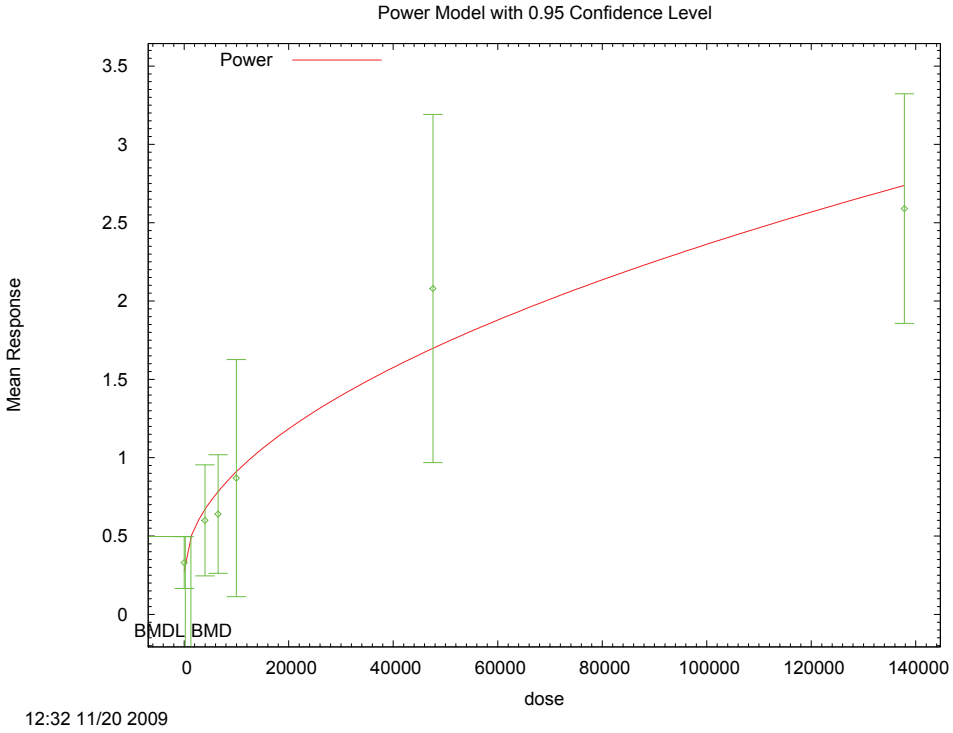
```
 ========================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_T4_UGT.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_T4_UGT.plt
                                                Fri Nov 20 12:32:14 2009
 ========================================================================

 Tbl2, T4 UGT
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 =    -0.462247
                           rho =            0
                     intercept =         0.33
                             v =         2.26
                             n =     0.525864
                             k =      66891.8


          Asymptotic Correlation Matrix of Parameter Estimates

                lalpha          rho    intercept            v            n            k

    lalpha           1        0.035        -0.26        -0.18       -0.017        0.038

       rho       0.035            1         0.48        -0.49        0.023        -0.21

 intercept       -0.26         0.48            1        -0.37         0.26        -0.14

         v       -0.18        -0.49        -0.37            1        -0.59         0.77

         n      -0.017        0.023         0.26        -0.59            1        -0.84

         k       0.038        -0.21        -0.14         0.77        -0.84            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        lalpha        -0.933225          0.25643           -1.43582           -0.430632
           rho          1.68188         0.441442           0.816665             2.54709
     intercept         0.294743        0.0705015           0.156563            0.432924
             v          2.10713         0.497534            1.13198             3.08228
             n          1.51694         0.601141            0.33872             2.69515
             k          14931.4          7059.91            1094.23             28768.6


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     8       0.33        0.295        0.198        0.224          0.444
 3969     8        0.6        0.544        0.424        0.376          0.424
 6479     8       0.64        0.758        0.453        0.497         -0.672
 9968     8       0.87         1.04        0.905        0.646         -0.723
4.761e+004     8       2.08         2.09         1.33         1.17        -0.0297
1.378e+005     8       2.59         2.33        0.877         1.28          0.571
```

```
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           -9.701316           7      33.402631
             A2            4.934967          12      14.130066
             A3            2.296438           8      11.407124
         fitted            1.684209           6       8.631582
              R          -29.519205           2      63.038411


                   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              68.9083         10          <.0001
  Test 2              29.2726          5          <.0001
  Test 3              5.27706          4            0.26
  Test 4              1.22446          2          0.5421

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 =        3674.98
```

```
BMDL =       1463.66
```

H.2.9.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



H.2.9.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_T4_UGT.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_T4_UGT.plt
                                                Fri Nov 20 12:32:14 2009
 ================================================================

 Tbl2, T4 UGT
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =    -0.462247
                             rho =            0
                         control =         0.33
                           slope =   0.00102277
                           power =     0.650735


            Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho      control        slope        power

     lalpha            1        0.031        -0.26        -0.13        0.074

        rho        0.031            1         0.58         0.11        -0.18

    control        -0.26         0.58            1        -0.13        0.067

      slope        -0.13         0.11        -0.13            1        -0.99

      power        0.074        -0.18        0.067        -0.99            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha        -0.836884         0.261303           -1.34903           -0.324739
            rho          1.68473         0.453932           0.795038             2.57442
        control           0.2748        0.0676712           0.142167            0.407433
          slope       0.00549254       0.00532631        -0.00494685           0.0159319
          power         0.516485        0.0924979           0.335192            0.697777


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     8       0.33        0.275        0.198        0.222          0.704
 3969     8        0.6        0.671        0.424        0.471          -0.43
 6479     8       0.64        0.786        0.453        0.537         -0.767
 9968     8       0.87        0.913        0.905         0.61          -0.2
4.761e+004     8       2.08         1.71         1.33         1.03           1.02
1.378e+005     8       2.59         2.75        0.877         1.54         -0.299


 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	-9.701316	7	33.402631
A2	4.934967	12	14.130066
A3	2.296438	8	11.407124
fitted	-0.712209	5	11.424417
R	-29.519205	2	63.038411

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	68.9083	10	<.0001
Test 2	29.2726	5	<.0001
Test 3	5.27706	4	0.26
Test 4	6.01729	3	0.1108

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 = 1286.41

BMDL = 212.264

H.2.10. Van Birgelen et al. (1995b): UGT 1A1

H.2.10.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	3	0.00	29.05	<0.0001	166.85	8.1E+04	2.4E+04	nonconstant variance, power restricted ≥1
exponential (M3)	3	0.00	29.05	<0.0001	166.85	8.1E+04	2.4E+04	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**2**	**0.00**	**1.04**	**0.60**	**140.83**	**4.0E+02**	**2.2E+02**	**nonconstant variance, power restricted ≥1**
exponential (M5)	1	0.00	0.97	0.32	142.77	5.0E+02	2.2E+02	nonconstant variance, power restricted ≥1
exponential (M5) [d]	1	0.00	0.97	0.32	142.77	5.0E+02	2.2E+02	nonconstant variance, power unrestricted
Hill	1	0.00	1.27	0.26	143.07	8.2E+02	error	nonconstant variance, n restricted >1
Hill [d]	1	0.00	1.27	0.26	143.07	8.2E+02	error	nonconstant variance, n unrestricted
linear	3	0.00	26.47	<.0001	164.27	1.8E+04	5.3E+02	nonconstant variance
polynomial	3	0.00	31.07	<.0001	168.87	3.5E+05	4.9E+02	nonconstant variance
power	3	0.00	26.47	<.0001	164.27	1.8E+04	5.3E+02	nonconstant variance, power restricted ≥1, bound hit
power [d]	2	0.00	5.95	0.05	145.75	3.8E+00	2.3E-04	nonconstant variance, power unrestricted
exponential (M2)	3	0.00	22.21	<0.0001	165.71	1.6E+05	8.3E+04	constant variance, power restricted ≥1
exponential (M3)	3	0.00	22.21	<0.0001	165.71	1.6E+05	8.3E+04	constant variance, power restricted ≥1
exponential (M4)	2	0.00	8.05	0.02	153.55	2.6E+03	1.2E+03	constant variance, power restricted ≥1
exponential (M5)	1	0.00	7.88	0.00	155.38	3.3E+03	1.2E+03	constant variance, power restricted ≥1
exponential (M5)	1	0.00	7.88	0.00	155.38	3.3E+03	1.2E+03	constant variance, power unrestricted
Hill	1	0.00	8.12	0.00	155.61	3.7E+03	9.6E+02	constant variance, n restricted >1
Hill	1	0.00	8.12	0.00	155.61	3.7E+03	8.8E+02	constant variance, n unrestricted
linear	3	0.00	21.83	<.0001	165.32	1.3E+05	6.2E+04	constant variance
polynomial	3	0.00	21.83	<.0001	165.32	1.3E+05	6.2E+04	constant variance
power	3	0.00	21.83	<.0001	165.32	1.3E+05	6.2E+04	constant variance, power restricted ≥1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
power	2	0.00	13.23	0.00	158.73	7.2E+01	1.6E-06	constant variance, power unrestricted

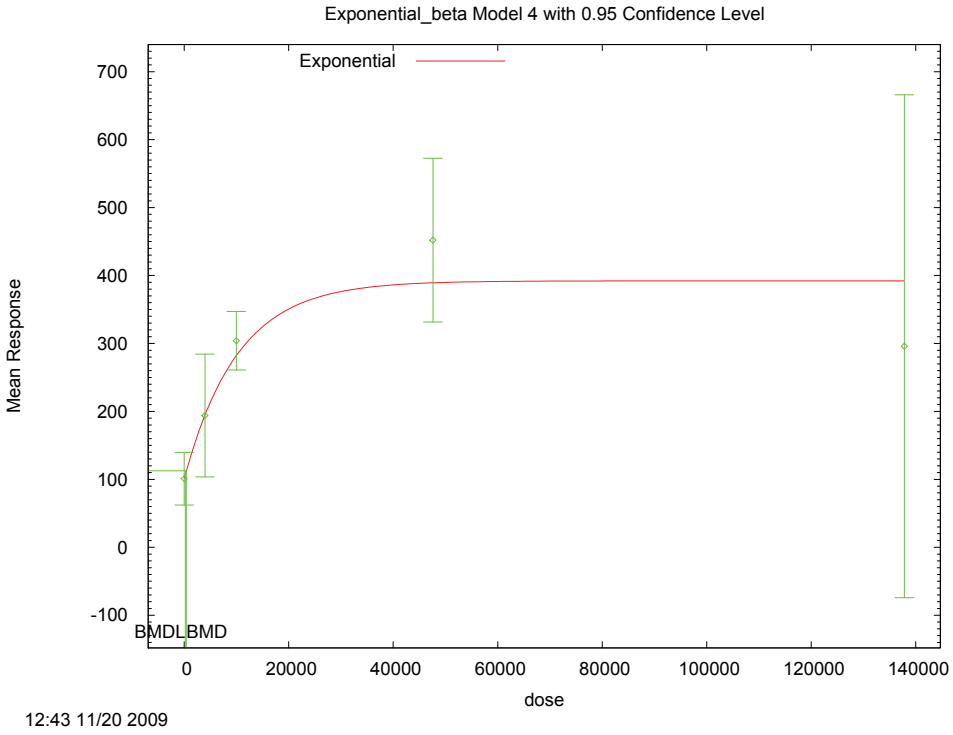
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.2.10.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



H.2.10.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

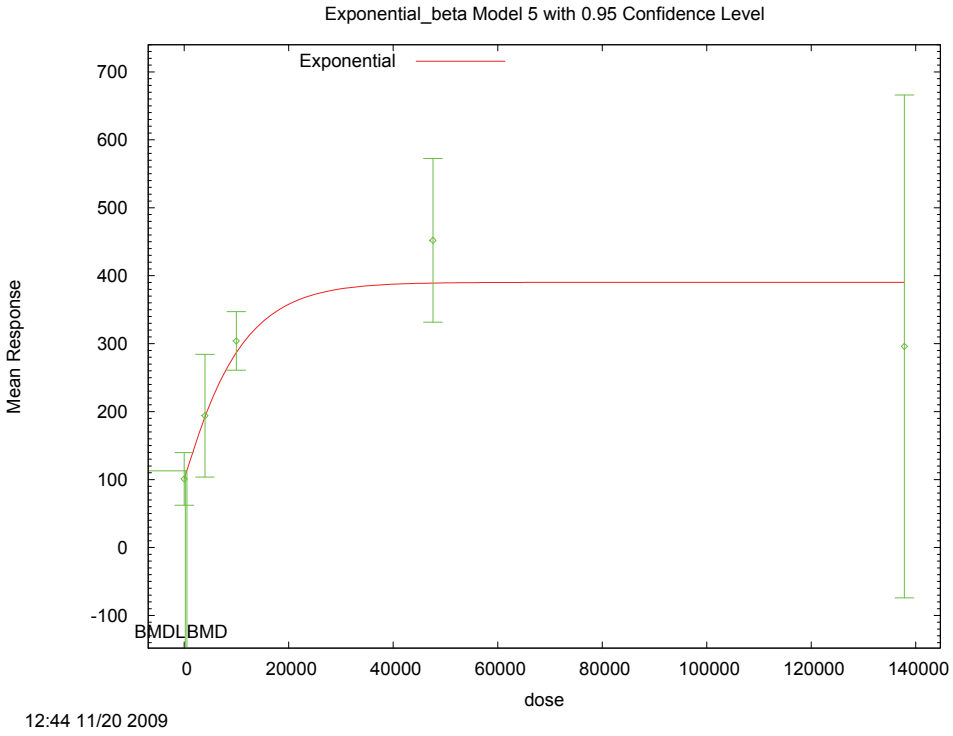
```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_BMR1_UGT_1A1.(d)
         Gnuplot Plotting File:
                                                Fri Nov 20 12:43:51 2009
 ========================================================================

 Tbl2, UGT_1A1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 4
                --------          --------
                  lnalpha            -1.53604
                      rho             1.59958
                        a               95.95
                        b         1.15499e-005
                        c              4.94633
                        d                    1


                  Parameter Estimates

                 Variable          Model 4
                 --------          -------
                  lnalpha          -10.3642
                      rho           3.29138
                        a           101.591
                        b       0.000102786
                        c           3.84125
                        d           1.08913


         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      3          101        15.59
   3969      3          194        36.37
   9968      3          304        17.32
  4.761e+004      3          452         48.5
  1.378e+005      3          296          149


                Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         101.5        11.18         -0.07335
   3969         194.7        32.89         -0.03837
   9968         282.1        60.75           0.6236
```

```
4.761e+004         389.3        103.5            1.049
1.378e+005         392.1        104.7           -1.589


   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       -68.74833           6      149.4967
                       A2       -58.69126          10      137.3825
                       A3       -64.89907           7      143.7981
                        R       -80.72265           2      165.4453
                        4       -65.41669           5      140.8334


   Additive constant for all log-likelihoods =     -13.78.  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                      44.06             8           < 0.0001
     Test 2                      20.11             4          0.0004741
     Test 3                      12.42             3           0.006087
    Test 6a                      1.035             2             0.5959


     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 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 =      402.539

                 BMDL =      221.776
```

H.2.10.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



H.2.10.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Exp_Unrest_BMR1_UGT_1A1.(d)
         Gnuplot Plotting File:
                                                 Fri Nov 20 12:44:01 2009
 ========================================================================

 Tbl2, UGT_1A1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 5
                --------          --------
                  lnalpha             -1.53604
                      rho              1.59958
                        a                95.95
                        b          1.15499e-005
                        c              4.94633
                        d                     1



                  Parameter Estimates

                 Variable          Model 5
                 --------          -------
                  lnalpha          -10.3642
                      rho           3.29138
                        a           101.591
                        b       0.000102786
                        c           3.84125
                        d           1.08913


          Table of Stats From Input Data

    Dose      N         Obs Mean     Obs Std Dev
    -----    ---       ----------   -------------
        0      3          101        15.59
     3969      3          194        36.37
     9968      3          304        17.32
    4.761e+004      3          452         48.5
    1.378e+005      3          296          149


                Estimated Values of Interest

     Dose      Est Mean      Est Std     Scaled Residual
    ------    ----------    ---------    ----------------
        0         101.6        11.28         -0.09081
     3969         192.2        32.19          0.09829
     9968         286.9        62.23           0.4773
4.761e+004         389.2        102.8            1.058
1.378e+005         390.2        103.3           -1.581
```

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	-68.74833	6	149.4967
A2	-58.69126	10	137.3825
A3	-64.89907	7	143.7981
R	-80.72265	2	165.4453
5	-65.38628	6	142.7726

Additive constant for all log-likelihoods = -13.78. 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	44.06	8	< 0.0001
Test 2	20.11	4	0.0004741
Test 3	12.42	3	0.006087
Test 7a	0.9744	1	0.3236

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.

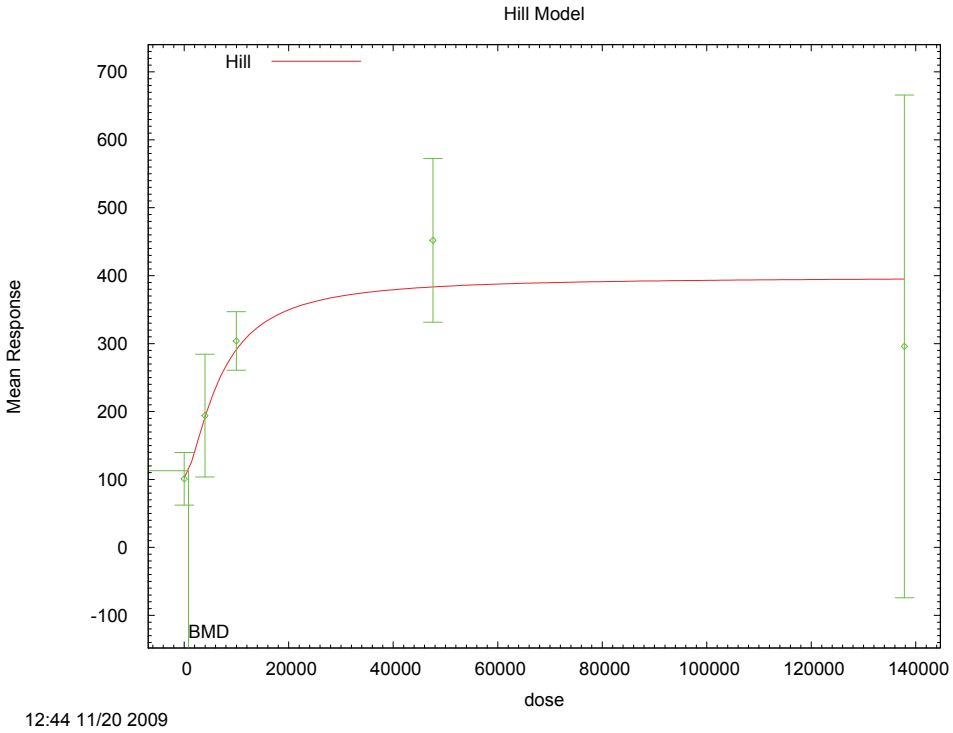
The p-value for Test 7a is greater than .1. Model 5 seems to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 1.000000

```
            Risk Type = Estimated standard deviations from control

      Confidence Level = 0.950000

                   BMD =      504.638

                  BMDL =      223.156
```

H.2.10.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



H.2.10.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ========================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_UGT_1A1.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Blood\Hill_Unrest_BMR1_UGT_1A1.plt
                                                 Fri Nov 20 12:44:02 2009
 ========================================================================

 Tbl2, UGT_1A1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =	8.57191
rho =	0
intercept =	101
v =	351
n =	0.350477
k =	11467.2

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	intercept	v	n	k
lalpha	1	-0.99	-0.19	0.14	0.12	-0.0083
rho	-0.99	1	0.18	-0.17	-0.12	-0.0038
intercept	-0.19	0.18	1	-0.12	0.031	0.1
v	0.14	-0.17	-0.12	1	-0.57	0.79
n	0.12	-0.12	0.031	-0.57	1	-0.73
k	-0.0083	-0.0038	0.1	0.79	-0.73	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-10.4997	3.7002	-17.752	-3.24748
rho	3.31877	0.67548	1.99485	4.64269
intercept	101.641	6.48455	88.9319	114.351
v	296.324	52.8989	192.644	400.003
n	1.52651	0.645076	0.262182	2.79084
k	6852.92	2333.57	2279.2	11426.6

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	3	101	102	15.6	11.2	-0.0989
3969	3	194	191	36.4	32.1	0.141
9968	3	304	291	17.3	64.4	0.348
4.761e+004	3	452	383	48.5	102	1.17
1.378e+005	3	296	395	149	107	-1.6

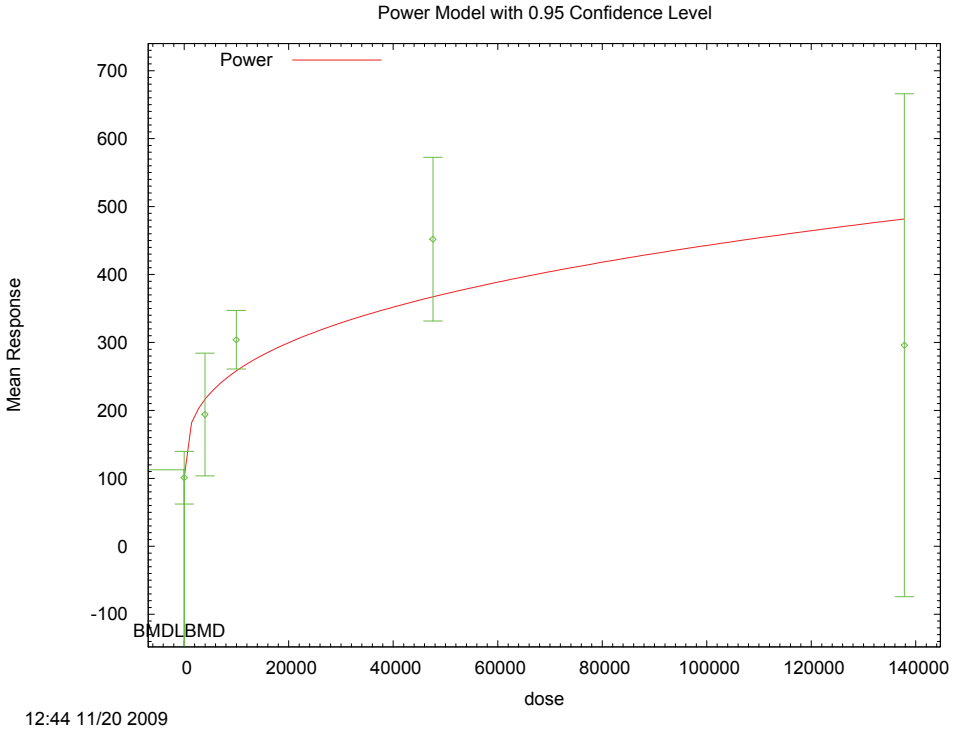
Model Descriptions for likelihoods calculated

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          -68.748326            6     149.496653
            A2          -58.691256           10     137.382511
            A3          -64.899072            7     143.798144
        fitted          -65.536514            6     143.073028
             R          -80.722651            2     165.445302


                  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              44.0628          8          <.0001
  Test 2              20.1141          4        0.0004741
  Test 3              12.4156          3         0.006087
  Test 4              1.27488          1           0.2589

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 =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =         823.8


BMDL computation failed.
```

H.2.10.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



H.2.10.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_UGT_1A1.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Blood\Pwr_Unrest_BMR1_UGT_1A1.plt
                                                Fri Nov 20 12:44:03 2009
 ================================================================

 Tbl2, UGT_1A1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =      8.57191
                             rho =            0
                         control =          101
                           slope =      19.8524
                           power =     0.225107


            Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho      control        slope        power

     lalpha            1        -0.99        -0.22       0.0058        0.021

        rho        -0.99            1         0.21        0.024       -0.057

    control        -0.22         0.21            1        -0.14         0.11

      slope       0.0058        0.024        -0.14            1        -0.99

      power        0.021       -0.057         0.11        -0.99            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -11.5995          3.46108           -18.3831            -4.81588
            rho          3.55351         0.629824            2.31908             4.78795
        control          101.406          6.37341            88.9147             113.898
          slope          7.06329          7.31729           -7.27833             21.4049
          power         0.337328         0.106575           0.128444            0.546212


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     3        101          101         15.6         11.1        -0.0634
 3969     3        194          217         36.4         42.9         -0.928
 9968     3        304          259         17.3         58.8           1.32
4.761e+004     3        452          369         48.5          110           1.31
1.378e+005     3        296          484          149          178          -1.82


 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          -68.748326           6     149.496653
```

A2	-58.691256	10	137.382511
A3	-64.899072	7	143.798144
fitted	-67.875596	5	145.751193
R	-80.722651	2	165.445302

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	44.0628	8	<.0001
Test 2	20.1141	4	0.0004741
Test 3	12.4156	3	0.006087
Test 4	5.95305	2	0.05097

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 = 3.82374

BMDL = 0.000231902

H.2.11. Vanden Heuvel et al. (1994): Hepatic CYP1A1 mRNA Expression

H.2.11.1. *Summary Table of BMDS Modeling Results*

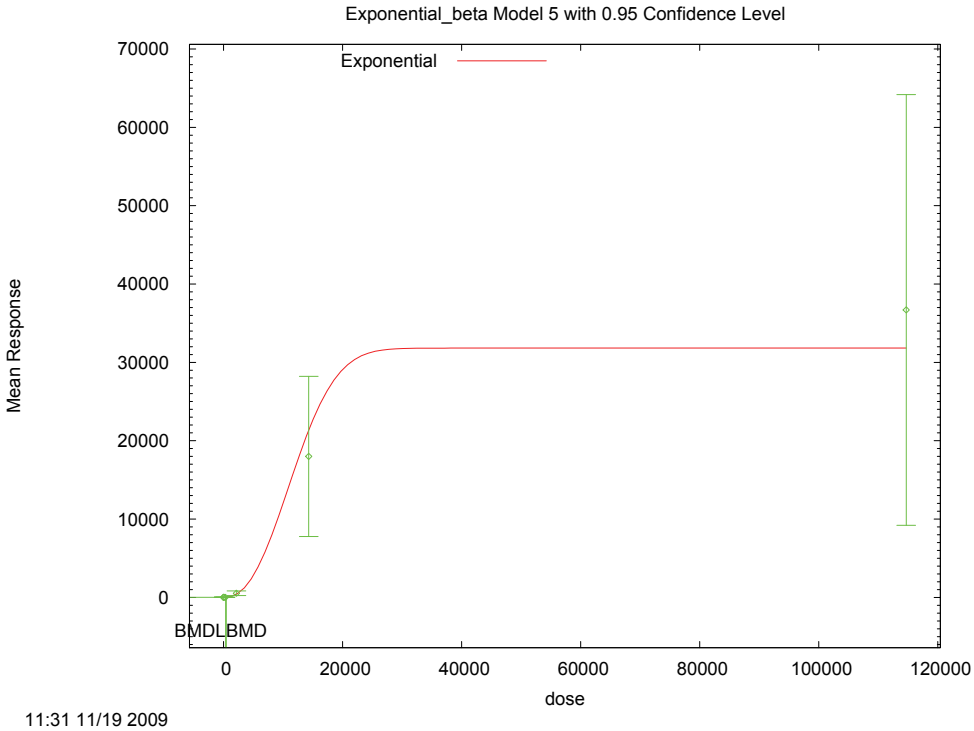
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	5	<0.0001	518.90	<0.0001	1114.48	4.2E+03	3.2E+03	nonconstant variance, power restricted ≥1
exponential (M3)	5	<0.0001	518.90	<0.0001	1114.48	4.2E+03	3.2E+03	nonconstant variance, power restricted ≥1
exponential (M4)	4	<0.0001	71.31	<0.0001	668.92	2.2E+01	1.0E+01	nonconstant variance, power restricted ≥1
exponential (M5) [c]	**3**	**<0.0001**	**35.23**	**<0.0001**	**634.84**	**4.5E+02**	**3.3E+02**	**nonconstant variance, power restricted ≥1**
Hill	3	<.0001	33.65	<.0001	633.26	5.3E+02	error	nonconstant variance, n restricted >1
linear	5	<.0001	79.92	<.0001	675.53	1.6E+01	8.5E+00	nonconstant variance
polynomial	5	<.0001	235.66	<.0001	831.27	1.4E+05	3.0E+02	nonconstant variance
power	4	<.0001	77.35	<.0001	674.96	2.1E+01	1.1E+01	nonconstant variance, power restricted ≥1
exponential (M2)	5	<0.0001	27.27	<0.0001	1178.21	6.7E+04	5.9E+04	constant variance, power restricted ≥1
exponential (M3)	4	<0.0001	62.38	<0.0001	1215.33	1.6E+09	6.0E+06	constant variance, power restricted ≥1
exponential (M4)	4	<0.0001	0.86	0.93	1153.81	5.8E+03	4.1E+03	constant variance, power restricted ≥1
exponential (M5)	3	<0.0001	0.00	1.00	1154.95	9.0E+03	4.4E+03	constant variance, power restricted ≥1
Hill	3	<.0001	0.00	1.00	1154.95	8.4E+03	3.5E+03	constant variance, n restricted >1
linear	5	<.0001	19.42	0.00	1170.37	3.0E+04	2.4E+04	constant variance
polynomial	5	<.0001	26.27	<.0001	1177.21	2.4E+04	2.1E+04	constant variance
power	5	<.0001	19.32	0.00	1170.27	3.1E+04	2.4E+04	constant variance, power restricted ≥1, bound hit

[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

H.2.11.2. *Figure for Selected Model: Exponential (M5), Nonconstant Variance, Power Restricted ≥1*



H.2.11.3. *Output File for Selected Model: Exponential (M5), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\AD\Blood\Exp_BMR1_hepatic_CYP1A1_mRNA_expression.(d)
         Gnuplot Plotting File:
                                                  Thu Nov 19 11:31:49 2009
 ================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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

MLE solution provided: Exact
```

Initial Parameter Values

Variable	Model 5
lnalpha	-0.89532
rho	2.01401
a	5.13
b	2.68046e-005
c	7511.7
d	1

Parameter Estimates

Variable	Model 5
lnalpha	0.166401
rho	1.90534
a	9.80088
b	7.30524e-005
c	3246.67
d	2.37353

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	13	5.4	3.606
3.805	5	7.2	5.59
35.91	12	14.8	14.9
301.9	7	12.8	4.498
2149	7	536	320.1
1.43e+004	11	1.8e+004	1.522e+004
1.147e+005	5	3.67e+004	2.214e+004

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	9.801	9.561	-1.66
3.805	9.801	9.561	-0.6083
35.91	9.825	9.583	1.799
301.9	13.52	12.99	-0.1474
2149	400.1	327.4	1.099
1.43e+004	2.133e+004	1.446e+004	-0.7638
1.147e+005	3.182e+004	2.117e+004	0.5154

```
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       -572.4744           8      1160.949
                      A2       -290.7965          14      609.5929
                      A3        -293.806           9      605.6119
                       R       -603.6646           2      1211.329
                       5       -311.4203           6      634.8406


Additive constant for all log-likelihoods =     -55.14.  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                       625.7            12           < 0.0001
  Test 2                       563.4             6           < 0.0001
  Test 3                       6.019             5             0.3044
 Test 7a                       35.23             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 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 =      449.252

              BMDL =      332.057
```

H.3. ADMINISTERED DOSE BMDS RESULTS

H.3.1. Hassoun et al. (2000): CytC Liver

H.3.1.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	4	0.39	15.15	0.00	-140.98	2.8E+01	1.9E+01	nonconstant variance, power restricted ≥1
exponential (M3)	4	0.39	15.15	0.00	-140.98	2.8E+01	1.9E+01	nonconstant variance, power restricted ≥1
exponential (M4)	3	0.39	1.73	0.63	-152.40	7.5E+00	4.6E+00	nonconstant variance, power restricted ≥1
exponential (M5)	2	0.39	0.56	0.76	-151.57	1.2E+01	5.2E+00	nonconstant variance, power restricted ≥1
exponential (M5)	2	0.39	0.56	0.76	-151.57	1.2E+01	5.2E+00	nonconstant variance, power unrestricted
Hill	2	0.39	0.67	0.72	-151.46	1.3E+01	error	nonconstant variance, n restricted >1
Hill	2	0.39	0.67	0.72	-151.46	1.3E+01	4.5E+00	nonconstant variance, n unrestricted
linear	4	0.39	7.87	0.10	-148.27	1.5E+01	1.0E+01	nonconstant variance
polynomial	4	0.39	7.87	0.10	-148.27	1.5E+01	1.0E+01	nonconstant variance
power	4	0.39	7.87	0.10	-148.27	1.5E+01	1.0E+01	nonconstant variance, power restricted ≥1, bound hit
power	3	0.39	3.95	0.27	-150.18	5.6E+00	1.7E+00	nonconstant variance, power unrestricted
exponential (M2)	4	0.39	16.43	0.00	-139.08	3.9E+01	3.3E+01	constant variance, power restricted ≥1
exponential (M3)	4	0.39	16.43	0.00	-139.08	3.9E+01	3.3E+01	constant variance, power restricted ≥1
exponential (M4) [c]	**3**	**0.39**	**1.70**	**0.64**	**-151.81**	**9.1E+00**	**5.9E+00**	**constant variance, power restricted ≥1**
exponential (M5)	2	0.39	0.48	0.79	-151.02	1.4E+01	6.5E+00	constant variance, power restricted ≥1
exponential (M5) [d]	2	0.39	0.48	0.79	-151.02	1.4E+01	6.5E+00	constant variance, power unrestricted
Hill	2	0.39	0.60	0.74	-150.90	1.5E+01	6.3E+00	constant variance, n restricted >1
Hill [d]	2	0.39	0.60	0.74	-150.90	1.5E+01	5.9E+00	constant variance, n unrestricted
linear	4	0.39	10.56	0.03	-144.95	2.5E+01	1.9E+01	constant variance
polynomial	4	0.39	10.56	0.03	-144.95	2.5E+01	1.9E+01	constant variance

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
power	4	0.39	10.56	0.03	-144.95	2.5E+01	1.9E+01	constant variance, power restricted ≥1, bound hit
power [d]	3	0.39	4.52	0.21	-148.99	6.6E+00	2.0E+00	constant variance, power unrestricted

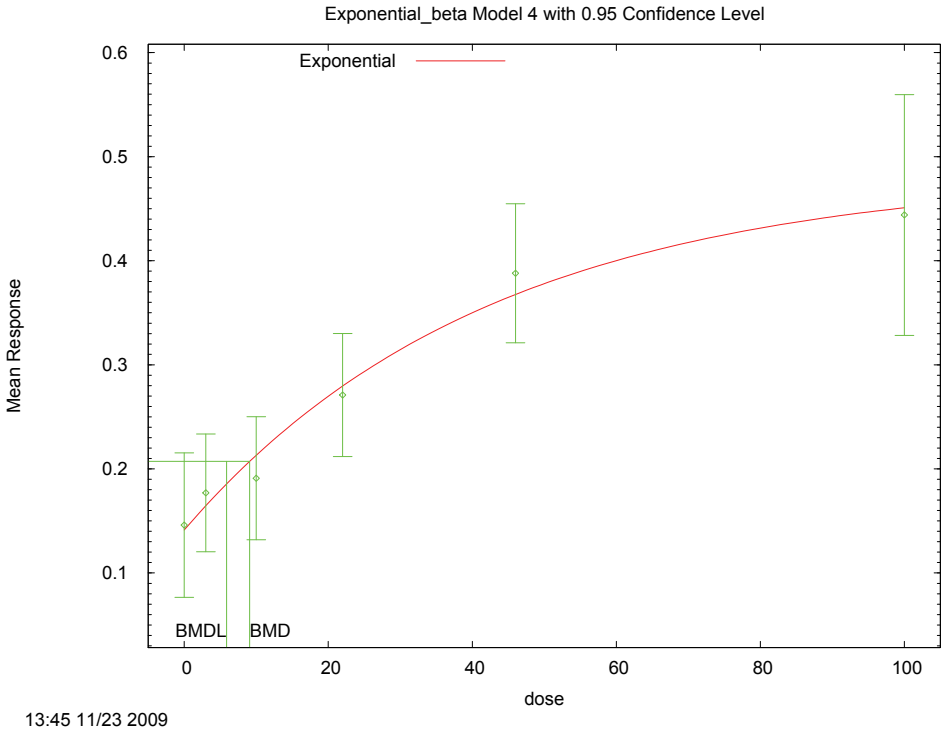
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]**Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix**

[d]Alternate model also presented in this appendix

H.3.1.2. *Figure for Selected Model: Exponential (M4), Constant Variance, Power Restricted ≥1*



H.3.1.3. *Output File for Selected Model: Exponential (M4), Constant Variance, Power Restricted ≥1*

```
================================================================
        Exponential Model. (Version: 1.5;  Date: 4/23/2009)
        Input Data File: C:\USEPA\BMDS21\Nov23\Exp_CV_BMR1_CytC_Liver.(d)
        Gnuplot Plotting File:
                                                Mon Nov 23 13:45:24 2009
================================================================

TBARs, liver only (Table 2)
```

```
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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             -5.48625
                        rho(S)                 0
                          a              0.1387
                          b             0.027423
                          c              3.36121
                          d                    1

     (S) = Specified


                    Parameter Estimates

                   Variable          Model 4
                   --------          -------
                    lnalpha          -5.47287
                        rho                 0
                          a          0.156285
                          b         0.0293581
                          c           2.85125
                          d           1.56807


           Table of Stats From Input Data

      Dose      N         Obs Mean     Obs Std Dev
      -----    ---       ----------   -------------
         0      6        0.146      0.06614
         3      6        0.177      0.05389
        10      6        0.191      0.05634
        22      6        0.271      0.05634
        46      6        0.388      0.06369
       100      6        0.444       0.1102
```

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.1413	0.06591	0.1762
3	0.1646	0.06591	0.4609
10	0.2131	0.06591	-0.8196
22	0.2796	0.06591	-0.3199
46	0.3676	0.06591	0.7587
100	0.4509	0.06591	-0.2564

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	80.75258	7	-147.5052
A2	83.37355	12	-142.7471
A3	80.75258	7	-147.5052
R	55.82002	2	-107.64
4	79.90337	4	-151.8067

Additive constant for all log-likelihoods = -33.08. 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

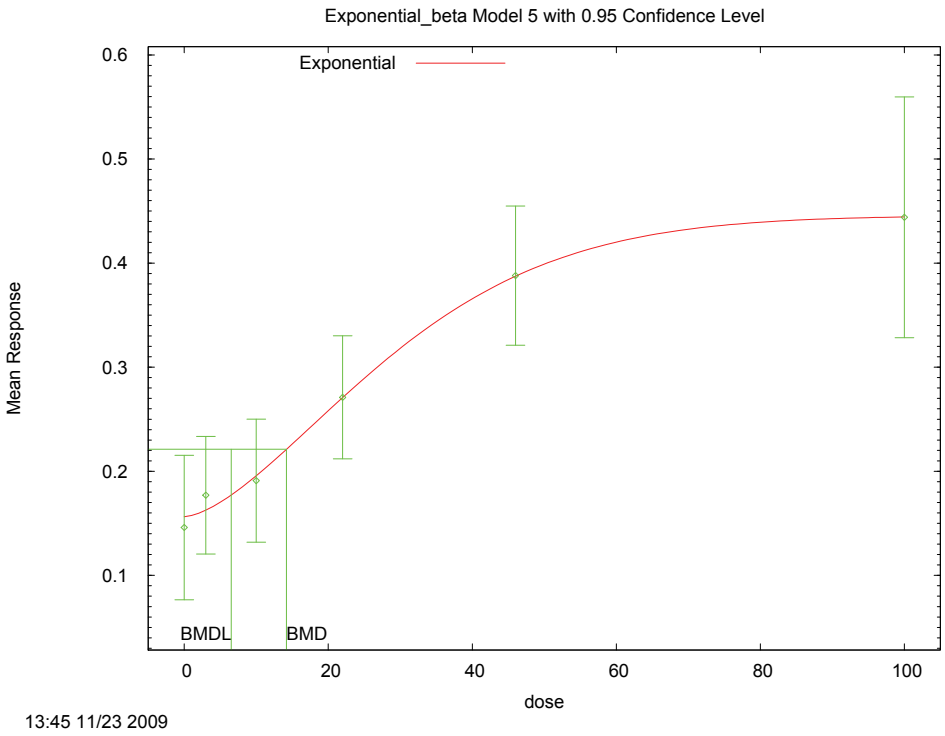
Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	55.11	10	< 0.0001
Test 2	5.242	5	0.3871
Test 3	5.242	5	0.3871
Test 6a	1.698	3	0.6373

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 =       9.0851

              BMDL =      5.88612
```

H.3.1.4. *Figure for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*



H.3.1.5. *Output File for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*

```
=================================================================
        Exponential Model. (Version: 1.5;  Date: 4/23/2009)
        Input Data File: C:\USEPA\BMDS21\Nov23\Exp_CV_Unrest_BMR1_CytC_Liver.(d)
        Gnuplot Plotting File:
                                                Mon Nov 23 13:45:31 2009
=================================================================
```

TBARs, liver only (Table 2)

~~~~~~

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 = 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 5
lnalpha	-5.48625
rho(S)	0
a	0.1387
b	0.027423
c	3.36121
d	1

(S) = Specified

Parameter Estimates

Variable	Model 5
lnalpha	-5.47287
rho	0
a	0.156285
b	0.0293581
c	2.85125
d	1.56807

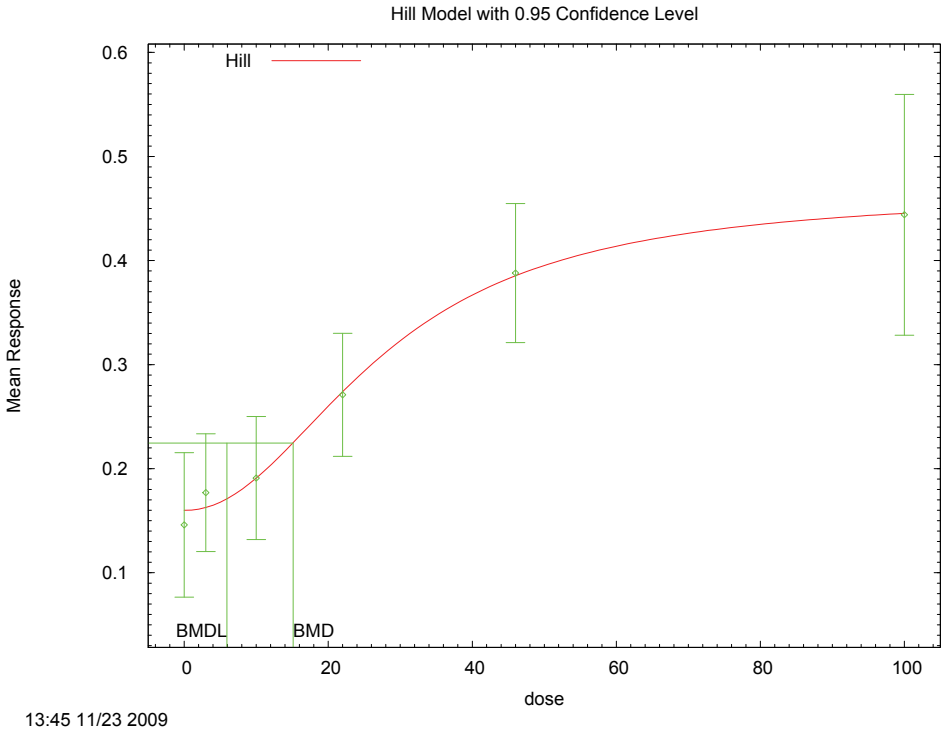
Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	6	0.146	0.06614
3	6	0.177	0.05389
10	6	0.191	0.05634
22	6	0.271	0.05634
46	6	0.388	0.06369
~~~~~~

```
   100      6        0.444       0.1102


                Estimated Values of Interest

    Dose      Est Mean      Est Std     Scaled Residual
  ------    ----------    ---------    ----------------
       0        0.1563       0.0648          -0.3888
       3        0.1626       0.0648           0.5434
      10        0.1957       0.0648          -0.1766
      22        0.2708       0.0648         0.007576
      46        0.3873       0.0648          0.02644
     100        0.4443       0.0648         -0.01203


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        80.75258            7     -147.5052
                    A2        83.37355           12     -142.7471
                    A3        80.75258            7     -147.5052
                     R        55.82002            2       -107.64
                     5        80.51171            5     -151.0234


Additive constant for all log-likelihoods =     -33.08.  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                      55.11            10           < 0.0001
  Test 2                      5.242             5             0.3871
  Test 3                      5.242             5             0.3871
 Test 7a                     0.4817             2             0.7859


  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 7a is greater than .1.  Model 5 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 =      14.1987

                BMDL =      6.53738
```

H.3.1.6. *Figure for Unrestricted Model: Hill, Constant Variance, n Unrestricted*



H.3.1.7. *Output File for Unrestricted Model: Hill, Constant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Hill_CV_Unrest_BMR1_CytC_Liver.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Hill_CV_Unrest_BMR1_CytC_Liver.plt
                                                Mon Nov 23 13:45:33 2009
 ================================================================
```

TBARs, liver only (Table 2)

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 = 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

alpha =	0.004972	
rho =	0	Specified
intercept =	0.146	
v =	0.298	
n =	17.5689	
k =	65.0769	

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	8.6e-008	-3.4e-008	3.4e-008	8.6e-008
intercept	8.6e-008	1	-0.61	0.53	0.069
v	-3.4e-008	-0.61	1	-0.84	0.64
n	3.4e-008	0.53	-0.84	1	-0.52
k	8.6e-008	0.069	0.64	-0.52	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.00421303	0.00099302	0.00226674	0.00615931
intercept	0.159748	0.0202818	0.119997	0.1995
v	0.305175	0.0615956	0.18445	0.4259
n	2.11196	1.024	0.104959	4.11895
k	28.1195	6.8986	14.5985	41.6405

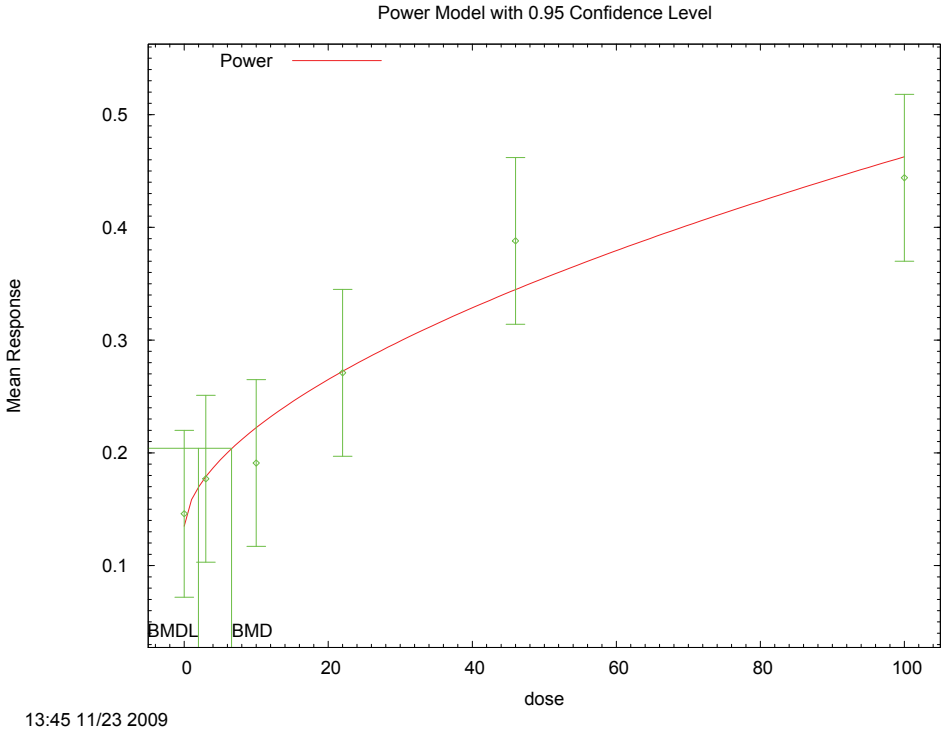
Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	0.146	0.16	0.0661	0.0649	-0.519
3	6	0.177	0.162	0.0539	0.0649	0.55

```
  10     6      0.191        0.191       0.0563       0.0649         0.0134
  22     6      0.271        0.274       0.0563       0.0649           -0.1
  46     6      0.388        0.385       0.0637       0.0649          0.106
 100     6      0.444        0.445         0.11       0.0649        -0.0503


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           80.752584           7    -147.505168
             A2           83.373547          12    -142.747094
             A3           80.752584           7    -147.505168
         fitted           80.452332           5    -150.904663
              R           55.820023           2    -107.640047


                   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               55.107         10          <.0001
  Test 2              5.24193          5          0.3871
  Test 3              5.24193          5          0.3871
  Test 4             0.600505          2          0.7406

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 =        15.1313

            BMDL =       5.93521
```

H.3.1.8. *Figure for Unrestricted Model: Power, Constant Variance, Power Unrestricted*



H.3.1.9. *Output File for Unrestricted Model: Power, Constant Variance, Power Unrestricted*

```
 ========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Pwr_CV_Unrest_BMR1_CytC_Liver.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Pwr_CV_Unrest_BMR1_CytC_Liver.plt
                                                Mon Nov 23 13:45:33 2009
 ========================================================================

 TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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

alpha =	0.004972	
rho =	0	Specified
control =	0.146	
slope =	0.0109242	
power =	0.717914	

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	-8.8e-010	-3.8e-009	4.5e-009
control	-8.8e-010	1	-0.77	0.68
slope	-3.8e-009	-0.77	1	-0.98
power	4.5e-009	0.68	-0.98	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.00469717	0.00110713	0.00252723	0.00686711
control	0.135495	0.0246289	0.0872229	0.183766
slope	0.0232652	0.013381	-0.00296103	0.0494915
power	0.573772	0.119032	0.340474	0.80707

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	0.146	0.135	0.0661	0.0685	0.375
3	6	0.177	0.179	0.0539	0.0685	-0.0784
10	6	0.191	0.223	0.0563	0.0685	-1.13
22	6	0.271	0.273	0.0563	0.0685	-0.056
46	6	0.388	0.345	0.0637	0.0685	1.54
100	6	0.444	0.462	0.11	0.0685	-0.653

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           80.752584            7    -147.505168
             A2           83.373547           12    -142.747094
             A3           80.752584            7    -147.505168
         fitted           78.494318            4    -148.988637
              R           55.820023            2    -107.640047


                    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               55.107         10          <.0001
  Test 2              5.24193          5          0.3871
  Test 3              5.24193          5          0.3871
  Test 4              4.51653          3          0.2108

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 = 6.57302


             BMDL = 1.96558
```

H.3.2. Hassoun et al. (2000): DNA SSB

H.3.2.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	4	0.75	47.92	<0.0001	121.75	3.8E+01	2.5E+01	nonconstant variance, power restricted ≥1
exponential (M3)	4	0.75	47.92	<0.0001	121.75	3.8E+01	2.5E+01	nonconstant variance, power restricted ≥1
exponential (M4)	3	0.75	8.98	0.03	84.81	3.7E+00	2.2E+00	nonconstant variance, power restricted ≥1
exponential (M5)	3	0.75	8.98	0.03	84.81	3.7E+00	2.2E+00	nonconstant variance, power restricted ≥1
exponential (M5)	3	0.75	8.98	0.03	84.81	3.7E+00	2.2E+00	nonconstant variance, power unrestricted
Hill	3	0.75	7.46	0.06	83.29	2.6E+00	1.4E+00	nonconstant variance, n restricted >1, bound hit
Hill	2	0.75	3.76	0.15	81.60	6.6E-01	1.8E-01	nonconstant variance, n unrestricted
linear	4	0.75	39.32	<.0001	113.16	1.9E+01	1.0E+01	nonconstant variance
polynomial	4	0.75	39.32	<.0001	113.16	1.9E+01	1.0E+01	nonconstant variance
power	4	0.75	39.32	<.0001	113.16	1.9E+01	1.0E+01	nonconstant variance, power restricted ≥1, bound hit
power	3	0.75	4.68	0.20	80.52	3.0E-01	8.5E-02	nonconstant variance, power unrestricted
exponential (M2)	4	0.75	48.54	<0.0001	120.83	3.0E+01	2.5E+01	constant variance, power restricted ≥1
exponential (M3)	4	0.75	48.54	<0.0001	120.83	3.0E+01	2.5E+01	constant variance, power restricted ≥1
exponential (M4)	3	0.75	8.53	0.04	82.81	3.7E+00	2.8E+00	constant variance, power restricted ≥1
exponential (M5)	3	0.75	8.53	0.04	82.81	3.7E+00	2.8E+00	constant variance, power restricted ≥1
exponential (M5) [d]	3	0.75	8.53	0.04	82.81	3.7E+00	2.8E+00	constant variance, power unrestricted
Hill [c]	**3**	**0.75**	**7.12**	**0.07**	**81.41**	**2.9E+00**	**2.0E+00**	**constant variance, n restricted >1, bound hit**
Hill [d]	2	0.75	4.03	0.13	80.32	9.6E-01	2.1E-01	constant variance, n unrestricted
linear	4	0.75	38.88	<.0001	111.16	1.8E+01	1.5E+01	constant variance
polynomial	4	0.75	38.88	<.0001	111.16	1.8E+01	1.5E+01	constant variance
power	4	0.75	38.88	<.0001	111.16	1.8E+01	1.5E+01	constant variance, power restricted ≥1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
power [d]	3	0.75	5.10	0.16	79.39	4.4E-01	1.5E-01	constant variance, power unrestricted

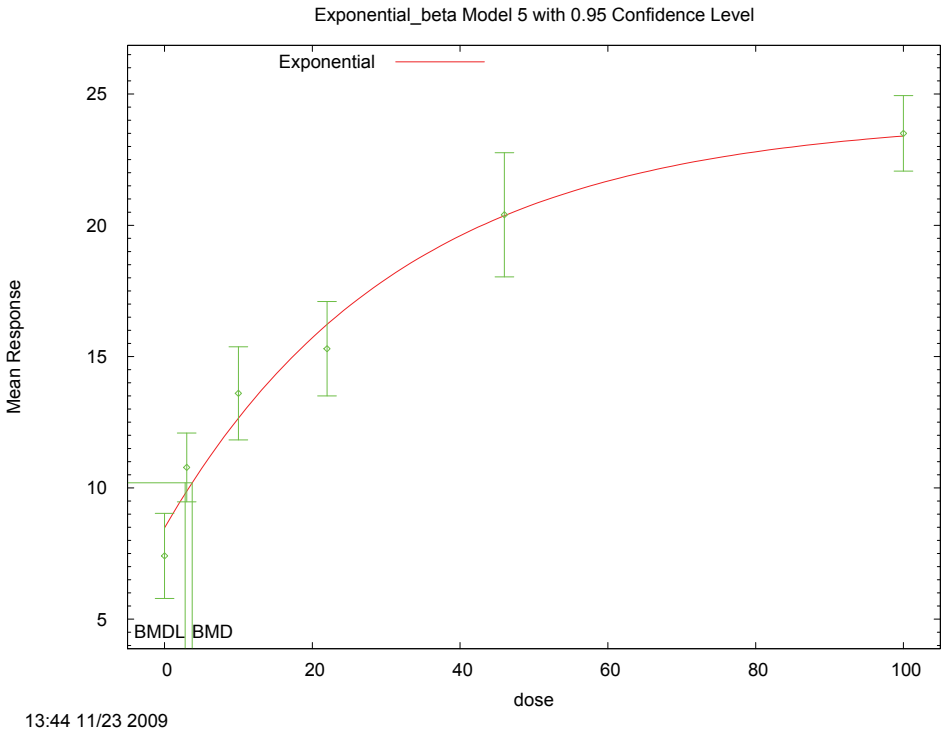
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.3.2.2. *Figure for Selected Model: Exponential (M5), Constant Variance, Power Unrestricted*



H.3.2.3. *Output File for Selected Model: Exponential (M5), Constant Variance, Power Unrestricted*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov23\Exp_CV_Unrest_BMR1_DNA_SSB.(d)
         Gnuplot Plotting File:
                                                Mon Nov 23 13:44:02 2009
 ================================================================

 DNA single-strand breaks, liver only (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 = 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 5
              --------          --------
                lnalpha            0.841244
                    rho(S)                0
                      a              7.0395
                      b           0.0279582
                      c             3.50522
                      d                   1

  (S) = Specified


                Parameter Estimates

               Variable          Model 5
               --------          -------
                lnalpha           1.07816
                    rho                 0
                      a           8.47733
                      b         0.0311513
                      c           2.84178
                      d                 1


        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
     0      6          7.41        1.543
     3      6         10.78        1.249
    10      6          13.6         1.69
    22      6          15.3        1.715
    46      6          20.4        2.254
   100      6          23.5        1.372


             Estimated Values of Interest

  Dose      Est Mean      Est Std     Scaled Residual
```

0	8.477	1.714	-1.525
3	9.87	1.714	1.3
10	12.66	1.714	1.348
22	16.22	1.714	-1.318
46	20.37	1.714	0.04957
100	23.4	1.714	0.1459

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	-33.14239	7	80.28478
A2	-31.81197	12	87.62394
A3	-33.14239	7	80.28478
R	-80.44209	2	164.8842
5	-37.40682	4	82.81364

Additive constant for all log-likelihoods = -33.08. 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	97.26	10	< 0.0001
Test 2	2.661	5	0.7521
Test 3	2.661	5	0.7521
Test 7a	8.529	3	0.03626

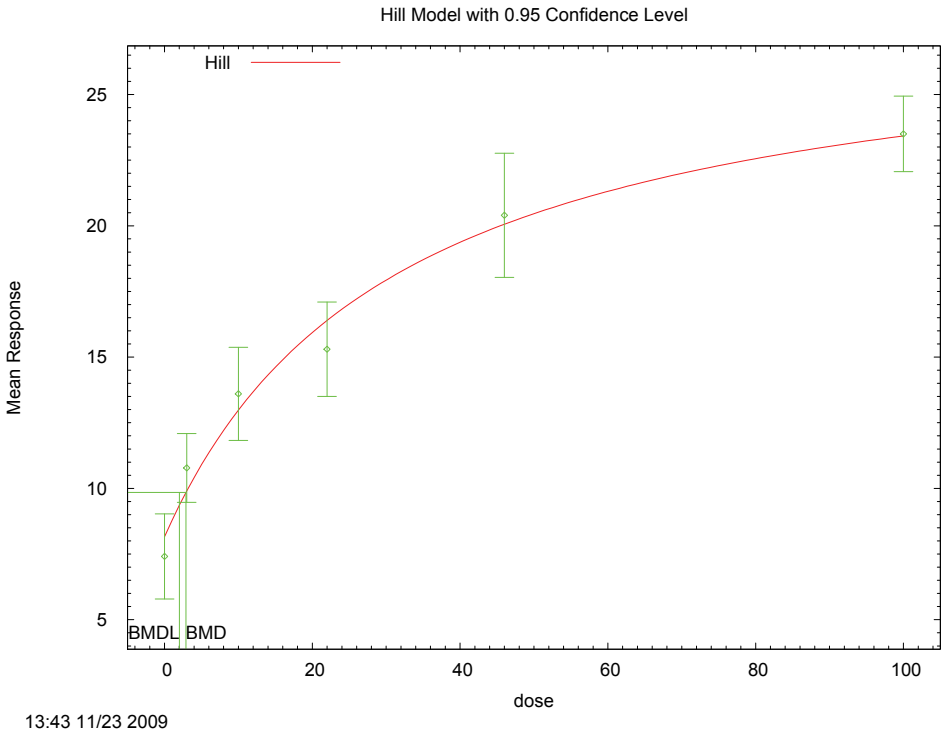
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

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 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 =      3.73387

               BMDL =      2.78339
```

H.3.2.4. *Figure for Unrestricted Model: Hill, Constant Variance, n Restricted >1, Bound Hit*



H.3.2.5. *Output File for Unrestricted Model: Hill, Constant Variance, n Restricted >1, Bound Hit*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Hill_CV_BMR1_DNA_SSB.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Hill_CV_BMR1_DNA_SSB.plt
                                              Mon Nov 23 13:43:57 2009
 ================================================================

 DNA single-strand breaks, liver only (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 = 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

alpha =	2.7831	
rho =	0	Specified
intercept =	7.41	
v =	16.09	
n =	0.174831	
k =	69.2706	

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	1.1e-007	1.9e-007	1.9e-007
intercept	1.1e-007	1	0.099	0.61
v	1.9e-007	0.099	1	0.79
k	1.9e-007	0.61	0.79	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	2.82659	0.666233	1.5208	4.13238
intercept	8.16404	0.581043	7.02522	9.30286
v	20.1253	1.69013	16.8127	23.4379
n	1	NA		
k	31.702	8.35815	15.3203	48.0836

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	7.41	8.16	1.54	1.68	-1.1
3	6	10.8	9.9	1.25	1.68	1.28
10	6	13.6	13	1.69	1.68	0.889

22	6	15.3	16.4	1.71	1.68	-1.62
46	6	20.4	20.1	2.25	1.68	0.469
100	6	23.5	23.4	1.37	1.68	0.0802

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	-33.142389	7	80.284779
A2	-31.811970	12	87.623940
A3	-33.142389	7	80.284779
fitted	-36.703273	4	81.406545
R	-80.442086	2	164.884172

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	97.2602	10	<.0001
Test 2	2.66084	5	0.7521
Test 3	2.66084	5	0.7521
Test 4	7.12177	3	0.06812

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

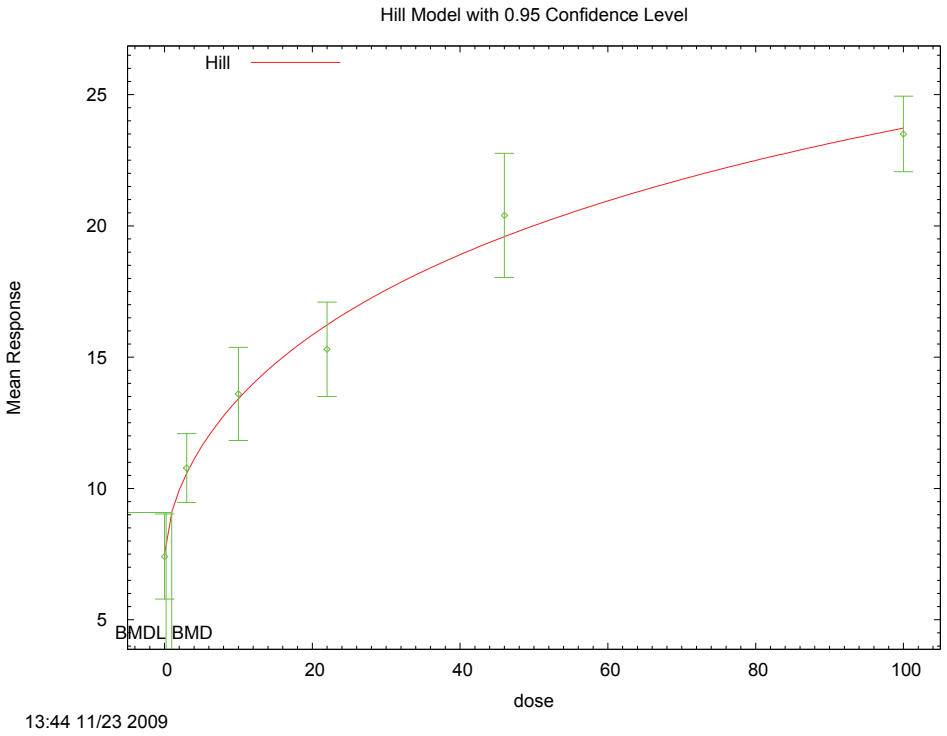
The p-value for Test 4 is less than .1. You may want to try a different
model

Benchmark Dose Computation

Specified effect = 1

```
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =        2.88976

            BMDL =       2.00669
```

H.3.2.6. *Figure for Unrestricted Model: Hill, Constant Variance, n Unrestricted*



H.3.2.7. *Output File for Unrestricted Model: Hill, Constant Variance, n Unrestricted*

```
 ========================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Hill_CV_Unrest_BMR1_DNA_SSB.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Hill_CV_Unrest_BMR1_DNA_SSB.plt
                                                Mon Nov 23 13:44:03 2009
 ========================================================================

 DNA single-strand breaks, liver only (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 is not restricted
```

A constant variance model is fit

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

alpha =	2.7831	
rho =	0	Specified
intercept =	7.41	
v =	16.09	
n =	0.174831	
k =	69.2706	

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	-2.2e-008	-4.6e-008	8.4e-009	-4.3e-008
intercept	-2.2e-008	1	-0.33	0.47	-0.29
v	-4.6e-008	-0.33	1	-0.95	1
n	8.4e-009	0.47	-0.95	1	-0.96
k	-4.3e-008	-0.29	1	-0.96	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	2.5942	0.611459	1.39576	3.79264
intercept	7.47627	0.665055	6.17278	8.77975
v	36.9014	25.5466	-13.1689	86.9718
n	0.612877	0.190055	0.240376	0.985377
k	148.104	303.532	-446.809	743.016

Table of Data and Estimated Values of Interest

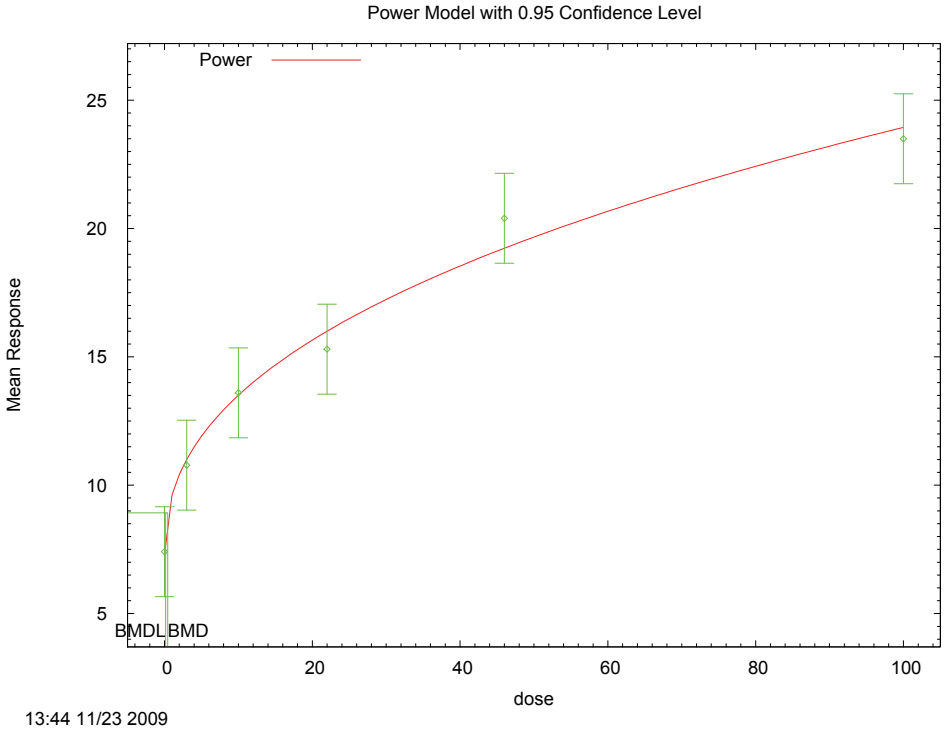
Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	7.41	7.48	1.54	1.61	-0.101
3	6	10.8	10.6	1.25	1.61	0.313
10	6	13.6	13.4	1.69	1.61	0.286
22	6	15.3	16.2	1.71	1.61	-1.41
46	6	20.4	19.6	2.25	1.61	1.24
100	6	23.5	23.7	1.37	1.61	-0.33

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          -33.142389           7      80.284779
             A2          -31.811970          12      87.623940
             A3          -33.142389           7      80.284779
         fitted          -35.159023           5      80.318046
              R          -80.442086           2     164.884172


                   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              97.2602         10          <.0001
  Test 2              2.66084          5          0.7521
  Test 3              2.66084          5          0.7521
  Test 4              4.03327          2          0.1331

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 =       0.961789

            BMDL =      0.211403
```

H.3.2.8. *Figure for Unrestricted Model: Power, Constant Variance, Power Unrestricted*



H.3.2.9. *Output File for Unrestricted Model: Power, Constant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Pwr_CV_Unrest_BMR1_DNA_SSB.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Pwr_CV_Unrest_BMR1_DNA_SSB.plt
                                                Mon Nov 23 13:44:04 2009
 ================================================================

 DNA single-strand breaks, liver only (Table 3)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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
                         alpha =       2.7831
```

```
                          rho =            0   Specified
                      control =         7.41
                        slope =      1.99047
                        power =       0.4538


          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-010     3.4e-009    -3.5e-009

   control       1e-010            1        -0.79         0.66

     slope     3.4e-009        -0.79            1        -0.97

     power    -3.5e-009         0.66        -0.97            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha          2.67247         0.629906             1.43787             3.90706
        control          7.29122         0.640201             6.03645             8.54599
          slope          2.31759         0.501503             1.33466             3.30051
          power         0.428335        0.0441267            0.341848            0.514821


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0       6       7.41         7.29         1.54         1.63          0.178
    3       6       10.8           11         1.25         1.63         -0.332
   10       6       13.6         13.5         1.69         1.63          0.142
   22       6       15.3           16         1.71         1.63          -1.05
   46       6       20.4         19.2         2.25         1.63           1.74
  100       6       23.5           24         1.37         1.63         -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)} = 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          -33.142389            7      80.284779
              A2          -31.811970           12      87.623940
              A3          -33.142389            7      80.284779
          fitted          -35.694033            4      79.388067
               R          -80.442086            2     164.884172


                    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              97.2602         10          <.0001
   Test 2              2.66084          5          0.7521
   Test 3              2.66084          5          0.7521
   Test 4              5.10329          3          0.1644

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 = 0.442709


            BMDL = 0.149473
```

H.3.3. Hassoun et al. (2000): TBARs Liver

H.3.3.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	4	0.33	20.31	0.00	-4.29	7.0E+01	3.4E+01	nonconstant variance, power restricted ≥1
exponential (M3)	4	0.33	20.31	0.00	-4.29	7.0E+01	3.4E+01	nonconstant variance, power restricted ≥1
exponential (M4)	3	0.33	3.08	0.38	-19.53	4.3E+00	1.9E+00	nonconstant variance, power restricted ≥1
exponential (M5)	2	0.33	2.78	0.25	-17.82	5.5E+00	2.0E+00	nonconstant variance, power restricted ≥1
exponential (M5)	2	0.33	2.78	0.25	-17.82	5.5E+00	2.0E+00	nonconstant variance, power unrestricted
Hill	2	0.33	2.52	0.28	-18.08	5.7E+00	2.0E+00	nonconstant variance, n restricted >1
Hill	2	0.33	2.52	0.28	-18.08	5.7E+00	error	nonconstant variance, n unrestricted
linear	4	0.33	19.16	0.00	-5.44	5.2E+01	2.2E+01	nonconstant variance
polynomial	4	0.33	19.16	0.00	-5.44	5.2E+01	2.2E+01	nonconstant variance
power	4	0.33	19.16	0.00	-5.44	5.2E+01	2.2E+01	nonconstant variance, power restricted ≥1, bound hit
power	3	0.33	8.22	0.04	-14.38	1.2E+00	5.2E-03	nonconstant variance, power unrestricted
exponential (M2)	4	0.33	20.40	0.00	-6.14	8.0E+01	5.3E+01	constant variance, power restricted ≥1
exponential (M3)	4	0.33	20.40	0.00	-6.14	8.0E+01	5.3E+01	constant variance, power restricted ≥1
exponential (M4) [c]	**3**	**0.33**	**3.36**	**0.34**	**-21.18**	**4.9E+00**	**2.3E+00**	**constant variance, power restricted ≥1**
exponential (M5)	2	0.33	2.86	0.24	-19.68	6.7E+00	2.5E+00	constant variance, power restricted ≥1
exponential (M5) [d]	2	0.33	2.86	0.24	-19.68	6.7E+00	2.5E+00	constant variance, power unrestricted
Hill	2	0.33	2.61	0.27	-19.93	6.3E+00	2.6E+00	constant variance, n restricted >1
Hill [d]	2	0.33	2.61	0.27	-19.93	6.3E+00	2.6E+00	constant variance, n unrestricted
linear	4	0.33	19.52	0.00	-7.02	6.9E+01	4.4E+01	constant variance
polynomial	4	0.33	19.52	0.00	-7.02	6.9E+01	4.4E+01	constant variance
power	4	0.33	19.52	0.00	-7.02	6.9E+01	4.4E+01	constant variance, power restricted ≥1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
power [d]	3	0.33	9.55	0.02	-14.99	2.9E+00	6.1E-02	constant variance, power unrestricted

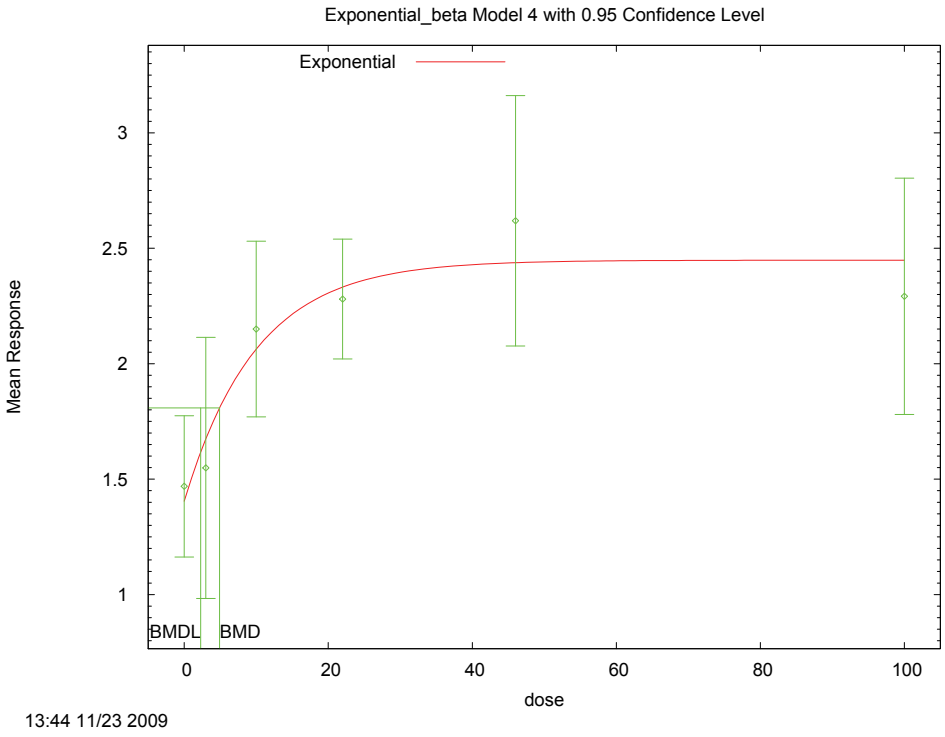
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.3.3.2. *Figure for Selected Model: Exponential (M4), Constant Variance, Power Restricted ≥1*



H.3.3.3. *Output File for Selected Model: Exponential (M4), Constant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov23\Exp_CV_BMR1_TBARs_Liver.(d)
         Gnuplot Plotting File:
                                                  Mon Nov 23 13:44:41 2009
 ================================================================

 TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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            -1.90388
                    rho(S)                0
                      a             1.39555
                      b           0.0194898
                      c             1.97051
                      d                    1

  (S) = Specified


                Parameter Estimates

               Variable          Model 4
               --------          -------
                lnalpha          -1.82448
                    rho                 0
                      a           1.46519
                      b          0.113543
                      c           1.63661
                      d           2.13652


        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
     0       6        1.469        0.2915
     3       6        1.549        0.5389
    10       6         2.15        0.3625
    22       6         2.28        0.2474
    46       6        2.619        0.5168
   100       6        2.292        0.4874


              Estimated Values of Interest
```

Dose	Est Mean	Est Std	Scaled Residual
0	1.404	0.4044	0.3915
3	1.674	0.4044	-0.7582
10	2.063	0.4044	0.527
22	2.332	0.4044	-0.3134
46	2.438	0.4044	1.099
100	2.448	0.4044	-0.9458

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	16.26977	7	-18.53954
A2	19.12783	12	-14.25565
A3	16.26977	7	-18.53954
R	2.44294	2	-0.8858799
4	14.5907	4	-21.18141

Additive constant for all log-likelihoods = -33.08. 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	33.37	10	0.000236
Test 2	5.716	5	0.3348
Test 3	5.716	5	0.3348
Test 6a	3.358	3	0.3396

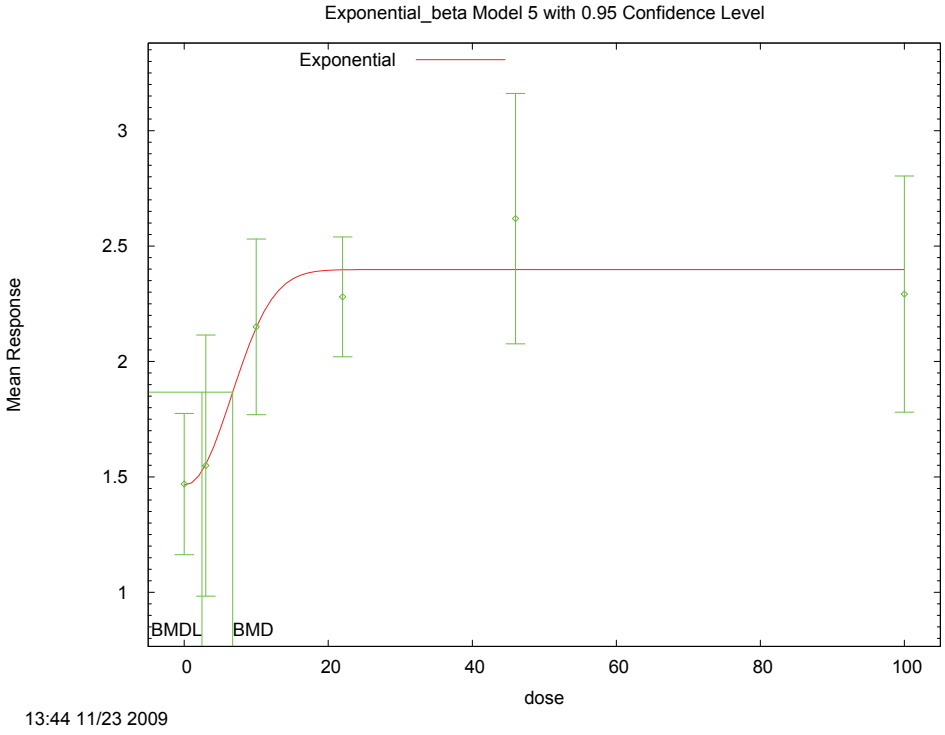
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

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 =      4.91639

                BMDL =      2.29952
```

H.3.3.4. *Figure for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*



H.3.3.5. *Output File for Unrestricted Model: Exponential (M5), Constant Variance, Power Unrestricted*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov23\Exp_CV_Unrest_BMR1_TBARs_Liver.(d)
         Gnuplot Plotting File:
                                                Mon Nov 23 13:44:47 2009
 ================================================================

 TBARs, liver only (Table 2)
```

```
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 5
                 --------          --------
                   lnalpha             -1.90388
                       rho(S)                0
                         a              1.39555
                         b            0.0194898
                         c              1.97051
                         d                    1

     (S) = Specified


                    Parameter Estimates

                  Variable          Model 5
                  --------          -------
                   lnalpha          -1.82448
                       rho                 0
                         a           1.46519
                         b          0.113543
                         c           1.63661
                         d           2.13652


           Table of Stats From Input Data

     Dose      N         Obs Mean     Obs Std Dev
     -----    ---       ----------   -------------
        0      6        1.469       0.2915
        3      6        1.549       0.5389
       10      6         2.15       0.3625
       22      6         2.28       0.2474
       46      6        2.619       0.5168
      100      6        2.292       0.4874
```

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	1.465	0.4016	0.02326
3	1.554	0.4016	-0.03103
10	2.147	0.4016	0.02011
22	2.397	0.4016	-0.7145
46	2.398	0.4016	1.348
100	2.398	0.4016	-0.6461

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	16.26977	7	-18.53954
A2	19.12783	12	-14.25565
A3	16.26977	7	-18.53954
R	2.44294	2	-0.8858799
5	14.8407	5	-19.68141

Additive constant for all log-likelihoods = -33.08. 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

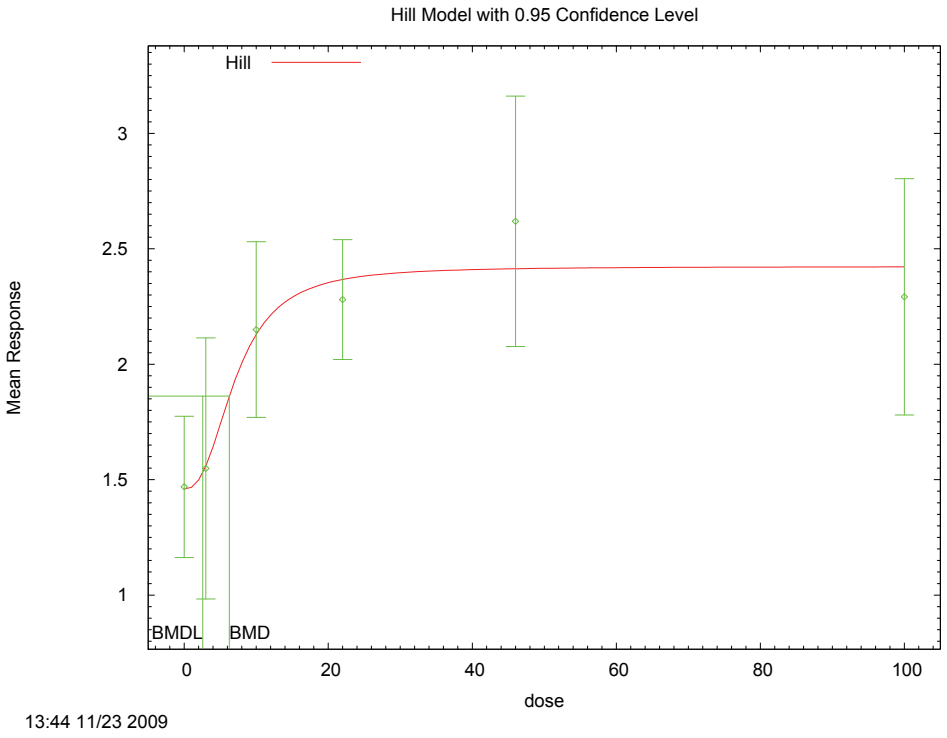
Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	33.37	10	0.000236
Test 2	5.716	5	0.3348
Test 3	5.716	5	0.3348
Test 7a	2.858	2	0.2395

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 7a is greater than .1.  Model 5 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 =      6.73152

              BMDL =      2.47029
```

H.3.3.6. *Figure for Unrestricted Model: Hill, Constant Variance, n Unrestricted*



H.3.3.7. *Output File for Unrestricted Model: Hill, Constant Variance, n Unrestricted*

```
========================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\USEPA\BMDS21\Nov23\Hill_CV_Unrest_BMR1_TBARs_Liver.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Hill_CV_Unrest_BMR1_TBARs_Liver.plt
                                                Mon Nov 23 13:44:49 2009
========================================================================

TBARs, liver only (Table 2)
```

~~~~~~

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 = 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

alpha =	0.178788	
rho =	0	Specified
intercept =	1.469	
v =	1.15	
n =	0.921061	
k =	11.2346	

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	4.6e-010	-1.2e-008	2.8e-009	3.8e-009
intercept	4.6e-010	1	-0.82	0.48	0.52
v	-1.2e-008	-0.82	1	-0.61	-0.22
n	2.8e-009	0.48	-0.61	1	0.29
k	3.8e-009	0.52	-0.22	0.29	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.160182	0.0377552	0.0861829	0.23418
intercept	1.4615	0.152914	1.16179	1.76121
v	0.962989	0.202872	0.565367	1.36061
n	2.4861	1.76422	-0.971707	5.94391
k	7.18099	2.79941	1.69424	12.6677

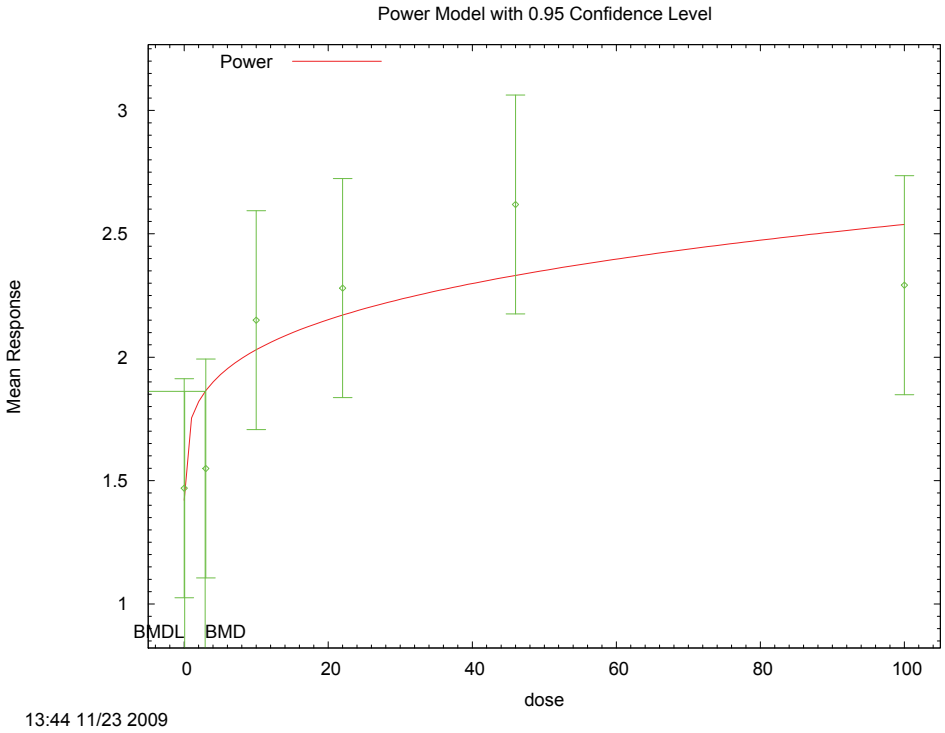
Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	1.47	1.46	0.291	0.4	0.0459
3	6	1.55	1.56	0.539	0.4	-0.0685
10	6	2.15	2.13	0.363	0.4	0.118
~~~~~~

```
  22     6       2.28         2.37        0.247          0.4         -0.541
  46     6       2.62         2.42        0.517          0.4           1.25
 100     6       2.29         2.42        0.487          0.4         -0.802


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           16.269770           7     -18.539539
            A2           19.127827          12     -14.255654
            A3           16.269770           7     -18.539539
        fitted           14.966039           5     -19.932079
             R            2.442940           2      -0.885880


                  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              33.3698         10        0.000236
  Test 2              5.71611          5          0.3348
  Test 3              5.71611          5          0.3348
  Test 4              2.60746          2          0.2715

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 =        6.26103

            BMDL =       2.57465
```

H.3.3.8. *Figure for Unrestricted Model: Power, Constant Variance, Power Unrestricted*



H.3.3.9. *Output File for Unrestricted Model: Power, Constant Variance, Power Unrestricted*

```
 ======================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov23\Pwr_CV_Unrest_BMR1_TBARs_Liver.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov23\Pwr_CV_Unrest_BMR1_TBARs_Liver.plt
                                                Mon Nov 23 13:44:49 2009
 ======================================================================

 TBARs, liver only (Table 2)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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

alpha =	0.178788	
rho =	0	Specified
control =	1.469	
slope =	0.0756538	
power =	0.652114	

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	1.1e-008	-1.1e-009	-1.5e-008
control	1.1e-008	1	-0.75	0.47
slope	-1.1e-009	-0.75	1	-0.91
power	-1.5e-008	0.47	-0.91	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.194232	0.0457809	0.104503	0.283961
control	1.42104	0.171077	1.08573	1.75634
slope	0.333105	0.166768	0.00624603	0.659963
power	0.262735	0.0983956	0.0698836	0.455587

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	6	1.47	1.42	0.291	0.441	0.267
3	6	1.55	1.87	0.539	0.441	-1.76
10	6	2.15	2.03	0.363	0.441	0.661
22	6	2.28	2.17	0.247	0.441	0.603
46	6	2.62	2.33	0.517	0.441	1.6
100	6	2.29	2.54	0.487	0.441	-1.37

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           16.269770            7     -18.539539
             A2           19.127827           12     -14.255654
             A3           16.269770            7     -18.539539
          fitted          11.496634            4     -14.993268
               R           2.442940            2      -0.885880


                    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              33.3698         10        0.000236
   Test 2              5.71611          5          0.3348
   Test 3              5.71611          5          0.3348
   Test 4              9.54627          3         0.02284

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 = 2.90232


             BMDL = 0.0614971
```

H.3.4. Kitchin et al. (1979): BaP Hydrolase Activity

H.3.4.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	9	<0.0001	247.00	<0.0001	452.67	2.6E+03	1.2E+03	nonconstant variance, power restricted ≥1
exponential (M3)	9	<0.0001	247.00	<0.0001	452.67	2.6E+03	1.2E+03	nonconstant variance, power restricted ≥1
exponential (M4)	8	<0.0001	18.96	0.02	226.60	1.8E+00	1.4E+00	nonconstant variance, power restricted ≥1
exponential (M5) [c]	**7**	**<0.0001**	**16.75**	**0.02**	**226.40**	**3.4E+00**	**1.6E+00**	**nonconstant variance, power restricted ≥1**
exponential (M5) [d]	7	<0.0001	16.75	0.02	226.40	3.4E+00	1.6E+00	nonconstant variance, power unrestricted
Hill	7	<.0001	296.88	<.0001	506.53	error	error	nonconstant variance, n restricted >1
Hill [d]	7	<.0001	296.88	<.0001	506.53	error	error	nonconstant variance, n unrestricted
linear	9	<.0001	94.11	<.0001	299.75	2.8E+00	2.0E+00	nonconstant variance
polynomial	9	<.0001	-197.64	<.0001	8.00	error	error	nonconstant variance
power	9	<.0001	94.11	<.0001	299.75	2.8E+00	2.0E+00	nonconstant variance, power restricted ≥1, bound hit
power [d]	8	<.0001	63.59	<.0001	271.23	3.0E-01	1.3E-01	nonconstant variance, power unrestricted
exponential (M2)	9	<0.0001	129.40	<0.0001	451.61	3.6E+03	3.1E+03	constant variance, power restricted ≥1
exponential (M3)	9	<0.0001	129.40	<0.0001	451.61	3.6E+03	3.1E+03	constant variance, power restricted ≥1
exponential (M4)	8	<0.0001	6.93	0.54	331.19	2.7E+01	2.1E+01	constant variance, power restricted ≥1
exponential (M5)	8	<0.0001	6.93	0.54	331.19	2.7E+01	2.1E+01	constant variance, power restricted ≥1
exponential (M5)	8	<0.0001	6.93	0.54	331.19	2.7E+01	2.1E+01	constant variance, power unrestricted
Hill	7	<.0001	67.64	<.0001	393.90	5.7E+02	5.2E+00	constant variance, n restricted >1
Hill	7	<.0001	2.70	0.91	328.96	2.0E+01	1.1E+01	constant variance, n unrestricted
linear	9	<.0001	120.31	<.0001	442.57	1.9E+03	1.4E+03	constant variance
polynomial	9	<.0001	120.31	<.0001	442.57	1.9E+03	1.4E+03	constant variance
power	9	<.0001	120.31	<.0001	442.57	1.9E+03	1.4E+03	constant variance, power restricted ≥1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
power	8	<.0001	51.05	<.0001	375.31	1.2E+00	2.5E-01	constant variance, power unrestricted

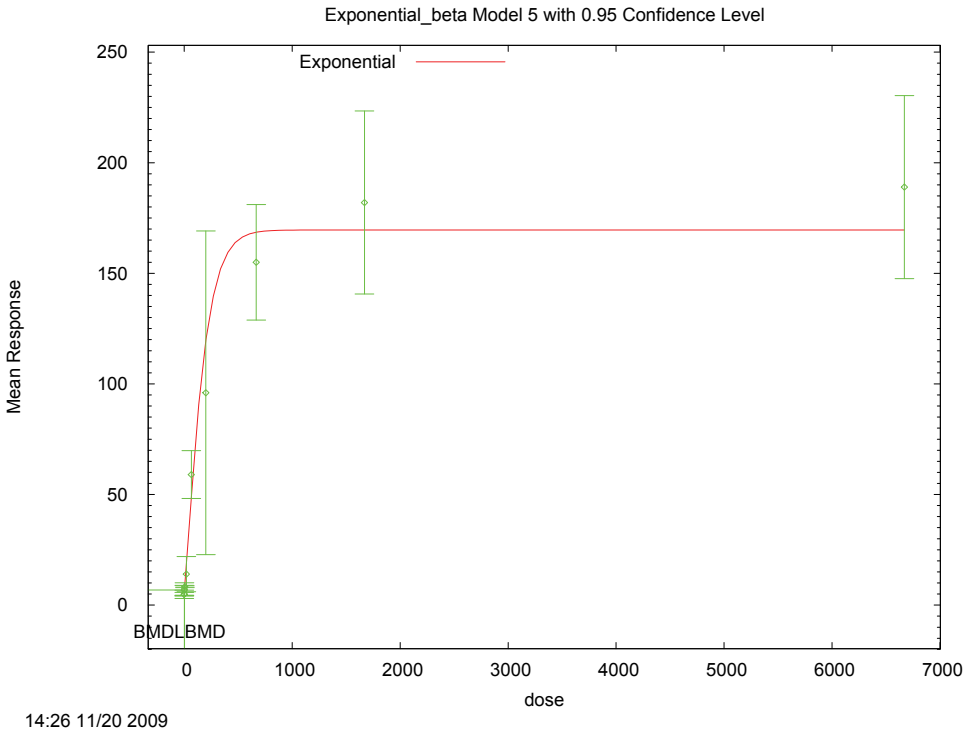
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.3.4.2. *Figure for Selected Model: Exponential (M5), Nonconstant Variance, Power Restricted ≥1*



H.3.4.3. *Output File for Selected Model: Exponential (M5), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_BMR1_BaP_hydro_act.(d)
         Gnuplot Plotting File:
                                                 Fri Nov 20 14:26:45 2009
 ================================================================

 Kitchin 1979, Tbl3, BaP hydrolase activity
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 11
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 5
              --------          --------
                lnalpha           -3.27793
                    rho            1.92227
                      a              4.655
                      b       0.000532066
                      c            42.6316
                      d                   1


                Parameter Estimates

               Variable          Model 5
               --------          -------
                lnalpha           -2.6425
                    rho           1.93734
                      a           5.43493
                      b        0.00574894
                      c           31.1998
                      d           1.21529


        Table of Stats From Input Data

 Dose      N         Obs Mean     Obs Std Dev
 -----    ---       ----------   -------------
     0      9          4.9          1.11
   0.2      4          4.9          1.18
 0.667      4          6.7           1.4
  1.33      4          7.2           1.8
  6.67      4          8.3          0.26
    20      4           14             5
  66.7      4           59           6.8
   200      4           96            46
   667      4          155          16.4
  1670      4          182            26
  6670      4          189            26
```

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	5.435	1.375	-1.167
0.2	5.479	1.386	-0.8354
0.667	5.625	1.422	1.513
1.33	5.874	1.483	1.789
6.67	8.524	2.127	-0.211
20	16.86	4.118	-1.391
66.7	49.42	11.67	1.642
200	119.4	27.42	-1.705
667	168.6	38.31	-0.7095
1670	169.6	38.52	0.6454
6670	169.6	38.52	1.009

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	-158.1306	12	340.2613
A2	-84.80028	22	213.6006
A3	-98.82189	13	223.6438
R	-234.6252	2	473.2504
5	-107.1994	6	226.3987

Additive constant for all log-likelihoods = -45.03. 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)

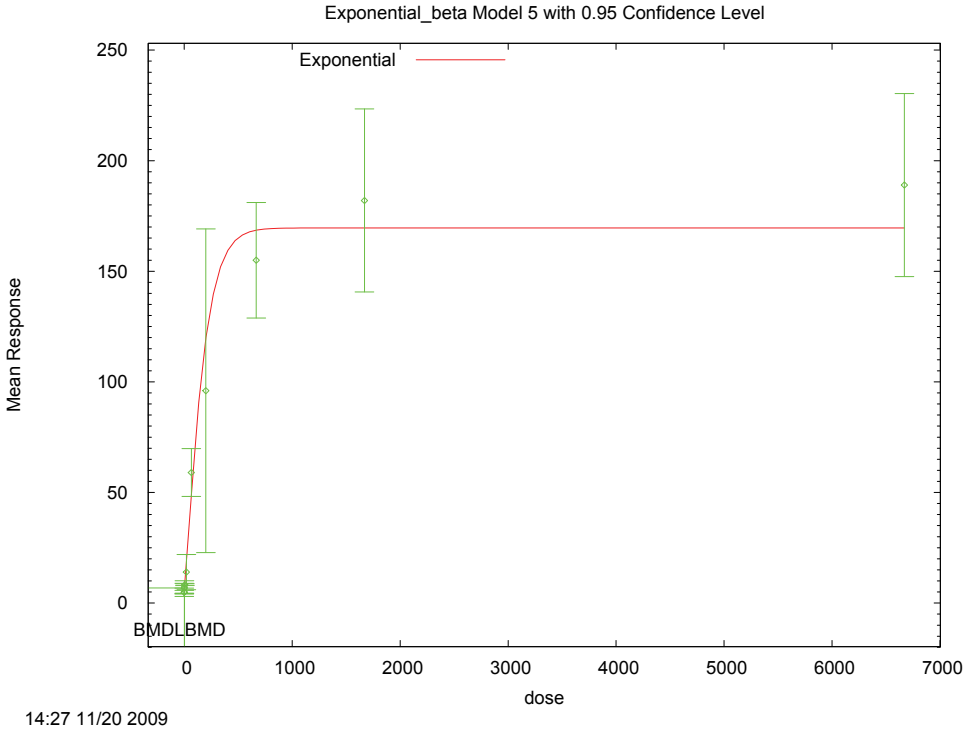
Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	299.6	20	< 0.0001
Test 2	146.7	10	< 0.0001
Test 3	28.04	9	0.0009381
Test 7a	16.75	7	0.01905

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 =      3.41185

                BMDL =      1.60436
```

H.3.4.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



H.3.4.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
=================================================================
```

```
          Exponential Model. (Version: 1.5;  Date: 4/23/2009)
          Input Data File: C:\USEPA\BMDS21\Nov20\Exp_Unrest_BMR1_BaP_hydro_act.(d)
          Gnuplot Plotting File:
                                                    Fri Nov 20 14:27:02 2009
 ========================================================================

 Kitchin 1979, Tbl3, BaP hydrolase activity
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 11
   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 5
                --------          --------
                  lnalpha          -3.27793
                      rho           1.92227
                        a             4.655
                        b       0.000532066
                        c           42.6316
                        d                 1



                  Parameter Estimates

                 Variable          Model 5
                 --------          -------
                  lnalpha           -2.6425
                      rho           1.93734
                        a           5.43493
                        b        0.00574894
                        c           31.1998
                        d           1.21529


          Table of Stats From Input Data

     Dose      N         Obs Mean     Obs Std Dev
     -----    ---       ----------   -------------
        0      9          4.9          1.11
      0.2      4          4.9          1.18
```

0.667	4	6.7	1.4
1.33	4	7.2	1.8
6.67	4	8.3	0.26
20	4	14	5
66.7	4	59	6.8
200	4	96	46
667	4	155	16.4
1670	4	182	26
6670	4	189	26

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	5.435	1.375	-1.167
0.2	5.479	1.386	-0.8354
0.667	5.625	1.422	1.513
1.33	5.874	1.483	1.789
6.67	8.524	2.127	-0.211
20	16.86	4.118	-1.391
66.7	49.42	11.67	1.642
200	119.4	27.42	-1.705
667	168.6	38.31	-0.7095
1670	169.6	38.52	0.6454
6670	169.6	38.52	1.009

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	-158.1306	12	340.2613
A2	-84.80028	22	213.6006
A3	-98.82189	13	223.6438
R	-234.6252	2	473.2504
5	-107.1994	6	226.3987

Additive constant for all log-likelihoods = -45.03. 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	299.6	20	< 0.0001
Test 2	146.7	10	< 0.0001
Test 3	28.04	9	0.0009381
Test 7a	16.75	7	0.01905

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

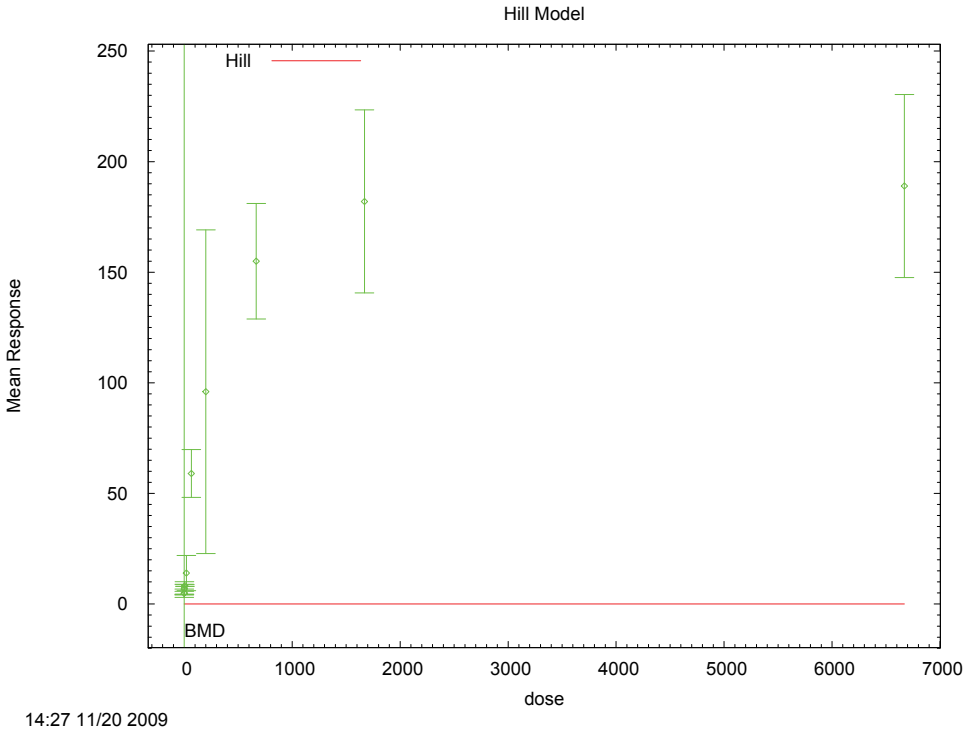
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 3.41185

BMDL = 1.60436

H.3.4.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



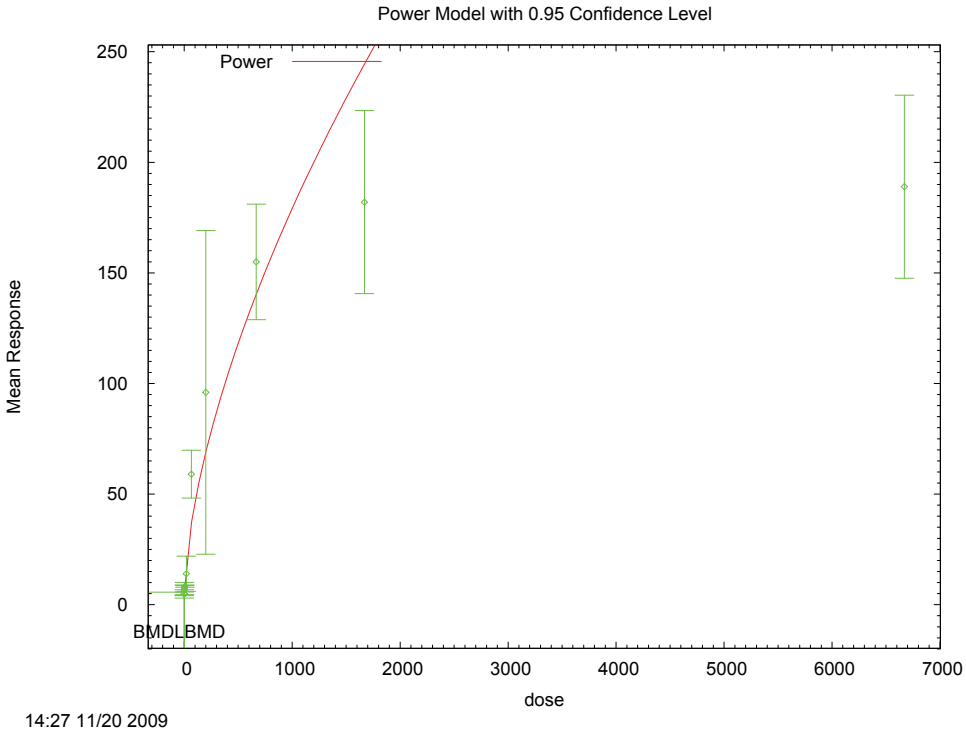
H.3.4.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_BaP_hydro_act.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_BaP_hydro_act.plt
                                              Fri Nov 20 14:27:04 2009
 ================================================================

 Kitchin 1979, Tbl3, BaP hydrolase activity
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 11
   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 =      5.70855
                           rho =            0
                     intercept =          4.9
                             v =        184.1
                             n =           18
                             k =      1126.48


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho    intercept            v            n            k

    lalpha       NA              NA             NA             NA             NA             NA

       rho       NA              NA             NA             NA             NA             NA

 intercept       NA              NA                   1       -0.012       NA             NA

         v       NA              NA              -0.012            1       NA             NA

         n       NA              NA             NA             NA             NA             NA

         k       NA              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           8.0472              NA                    NA                  NA
           rho       -0.0780259              NA                    NA                  NA
```

```
      intercept    -1.52215e-006              NA                 NA                 NA
              v          185.167              NA                 NA                 NA
              n          17.9979              NA                 NA                 NA
              k           117036              NA                 NA                 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     9        4.9   -1.52e-006         1.11         94.3          0.156
  0.2     4        4.9   -1.52e-006         1.18         94.3          0.104
0.667     4        6.7   -1.52e-006          1.4         94.3          0.142
 1.33     4        7.2   -1.52e-006          1.8         94.3          0.153
 6.67     4        8.3   -1.52e-006         0.26         94.3          0.176
   20     4         14   -1.52e-006            5         94.3          0.297
 66.7     4         59   -1.52e-006          6.8         94.3           1.25
  200     4         96   -1.52e-006           46         94.3           2.04
  667     4        155   -1.52e-006         16.4         94.3           3.29
 1670     4        182   -1.52e-006           26         94.3           3.86
 6670     4        189   -1.52e-006           26         94.3           4.01



 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         -158.130647          12     340.261294
             A2          -84.800279          22     213.600558
             A3          -98.821893          13     223.643786
         fitted         -247.263464           6     506.526928
              R         -234.625213           2     473.250426


                   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              299.65         20          <.0001
   Test 2             146.661         10          <.0001
   Test 3             28.0432          9       0.0009381
   Test 4             296.883          7          <.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 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 =        1.#QNAN


BMDL computation failed.
```

H.3.4.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



H.3.4.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_BaP_hydro_act.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_BaP_hydro_act.plt
                                                Fri Nov 20 14:27:04 2009
 ================================================================

 Kitchin 1979, Tbl3, BaP hydrolase activity
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 11
   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 =      5.70855
                          rho =            0
                      control =          4.9
                        slope =     0.984853
                        power =      0.59404


          Asymptotic Correlation Matrix of Parameter Estimates

               lalpha          rho      control        slope        power

    lalpha          1         -0.9        -0.45         0.26        -0.23

       rho       -0.9            1         0.35        -0.24         0.12

   control      -0.45         0.35            1        -0.45         0.42

     slope       0.26        -0.24        -0.45            1        -0.92

     power      -0.23         0.12         0.42        -0.92            1


                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        lalpha         -3.42083         0.570828          -4.53963           -2.30202
           rho          2.42943         0.164289           2.10743            2.75143
       control          4.52619         0.315826           3.90719             5.1452
         slope           2.4104         0.540821           1.35041            3.47039
         power         0.619986        0.0482232          0.525471           0.714502


     Table of Data and Estimated Values of Interest
```

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	9	4.9	4.53	1.11	1.13	0.991
0.2	4	4.9	5.41	1.18	1.41	-0.732
0.667	4	6.7	6.4	1.4	1.72	0.346
1.33	4	7.2	7.4	1.8	2.06	-0.197
6.67	4	8.3	12.3	0.26	3.83	-2.11
20	4	14	20	5	6.87	-1.74
66.7	4	59	37.1	6.8	14.6	3
200	4	96	68.9	46	30.9	1.75
667	4	155	140	16.4	73.4	0.399
1670	4	182	244	26	144	-0.868
6670	4	189	571	26	403	-1.89

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	-158.130647	12	340.261294
A2	-84.800279	22	213.600558
A3	-98.821893	13	223.643786
fitted	-130.616947	5	271.233893
R	-234.625213	2	473.250426

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	299.65	20	<.0001
Test 2	146.661	10	<.0001
Test 3	28.0432	9	0.0009381
Test 4	63.5901	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 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 = 0.29535


             BMDL = 0.12727
```

H.3.5. National Toxicology Program. (2006): EROD Liver Week 53

H.3.5.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	4	<0.0001	121.00	<0.0001	210.78	5.7E+01	4.0E+01	nonconstant variance, power restricted ≥1
exponential (M3)	4	<0.0001	121.00	<0.0001	210.78	5.7E+01	4.0E+01	nonconstant variance, power restricted ≥1
exponential (M4)	3	<0.0001	7.05	0.07	98.86	2.7E-01	1.9E-01	nonconstant variance, power restricted ≥1
exponential (M5)	2	<0.0001	6.44	0.04	100.25	3.4E-01	2.0E-01	nonconstant variance, power restricted ≥1
Hill [c]	**2**	**<.0001**	**3.05**	**0.22**	**96.86**	**5.4E-01**	**3.3E-01**	**nonconstant variance, n restricted >1**
Hill [d]	2	<.0001	3.05	0.22	96.86	5.4E-01	3.3E-01	nonconstant variance, n unrestricted
linear	4	<.0001	113.79	<.0001	203.61	2.9E+01	1.1E+01	nonconstant variance
polynomial	4	<.0001	113.79	<.0001	203.61	2.9E+01	1.1E+01	nonconstant variance
power	4	<.0001	113.79	<.0001	203.61	2.9E+01	1.1E+01	nonconstant variance, power restricted ≥1, bound hit
exponential (M2)	4	<0.0001	85.26	<0.0001	209.43	5.0E+01	4.1E+01	constant variance, power restricted ≥1

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M3)	4	<0.0001	85.26	<0.0001	209.43	5.0E+01	4.1E+01	constant variance, power restricted ≥1
exponential (M4)	3	<0.0001	4.50	0.21	130.67	1.5E+00	1.2E+00	constant variance, power restricted ≥1
exponential (M5)	3	<0.0001	4.50	0.21	130.67	1.5E+00	1.2E+00	constant variance, power restricted ≥1
Hill	2	<.0001	2.30	0.32	130.48	1.7E+00	9.3E-01	constant variance, n restricted >1
Hill	2	<.0001	2.30	0.32	130.48	1.7E+00	9.3E-01	constant variance, n unrestricted
linear	4	<.0001	77.49	<.0001	201.66	3.2E+01	2.5E+01	constant variance
polynomial	4	<.0001	77.49	<.0001	201.66	3.2E+01	2.5E+01	constant variance
power	4	<.0001	77.49	<.0001	201.66	3.2E+01	2.5E+01	constant variance, power restricted ≥1, bound hit

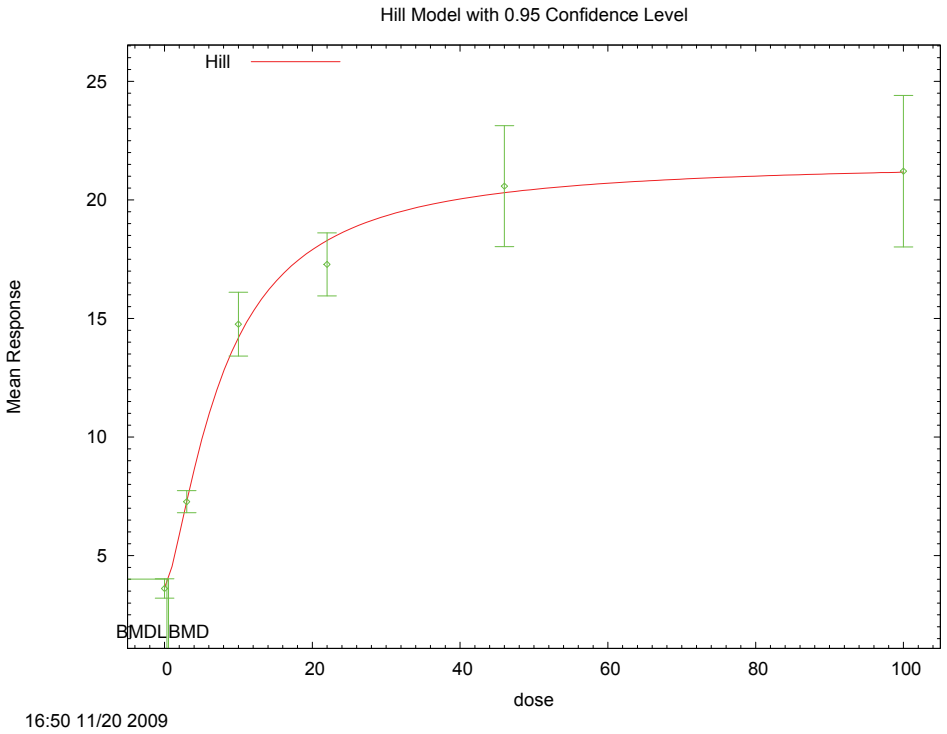
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.3.5.2. *Figure for Selected Model: Hill, Nonconstant Variance, n Restricted >1*



H.3.5.3. *Output File for Selected Model: Hill, Nonconstant Variance, n Restricted >1*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Hill_BMR1_Tbl12_wk53_EROD_liv.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Hill_BMR1_Tbl12_wk53_EROD_liv.plt
                                                 Fri Nov 20 16:50:09 2009
 ================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 =      1.59547
                           rho =            0
                     intercept =        3.614
                             v =       17.599
                             n =      1.38584
                             k =      12.1933


           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho    intercept            v            n            k

    lalpha            1        -0.96        -0.16        0.086       -0.057        0.041

       rho        -0.96            1         0.14        -0.11         0.06       -0.045

 intercept        -0.16         0.14            1        -0.18         0.13        0.069

         v        0.086        -0.11        -0.18            1        -0.72         0.84

         n       -0.057         0.06         0.13        -0.72            1        -0.79

         k        0.041       -0.045        0.069         0.84        -0.79            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        lalpha         -4.86544         0.741662           -6.31907            -3.4118
           rho          2.26969         0.287261            1.70667            2.83271
     intercept          3.62908         0.133826            3.36679            3.89138
             v          17.9785         0.989021            16.0401             19.917
             n          1.43249         0.162632            1.11374            1.75124
             k          7.81956          1.00384            5.85206            9.78706
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	3.61	3.63	0.486	0.379	-0.113
3	8	7.27	7.27	0.557	0.833	0.0201
10	8	14.8	14.2	1.61	1.78	0.912
22	8	17.3	18.3	1.59	2.37	-1.19
46	8	20.6	20.3	3.05	2.67	0.306
100	8	21.2	21.2	3.82	2.8	0.061

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	-59.086537	7	132.173073
A2	-37.515858	12	99.031716
A3	-40.906180	8	97.812359
fitted	-42.430348	6	96.860697
R	-116.710291	2	237.420582

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	158.389	10	<.0001
Test 2	43.1414	5	<.0001
Test 3	6.78064	4	0.1479
Test 4	3.04834	2	0.2178

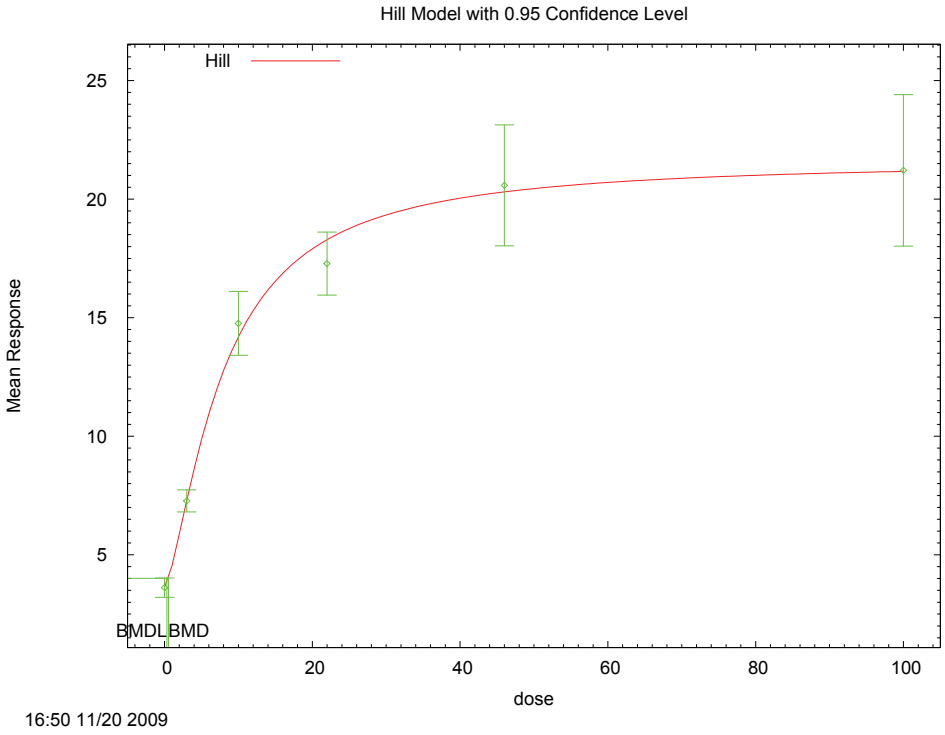
The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

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 =       0.536614

            BMDL =      0.328003
```

H.3.5.4. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



H.3.5.5. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ========================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_Tbl12_wk53_EROD_liv.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_Tbl12_wk53_EROD_liv.plt
                                                 Fri Nov 20 16:50:14 2009
 ========================================================================

 0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 =      1.59547
                           rho =            0
                     intercept =        3.614
                             v =       17.599
                             n =      1.38584
                             k =      12.1933


          Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho    intercept            v            n            k

    lalpha            1        -0.96        -0.16        0.086       -0.057        0.041

       rho        -0.96            1         0.14        -0.11         0.06       -0.045

 intercept        -0.16         0.14            1        -0.18         0.13        0.069

         v        0.086        -0.11        -0.18            1        -0.72         0.84

         n       -0.057         0.06         0.13        -0.72            1        -0.79

         k        0.041       -0.045        0.069         0.84        -0.79            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        lalpha         -4.86544         0.741662           -6.31907            -3.4118
           rho          2.26969         0.287261            1.70667            2.83271
     intercept          3.62908         0.133826            3.36679            3.89138
             v          17.9785         0.989021            16.0401             19.917
             n          1.43249         0.162632            1.11374            1.75124
             k          7.81956          1.00384            5.85206            9.78706


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

   0        8       3.61         3.63        0.486        0.379         -0.113
   3        8       7.27         7.27        0.557        0.833         0.0201
  10        8       14.8         14.2         1.61         1.78          0.912
  22        8       17.3         18.3         1.59         2.37          -1.19
  46        8       20.6         20.3         3.05         2.67          0.306
 100        8       21.2         21.2         3.82          2.8          0.061
```

```
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          -59.086537            7     132.173073
             A2          -37.515858           12      99.031716
             A3          -40.906180            8      97.812359
         fitted          -42.430348            6      96.860697
              R         -116.710291            2     237.420582


                   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              158.389         10          <.0001
   Test 2              43.1414          5          <.0001
   Test 3              6.78064          4          0.1479
   Test 4              3.04834          2          0.2178

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 =       0.536614
```

```
BMDL =      0.328003
```

H.3.6. National Toxicology Program. (2006): Lung EROD Week 31

H.3.6.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	4	<0.0001	129.30	<0.0001	396.45	8.9E+01	6.2E+01	nonconstant variance, power restricted ≥1
exponential (M3)	4	<0.0001	129.30	<0.0001	396.45	8.9E+01	6.2E+01	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**3**	**<0.0001**	**20.80**	**0.00**	**289.99**	**1.0E-01**	**6.9E-02**	**nonconstant variance, power restricted ≥1**
exponential (M5)	3	<0.0001	20.80	0.00	289.99	1.0E-01	6.9E-02	nonconstant variance, power restricted ≥1
exponential (M5) [d]	3	<0.0001	20.80	0.00	289.99	1.0E-01	6.9E-02	nonconstant variance, power unrestricted
Hill	3	<.0001	78.84	<.0001	348.02	9.6E+00	error	nonconstant variance, n restricted >1, bound hit
Hill [d]	3	<.0001	78.84	<.0001	348.02	9.6E+00	error	nonconstant variance, n unrestricted
linear	4	<.0001	125.96	<.0001	393.15	6.3E+01	3.1E+01	nonconstant variance
polynomial	4	<.0001	128.35	<.0001	395.53	1.0E+02	2.3E+01	nonconstant variance
power	4	<.0001	125.96	<.0001	393.15	6.3E+01	3.1E+01	nonconstant variance, power restricted ≥1, bound hit
power [d]	3	<.0001	22.50	<.0001	291.68	1.9E-06	1.9E-06	nonconstant variance, power unrestricted
exponential (M2)	4	<0.0001	87.28	<0.0001	397.44	6.6E+01	5.3E+01	constant variance, power restricted ≥1
exponential (M3)	4	<0.0001	87.28	<0.0001	397.44	6.6E+01	5.3E+01	constant variance, power restricted ≥1
exponential (M4)	3	<0.0001	15.56	0.00	327.72	1.7E+00	1.2E+00	constant variance, power restricted ≥1
exponential (M5)	3	<0.0001	15.56	0.00	327.72	1.7E+00	1.2E+00	constant variance, power restricted ≥1
exponential (M5)	3	<0.0001	15.56	0.00	327.72	1.7E+00	1.2E+00	constant variance, power unrestricted
Hill	2	<.0001	34.01	<.0001	348.17	2.8E+00	2.4E-01	constant variance, n restricted >1
Hill	2	<.0001	34.01	<.0001	348.17	2.8E+00	5.0E-05	constant variance, n unrestricted
linear	4	<.0001	81.72	<.0001	391.88	4.6E+01	3.5E+01	constant variance

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
polynomial	4	<.0001	81.72	<.0001	391.88	4.6E+01	3.5E+01	constant variance
power	4	<.0001	81.72	<.0001	391.88	4.6E+01	3.5E+01	constant variance, power restricted ≥1, bound hit
power	3	<.0001	22.22	<.0001	334.38	1.0E-02	6.9E-04	constant variance, power unrestricted

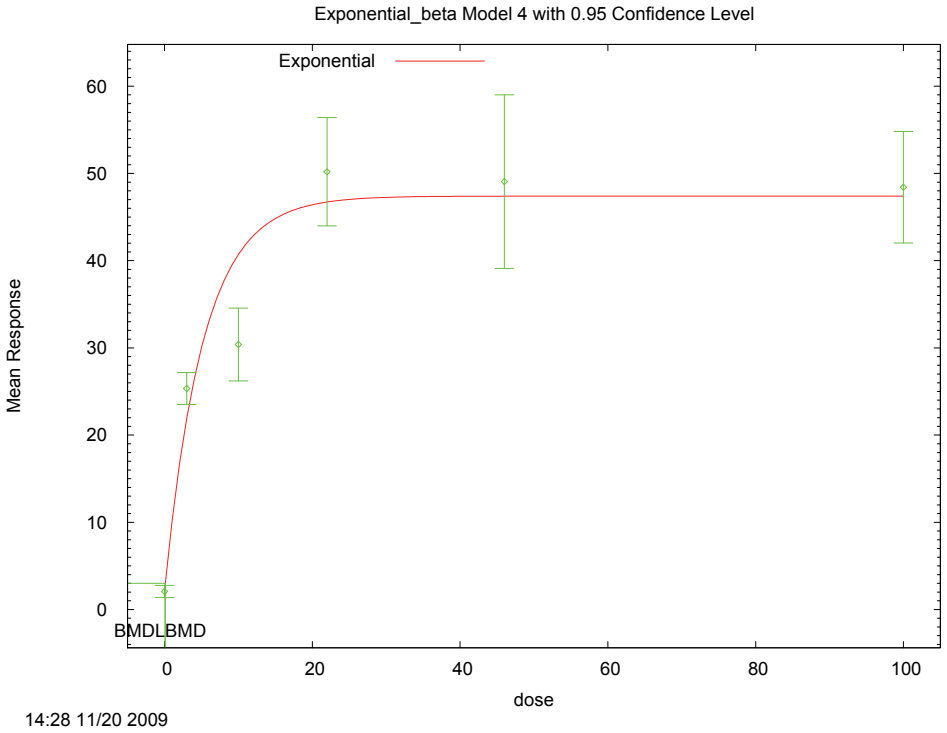
[a]Values < 0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.3.6.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



H.3.6.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_BMR1_Lung_EROD_wk31.(d)
         Gnuplot Plotting File:
```

Fri Nov 20 14:28:10 2009

Tbl 12, Week 31, Lung Microsomes EROD

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 = 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	-1.42653
rho	1.46168
a	1.96745
b	0.034997
c	26.7857
d	1

Parameter Estimates

Variable	Model 4
lnalpha	-1.46439
rho	1.61106
a	2.12443
b	0.19145
c	22.311
d	1

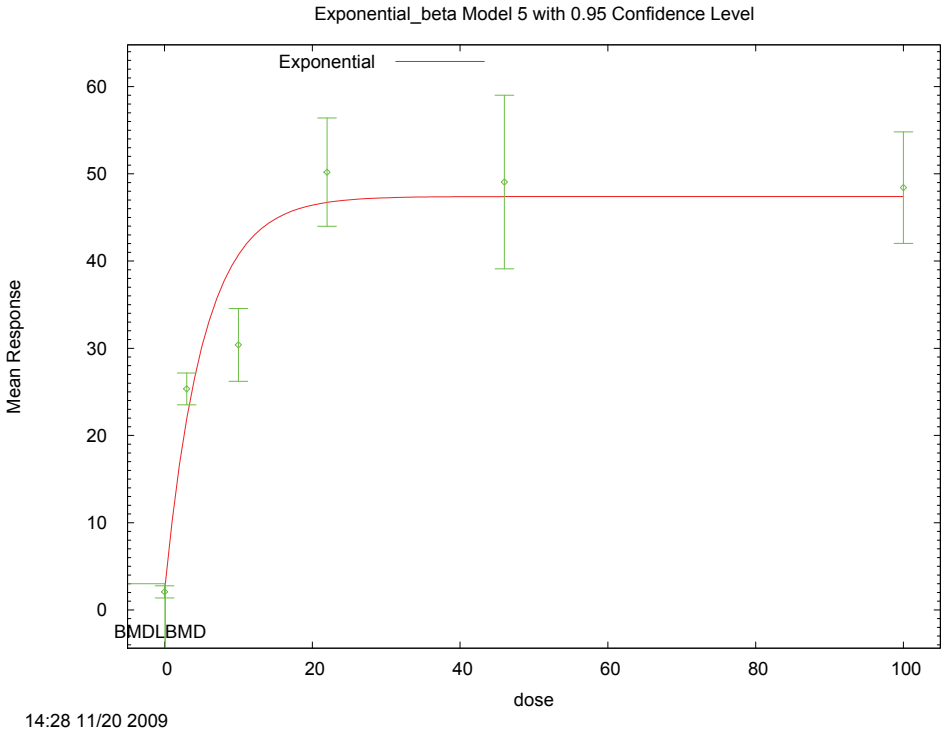
Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	2.071	0.9708
3	10	25.34	2.549
10	10	30.39	5.831
22	10	50.19	8.68
46	10	49.07	13.91

```
   100     10        48.42        8.933


                Estimated Values of Interest

    Dose      Est Mean      Est Std     Scaled Residual
  ------    ----------    ---------    ----------------
       0         2.124       0.8823          -0.1915
       3         21.91        5.779             1.88
      10         40.72        9.524           -3.432
      22         46.73        10.64            1.029
      46         47.39        10.76           0.4921
     100          47.4        10.76           0.3006


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       -152.0793           7      318.1586
                     A2        -123.367          12       270.734
                     A3       -129.5911           8      275.1823
                      R       -206.5175           2      417.0349
                      4       -139.9927           5      289.9853


Additive constant for all log-likelihoods =     -55.14.  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                      166.3             10           < 0.0001
  Test 2                      57.42              5           < 0.0001
  Test 3                      12.45              4            0.01431
 Test 6a                       20.8              3          0.0001157


  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 =     0.102798

                BMDL =     0.069311
```

H.3.6.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



H.3.6.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_Unrest_BMR1_Lung_EROD_wk31.(d)
         Gnuplot Plotting File:
```

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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 = 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 5
lnalpha	-1.42653
rho	1.46168
a	1.96745
b	0.034997
c	26.7857
d	1

Parameter Estimates

Variable	Model 5
lnalpha	-1.46439
rho	1.61106
a	2.12443
b	0.19145
c	22.311
d	1

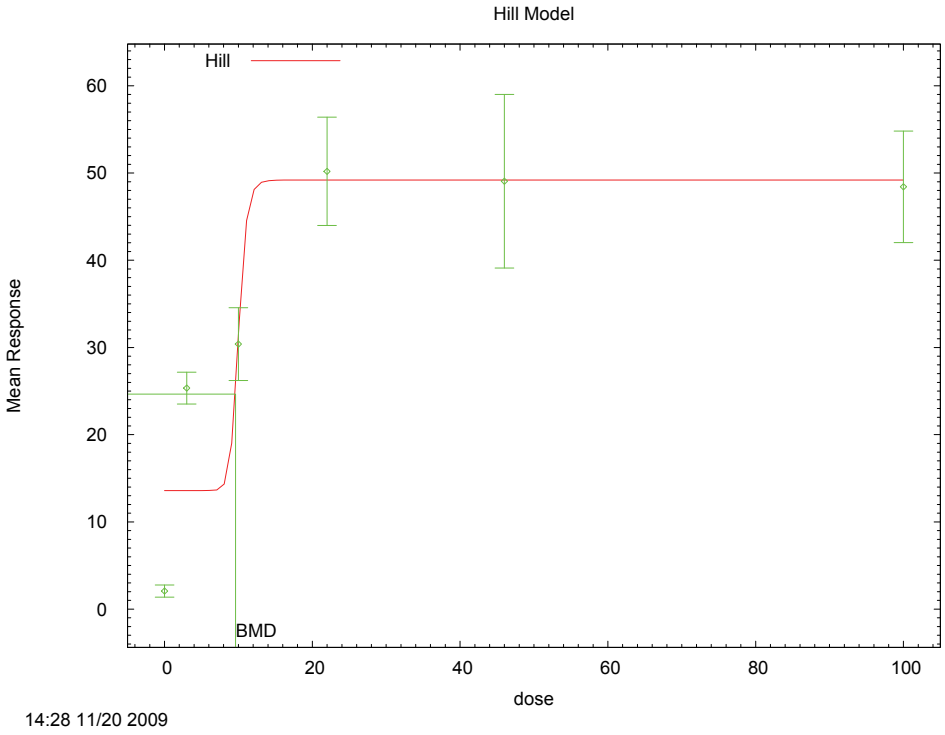
Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	10	2.071	0.9708
3	10	25.34	2.549
10	10	30.39	5.831
22	10	50.19	8.68
46	10	49.07	13.91

```
   100     10        48.42        8.933


                Estimated Values of Interest

    Dose      Est Mean      Est Std     Scaled Residual
  ------    ----------    ---------    ----------------
       0         2.124       0.8823          -0.1915
       3         21.91        5.779             1.88
      10         40.72        9.524           -3.432
      22         46.73        10.64            1.029
      46         47.39        10.76           0.4921
     100          47.4        10.76           0.3006


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       -152.0793           7      318.1586
                     A2        -123.367          12       270.734
                     A3       -129.5911           8      275.1823
                      R       -206.5175           2      417.0349
                      5       -139.9927           5      289.9853


Additive constant for all log-likelihoods =     -55.14.  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                      166.3             10           < 0.0001
  Test 2                      57.42              5           < 0.0001
  Test 3                      12.45              4            0.01431
 Test 7a                       20.8              3          0.0001157


  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 =     0.102798

                BMDL =    0.0693109
```

H.3.6.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



H.3.6.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ========================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_Lung_EROD_wk31.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_Lung_EROD_wk31.plt
                                                 Fri Nov 20 14:28:19 2009
 ========================================================================
```

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~~~~~~

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 = 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 =	4.17467
rho =	0
intercept =	2.071
v =	48.119
n =	18
k =	15.9059

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	0.04	-0.054	-0.092
rho	-0.98	1	-0.027	0.046	0.096
intercept	0.04	-0.027	1	-0.82	0.36
v	-0.054	0.046	-0.82	1	-0.16
k	-0.092	0.096	0.36	-0.16	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	5.40756	1.03169	3.38548	7.42964
rho	-0.228427	0.299513	-0.815462	0.358608
intercept	13.5736	2.48089	8.71112	18.436
v	35.6207	3.03486	29.6725	41.5689
n	18	NA		
k	10.0457	0.22238	9.60987	10.4816

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	2.07	13.6	0.971	11.1	-3.28
3	10	25.3	13.6	2.55	11.1	3.36
10	10	30.4	30.7	5.83	10.1	-0.0833
22	10	50.2	49.2	8.68	9.57	0.329
46	10	49.1	49.2	13.9	9.57	-0.0424
100	10	48.4	49.2	8.93	9.57	-0.255

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	-152.079318	7	318.158637
A2	-123.366985	12	270.733969
A3	-129.591134	8	275.182269
fitted	-169.011448	5	348.022896
R	-206.517459	2	417.034919

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	166.301	10	<.0001
Test 2	57.4247	5	<.0001
Test 3	12.4483	4	0.01431
Test 4	78.8406	3	<.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

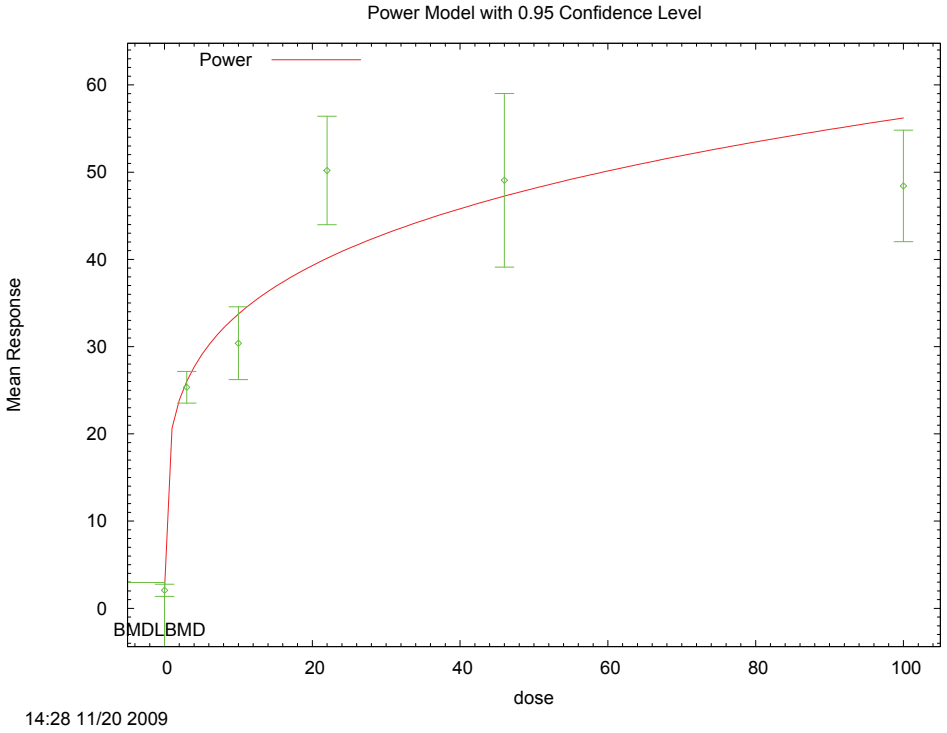
The p-value for Test 3 is less than .1. You may want to consider a
different variance model

The p-value for Test 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 =       9.61218


BMDL computation failed.
```

H.3.6.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



H.3.6.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_Lung_EROD_wk31.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_Lung_EROD_wk31.plt
                                                 Fri Nov 20 14:28:19 2009
 ========================================================================

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   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 =      4.17467
                           rho =            0
                       control =        2.071
                         slope =      18.9386
                         power =     0.224076


          Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho      control        slope        power

  lalpha            1        -0.94        -0.42         0.15        -0.13

     rho        -0.94            1         0.38        -0.19         0.14

 control        -0.42         0.38            1        -0.15        0.093

   slope         0.15        -0.19        -0.15            1        -0.94

   power        -0.13         0.14        0.093        -0.94            1


                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        lalpha         -1.53358         0.571219           -2.65315           -0.414007
           rho           1.6412         0.166321            1.31521             1.96718
       control          2.10983         0.270093            1.58046              2.6392
         slope          18.5389          2.01491            14.5897              22.488
         power         0.233238        0.0324661           0.169605             0.29687


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    10       2.07         2.11        0.971        0.857         -0.143
    3    10       25.3         26.1         2.55         6.74         -0.338
   10    10       30.4         33.8         5.83         8.35           -1.3
   22    10       50.2         40.2         8.68         9.63           3.27
   46    10       49.1         47.4         13.9           11          0.481
  100    10       48.4         56.4         8.93         12.7          -1.98


 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         -152.079318            7     318.158637
             A2         -123.366985           12     270.733969
             A3         -129.591134            8     275.182269
          fitted        -140.838955            5     291.677909
              R         -206.517459            2     417.034919


                    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              166.301         10          <.0001
  Test 2              57.4247          5          <.0001
  Test 3              12.4483          4         0.01431
  Test 4              22.4956          3          <.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 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 = 1.88864e-006


             BMDL = 1.88864e-006
```

H.3.7. National Toxicology Program. (2006): Lung EROD Week 53

H.3.7.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	4	<0.0001	66.01	<0.0001	316.32	1.3E+02	8.1E+01	nonconstant variance, power restricted ≥1
exponential (M3)	4	<0.0001	66.01	<0.0001	316.32	1.3E+02	8.1E+01	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**3**	**<0.0001**	**2.82**	**0.42**	**255.12**	**1.2E-01**	**7.5E-02**	**nonconstant variance, power restricted ≥1**
exponential (M5)	2	<0.0001	16.10	0.00	270.40	2.6E-01	1.5E-04	nonconstant variance, power restricted ≥1
exponential (M5) [d]	2	<0.0001	16.10	0.00	270.40	2.6E-01	1.5E-04	nonconstant variance, power unrestricted
Hill	2	<.0001	81.88	<.0001	336.18	3.0E+02	error	nonconstant variance, n restricted >1
Hill [d]	2	<.0001	81.88	<.0001	336.18	3.0E+02	error	nonconstant variance, n unrestricted
linear	4	<.0001	65.65	<.0001	315.96	1.2E+02	6.3E+01	nonconstant variance
polynomial	4	<.0001	65.65	<.0001	315.96	1.2E+02	6.3E+01	nonconstant variance
power	4	<.0001	65.65	<.0001	315.96	1.2E+02	6.3E+01	nonconstant variance, power restricted ≥1, bound hit
power [d]	3	<.0001	8.50	0.04	260.80	3.8E-10	3.8E-10	nonconstant variance, power unrestricted
exponential (M2)	4	<0.0001	43.26	<0.0001	319.80	8.0E+01	6.0E+01	constant variance, power restricted ≥1
exponential (M3)	4	<0.0001	43.26	<0.0001	319.80	8.0E+01	6.0E+01	constant variance, power restricted ≥1
exponential (M4)	3	<0.0001	3.04	0.39	281.57	9.2E-01	5.5E-01	constant variance, power restricted ≥1
exponential (M5)	2	<0.0001	2.71	0.26	283.24	2.2E+00	5.7E-01	constant variance, power restricted ≥1
exponential (M5)	2	<0.0001	2.71	0.26	283.24	2.2E+00	5.7E-01	constant variance, power unrestricted
Hill	2	<.0001	2.71	0.26	283.24	2.7E+00	3.2E-01	constant variance, n restricted >1
Hill	2	<.0001	2.71	0.26	283.24	2.7E+00	1.2E-02	constant variance, n unrestricted
linear	4	<.0001	41.45	<.0001	317.99	6.5E+01	4.4E+01	constant variance
polynomial	4	<.0001	41.45	<.0001	317.99	6.5E+01	4.4E+01	constant variance
power	4	<.0001	41.45	<.0001	317.99	6.5E+01	4.4E+01	constant variance, power restricted ≥1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
power	3	<.0001	5.93	0.11	284.47	5.3E-04	5.3E-04	constant variance, power unrestricted

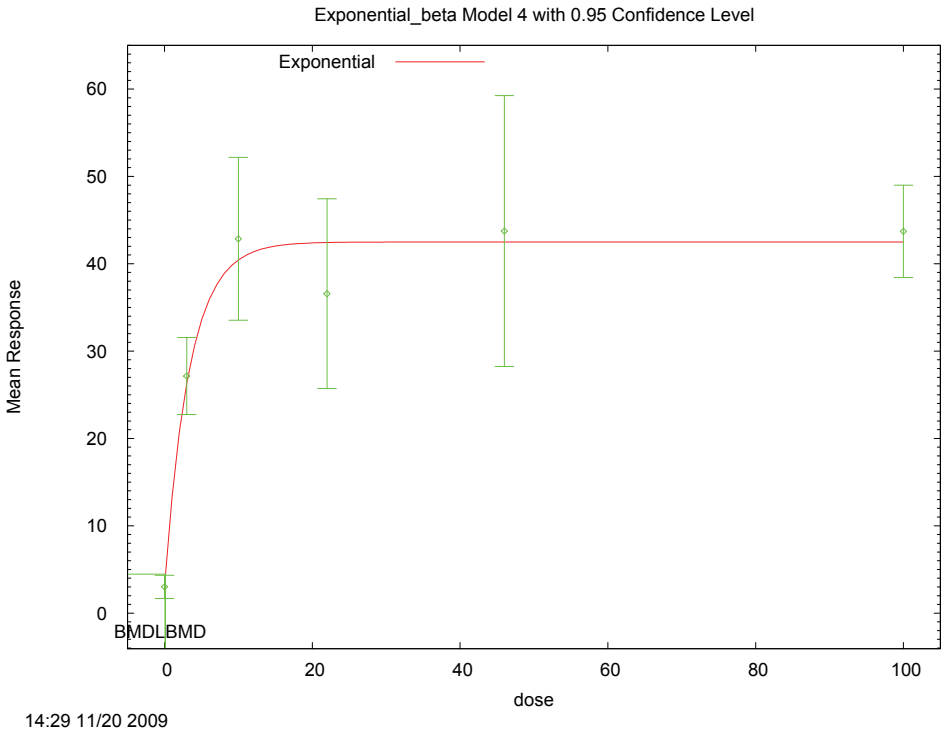
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.3.7.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



H.3.7.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_BMR1_Lung_EROD_wk53.(d)
         Gnuplot Plotting File:
                                                 Fri Nov 20 14:29:03 2009
 ================================================================

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   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 = 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             -0.80064
                    rho              1.47683
                      a              2.86045
                      b            0.0390303
                      c              16.0581
                      d                    1



                Parameter Estimates

               Variable          Model 4
               --------          -------
                lnalpha          -1.07501
                    rho           1.68859
                      a             3.011
                      b           3.22004
                      c           12.8877
                      d                18


        Table of Stats From Input Data

 Dose      N         Obs Mean     Obs Std Dev
 -----    ---       ----------   -------------
    0      8        3.011        1.584
    3      8        27.15        5.269
   10      8        42.85        11.15
   22      8        36.57        12.99
   46      8        43.75        18.55
  100      8        43.71        6.322


              Estimated Values of Interest

  Dose      Est Mean      Est Std     Scaled Residual
------    ----------    ---------    ----------------
```

0	3.068	1.404	-0.1156
3	26.26	8.088	0.3111
10	40.44	11.5	0.5912
22	42.43	11.96	-1.386
46	42.49	11.98	0.2969
100	42.49	11.98	0.2891

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	-135.2677	7	284.5353
A2	-115.6885	12	255.3771
A3	-121.1517	8	258.3034
R	-162.0902	2	328.1805
4	-122.5608	5	255.1215

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	92.8	10	< 0.0001
Test 2	39.16	5	< 0.0001
Test 3	10.93	4	0.0274
Test 6a	2.818	3	0.4205

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.

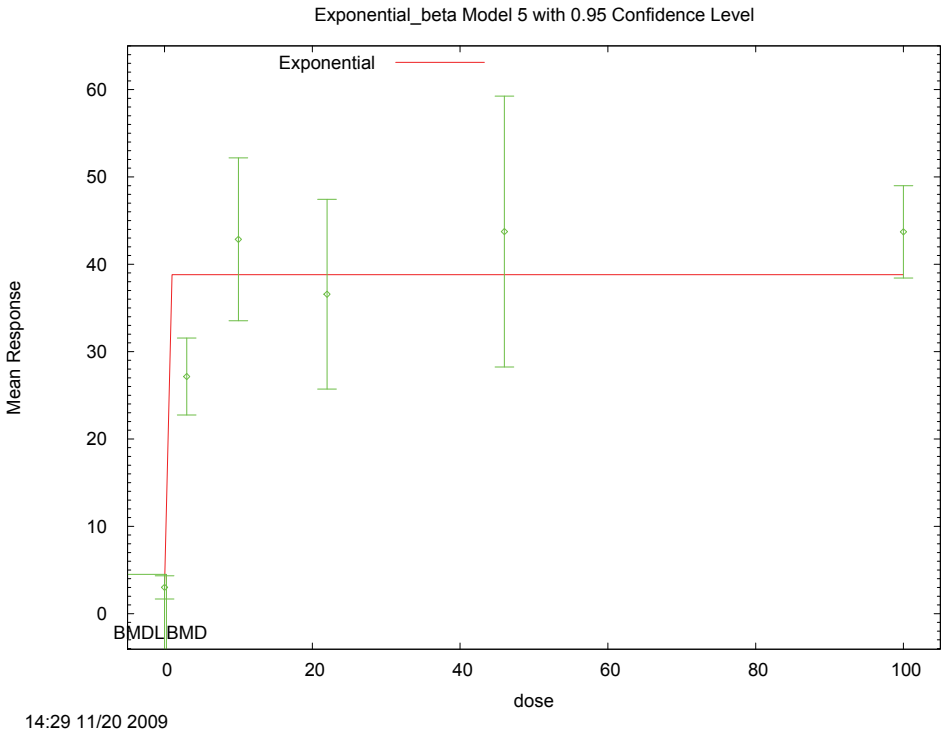
The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

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 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 =     0.122595

               BMDL =    0.0752795
```

H.3.7.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



H.3.7.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_Unrest_BMR1_Lung_EROD_wk53.(d)
         Gnuplot Plotting File:
                                                Fri Nov 20 14:29:09 2009
 ================================================================

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```

```
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 = 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 5
               --------          --------
                 lnalpha            -0.80064
                     rho             1.47683
                       a             2.86045
                       b           0.0390303
                       c             16.0581
                       d                   1


                  Parameter Estimates

                Variable          Model 5
                --------          -------
                 lnalpha          -1.07501
                     rho           1.68859
                       a             3.011
                       b           3.22004
                       c           12.8877
                       d                18


        Table of Stats From Input Data

 Dose      N         Obs Mean     Obs Std Dev
 -----    ---       ----------   -------------
    0      8        3.011        1.584
    3      8        27.15        5.269
   10      8        42.85        11.15
   22      8        36.57        12.99
   46      8        43.75        18.55
  100      8        43.71        6.322


              Estimated Values of Interest

 Dose      Est Mean      Est Std     Scaled Residual
```

0	3.011	1.482	-4.539e-008
3	38.8	12.82	-2.571
10	38.8	12.82	0.8915
22	38.8	12.82	-0.4931
46	38.8	12.82	1.09
100	38.8	12.82	1.082

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	-135.2677	7	284.5353
A2	-115.6885	12	255.3771
A3	-121.1517	8	258.3034
R	-162.0902	2	328.1805
5	-129.2006	6	270.4011

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 7a: Does Model 5 fit the data? (A3 vs 5)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	92.8	10	< 0.0001
Test 2	39.16	5	< 0.0001
Test 3	10.93	4	0.0274
Test 7a	16.1	2	0.0003195

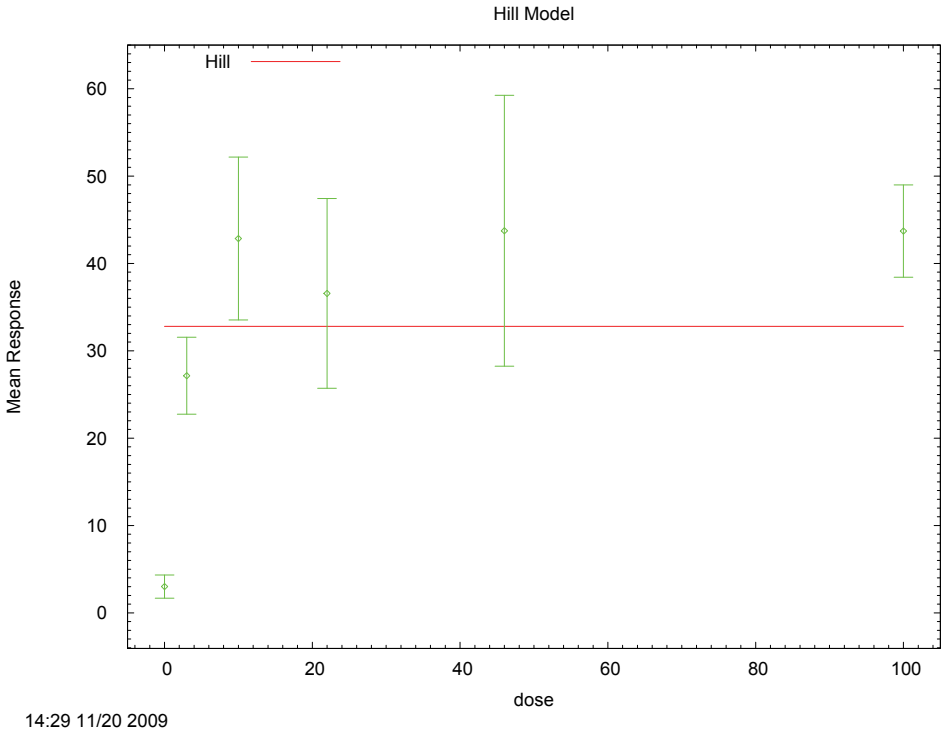
The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

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 =     0.260501

              BMDL =  0.000148718
```

H.3.7.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



H.3.7.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_Lung_EROD_wk53.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_Lung_EROD_wk53.plt
                                                Fri Nov 20 14:29:11 2009
 ================================================================

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   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 = 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 =	4.76968
rho =	0
intercept =	3.011
v =	40.735
n =	1.63324
k =	3.46862

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	intercept	v	n	k
lalpha	1	-1	0.00098	-0.015	NA	NA
rho	-1	1	-0.00098	0.015	NA	NA
intercept	0.00098	-0.00098	1	-1.5e-005	NA	NA
v	-0.015	0.015	-1.5e-005	1	NA	NA
n	NA	NA	NA	NA	NA	NA
k	NA	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

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	16.2956	NA	NA	NA
rho	-3.01917	NA	NA	NA
intercept	32.8392	NA	NA	NA
v	81.7793	NA	NA	NA
n	17.5977	NA	NA	NA
k	324.491	NA	NA	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	8	3.01	32.8	1.58	17.8	-4.75
3	8	27.1	32.8	5.27	17.8	-0.906

10	8	42.8	32.8	11.2	17.8	1.59
22	8	36.6	32.8	13	17.8	0.594
46	8	43.7	32.8	18.5	17.8	1.74
100	8	43.7	32.8	6.32	17.8	1.73

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	-135.267662	7	284.535325
A2	-115.688533	12	255.377067
A3	-121.151707	8	258.303413
fitted	-162.090242	6	336.180484
R	-162.090242	2	328.180484

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	92.8034	10	<.0001
Test 2	39.1583	5	<.0001
Test 3	10.9263	4	0.0274
Test 4	81.8771	2	<.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 4 is less than .1. You may want to try a different
model

Benchmark Dose Computation

Specified effect = 1

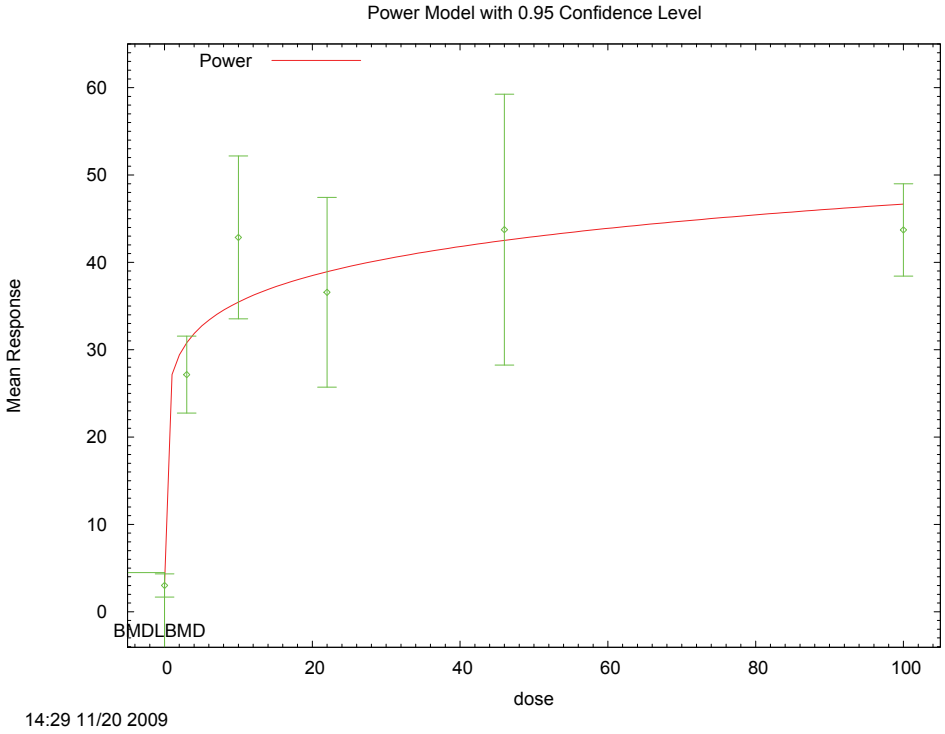
```
Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =        301.687


BMDL computation failed.
```

H.3.7.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



H.3.7.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_Lung_EROD_wk53.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_Lung_EROD_wk53.plt
                                                 Fri Nov 20 14:29:12 2009
 ========================================================================

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   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 =	4.76968
rho =	0
control =	3.011
slope =	23.6162
power =	0.133025

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	control	slope	power
lalpha	1	-0.96	-0.48	0.11	-0.048
rho	-0.96	1	0.45	-0.14	0.053
control	-0.48	0.45	1	-0.14	0.05
slope	0.11	-0.14	-0.14	1	-0.93
power	-0.048	0.053	0.05	-0.93	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	-1.03233	0.815925	-2.63152	0.566849
rho	1.63033	0.23978	1.16037	2.10029
control	3.01788	0.518168	2.00229	4.03347
slope	24.0756	3.58644	17.0463	31.1049
power	0.128899	0.0448635	0.040968	0.21683

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	3.01	3.02	1.58	1.47	-0.0133
3	8	27.1	30.8	5.27	9.74	-1.05
10	8	42.8	35.4	11.2	10.9	1.92
22	8	36.6	38.9	13	11.8	-0.554
46	8	43.7	42.5	18.5	12.7	0.288
100	8	43.7	46.6	6.32	13.7	-0.599

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         -135.267662            7     284.535325
              A2         -115.688533           12     255.377067
              A3         -121.151707            8     258.303413
           fitted        -125.400472            5     260.800944
               R         -162.090242            2     328.180484


                    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              92.8034         10          <.0001
   Test 2              39.1583          5          <.0001
   Test 3              10.9263          4          0.0274
   Test 4              8.49753          3         0.03677

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 = 3.76923e-010


             BMDL = 3.76923e-010
```

H.3.8. National Toxicology Program. (2006): Tbl11 Index Week 31

H.3.8.1. *Summary Table of BMDS Modeling Results*

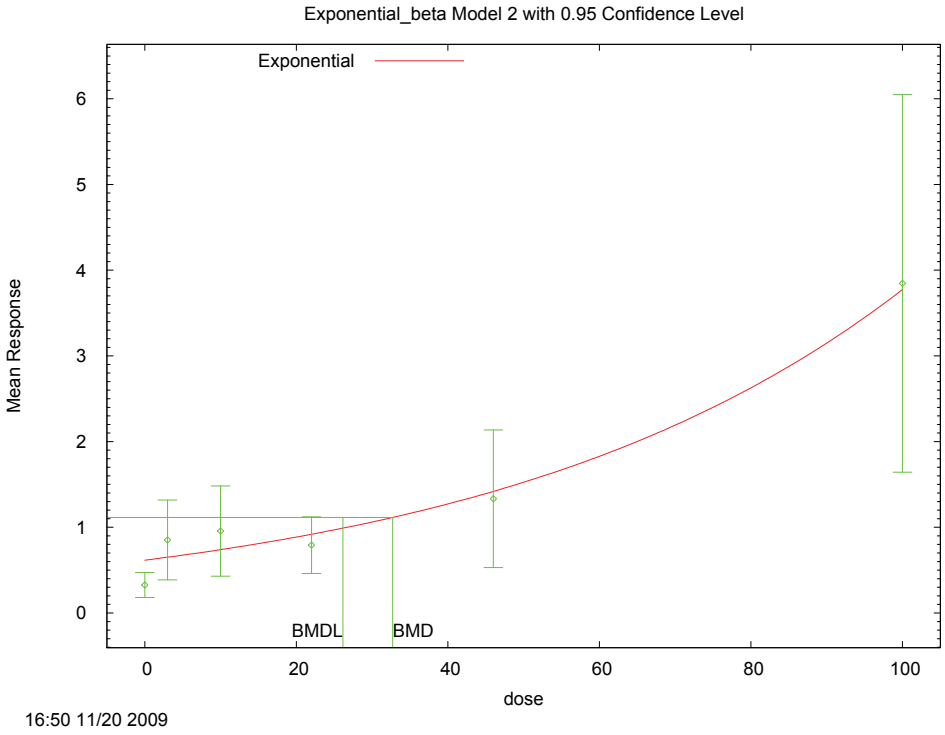
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2) [c]	**4**	**<0.0001**	**21.34**	**0.00**	**47.30**	**3.3E+01**	**2.6E+01**	**nonconstant variance, power restricted ≥1**
exponential (M3)	4	<0.0001	21.34	0.00	47.30	3.3E+01	2.6E+01	nonconstant variance, power restricted ≥1
exponential (M4)	3	<0.0001	25.36	<0.0001	53.32	1.7E+01	1.1E+01	nonconstant variance, power restricted ≥1
exponential (M5)	2	<0.0001	21.10	<0.0001	51.06	4.6E+01	2.9E+01	nonconstant variance, power restricted ≥1
Hill	3	<.0001	21.10	0.00	49.06	4.6E+01	error	nonconstant variance, n restricted >1, bound hit
linear	4	<.0001	25.36	<.0001	51.32	1.7E+01	1.1E+01	nonconstant variance
polynomial	3	<.0001	21.87	<.0001	49.83	3.9E+01	1.7E+01	nonconstant variance
power	3	<.0001	21.87	<.0001	49.83	4.5E+01	2.4E+01	nonconstant variance, power restricted ≥1
exponential (M2)	4	<0.0001	1.02	0.91	101.49	6.4E+01	5.7E+01	constant variance, power restricted ≥1
exponential (M3)	3	<0.0001	1.00	0.80	103.47	6.7E+01	5.7E+01	constant variance, power restricted ≥1
exponential (M4)	3	<0.0001	3.38	0.34	105.85	4.4E+01	3.3E+01	constant variance, power restricted ≥1
exponential (M5)	2	<0.0001	1.10	0.58	105.57	6.6E+01	3.9E+01	constant variance, power restricted ≥1
Hill	2	<.0001	1.10	0.58	105.57	6.6E+01	3.9E+01	constant variance, n restricted >1
linear	4	<.0001	3.38	0.50	103.85	4.4E+01	3.3E+01	constant variance
polynomial	3	<.0001	1.08	0.78	103.55	6.4E+01	3.9E+01	constant variance
power	3	<.0001	1.10	0.78	103.57	6.6E+01	3.9E+01	constant variance, power restricted ≥1

[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

H.3.8.2. *Figure for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*



H.3.8.3. *Output File for Selected Model: Exponential (M2), Nonconstant Variance, Power Restricted ≥1*

```
 ======================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_BMR1_Tbl11_31wk.(d)
         Gnuplot Plotting File:
                                                  Fri Nov 20 16:50:52 2009
 ======================================================================

 Tbl 11, 31wk, Hep Cell Proliferation Labeling Index
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   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 = 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 2
lnalpha	-0.674004
rho	2.29189
a	0.31065
b	0.024912
c	12.9995
d	1

Parameter Estimates

Variable	Model 2
lnalpha	-0.495833
rho	1.97486
a	0.740304
b	0.0199927
c	5.16751
d	18

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	9	0.327	0.189
3	10	0.852	0.6514
10	10	0.956	0.7368
22	10	0.792	0.4617
46	10	1.333	1.123
100	10	3.846	3.08

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	0.6166	0.4987	-1.742
3	0.651	0.5251	1.21
10	0.7391	0.5925	1.158
22	0.9186	0.7287	-0.5493
46	1.419	1.102	-0.2466
100	3.775	2.796	0.08069

```
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       -47.23498           7        108.47
                    A2       -8.679256          12       41.35851
                    A3       -8.980651           8        33.9613
                     R       -63.44829           2       130.8966
                     2        -19.6508           4       47.30161


Additive constant for all log-likelihoods =     -54.22.  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                        109.5           10           < 0.0001
  Test 2                        77.11            5           < 0.0001
  Test 3                       0.6028            4             0.9628
  Test 4                        21.34            4          0.0002711


  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 =      32.7092

             BMDL =      26.1405
```

H.3.9. Van Birgelen et al. (1995b): T4 UGT

H.3.9.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	4	<0.0001	35.16	<0.0001	38.57	5.0E+02	3.5E+02	nonconstant variance, power restricted ≥1
exponential (M3)	4	<0.0001	35.16	<0.0001	38.57	5.0E+02	3.5E+02	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**3**	**<0.0001**	**1.01**	**0.80**	**6.42**	**1.2E+01**	**6.2E+00**	**nonconstant variance, power restricted ≥1**
exponential (M5)	3	<0.0001	1.01	0.80	6.42	1.2E+01	6.2E+00	nonconstant variance, power restricted ≥1
exponential (M5) [d]	3	<0.0001	1.01	0.80	6.42	1.2E+01	6.2E+00	nonconstant variance, power unrestricted
Hill	2	<.0001	1.12	0.57	8.52	1.3E+01	6.1E+00	nonconstant variance, n restricted >1
Hill [d]	2	<.0001	1.12	0.57	8.52	1.3E+01	3.7E+00	nonconstant variance, n unrestricted
linear	4	<.0001	23.17	0.00	26.57	1.7E+02	9.4E+01	nonconstant variance
polynomial	4	<.0001	23.17	0.00	26.57	1.7E+02	9.4E+01	nonconstant variance
power	4	<.0001	23.17	0.00	26.57	1.7E+02	9.4E+01	nonconstant variance, power restricted ≥1, bound hit
power [d]	3	<.0001	5.05	0.17	10.45	4.0E+00	4.8E-01	nonconstant variance, power unrestricted
exponential (M2)	4	<0.0001	14.22	0.01	39.63	6.1E+02	5.2E+02	constant variance, power restricted ≥1
exponential (M3)	4	<0.0001	14.22	0.01	39.63	6.1E+02	5.2E+02	constant variance, power restricted ≥1
exponential (M4)	3	<0.0001	0.16	0.98	27.56	8.8E+01	3.6E+01	constant variance, power restricted ≥1
exponential (M5)	3	<0.0001	0.16	0.98	27.56	8.8E+01	3.6E+01	constant variance, power restricted ≥1
exponential (M5)	3	<0.0001	0.16	0.98	27.56	8.8E+01	3.6E+01	constant variance, power unrestricted
Hill	2	<.0001	0.10	0.95	29.51	7.1E+01	2.7E+01	constant variance, n restricted >1
Hill	2	<.0001	0.10	0.95	29.51	7.1E+01	1.9E+01	constant variance, n unrestricted
linear	4	<.0001	9.68	0.05	35.08	4.0E+02	3.0E+02	constant variance
polynomial	4	<.0001	9.68	0.05	35.08	4.0E+02	3.0E+02	constant variance
power	4	<.0001	9.68	0.05	35.08	4.0E+02	3.0E+02	constant variance, power restricted ≥1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
power	3	<.0001	2.09	0.55	29.49	5.7E+01	9.9E+00	constant variance, power unrestricted

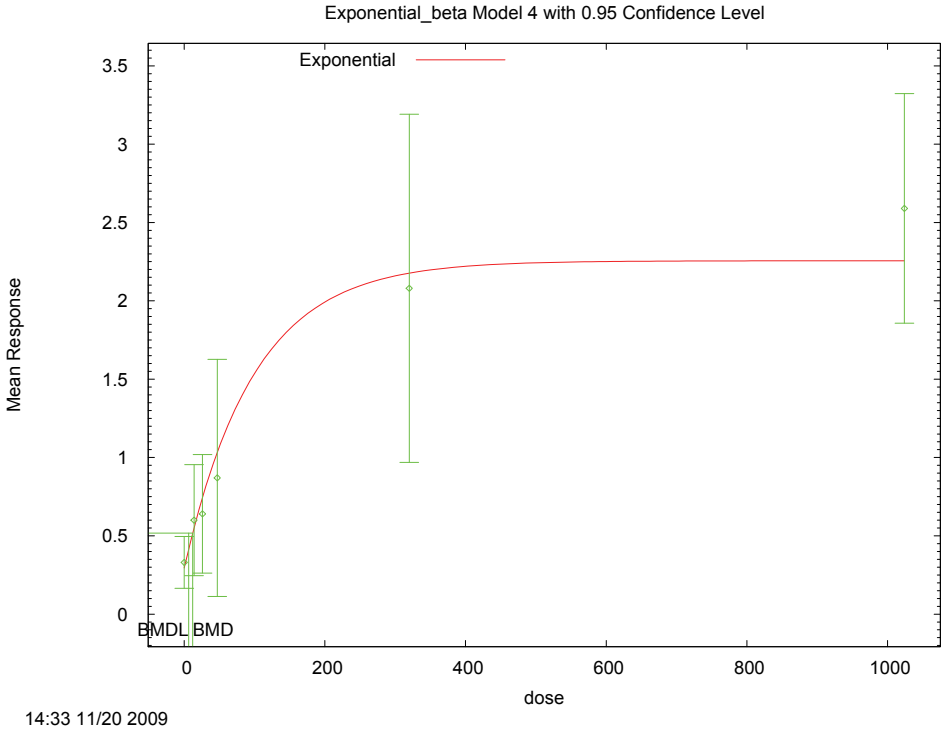
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.3.9.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



H.3.9.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_BMR1_T4_UGT.(d)
         Gnuplot Plotting File:
                                                 Fri Nov 20 14:33:47 2009
 ========================================================================

 Tbl2, T4 UGT
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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           -0.937573
                    rho             1.54913
                      a              0.3135
                      b           0.00297568
                      c              8.67464
                      d                    1


                Parameter Estimates

               Variable          Model 4
               --------          -------
                lnalpha         -0.937201
                    rho            1.6967
                      a          0.294922
                      b         0.0100397
                      c           7.64822
                      d                 1


        Table of Stats From Input Data

 Dose      N         Obs Mean     Obs Std Dev
 -----    ---       ----------   -------------
    0      8         0.33        0.198
   14      8          0.6        0.4243
   26      8         0.64        0.4525
   47      8         0.87        0.9051
  320      8         2.08         1.329
 1024      8         2.59        0.8768


              Estimated Values of Interest

  Dose      Est Mean      Est Std     Scaled Residual
------    ----------    ---------    ----------------
```

0	0.2949	0.2221	0.4466
14	0.552	0.3781	0.3589
26	0.7454	0.4878	-0.6111
47	1.032	0.6431	-0.7146
320	2.177	1.211	-0.2259
1024	2.256	1.248	0.758

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	-9.701316	7	33.40263
A2	4.934967	12	14.13007
A3	2.296438	8	11.40712
R	-29.51921	2	63.03841
4	1.790563	5	6.418874

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	68.91	10	< 0.0001
Test 2	29.27	5	< 0.0001
Test 3	5.277	4	0.26
Test 6a	1.012	3	0.7984

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.

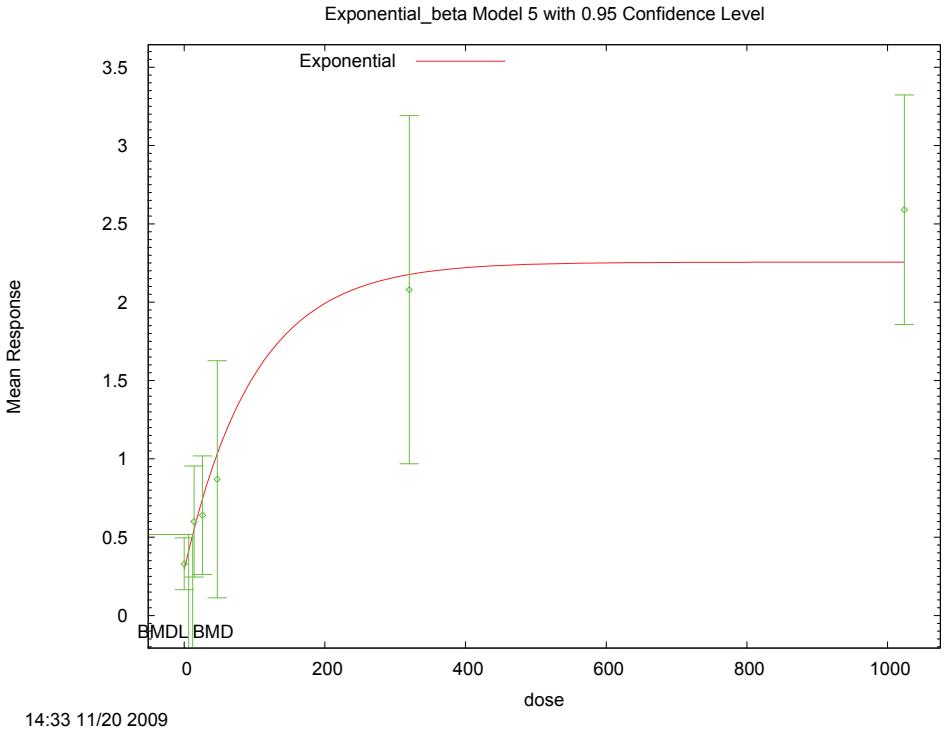
The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

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 =      11.9766

               BMDL =      6.23544
```

H.3.9.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



H.3.9.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_Unrest_BMR1_T4_UGT.(d)
         Gnuplot Plotting File:
                                                 Fri Nov 20 14:33:53 2009
 ========================================================================

 Tbl2, T4 UGT
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 5
              --------          --------
                lnalpha           -0.937573
                    rho             1.54913
                      a              0.3135
                      b           0.00297568
                      c              8.67464
                      d                    1


                Parameter Estimates

               Variable          Model 5
               --------          -------
                lnalpha         -0.937201
                    rho            1.6967
                      a          0.294922
                      b         0.0100397
                      c           7.64822
                      d                 1


        Table of Stats From Input Data

 Dose      N         Obs Mean     Obs Std Dev
 -----    ---       ----------   -------------
    0      8          0.33         0.198
   14      8           0.6        0.4243
   26      8          0.64        0.4525
   47      8          0.87        0.9051
  320      8          2.08         1.329
 1024      8          2.59        0.8768


              Estimated Values of Interest

  Dose      Est Mean      Est Std     Scaled Residual
------    ----------    ---------    ----------------
```

0	0.2949	0.2221	0.4466
14	0.552	0.3781	0.3589
26	0.7454	0.4878	-0.6111
47	1.032	0.6431	-0.7146
320	2.177	1.211	-0.2259
1024	2.256	1.248	0.758

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	-9.701316	7	33.40263
A2	4.934967	12	14.13007
A3	2.296438	8	11.40712
R	-29.51921	2	63.03841
5	1.790563	5	6.418874

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 7a: Does Model 5 fit the data? (A3 vs 5)
```

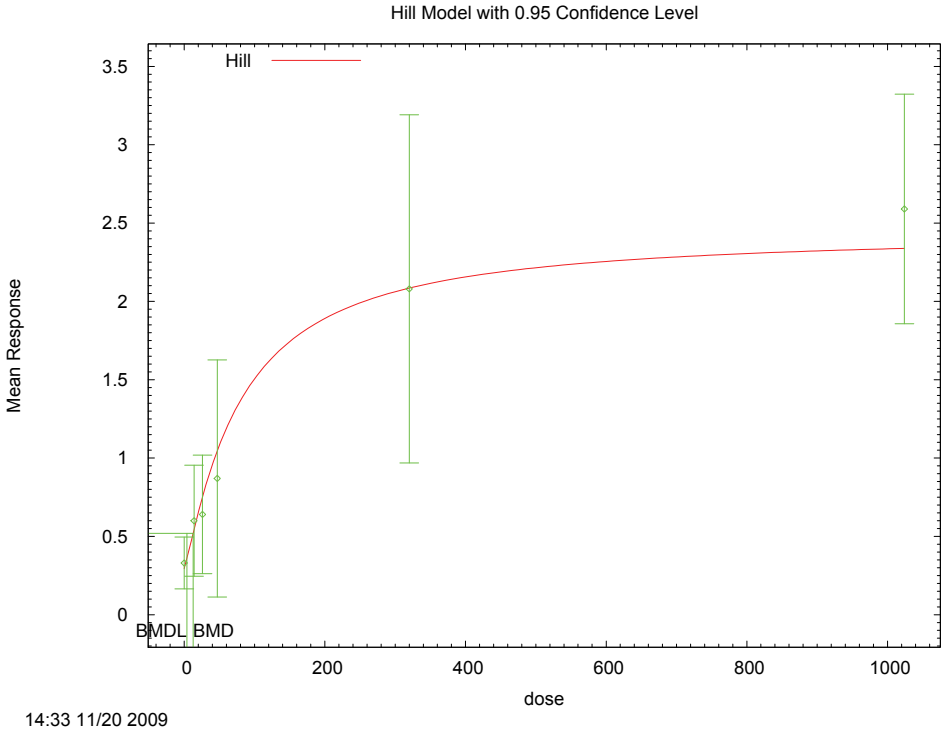
Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	68.91	10	< 0.0001
Test 2	29.27	5	< 0.0001
Test 3	5.277	4	0.26
Test 7a	1.012	3	0.7984

```
  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 7a is greater than .1.  Model 5 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 =      11.9766

              BMDL =      6.23544
```

H.3.9.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



H.3.9.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_T4_UGT.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_T4_UGT.plt
                                                Fri Nov 20 14:33:54 2009
 ================================================================

 Tbl2, T4 UGT
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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 =	-0.462247
rho =	0
intercept =	0.33
v =	2.26
n =	0.430022
k =	459.884

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	intercept	v	n	k
lalpha	1	0.036	-0.26	-0.16	-0.017	0.037
rho	0.036	1	0.48	-0.46	0.02	-0.2
intercept	-0.26	0.48	1	-0.37	0.26	-0.15
v	-0.16	-0.46	-0.37	1	-0.64	0.81
n	-0.017	0.02	0.26	-0.64	1	-0.85
k	0.037	-0.2	-0.15	0.81	-0.85	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-0.935113	0.256585	-1.43801	-0.432217
rho	1.68648	0.441197	0.821746	2.55121
intercept	0.295265	0.0703668	0.157348	0.433181
v	2.14661	0.547941	1.07267	3.22056
n	1.16336	0.46393	0.25407	2.07264
k	80.2777	52.4068	-22.4378	182.993

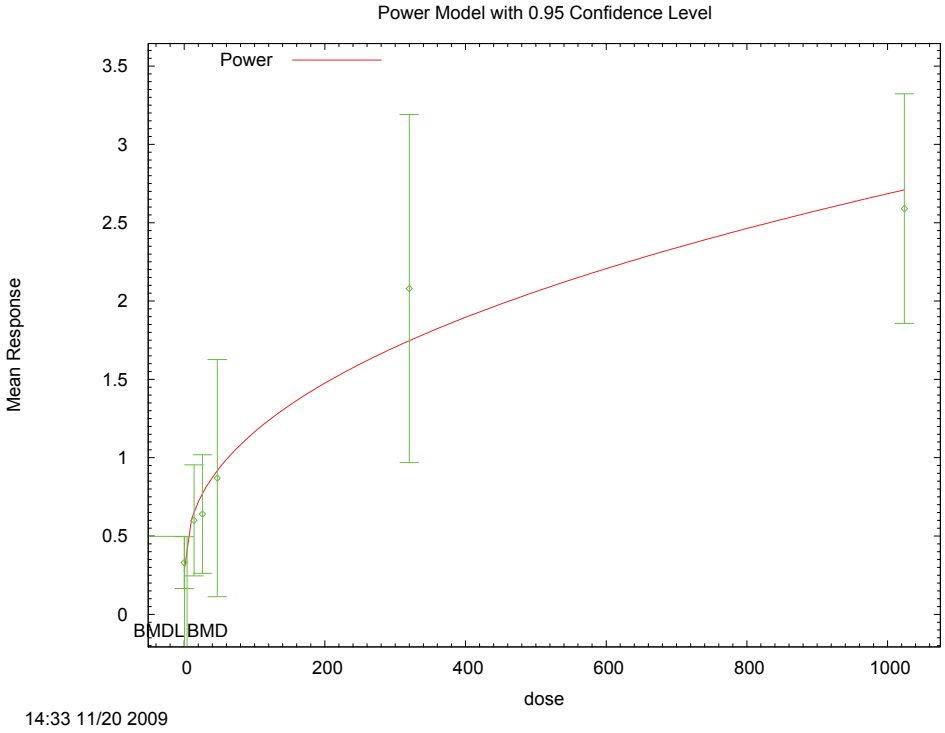
Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	0.33	0.295	0.198	0.224	0.439
14	8	0.6	0.544	0.424	0.375	0.422
26	8	0.64	0.751	0.453	0.492	-0.637
47	8	0.87	1.04	0.905	0.65	-0.76
320	8	2.08	2.08	1.33	1.16	-0.00947
1024	8	2.59	2.34	0.877	1.28	0.56

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           -9.701316            7      33.402631
            A2            4.934967           12      14.130066
            A3            2.296438            8      11.407124
         fitted           1.738274            6       8.523453
             R          -29.519205            2      63.038411


                  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              68.9083         10          <.0001
  Test 2              29.2726          5          <.0001
  Test 3              5.27706          4            0.26
  Test 4              1.11633          2          0.5723

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 =        12.6477

            BMDL =       3.73502
```

H.3.9.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



H.3.9.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_T4_UGT.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_T4_UGT.plt
                                              Fri Nov 20 14:33:55 2009
 ========================================================================

 Tbl2, T4 UGT
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =    -0.462247
                       rho =            0
                   control =         0.33
                     slope =    0.0542809
                     power =     0.537973


          Asymptotic Correlation Matrix of Parameter Estimates

                lalpha          rho      control        slope        power

    lalpha           1        0.032        -0.26        -0.19        0.071

       rho       0.032            1         0.57        0.021        -0.19

   control       -0.26         0.57            1        -0.23        0.077

     slope       -0.19        0.021        -0.23            1        -0.94

     power       0.071        -0.19        0.077        -0.94            1


                              Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        lalpha         -0.85465         0.259915           -1.36407           -0.345225
           rho          1.67517         0.448857           0.795428            2.55492
       control         0.275898        0.0675474           0.143507           0.408288
         slope          0.12137        0.0517127          0.0200146           0.222725
         power          0.43322        0.0764873           0.283308           0.583132


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0       8       0.33        0.276        0.198        0.222           0.69
   14       8        0.6        0.657        0.424        0.459         -0.349
   26       8       0.64        0.774        0.453        0.526         -0.719
   47       8       0.87        0.919        0.905        0.608         -0.229
  320       8       2.08         1.75         1.33         1.04          0.886
 1024       8       2.59         2.72        0.877         1.51         -0.245


 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           -9.701316            7      33.402631
              A2            4.934967           12      14.130066
              A3            2.296438            8      11.407124
          fitted           -0.226526            5      10.453053
               R          -29.519205            2      63.038411


                    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              68.9083         10          <.0001
   Test 2              29.2726          5          <.0001
   Test 3              5.27706          4            0.26
   Test 4              5.04593          3          0.1685

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 = 4.02257


            BMDL = 0.480637
```

H.3.10. Van Birgelen et al. (1995b): UGT 1A1

H.3.10.1. *Summary Table of BMDS Modeling Results*

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	3	0.00	29.54	<0.0001	167.34	7.4E+02	2.1E+02	nonconstant variance, power restricted ≥1
exponential (M3)	3	0.00	29.54	<0.0001	167.34	7.4E+02	2.1E+02	nonconstant variance, power restricted ≥1
exponential (M4) [c]	**2**	**0.00**	**1.28**	**0.53**	**141.08**	**1.6E+00**	**8.5E-01**	**nonconstant variance, power restricted ≥1**
exponential (M5)	2	0.00	1.28	0.53	141.08	1.6E+00	8.5E-01	nonconstant variance, power restricted ≥1
exponential (M5) [d]	2	0.00	1.28	0.53	141.08	1.6E+00	8.5E-01	nonconstant variance, power unrestricted
Hill	1	0.00	1.31	0.25	143.11	1.8E+00	error	nonconstant variance, n restricted >1
Hill [d]	1	0.00	1.31	0.25	143.11	1.8E+00	error	nonconstant variance, n unrestricted
linear	3	0.00	27.83	<.0001	165.63	2.1E+02	5.8E+01	nonconstant variance
polynomial	3	0.00	30.93	<.0001	168.73	1.8E+03	2.9E+01	nonconstant variance
power	3	0.00	27.83	<.0001	165.63	2.1E+02	5.8E+01	nonconstant variance, power restricted ≥1, bound hit
power [d]	2	0.00	5.39	0.07	145.19	3.4E-03	3.4E-03	nonconstant variance, power unrestricted
exponential (M2)	3	0.00	22.45	<0.0001	165.95	1.3E+03	6.4E+02	constant variance, power restricted ≥1
exponential (M3)	3	0.00	22.45	<0.0001	165.95	1.3E+03	6.4E+02	constant variance, power restricted ≥1
exponential (M4)	2	0.00	7.89	0.02	153.38	1.1E+01	4.7E+00	constant variance, power restricted ≥1
exponential (M5)	2	0.00	7.89	0.02	153.38	1.1E+01	4.7E+00	constant variance, power restricted ≥1
exponential (M5)	2	0.00	7.89	0.02	153.38	1.1E+01	4.7E+00	constant variance, power unrestricted
Hill	1	0.00	8.15	0.00	155.65	1.3E+01	3.0E+00	constant variance, n restricted >1
Hill	1	0.00	8.15	0.00	155.65	1.3E+01	1.9E+00	constant variance, n unrestricted
linear	3	0.00	22.15	<.0001	165.65	1.1E+03	4.9E+02	constant variance
polynomial	3	0.00	22.15	<.0001	165.65	1.1E+03	4.9E+02	constant variance
power	3	0.00	22.15	<.0001	165.65	1.1E+03	4.9E+02	constant variance, power restricted ≥1, bound hit

Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
power	2	0.00	12.90	0.00	158.40	1.6E-01	5.2E-06	constant variance, power unrestricted

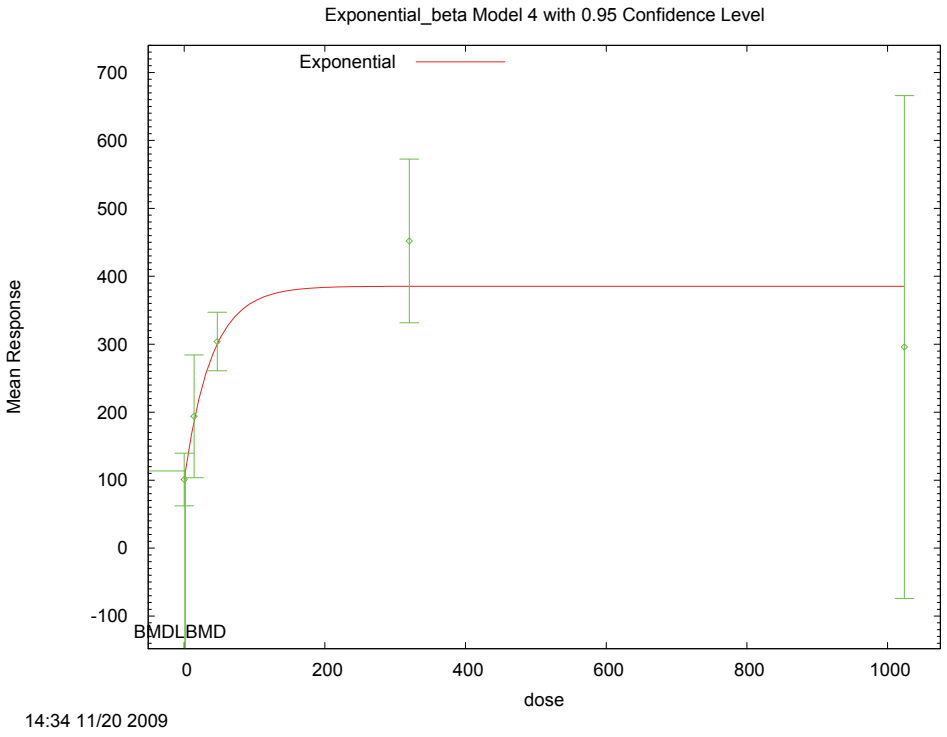
[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

[d]Alternate model also presented in this appendix

H.3.10.2. *Figure for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*



H.3.10.3. *Output File for Selected Model: Exponential (M4), Nonconstant Variance, Power Restricted ≥1*

```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_BMR1_UGT_1A1.(d)
         Gnuplot Plotting File:
                                                 Fri Nov 20 14:34:36 2009
 ========================================================================

 Tbl2, UGT_1A1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 4
              --------          --------
                lnalpha            -1.53604
                    rho             1.59958
                      a               95.95
                      b          0.00148532
                      c             4.94633
                      d                    1


                Parameter Estimates

               Variable          Model 4
               --------          -------
                lnalpha          -10.1636
                    rho           3.25851
                      a           101.863
                      b         0.0256373
                      c           3.78343
                      d                 1


        Table of Stats From Input Data

 Dose      N         Obs Mean     Obs Std Dev
 -----    ---       ----------   -------------
    0      3          101         15.59
   14      3          194         36.37
   47      3          304         17.32
  320      3          452          48.5
 1024      3          296           149


              Estimated Values of Interest

  Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
    0         101.9         11.6          -0.1288
```

14	187.4	31.32	0.3668	
47	300.4	67.58	0.09183	
320	385.3	101.4	1.139	
1024	385.4	101.4	-1.527	

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	-68.74833	6	149.4967
A2	-58.69126	10	137.3825
A3	-64.89907	7	143.7981
R	-80.72265	2	165.4453
4	-65.54073	5	141.0815

Additive constant for all log-likelihoods = -13.78. 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	44.06	8	< 0.0001
Test 2	20.11	4	0.0004741
Test 3	12.42	3	0.006087
Test 6a	1.283	2	0.5264

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.

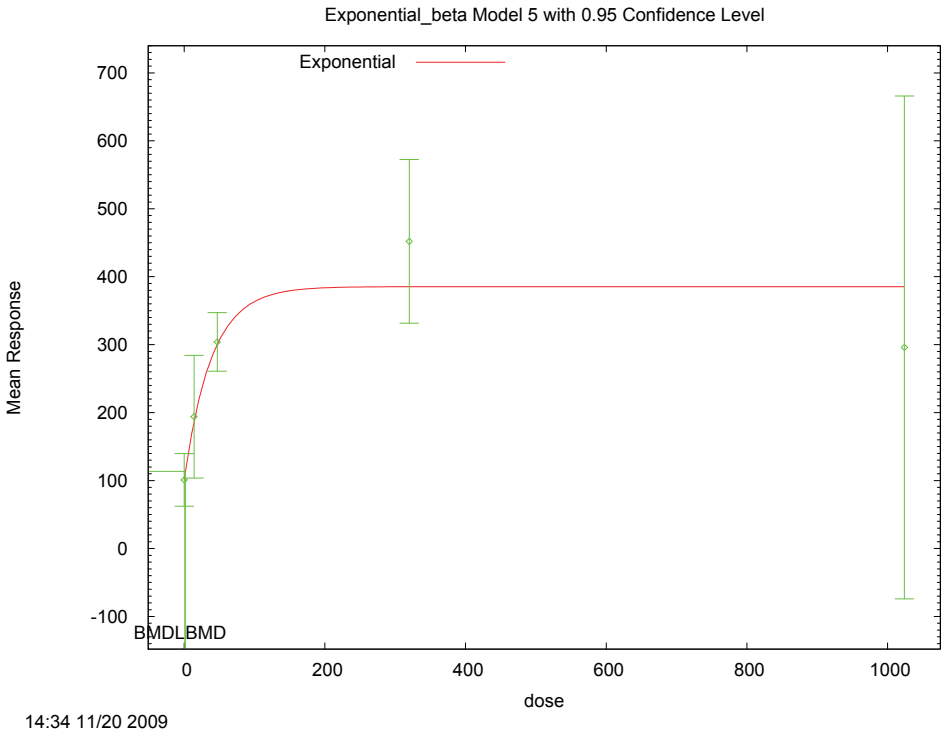
The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

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 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 =      1.62983

                BMDL =     0.853335
```

H.3.10.4. *Figure for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*



H.3.10.5. *Output File for Unrestricted Model: Exponential (M5), Nonconstant Variance, Power Unrestricted*

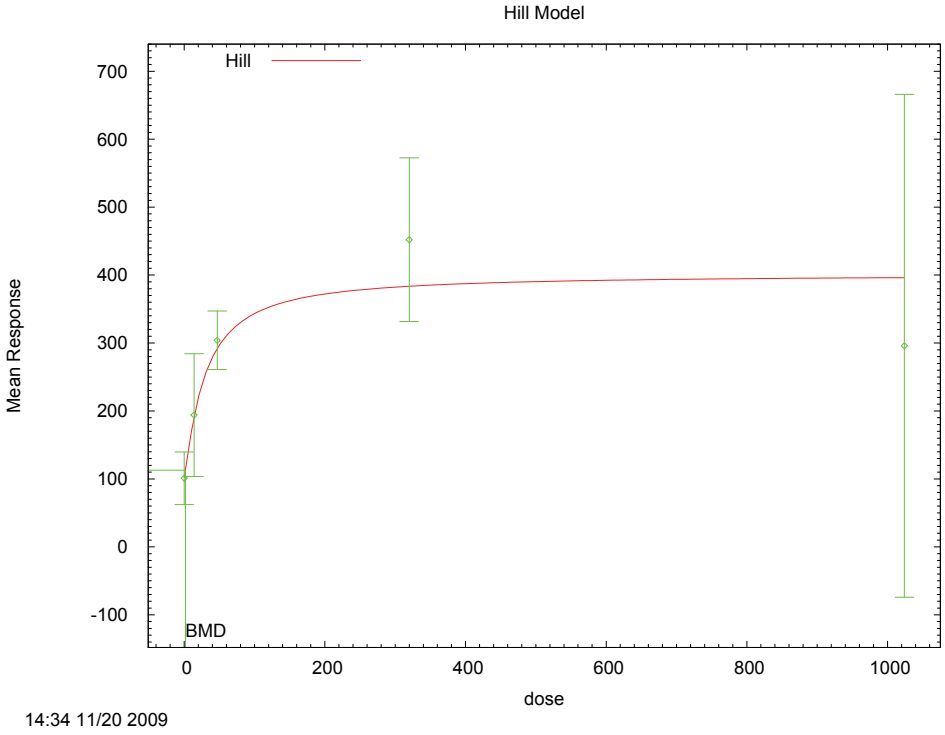
```
 ========================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_Unrest_BMR1_UGT_1A1.(d)
         Gnuplot Plotting File:
                                                 Fri Nov 20 14:34:44 2009
 ========================================================================

 Tbl2, UGT_1A1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 5
              --------          --------
                lnalpha            -1.53604
                    rho             1.59958
                      a               95.95
                      b           0.00148532
                      c              4.94633
                      d                     1



                Parameter Estimates

               Variable          Model 5
               --------          -------
                lnalpha          -10.1636
                    rho           3.25851
                      a           101.863
                      b         0.0256373
                      c           3.78343
                      d                 1


        Table of Stats From Input Data

 Dose      N         Obs Mean     Obs Std Dev
 -----    ---       ----------   -------------
    0      3          101         15.59
   14      3          194         36.37
   47      3          304         17.32
  320      3          452          48.5
 1024      3          296           149


              Estimated Values of Interest

  Dose      Est Mean      Est Std     Scaled Residual
------    ----------    ---------    ----------------
     0         101.9         11.6          -0.1288
    14         187.4        31.32           0.3668
    47         300.4        67.58          0.09183
   320         385.3        101.4            1.139
```

```
   1024         385.4        101.4           -1.527


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       -68.74833           6      149.4967
                    A2       -58.69126          10      137.3825
                    A3       -64.89907           7      143.7981
                     R       -80.72265           2      165.4453
                     5       -65.54073           5      141.0815


Additive constant for all log-likelihoods =     -13.78.  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                      44.06             8            < 0.0001
  Test 2                      20.11             4           0.0004741
  Test 3                      12.42             3            0.006087
 Test 7a                      1.283             2              0.5264


  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 greater than .1.  Model 5 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 =      1.62983

                  BMDL =     0.853335
```

H.3.10.6. *Figure for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*



H.3.10.7. *Output File for Unrestricted Model: Hill, Nonconstant Variance, n Unrestricted*

```
 ========================================================================
         Hill Model. (Version: 2.14;  Date: 06/26/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_UGT_1A1.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Hill_Unrest_BMR1_UGT_1A1.plt
                                                Fri Nov 20 14:34:45 2009
 ========================================================================

 Tbl2, UGT_1A1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =	8.57191
rho =	0
intercept =	101
v =	351
n =	0.273231
k =	55.25

Asymptotic Correlation Matrix of Parameter Estimates

	lalpha	rho	intercept	v	n	k
lalpha	1	-0.99	-0.19	0.12	0.12	-0.017
rho	-0.99	1	0.18	-0.16	-0.12	0.0049
intercept	-0.19	0.18	1	-0.11	0.031	0.096
v	0.12	-0.16	-0.11	1	-0.61	0.82
n	0.12	-0.12	0.031	-0.61	1	-0.76
k	-0.017	0.0049	0.096	0.82	-0.76	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-10.516	3.69809	-17.7641	-3.26786
rho	3.32204	0.675078	1.99891	4.64517
intercept	101.644	6.48157	88.9405	114.348
v	298.646	56.3141	188.273	409.02
n	1.1568	0.50134	0.17419	2.13941
k	29.0772	13.7717	2.08512	56.0693

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	3	101	102	15.6	11.2	-0.0994
14	3	194	191	36.4	32.1	0.143
47	3	304	291	17.3	64.6	0.338
320	3	452	383	48.5	102	1.18
1024	3	296	396	149	107	-1.61

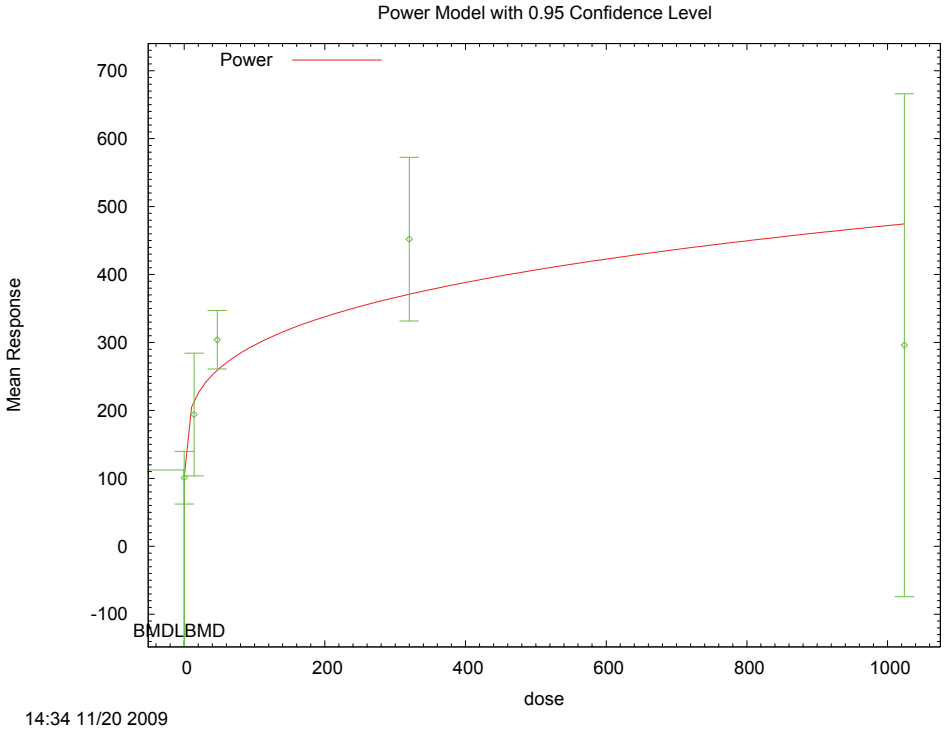
Model Descriptions for likelihoods calculated

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          -68.748326            6     149.496653
              A2          -58.691256           10     137.382511
              A3          -64.899072            7     143.798144
          fitted          -65.554216            6     143.108432
               R          -80.722651            2     165.445302


                    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              44.0628          8          <.0001
   Test 2              20.1141          4        0.0004741
   Test 3              12.4156          3         0.006087
   Test 4              1.31029          1           0.2523

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 =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =           0.95

             BMD =        1.76282


BMDL computation failed.
```

H.3.10.8. *Figure for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*



H.3.10.9. *Output File for Unrestricted Model: Power, Nonconstant Variance, Power Unrestricted*

```
 ========================================================================
         Power Model. (Version: 2.15;  Date: 04/07/2008)
         Input Data File: C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_UGT_1A1.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS21\Nov20\Pwr_Unrest_BMR1_UGT_1A1.plt
                                                Fri Nov 20 14:34:47 2009
 ========================================================================

 Tbl2, UGT_1A1
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 =      8.57191
                            rho =            0
                        control =          101
                          slope =      75.1984
                          power =      0.19277


            Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho      control        slope        power

     lalpha            1        -0.99        -0.22        0.054        0.018

        rho        -0.99            1          0.2       -0.038       -0.052

    control        -0.22          0.2            1         -0.2         0.11

      slope        0.054       -0.038         -0.2            1        -0.95

      power        0.018       -0.052         0.11        -0.95            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         lalpha         -11.5264          3.45692           -18.3019            -4.75098
            rho          3.53579         0.629031            2.30291             4.76867
        control          101.425          6.34917             88.981             113.869
          slope          53.9904          20.7283             13.3638              94.617
          power         0.279427        0.0834726            0.115823             0.44303


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0       3        101          101         15.6         11.1        -0.0666
   14       3        194          214         36.4         41.5         -0.847
   47       3        304          260         17.3         58.3           1.31
  320       3        452          372         48.5          110           1.26
 1024       3        296          476          149          170          -1.83


 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          -68.748326           6     149.496653
```

A2	-58.691256	10	137.382511
A3	-64.899072	7	143.798144
fitted	-67.596085	5	145.192170
R	-80.722651	2	165.445302

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	44.0628	8	<.0001
Test 2	20.1141	4	0.0004741
Test 3	12.4156	3	0.006087
Test 4	5.39403	2	0.06741

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 = 0.00343319

BMDL = 0.00343312

H.3.11. Vanden Heuvel et al. (1994): Hepatic CYP1A1 mRNA Expression

H.3.11.1. *Summary Table of BMDS Modeling Results*

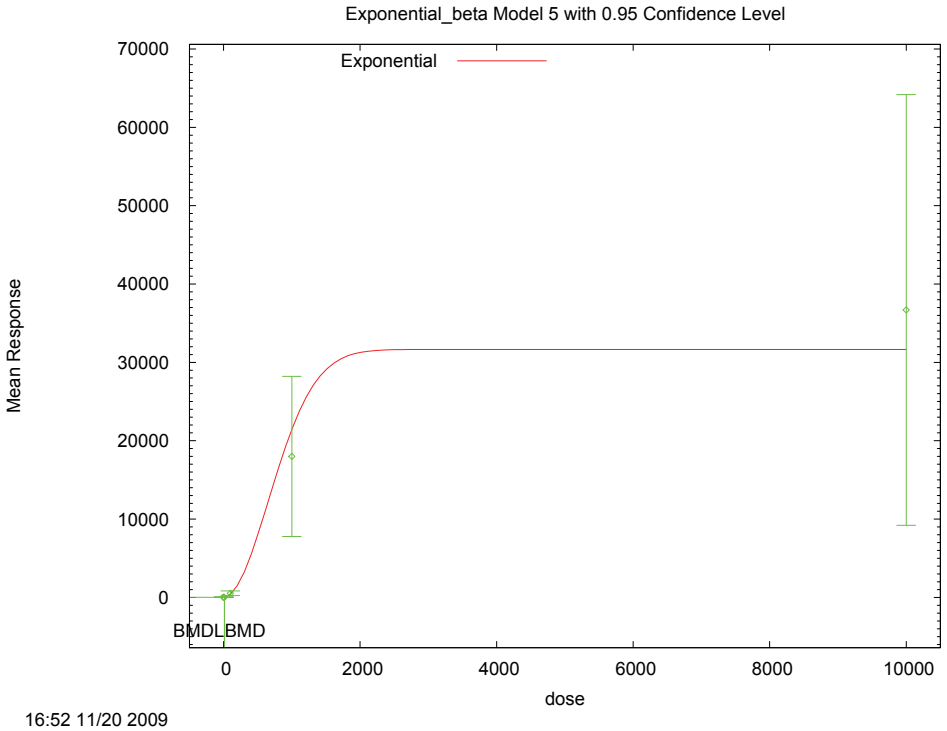
Model	Degrees of Freedom	Variance *p*-Value [a]	χ^2 Test Statistic	χ^2 *p*-Value [b]	AIC	BMD (ng/kg-day)	BMDL (ng/kg-day)	Model Notes
exponential (M2)	5	<0.0001	568.80	<0.0001	1164.38	4.7E+03	1.7E+03	nonconstant variance, power restricted ≥1
exponential (M3)	5	<0.0001	568.80	<0.0001	1164.38	4.7E+03	1.7E+03	nonconstant variance, power restricted ≥1
exponential (M4)	4	<0.0001	63.39	<0.0001	661.01	4.5E-01	2.6E-01	nonconstant variance, power restricted ≥1
exponential (M5) [c]	**3**	**<0.0001**	**35.71**	**<0.0001**	**635.33**	**1.5E+01**	**1.0E+01**	**nonconstant variance, power restricted ≥1**
Hill	3	<.0001	33.98	<.0001	633.59	1.9E+01	error	nonconstant variance, n restricted >1
linear	5	<.0001	71.94	<.0001	667.55	5.0E-01	3.1E-01	nonconstant variance
polynomial	5	<.0001	137.66	<.0001	733.28	5.4E+03	1.7E+01	nonconstant variance
power	4	<.0001	71.83	<.0001	669.44	5.6E-01	3.2E-01	nonconstant variance, power restricted ≥1
exponential (M2)	5	<0.0001	27.93	<0.0001	1178.88	5.9E+03	5.1E+03	constant variance, power restricted ≥1
exponential (M3)	5	<0.0001	27.93	<0.0001	1178.88	5.9E+03	5.1E+03	constant variance, power restricted ≥1
exponential (M4)	4	<0.0001	0.34	0.99	1153.28	4.0E+02	2.8E+02	constant variance, power restricted ≥1
exponential (M5)	3	<0.0001	0.00	1.00	1154.95	5.7E+02	2.9E+02	constant variance, power restricted ≥1
Hill	3	<.0001	0.00	1.00	1154.95	5.3E+02	2.1E+02	constant variance, n restricted >1
linear	5	<.0001	21.45	0.00	1172.40	2.8E+03	2.2E+03	constant variance
polynomial	5	<.0001	22.53	0.00	1173.48	3.1E+03	2.1E+03	constant variance
power	5	<.0001	21.45	0.00	1172.40	2.8E+03	2.2E+03	constant variance, power restricted ≥1, bound hit

[a]Values <0.1 means nonconstant variance model should be selected; Values ≥0.1 means a constant variance model should be selected

[b]Values <0.1 fail to meet BMDS goodness-of-fit criteria

[c]Best-fitting model as assessed by lowest-AIC criterion, bolded, presented in this appendix

H.3.11.2. *Figure for Selected Model: Exponential (M5), Nonconstant Variance, Power Restricted ≥1*



H.3.11.3. *Output File for Selected Model: Exponential (M5), Nonconstant Variance, Power Restricted ≥1*

```
 ================================================================
         Exponential Model. (Version: 1.5;  Date: 4/23/2009)
         Input Data File: C:\USEPA\BMDS21\Nov20\Exp_BMR1_hepatic_CYP1A1_mRNA_expression.(d)
         Gnuplot Plotting File:
                                                  Fri Nov 20 16:52:21 2009
 ================================================================

 [insert study notes]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   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 = 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

MLE solution provided: Exact
```

Initial Parameter Values

Variable	Model 5
lnalpha	-0.89532
rho	2.01401
a	5.13
b	0.000307638
c	7511.7
d	1

Parameter Estimates

Variable	Model 5
lnalpha	0.176234
rho	1.90467
a	9.74751
b	0.00106447
c	3247.52
d	1.96414

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	13	5.4	3.606
0.1	5	7.2	5.59
1	12	14.8	14.9
10	7	12.8	4.498
100	7	536	320.1
1000	11	1.8e+004	1.522e+004
1e+004	5	3.67e+004	2.214e+004

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	9.748	9.551	-1.641
0.1	9.748	9.551	-0.5965
1	9.793	9.593	1.808
10	13.97	13.45	-0.2296
100	395.9	325.2	1.14
1000	2.144e+004	1.456e+004	-0.7835
1e+004	3.166e+004	2.11e+004	0.5347

```
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       -572.4744           8      1160.949
                       A2       -290.7965          14      609.5929
                       A3        -293.806           9      605.6119
                        R       -603.6646           2      1211.329
                        5       -311.6633           6      635.3266


Additive constant for all log-likelihoods =     -55.14.  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                        625.7           12           < 0.0001
  Test 2                        563.4            6           < 0.0001
  Test 3                        6.019            5             0.3044
 Test 7a                        35.71            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 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 =      15.1574

             BMDL =      10.4625
```

H.4. REFERENCES

Hassoun, EA; Li, F; Abushaban, A; 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. Toxicology 145:103−113.

NTP (National Toxicology Program). (2006) Studies of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in female Harlan Sprague-Dawley rats (gavage studies) Tech. Rep. Ser. No. 521. U.S. Department of Health and Human Services, Public Health Service, Research Triangle Park, NC.

Van Birgelen et al. 1995a and 1995b – I assume below is one of them?

Van Birgelen, AP; Van der Kolk, J; Fase, KM; et al. (1995) Subchronic dose-response study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in female Sprague-Dawley rats. Toxicol Appl Pharmacol 132:1-13.

van den Heuvel, JP; Clark, GC; Kohn, MC; et al. (1994) Dioxin-responsive genes: examination of dose-response relationships using quantitative reverse transcriptase-polymerase chain reaction. Cancer Res 54:62–68.