1. INTRODUCTION

Dioxins and dioxin-like compounds (DLCs), including polychlorinated dibenzo-dioxins, polychlorinated dibenzofurans, and polychlorinated biphenyls are structurally and toxicologically related halogenated dicyclic aromatic hydrocarbons.[1] Dioxins and DLCs are released into the environment from several industrial sources such as chemical manufacturing, combustion, and metal processing; from individual activities including the burning of household waste; and from natural processes such as forest fires. Dioxins and DLCs are widely distributed throughout the environment and typically occur as chemical mixtures. Additionally, they do not readily degrade; therefore, levels persist in the environment, build up in the food chain, and accumulate in the tissues of animals. Human exposure to these compounds occurs primarily through the ingestion of contaminated foods (Lorber et al., 2009), although exposures to other environmental media and by other routes and pathways do occur.

The health effects from exposures to dioxins and DLCs have been documented extensively in epidemiologic and toxicological studies. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is one of the most toxic members of this class of compounds and has a robust toxicological database. Characterization of TCDD toxicity is critical to the risk assessment of mixtures of dioxins and DLCs because it has been selected repeatedly as the "index chemical" for the dioxin toxicity equivalence factors (TEF) approach. In this approach, the toxicity of individual components of dioxin and DLC mixtures is scaled to that of TCDD. Then, the dose-response information for TCDD is used by the U.S. Environmental Protection Agency (EPA) and other organizations to evaluate risks from exposure to mixtures of DLCs (U.S. EPA, 2010b; Van den Berg et al., 2006; 1998) (also see the World Health Organization's Web site for the dioxin toxicity equivalence factors [TEFs]).[2]

In 2010, EPA completed and published a report entitled, *Recommended Toxicity Equivalence Factors (TEFs) for Human Health Risk Assessments of 2,3,7,8-Tetrachlorodibenzo-p-dioxin and Dioxin-Like Compounds* (TEF report) (U.S. EPA, 2010b). The TEF report describes EPA's updated approach for evaluating the human health risks from exposures to environmental media containing DLCs. In the TEF report, EPA recommends use of the

[1] For further information on the chemical structures of these compounds, see U.S. EPA (2010b, 2008b, 2003).
[2] Available online at http://www.who.int/ipcs/assessment/tef_update/en/.

consensus TEF values for TCDD and DLCs published in 2005 by the World Health Organization (Van den Berg et al., 2006) for all cancer and noncancer effects mediated through aryl hydrocarbon receptor binding. Further, EPA recommends that the TEF methodology, a component mixture method, be used to evaluate human health risks posed by these mixtures, using TCDD as the index chemical. The TEFs are factors that scale individual DLC exposures to toxicity equivalence (TEQ)[3] units of TCDD. To assess health risks for a given exposure to a mixture of DLCs, the TEQ's of those DLCs are summed, and the sum (i.e., total TEQ) is compared to dose-response information for TCDD. Therefore, it is imperative to correctly assess the dose response of TCDD and understand the uncertainties and limitations therein.

In 2003, EPA produced an external review draft of the multiyear comprehensive reassessment of dioxin exposure and human health effects entitled, *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (U.S. EPA, 2003). This draft report, herein called the "2003 Reassessment," consisted of (1) a scientific review of information relating to sources of and exposures to TCDD, other dioxins, and DLCs in the environment; (2) detailed reviews of scientific information on the health effects of TCDD, other dioxins, and DLCs; and (3) an integrated risk characterization for TCDD and related compounds.

In 2004, EPA asked the National Research Council of the National Academy of Sciences (NAS) to review the 2003 Reassessment. The NAS Statement of Task was as follows:

[3] Toxicity equivalence (TEQ) is the product of the concentration of an individual DLC in an environmental mixture and the corresponding TCDD TEF for that compound. These products are summed to yield the TEQ of the mixture.

> The National Academies' National Research Council will convene an expert committee that will review EPA's 2003 draft reassessment of the risks of dioxins and dioxin-like compounds to assess whether EPA's risk estimates are scientifically robust and whether there is a clear delineation of all substantial uncertainties and variability. To the extent possible, the review will focus on EPA's modeling assumptions, including those associated with the dose-response curve and points of departure; dose ranges and associated likelihood estimates for identified human health outcomes; EPA's quantitative uncertainty analysis; EPA's selection of studies as a basis for its assessments; and gaps in scientific knowledge. The study will also address the following aspects of EPA's 2003 Reassessment: (1) the scientific evidence for classifying dioxin as a human carcinogen; and (2) the validity of the nonthreshold linear dose-response model and the cancer slope factor calculated by EPA through the use of this model. The committee will also provide scientific judgment regarding the usefulness of toxicity equivalence factors (TEFs) in the risk assessment of complex mixtures of dioxins and the uncertainties associated with the use of TEFs. The committee will also review the uncertainty associated with the 2003 Reassessment's approach regarding the analysis of food sampling and human dietary intake data, and, therefore, human exposures, taking into consideration the Institute of Medicine's report Dioxin and Dioxin-Like Compounds in the Food Supply: Strategies to Decrease Exposure. The committee will focus particularly on the risk characterization section of EPA's 2003 Reassessment report and will endeavor to make the uncertainties in such risk assessments more fully understood by decision makers. The committee will review the breadth of the uncertainty and variability associated with risk assessment decisions and numerical choices, including, for example, modeling assumptions, including those associated with the dose-response curve and points of departure. The committee will also review quantitative uncertainty analyses, as feasible and appropriate. The committee will identify gaps in scientific knowledge that are critical to understanding dioxin reassessment (NAS, 2006b, p. 43, Box 1-1).

In 2006, the NAS published its review of EPA's 2003 Reassessment titled *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment* (NAS, 2006b).

1.1. SUMMARY OF KEY NAS (2006B) COMMENTS ON DOSE-RESPONSE MODELING IN THE 2003 REASSESSMENT

While recognizing the effort that EPA expended to prepare the 2003 Reassessment, the NAS committee identified three key areas that they believed required improvement to support a scientifically robust health assessment. These three key areas are

- Transparency and clarity in selection of key data sets for analysis;
- Justification of approaches to dose-response modeling for cancer and noncancer endpoints; and
- Transparency, thoroughness, and clarity in quantitative uncertainty analysis.

In their Public Summary, the NAS made the following overall recommendations to aid EPA in addressing their key concerns:

- EPA should identify the most important data sets to be used for quantitative risk assessment for each of the four key end points (cancer, immunotoxicity, reproductive effects, and developmental effects). EPA should specify inclusion criteria for the studies (animal and human) used for derivation of the benchmark dose (BMD) for different noncancer effects and potentially for the development of RfD (reference dose) values and discuss the strengths and limitations of those key studies; describe and define (quantitatively to the extent possible) the variability and uncertainty for key assumptions used for each key end-point-specific risk assessment (choices of data set, POD [point of departure],[4] model, and dose metric); incorporate probabilistic models to the extent possible to represent the range of plausible values; and assess goodness-of-fit of dose-response models for data sets and provide both upper and lower bounds on central estimates for all statistical estimates. When quantitation is not possible, EPA should clearly state it and explain what would be required to achieve quantitation (NAS, 2006b, p. 9).

- EPA should continue to use body burden as the preferred dose metric but should also consider physiologically based pharmacokinetic modeling as a means to adjust for differences in body fat composition and for other differences between rodents and humans (NAS, 2006b, p. 9).

- When selecting a BMD as a POD, EPA should provide justification for selecting a response level (e.g., at the 10%, 5%, or 1% level). In either case, the effects of this choice on the final risk assessment values should be illustrated by comparing point estimates and lower bounds derived from selected PODs (NAS, 2006b, p. 9).

- EPA should compare cancer risks by using nonlinear models consistent with a receptor mediated mechanism of action and by using epidemiological data and the new National Toxicology Program (NTP) animal bioassay data (NTP, 2006a). The comparison should include upper and lower bounds, as well as central estimates of risk. EPA should clearly communicate this information as part of its risk characterization (NAS, 2006b, p. 9).

- Although EPA addressed many sources of variability and uncertainty qualitatively, the committee noted that the 2003 Reassessment would be substantially improved if its risk characterization included more quantitative approaches. Failure to characterize variability and uncertainty thoroughly can convey a false sense of precision in the conclusions of the risk assessment (NAS, 2006b, p. 5).

[4] Point of departure: The dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD), or a NOAEL or LOAEL for an observed incidence, or change in level of response (available online at http://www.epa.gov/iris/help_gloss.htm#p).

Importantly, the NAS encouraged EPA to calculate an RfD as the 2003 Reassessment does not contain an RfD derivation. The committee suggested that:

> …estimating an RfD would provide useful guidance to risk managers to help them (1) assess potential health risks in that portion of the population with intakes above the RfD, (2) assess risks to population subgroups, such as those with occupational exposures, and (3) estimate the contributions to risk from the major food sources and other environmental sources of TCDD, other dioxins, and DLCs for those individuals with high intakes (NAS, 2006b, p. 6).

The NAS made many other thoughtful and specific recommendations throughout their review; additional NAS recommendations and comments pertaining to the dose-response assessment of TCDD will be presented and addressed in various sections throughout this document.

1.2. EPA'S SCIENCE PLAN

In May 2009, EPA Administrator Lisa P. Jackson announced the "*Science Plan for Activities Related to Dioxins in the Environment*" ("Science Plan") that addressed the need to finish EPA's dioxin reassessment and provide a completed health assessment on this high profile chemical to the American public.[5]

The Science Plan outlined EPA's interim milestones for addressing several issues related to dioxins and DLCs. With regard to EPA's response to the NAS comments on the 2003 Dioxin Reassessment, the Science Plan stated the following:

1. EPA will release a draft report that responds to the recommendations and comments included in the National Academy of Sciences' (NAS) 2006 review of EPA's 2003 Dioxin Reassessment.

    a. EPA's National Center for Environment Assessment (NCEA) in the Office of Research and Development, will prepare a limited response to key comments and recommendations in the NAS report.

    b. The draft response will focus on dose-response issues raised by the NAS and will include an analysis of relevant new key studies.

[5] Available at http://www.epa.gov/dioxin/scienceplan.

2. EPA will provide the draft response to comments report for internal and external review.

    a. The draft response to comments report will also undergo both internal EPA review and interagency review.

    b. The draft response will be provided for public review and comment and independent external peer review.

3. The EPA Science Advisory Board (SAB) will review the science content of the response to comments report.

As required in the Science Plan, in 2009, EPA developed a draft report titled *EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* (draft Reanalysis) that responded to the key comments and recommendations in the NAS report (U.S. EPA, 2010a). The draft Reanalysis focused on TCDD dose-response issues and included analyses of relevant new studies and the derivation of an oral RfD. The draft Reanalysis was reviewed internally by EPA scientists and externally by other federal agencies and  e House Offices. On May 21, 2010, the draft Reanalysis was released for public review and comment and independent external peer review by EPA's SAB.

1.3. SAB REVIEW OF EPA'S DRAFT REANALYSIS

For their review, the SAB convened an expert panel composed of scientists knowledgeable about technical issues related to dioxins and risk assessment. The SAB held public meetings in June, July, and October 2010 and March and June 2011. They released their final report reviewing the draft Reanalysis on August 26, 2011 (SAB, 2011).[6] In their report, the SAB made the following overarching observations:

- They found that the draft Reanalysis was clear, logical and responsive to many, but not all, of the NAS recommendations; they were impressed with the comprehensive and rigorous study selection process that was used to identify, review and evaluate the scientific literature on TCDD dose response;

    - …the SAB finds that the *Report* is generally clear, logical, and responsive to many but not all of the recommendations of the NAS. The SAB has, however, provided many recommendations to further improve the clarity, organization, and

[6] Available online at http://yosemite.epa.gov/sab/sabproduct.nsf/2A45B492EBAA8553852578F9003ECBC5/$File/EPA-SAB-11-014-unsigned.pdf.

responsiveness of various parts of the *Report*. The SAB was impressed with the process that EPA used to identify, review, and evaluate the relevant literature. The SAB finds that EPA's process was comprehensive and rigorous and included public participation. (SAB, 2011, p. 1)

- They agreed with the choice of the Emond physiologically based pharmacokinetic (PBPK) model for dose metric calculations and with whole blood as the appropriate dose metric;
    - The SAB agrees with EPA's use of blood TCDD concentration as a surrogate for tissue exposure to TCDD. Blood TCDD concentration is a better choice than using body burden (as in the 2003 Reassessment) because it is more closely related to the biologically relevant dose metric: the free concentration of dioxin in the target tissues. It is important to recognize, however, that TCDD distribution within tissues such as the liver can be nonuniform. The SAB further agrees that the PBPK model developed by Emond et al. (2006; 2005; 2004) provides the best available basis for the dose metric calculations in the assessment. (SAB, 2011, p. 2)
- They agreed with the choice of two epidemiologic studies as co-critical studies whose developmental toxicity data were used to derive the RfD for TCDD;
    - The SAB supports EPA's selection of the Mocarelli et al. (2008) and Baccarelli et al. (2008) studies for identifying "cocritical" effects for the derivation of the reference dose (RfD). These two human epidemiological studies are well designed and provide sufficient exposure information, including biological concentrations that could be used to establish acceptable lifetime daily exposure levels. (SAB, 2011, p. 3)
- They agreed with EPA's evaluation of TCDD carcinogenicity (with the exception of one panelist with a dissenting view);
    - The SAB agrees with EPA's conclusion that TCDD is "*Carcinogenic to Humans*." (SAB, 2011, p. 5).

The SAB also noted two deficiencies in EPA's draft Reanalysis with respect to the completeness of the consideration of two critical elements:

- Nonlinear dose response for TCDD carcinogenicity, and
- Uncertainty analysis

The SAB recommended that EPA fully evaluate both linear and nonlinear dose-response approaches to TCDD cancer dose-response assessment, including a discussion of carcinogenic mode of action. The SAB also recommended a number of approaches to quantitative uncertainty analysis that could be implemented by EPA, including the use of sensitivity analyses and probability trees.

- The SAB finds that the Report did not respond adequately to the NAS recommendation to adopt "both linear and nonlinear methods of risk characterization to account for the uncertainty of dose-response relationship shape below the ED01." EPA should present both linear and nonlinear risk assessment approaches. In the absence of a definitive nonlinear mode of action, the linear option results can serve as the baseline for comparison with other estimates. (SAB, 2011, p. 6)

- …the SAB does not agree with EPA's argument that conducting a unified quantitative uncertainty analysis for TCDD toxicity is unfeasible…..EPA argues that a complete quantitative uncertainty analysis would require data and resources not available. The SAB disagrees with this logic. While EPA may lack an adequate empirical basis for full Monte-Carlo propagation of input distributions, there are other options available. More limited evaluations can, and should, be implemented to inform critical issues in the dioxin reassessment. (SAB, 2011, p. 7)

The SAB made many additional thoughtful comments and specific recommendations throughout their review pertaining to the dose-response assessment of TCDD (SAB, 2011).

1.4. SCOPE OF EPA'S REANALYSIS VOLUMES 1 AND 2

In August 2011, EPA announced a plan for moving forward to complete the draft Reanalysis.[7] This plan includes the completion and posting to the IRIS database of the noncancer portion of the draft Reanalysis separately followed soon thereafter by the completion and posting to the IRIS database of the cancer portion of the draft Reanalysis. As such, this document comprises the first of two EPA reports (U.S. EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments Volumes 1 and 2 [Reanalysis Volumes 1 and 2]) that together will respond to the recommendations and comments on TCDD dose-response assessment included in the NAS review of EPA's 2003 Reassessment. Both Volumes focus on TCDD only. This report, Reanalysis Volume 1, completes and publishes EPA's study

[7] Available online at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=209690.

selection criteria and results for both noncancer and cancCDD dose-response assessment; choice of kinetic model; noncancer RfD for TCDD; and a qualitative discussion of uncertainties in the RfD with a focused quantitative uncertainty analysis.

These information and analyses have undergone revisions in response to SAB comments and recommendations (see Appendix A). Reanalysis Volume 2 will address the two deficiencies identified by the SAB, i.e., nonlinear dose response for TCDD carcinogenicity and quantitative uncertainty analysis. In Volume 2, EPA will complete the evaluation of cancer mode-of-action, cancer dose-response modeling, including justification of the approaches used for dose-response modeling of the cancer endpoints, and an associated quantitative uncertainty analysis. The information provided in Volume 1 will be used in three ways: (1) as the first of two reports that contain EPA's response to the NAS (2006b) report, (2) as the Support Document for the TCDD noncancer IRIS Summary and TCDD oral RfD, and (3) as technical support for Reanalysis Volume 2.

1.5. OVERVIEW OF EPA'S RESPONSE TO NAS (2006B)

In their key recommendations, the NAS commented that EPA should thoroughly justify and communicate approaches to dose-response modeling, increase transparency in the selection of key data sets, and improve the communication of uncertainty (particularly quantitative uncertainty). They also encouraged EPA to calculate an RfD. These main areas of improvement refer to issues specifically related to TCDD dose-response assessment (and uncertainty analysis); therefore, as noted in the Science Plan, EPA's response to the NAS is particularly focused on these issues.

EPA thoroughly considered the recommendations of the NAS and, in Reanalysis Volume 1, responds with scientific and technical evaluation of TCDD dose–response data via the following:

- An updated literature search that identified new TCDD dose-response studies (see Section 2/Appendix J);
- A kickoff workshop that included the participation of external experts in TCDD health effects, toxicokinetics, dose-response assessment and quantitative uncertainty analysis; these experts discussed potential approaches to TCDD dose-response assessment and considerations for EPA's response to NAS (U.S. EPA, 2009b) (see Appendix B);

- Detailed study inclusion criteria and processes for the selection of key studies (see Section 2.3) and epidemiologic and animal bioassay data for quantitative TCDD dose-response assessment (see Section 2.4.1/Appendix C and Section 2.4.2/Appendix D respectively);

- Kinetic modeling that quantifies appropriate dose metrics for use in TCDD dose-response assessment (see Section 3 and Appendices E and F);

- Sensitivity analyses that were performed on each of the animal and human Emond PBPK models that identify the most sensitive variables in each model (see Section 3.3.4);

- Dose-response modeling for all appropriate noncancer data sets (see Section 4.2/Appendix G);

- Thorough and transparent evaluation of the selected TCDD data for use in the derivation of an RfD, including justification of approaches used for dose-response modeling of noncancer endpoints (see Section 4.2 and Appendix H);

- The development of an RfD (see Section 4.3);

- A qualitative discussion of the uncertainty in the RfD and a focused quantitative uncertainty analyses of the RfD (see Sections 4.4 and 4.5, respectively); and

- Responses to the comments and recommendations made by the SAB in their final report (SAB, 2011) (see Appendix A).

Each of those activities is described in detail in subsequent sections of this document.

In addition to this document, it should be noted that several additional EPA activities address other TCDD issues, specifically related to the application of dioxin TEFs and to TCDD and DLC background exposure levels. Information on the application of the dioxin TEFs is published elsewhere by EPA for both ecological (U.S. EPA, 2008b) and human health risk assessment (U.S. EPA, 2010b). As a consequence, EPA does not directly address TEFs herein, but makes use of the concept of toxicity equivalence as applicable to the analysis of exposure dose in epidemiologic studies. Furthermore, this document does not address the NAS recommendations pertaining to the assessment of human exposures to TCDD and other dioxins. Information on updated background levels of dioxin in the U.S. population has been recently reported (Lorber et al., 2009). In 2006, EPA also released a report titled *An Inventory of Sources and Environmental Releases of Dioxin-Like Compounds in the United States for the Years 1987, 1995 and 2000,* which presents an evaluation of sources and emissions of dioxins, dibenzofurans,

and coplanar polychlorinated biphenyls (PCBs) to the air, land and water of the United States (U.S. EPA, 2006).

1.5.1. TCDD Literature Update

EPA has developed a literature database of peer-reviewed studies on TCDD toxicity, including in vivo mammalian dose-response studies and epidemiologic studies for use in quantitative TCDD dose-response assessment and supporting qualitative discussions. An initial literature search for studies published since the 2003 Reassessment was conducted by the U.S. Department of Energy's Argonne National Laboratory (ANL) through an Interagency Agreement with EPA. ANL used the online National Library of Medicine database (PubMed) and identified studies published between the year 2000 and October 31, 2008 (see Appendix J). Supporting references published since the release of the 2003 Reassessment were also identified. Supporting studies were classified as studies pertaining to TCDD kinetics, TCDD mode-of-action, in vitro TCDD studies, and TCDD risk assessment approaches. The literature search strategy explicitly excluded studies addressing: (1) analytical/detection data and cellular screening assays; (2) environmental fate, transport and concentration data; (3) dioxin-like compounds and toxic equivalents; (4) nonmammalian dose-response data; (5) human exposure analyses only, including body burden data; and (6) combustor or incinerator or other facility-related assessments absent primary dose-response data.

EPA published the initial literature search results in the Federal Register on November 24, 2008 (73 FR 70999; November 24, 2008) and invited the public to review the list and submit additional peer-reviewed in vivo mammalian dose-response studies for TCDD, including epidemiologic studies that were absent from the list (U.S. EPA, 2008a). Submissions were accepted by the EPA through an electronic docket, email, and hand delivery, and they were evaluated for use in TCDD dose-response assessment. The literature search results and subsequent submissions were used during a 2009 scientific workshop, which was open to the public and featured a panel of experts on TCDD toxicity and dose-response modeling (discussed below). Additional studies identified during the workshop, and those collected by EPA scientists during the development of this report through October 2009, have been incorporated into the final set of studies for TCDD quantitative dose-response assessment.

Since release of the draft Reanalysis for public comment and external peer review in 2010, EPA has collected a limited number of additional studies published since October 2009 that also inform EPA's derivation of an RfD for TCDD. These studies were identified by EPA scientists, the SAB, and the public, and they have been used to further evaluate the biological significance of the endpoints used to derive the RfD and to develop information on uncertainty in the RfD. These additional studies are cited in the appropriate sections of this document. No data sets collected since October 2009 were used quantitatively in the noncancer dose-response assessment of TCDD.

1.5.2. EPA's 2009 Workshop on TCDD Dose Response

To assist EPA in responding to the NAS, EPA and ANL convened a scientific workshop (the "Dioxin Workshop") on February 18–20, 2009, in Cincinnati, OH. The goals of the Dioxin Workshop were to identify and address issues related to the dose-response assessment of TCDD and to ensure that EPA's response to the NAS focused on the key issues and reflected the most meaningful science. The Dioxin Workshop included seven scientific sessions: quantitative dose-response modeling issues, immunotoxicity, neurotoxicity and nonreproductive endocrine effects, cardiovascular toxicity and hepatotoxicity, cancer, reproductive and developmental toxicity, and quantitative uncertainty analysis of dose response. During each session, EPA asked a panel of expert scientists to perform the following tasks:

- Identify and discuss the technical challenges involved in addressing the NAS comments related to the dose-response issues within each specific session topic and the TCDD quantitative dose-response assessment.
- Discuss approaches for addressing the key NAS recommendations.
- Identify important published, independently peer-reviewed literature—particularly studies describing epidemiologic studies and in vivo mammalian bioassays expected to be most useful for informing EPA's response.

The sessions were followed by open comment periods during which members of the audience were invited to address the expert panels. The session's Panel Co-chairs were asked to summarize and present the results of the panel discussions—including the open comment periods. The summaries were intended to reflect the core of the panel discussions and

incorporated points of agreement as well as minority opinions. Final session summaries were prepared by the session Panel Co-chairs with input from the panelists, and they formed the basis of a final workshop report (U.S. EPA, 2009b) (Appendix B of this report). Because the sessions were not designed to achieve consensus among the panelists, the summaries do not necessarily represent the opinions of all the scientists that attended the meeting. Some of the key discussion points from the workshop that influenced EPA's development of this document are listed below (see Appendix B for detail):

- In the development of study selection criteria, more relevant exposure-level decision points using tissue concentrations could be defined.

- A linear approach to body-burden estimation, which was utilized in the 2003 Reassessment (U.S. EPA, 2003), does not fully consider key toxicokinetic issues related to TCDD—e.g., sequestration in the liver and fat, age-dependent elimination, and changing elimination rates over time. Thus, kinetic/mechanistic modeling could be used to quantify tissue-based metrics. In considering human data, lipid-adjusted serum levels may be preferable over body burden, although the assumptions used in the back calculation of the body burden in epidemiologic cohorts are of concern. In considering rat bioassay data, lipid-adjusted body-burden estimates may be preferable.

- New epidemiologic studies on noncancer endpoints have been published since the 2003 Reassessment that may need to be considered (e.g., thyroid dysfunction literature from Wang et al. (2005) and Baccarelli et al. (2008).

- The 1% of maximal response (ED_{01}) that was utilized in the 2003 Reassessment has not typically been used in dose-response assessment. Some alternative ideas were as follows: (1) the POD should depend on the specific endpoint; (2) for continuous measures, the benchmark response (BMR) could be based on the difference from control and consider the adversity level; and (3) for incidence data, the BMR should be set to a fixed-risk level.

- The quantitative dose-response modeling for cancer could be based on human or animal data. There are new publications in the literature for four epidemiological cohort studies (Dutch cohort, NIOSH cohort, BASF accident cohort, and Hamburg cohort). The increase in total cancers could be considered for modeling human cancer data. However, non-Hodgkin lymphoma and lung tumors are the main TCDD-related cancer types seen from human exposure. In reviewing the rat data, the NTP (2006a) data sets are new and can be modeled. Although the liver and lungs are the main target organs, modeling all cancers, as well as using tumor incidence in lieu of individual rats as a measure, should be considered.

- Both linear and nonlinear model functions should be considered in the cancer dose-response analysis because there are data and rationales to support use of either below the POD.

- For quantitative uncertainty analysis, consider the impacts of choices among plausible alternative data sets, dose metrics, models, and other more qualitative choices. Issues to consider include how much difference these choices make and, also, how much relative credence should be put toward each alternative as a means to gauge and describe the landscape of imperfect knowledge with respect to possibilities for the true dose response. This may be difficult to do quantitatively because the factors are not readily expressed as statistical distributions. However, the rationale for accepting or questioning each alternative in terms of the available supporting evidence, contrary evidence, and needed assumptions, can be delineated.

1.5.3. Organization of EPA's Response to NAS Recommendations (Reanalysis Volume 1)

The remainder of this document, Reanalysis Volume 1, is divided into three sections that address the three primary areas of concern resulting from the NAS (2006b) review. Section 2 describes EPA's approach to the recommendation for transparency and clarity during selection of key data sets suitable for TCDD dose-response assessment—including criteria for the selection of key dose-response studies and results of the evaluations of the important epidemiologic studies and animal bioassays (Appendices C and D contain study summaries and additional details on study evaluations for the epidemiologic and animal bioassays, respectively). Sections 3 and 4 present EPA's response to the NAS recommendation to better justify the approaches used in dose-response modeling of TCDD for noncancer endpoints. Section 3 discusses the toxicokinetic modeling EPA conducted to support the dose-response analyses. Section 4 presents EPA's noncancer data set selection, the noncancer dose-response modeling results, the RfD derivation for TCDD, a qualitative discussion of the uncertainties associated with the RfD, and a focused quantitative uncertainty analysis of the PODs considered for RfD derivation.