UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL CENTER FOR ENVIRONMENTAL ASSESSMENT
WASHINGTON, DC 20460

May 27, 2010

OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

SUBJECT: Request for Science Advisory Board Review of the Draft Report, "EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments"

FROM: Becki Clark, Deputy Director
National Center for Environmental Assessment (8601P)
Office of Research and Development

TO: Vanessa T. Vu, Ph.D., Director
EPA Science Advisory Board (1400F)

This is to request a review by the Science Advisory Board of the draft report entitled "EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments" (EPA/600/R-10/038A). This draft report details the Environmental Protection Agency's (EPA) response to key comments and recommendations included in the 2006 NAS report ("Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment") on their review of the (EPA) 2003 draft dioxin reassessment. This draft report also includes significant new analyses on both the potential cancer and noncancer human health effects that may result from chronic exposures to dioxins.

Attached is the Charge that provides background information as well as questions that are to be the focus of the Science Advisory Board review of this draft report.

Please let me know if you have any questions. Thank you.

Attachment: Charge for EPA's Science Advisory Board – Review of the Draft Report, "EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments"

cc: Peter W. Preuss
Annette Gatchett
Glenn Rice
Cheryl Itkin

Proposed Charge to the Science Advisory Board for Peer Review
of Draft Report,
"EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments"
May, 2010

EPA has been preparing an assessment of the potential health impacts of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) for many years. In 2003, EPA released an external review draft report entitled, *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (U.S. EPA, 2003) (herein referred to as "*2003 Reassessment*") that was reviewed by the EPA Science Advisory Board (SAB), and then by the National Academy of Sciences (NAS). In 2006, the National Research Council (NRC) of the National Academies published their report of EPA's reassessment, *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment* (NRC, 2006).

The current draft document *EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* ("*Response to Comments*") before the SAB is a response to the review by the NRC, and includes new analyses completed in response to the NRC recommendations and recently published literature, as well as a discussion of topics where our views differed. The draft *Response to Comments* document is not an assessment per se; it is designed to supplement the information provided in the *2003 Reassessment*. However, the draft *Response to Comments* provides a noncancer reference dose and updated cancer values. Detailed discussions of many of the issues addressed in the draft *Response to Comments* are available in the *2003 Reassessment* and have not been reproduced in the current draft document– whenever appropriate; the reader is directed to the pertinent chapters of the *2003 Reassessment*.

The NRC identified three key recommendations that they believed would result in substantial improvement to the EPA *2003 Reassessment* and thus support a scientifically robust characterization of human responses to exposures to TCDD. These three key areas are (1) improved transparency and clarity in the selection of key data sets for dose-response analysis, (2) further justification of approaches to dose-response modeling for cancer and noncancer endpoints, and (3) improved transparency, thoroughness, and clarity in quantitative uncertainty analysis. The NRC Report also encouraged EPA to calculate a reference dose (RfD), which had not been derived in the *2003 Reassessment*. The draft *Response to Comments* document addresses each of these issues. Please consider the accuracy, objectivity, and transparency of EPA's reanalysis and responses in your review.

General Charge Questions

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

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

Specific Charge Questions

Section 2. Transparency and Clarity in the Selection of Key Data Sets for Dose-Response Analysis

2.1. Is this Section responsive to the NAS concern about transparency and clarity in data-set selection for dose-response analysis?

2.2. Are the epidemiology and animal bioassay study criteria/considerations scientifically justified and clearly described?

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

Section 3. The Use of Toxicokinetics in the Dose-Response Modeling for Cancer and Noncancer Endpoints

3.1. The *2003 Reassessment* utilized first-order body burden as the dose metric. In the draft *Response to Comments* document, EPA used a physiologically-based pharmacokinetic (PBPK) model (Emond et al., 2004, 2005, 2006) with whole blood concentration as the dose metric rather than first-order body burden. This PBPK model was chosen, in part, because it includes a biological description of the dose-dependent elimination rate of TCDD. EPA made specific modifications to the published model based on more recent data. Although lipid-adjusted serum concentrations (LASC) for TCDD are commonly used as a dose metric in the literature, EPA chose whole blood TCDD concentrations as the relevant dose metric because serum and serum lipid are not true compartments in the Emond PBPK models (LASC is a side calculation proportional to blood concentration).

Please comment on:

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

3.1.b. The scientific justification for using the Emond et al. model as opposed to other available TCDD kinetic models.

3.1.c. The modifications implemented by EPA to the published Emond et al. model.

3.1.d. Whether EPA adequately characterized the uncertainty in the kinetic models.

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

Please comment on:

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

3.2.b. The performance of the mouse model in reference to the available data.

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

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

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

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

Section 4. Reference Dose

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

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

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

4.2.a.i. EPA's approach for identifying the exposure window and calculating average exposure for this study.

4.2.a.ii. EPA's designation of a 20% decrease in sperm count (and an 11% decrease in sperm motility) as a LOAEL for Mocarelli et al. (2008).

4.2.b. For Baccarelli et al. (2008), the critical exposure window occurs long after the high-dose pulse exposure. Therefore, the variability in the exposure over the

critical exposure window is likely to be less than the variability in the Mocarelli et al. subjects. EPA concluded that the reported maternal exposures from the regression model developed by Baccarelli et al. provide an appropriate estimate of the relevant effective dose as opposed to extrapolating from the measured infant TCDD concentrations to maternal exposures. Additionally, EPA selected a LOAEL of 5 μ-units TSH per ml blood in neonates; as this was established by World Health Organization (WHO) as a level above which there was concern about abnormal thyroid development later in life. Please comment on the following:

4.2.b.i. EPA's decision to use the reported maternal levels and the appropriateness of this exposure estimate for the Baccarelli et al. study.

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

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

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

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

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

4.7. For the animal bioassay modeling, EPA applied the kinetic extrapolation at the level of the POD prior to applying the uncertainty factors because EPA has less confidence in the kinetic model output at lower doses reflective of the RfD. Please comment on whether this approach was scientifically justified and clearly described.

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

Section 5. Cancer Assessment

5.1. Weight of Evidence Cancer Descriptor: The *2003 Reassessment* concluded that TCDD is a "known human carcinogen." In the current draft *Response to Comments* document, EPA concluded that under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005) TCDD is "carcinogenic to humans." Is the weight-of-evidence characterization scientifically justified and clearly
described?

5.2. Mode of Action: The mode of action of a carcinogen can inform identification of hazards and approaches used for a dose-response assessment. The mode of carcinogenic action for TCDD has not been elucidated for any tumor type. EPA concluded that, while interaction with the Ah receptor is likely to be a necessary early event in TCDD carcinogenicity in experimental animals, the downstream events involved are unknown.

5.2.a. Are the available data related to mode(s) of action for the carcinogenicity of TCDD appropriately characterized and clearly presented?

5.2.b. Do the available data support EPA's conclusion that the overall mode(s) of action for TCDD-induced carcinogenesis is largely unknown? Please comment on whether this evaluation is clearly described.

5.3. Is EPA's approach for selecting data sets from the key epidemiologic studies and animal bioassays identified for cancer dose response modeling scientifically justified and clearly described?

5.4. For the animal bioassay data, potential cancer oral slope factors (OSFs) were calculated by linear extrapolation (using a linear, nonthreshold cancer approach) from the point of departure (POD). EPA also estimated the composite risk of the occurrence of several tumor types from the animal cancer bioassay data.

5.4.a. Please comment on whether the approach for estimating cancer risk, including the use of tumor modeling of the TCDD animal cancer bioassay data, is scientifically justified and clearly described.

5.4.b. Please comment on the choice of using a $BMDL_{01}$ as the POD for the development of candidate oral slope factors derived from the TCDD animal cancer bioassays.

5.5. EPA selected Cheng et al. (2006) -- an analysis of the NIOSH occupational cohort-- as the critical study for oral slope factor (OSF) development. This study was chosen because it considers dose-dependent elimination of TCDD rather than first-order kinetics.

5.5.a. Please comment on whether the rationale for this selection is scientifically justified and clearly described. Please identify and provide the rationale for any other studies that should be considered and provide a critical evaluation of the study and of its suitability for meeting the goals of a quantitative cancer assessment.

5.5.b. Cheng et al. (2006) analyzed all-cancer mortality. Please comment on the use of all-cancer mortality as the basis of the OSF.

5.5.c. Please comment on whether the use of the Emond PBPK model in the estimation of risk-specific doses from the Cheng et al. dose-response modeling results is scientifically justified and clearly described.

5.5.d. EPA elected to use the log linear relationship of fat concentration and rate ratio to estimate risk-specific doses at all risk levels. EPA could have estimated a POD for cancer risk itself at a single risk level (BMR) for extrapolation to the origin. Please comment on EPA's choice of extrapolation approach.

5.5.e. The slope factor derived from Cheng et al. (2006) was extrapolated below the background TCDD exposure levels experienced by the NIOSH cohort. Please comment on this extrapolation.

5.6. Please comment on whether EPA has clearly described the major qualitative uncertainties in the derivation of the OSF.

5.7. EPA did not consider dioxin-like compounds (DLCs) in the cancer dose-response modeling because the occupational exposures in the available cohorts were primarily to TCDD. Background DLC exposures were not incorporated in the dose-response modeling because EPA judged that it was not possible to disaggregate the responses from background exposure to DLCs and occupational exposure to TCDD. Please comment on whether this approach is scientifically justified and clearly described.

5.8. The NRC suggested that EPA consider nonlinear approaches for the assessment of TCDD carcinogenicity. In the *Response to Comments*, EPA presents two illustrative nonlinear approaches for cancer, but considers both inappropriate to use because of the lack of MOA information.

5.8.a. Please comment on these two illustrative nonlinear approaches including EPA's conclusions regarding the limitations of these approaches.

5.8.b. Are there other nonlinear approaches that could be readily developed based on existing data for the assessment of TCDD carcinogenicity? If so, please suggest alternative approaches and describe their utility and suitability for meeting the goals of a quantitative cancer assessment.

Section 6. Feasibility of Quantitative Uncertainty Analysis from NAS Evaluation of the 2003 Reassessment

6.1. Please comment on the discussion in this Section. Is the response clearly presented and scientifically justified?

6.2. Please comment on EPA's overall conclusion that a comprehensive quantitative uncertainty analysis is not feasible.

6.2.a. Please comment on the discussion in Section 6 regarding volitional uncertainty and how this type of uncertainty limits the ability to conduct a quantitative uncertainty analysis.

6.3. Throughout the document (including the Appendices), EPA presents a number of limited sensitivity analyses (e.g., toxicokinetic modeling, RfD ranges, cancer OSF ranges, cancer RfD development). Please comment on the approaches used, and the utility of these sensitivity analyses in clarifying potential significant uncertainties.