Center for Health, Environment & Justice
P.O. Box 6806 • Falls Church, VA 22040 • Phone: 703.237.2249 • Fax: 703.237.8389 • www.chej.org

September 20, 2010

Office of Environmental Information (OEI) Docket
Mail Code 2822
US Environmental Protection Agency
1200 Pennsylvania Ave., NW.
Washington, DC 20460

RE: Comments on "EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments," May 27, 2010: Docket ID No. EPA-HQ-ORD-2010-0395.

These comments are submitted on behalf of the Center for Health, Environment & Justice on the report "EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments," May 27, 2010.

CHEJ has been following and participating in EPA's activities on dioxin since 1994. We have submitted comments on the draft reassessment document released in 1994 and 2000. We have participated and submitted comments to the EPA's Science Advisory Board (SAB) when they reviewed the agency's draft reassessment documents in 1995 and 2001. We provided public comments to the NAS committee that reviewed EPA's 2003 draft reassessment document. We have published two significant reports on dioxin, *Dying from Dioxin* in 1995 and *The American People's Report on Dioxin* in 1999. We have contributed to the organization of two major citizen's conferences on dioxin in Baton Rouge, LA in 1996 and Berkeley, CA in 2000. We have contributed to the organization of numerous sign-on letters with communities impacted by dioxins, local, state and national environmental health, environmental justice, consumer, labor, parenting and health-affected organizations encouraging the agency to finish its work on dioxin and release the reassessment report.

I have presented papers at the Dioxin 1997 and Dioxin 2000 conferences that summarize many of these activities. I have also traveled to Russia with a delegation of American scientists and to Hanoi, Vietnam to present my experiences working with grassroots community organizations in the U.S. that have been impacted by exposures to dioxins and dioxin-like compounds. In my capacity as Science Director at CHEJ (since 1983), I have worked with hundreds if not thousands of grassroots communities where exposure to dioxins was a major concern for the community. These communities include Superfund sites in Jacksonville and Pensacola, FL, Lock Haven, PA, Columbia, MS, Jacksonville, AR, and Times Beach, MO; other contaminated sites including New Bedford, MA, Missoula, MT, Quincy, WA, and Mossville, LA; communities impacted by waste incinerators including Columbus, OH, Hemtramck, MI, and Rosamond, CA. The experiences of these and other dioxin-impacted communities are summarized in our report published in 1998

Standing our Ground. The organized opposition of many of these grassroots community organizations is directly responsible for shutting down some of the worst incinerators and other sources of dioxin releases to the environment including the Columbus, OH garbage incinerator, the Miami "monster" garbage incinerator in Miami, FL, and the Occidental Petroleum garbage incinerator in Niagara Falls, NY. These groups took matters into their own hands because of inaction on the part of the government. This experience is the basis for the comments that we submit today.

Completing the Dioxin Reassessment

We want to begin by commending the agency for moving forward with its plan to complete the dioxin reassessment document and release this report to the public. It is long overdue. We urge EPA to complete its response to the comments it received from the NAS in 2006, to update the reassessment as appropriate and as quickly as possible, and to finally release the reassessment report to the public. After more than 20 years, the American public deserves to know what the risks of exposure to dioxin are and what steps the agency plans to take to protect the health of the American people.

In relation to the *EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments*, we offer the following comments and recommendations. Our comments address three specific issue areas: 1) Transparency and clarity in the selection of key data sets; 2) Cancer risk assessment; and 3) The reference dose.

Overview

The "EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments" (hereafter referred to as the Response to NAS Comments) is very thorough, well written, and well documented. This report is the agency's response to comments prepared by a committee of the National Academy of Sciences (NAS) in 2006. The Response to the NAS comments provides the transparency and clarity on EPA positions that the National Academies has requested. It also provides clear logical responses to the questions and issues raised by the NAS committee about the agency's draft report entitled "Exposure and Human Health Reassessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds." The agency has clearly and objectively summarized and presented the three key recommendations from the NAS report and provided detailed analyses and extensive documentation of their responses that makes it clear and transparent what they have done and why.

The EPA has concluded that TCDD is carcinogenic to humans. The basis for this determination is the criteria defined in the agency's *2005 Guidelines for Carcinogenic Risk Assessment* (Response to NAS Comments, p. 5-3). These guidelines call for using a weight of the evidence approach in which all available information is considered in making a determination on the carcinogenicity of a substance. The human epidemiological and animal bioassay data presented by EPA make it

clear how and why the agency has come to this conclusion. We support and commend the agency for this clear and transparent presentation that scientifically justifies its determination that TCDD is carcinogenic to humans.

EPA calculated oral slope factors using human epidemiological and animal data by extrapolating from a point of departure (POD) using a linear non-threshold dose response model. We find that the approach EPA used to estimate cancer risk is scientifically justified and clearly described and documented. We further agree that it is appropriate for EPA to take a public health protective default position regarding the interpretation of toxicological and epidemiological data, especially when there is no information on the mode of action following the binding of TCDD to the AhR that ultimately leads to the development of cancer. We strongly support the EPA's decision to follow its 2005 cancer guidelines that calls for the use of a linear no threshold model for extrapolating to low doses when calculating the cancer risk for TCDD. EPA chose to derive a reference dose (RfD) for TCDD based on co-critical effects - male reproductive effects (Mocarelli et al. 2008) and changes in neonatal thyroid hormone levels (Baccarelli et al. 2008). We feel that the rationale for the selection of these critical effects is clearly described and scientifically justified. However, one concern we have about this process is that the final RfD value was derived using uncertainty factors that did not take into account the unique susceptibility and vulnerability of children. The agency needs to explain why this was done and incorporate this factor into the final RfD.

I. Transparency and Clarity in Selection of Key Data Sets

A key issue raised by the NAS was the lack of transparency and clarity in selection of key data sets for dose-response analysis. We feel that the agency has prepared an extensive detailed response that adequately and appropriately addresses this concern. They did this by including the public at numerous stages in the development of their response to the NAS. This provided a peer-to-peer transparent and rigorous evaluation of the scientific quality of each study in the data base. This process also provided a transparent method for screening studies to be considered for TCDD dose response analysis.

EPA began this process by conducting an exhaustive literature search to identify peer reviewed, dose response studies for TCDD that have been published since the 2003 reassessment report (Response to NAS Comments, p. 2.2). This search included both animal bioassays and human epidemiological studies of TCDD conducted from 2000 to the 2008. More than 500 studies were identified. These studies were published in the federal register and the public was given the opportunity to review this list and identify any additional studies that were not included. Several additional studies were identified in this process and included in the final TCDD literature data base. We agree with the agency that the implementation of this rigorous search strategy ensures that the most current and relevant studies would be considered in their technical response to NAS and in the TCDD dose-response assessment. It also ensures that the most current and relevant studies would be included in the dioxin reassessment report.

The agency then developed specific criteria to evaluate these studies in order to decide which were appropriate to include in the agency's assessment of the TCDD's dose response. We agree that these criteria are based on common practices and current guidance and are appropriate for identification of point-of-departure (POD) effect levels and for deriving reference dose (RfD) and oral slope factor (OSF) estimates. Criteria were developed for both animal studies and human epidemiological studies. Key criteria included whether the study was published in the peer-reviewed literature; whether the exposure was primarily to TCDD, rather than to dioxin-like compounds (DLCs); and whether the specified dose and oral exposure was reasonably estimable (Response to NAS Comments, p. xxxi).

The agency solicited feed-back and included the public in the preparation of their response to the NAS by convening a scientific workshop in February of 2009 that was open to the public. The primary goal of the workshop was to identify and address the issues related to the dose-response assessment of TCDD and to ensure that the EPA's response to the NAS focused on the key issues, while reflecting the most meaningful science (Response to NAS Comments, p. xxix). At this workshop, the agency solicited further comments on the TCDD data base and further refined the selection criteria for inclusion of studies in the TCDD dose response analysis. As part of the study selection process, the agency developed criteria for identifying studies that had administered doses where adverse effects were observed that would be suitable to cancer slope factor derivation (Response to NAS Comments, p. 2-9). We believe that the agency appropriately developed criteria that provided reasonable cut-offs that restrict the number of studies that would need to be modeled while ensuring that appropriate study/data set combinations that were good candidates for deriving the cancer oral slop factor (OSF) or the reference dose (RfD) were modeled.

The agency selected an administered dose of less than or equal to 1 nanogram per kilogram per day (ng/kg-day) for cancer studies in animal bioassays and less than or equal to 30 ng/kg-day as a reasonable cut-off for non-cancer studies. These dose requirements were used to eliminate those studies that would not be selected for development of a RfD or an OSF because the lowest tested dose would be too high relative to other TCDD studies of acceptable quality (Response to NAS Comments, p. 2-10). The agency also required that the bioassays exposed animals via the oral route to TCDD only and that the purity of the TCDD was specified (Response to NAS Comments, p. xxxii).

We feel these criteria are clearly defined and described and are scientifically justified for selecting the most appropriate studies to conduct dose-response modeling for TCDD. In addition, EPA also required that the considered studies be further evaluated using four additional criteria: 1) Is the strain, gender, and age of test species identified; 2) Is the testing protocol, including the duration and timing of dosing clear; 3) Is the study design consistent with standard toxicological practices; and 4) Is the magnitude of the animal responses outside the range of normal variability (see Response to NAS Comments, Figure ES-2, p. lvi). These additional criteria further ensure the scientific rigor of the selected studies and that the most relevant information for development of quantitative human risk analysis from animal bioassay has been identified and selected for dose-response modeling for TCDD.

The agency provided an extensive detailed analysis of each key human epidemiological and animal study assessed against the developed criteria. Each study is briefly summarized, assessed against the criteria and evaluated for suitability for TCDD dose response modeling (see Response to NAS Comments, pp. 2-25 to 2-210). We feel that this open and transparent process has made it easy to see how the agency has applied the study inclusion criteria for both epidemiological and mammalian bioassay data-sets. Consequently, we feel that EPA has applied these criteria in a scientifically sound manner and has appropriately identified the key non-cancer and cancer studies to conduct appropriate quantitative dose response analyses for TCDD. Subsequently, the agency was able to develop appropriate reference dose and cancer slope factor values for TCDD.

II. Cancer Assessment

The EPA has concluded that TCDD is carcinogenic to humans. The basis for this determination is the criteria defined in the agency's *2005 Guidelines for Carcinogenic Risk Assessment* (Response to NAS Comments, p. 5-3). These guidelines call for using a weight of the evidence approach in which all available information is considered in making a determination on the carcinogenicity of a substance. These guidelines were vetted through the usual agency public review process before being finalized and have been generally accepted by the public including the regulated community.

According to these guidelines, a determination that a substance is carcinogenic to humans is appropriate when the following conditions are met: 1) there is strong evidence of an association between human exposure and either cancer or the key precursor events of an agent's mode of action, but not enough for a causal association; 2) there is extensive evidence of carcinogenicity in animals; 3) the mode (s) of carcinogenic action and associated key precursor events have been identified in animals; and 4) there is strong evidence that the key precursor events that precede the carcinogenic response in animals are anticipated to occur in humans and progress to tumors, based on available biological information (Response to NAS Comments, p. 5-3).

We find that the criteria considered in the weight-of-evidence approach are clearly identified and discussed by EPA and that the use of this approach is scientifically justified. EPA presents and evaluates the human epidemiological data and animal bioassay results in significant detail (see Response to NAS Comments, pp. 5-3 to 5-21). For epidemiological data, the agency considered and discussed factors such as the evidence of causality, temporality, strength of association, consistency, biological gradient, biological plausibility, and specificity. The analysis of these factors allows the reader to fully consider all the relevant evidence of carcinogenicity for both human epidemiological data and animal bioassay data.

The evidence that TCDD is a carcinogenic to humans is summarized on pages 5-20 to 5-21. This conclusion is based on the following evidence:

- Multiple occupational epidemiological studies showing strong evidence of an association between TCDD exposure and increased mortality from all cancers.
- Epidemiological studies showing an association between TCDD exposure and certain cancers in individuals accidentally exposed to TCDD in Seveso, Italy.
- Extensive evidence of carcinogenicity at multiple tumor sites in both sexes of multiple species of experimental animals.
- General scientific consensus that the mode of TCDD's carcinogenic action in animals involves Ah Receptor (AhR)-dependent key precursor events and proceeds through modification of one or more of a number of cellular processes, such as induction of enzymes, changes in growth factors and/or hormone regulation, and/or alterations in cellular proliferation and differentiation.
- The human AhR and rodent AhR are similar in structure and function and human and rodent tissue and organ cultures respond to TCDD in a similar manner and at similar concentrations.
- General scientific consensus that AhR activation is anticipated to occur in humans and may progress to cancers.

When presented in this format following the detailed discussion of both the human epidemiological and animal bioassay data, it is clear how and why the agency has made its conclusion. We support and commend the agency for this clear and transparent presentation that scientifically justifies its determination that TCDD is carcinogenic to humans.

EPA does not stand alone in this reaching this conclusion. The U.S. National Toxicology Program (NTP), a program of the National Institute of Environmental Health Sciences (NIEHS) and the lead agency in this country that evaluates the potential for chemicals to cause cancer, has classified TCDD as a human carcinogen. In addition, the World Health Organization's International Agency for Research on Cancer (IARC), the most prestigious cancer research group in the world, has also concluded that TCDD is carcinogenic to humans. The review process used by both these institutions involved the best and most knowledgeable (on dioxin) cancer researchers in the world. These institutions have come to the same conclusion that EPA reached on the classification of TCDD as a human carcinogen.

Mode of Action

EPA presents the available data related to the mode of action for the carcinogenicity of TCDD in detail in the 2003 reassessment document (see Part II, Chapter 2 and Part III, Chapter 3) and in summarized form in the Response to NAS Comments document (see pp. 5-11 to 5-15). We feel that the data presented in this discussion is adequate and sufficient and appropriately characterizes the available data related to the mode of action for the carcinogenicity of TCDD.

Following presentation and discussion about what is known about the mode of action for the carcinogenicity of TCDD, the agency made these conclusions: 1) interaction with the Ah receptor (AhR) is a necessary early event in TCDD carcinogenicity in experimental animals; 2) through interaction with the AhR, TCDD modifies one or more of a number of cellular processes, such as induction of enzymes, changes in growth factor and/or hormone regulation, and/or alterations in cellular proliferation and differentiation; 3) AhR activation is anticipated to occur in humans and may progress to tumors. AhR is present in human cells and tissues; studies using human cells are consistent with the hypothesis that the AhR mediates TCDD toxicity; and no data exist to suggest that the biological effects of AhR activation by TCDD are precluded in humans; and 4) non-AhR mediated effects of TCDDD are possible (Response to NAS Comments, p. 5-20).

We feel that the data presented by EPA does support the findings above including the conclusion that the overall mode of action for TCDD-induced carcinogenesis is largely unknown. We feel that the agency's evaluation of the data supporting this conclusion is clearly presented and described.

Key Data Sets

EPA selected key epidemiological studies and animal bioassays for cancer dose response modeling based on extensive study selection criteria. We found that the agency's approach for selecting these key data sets to be scientifically justified and clearly described (see Section I above). The key epidemiological data studies are summarized (for a second time) in the cancer assessment chapter (see Response to NAS Comments, Chapter 5) and the basis for deriving a central tendency estimate and lower bound Effective Dose eliciting a 1 percent response (ED_{01}) from a linear dose response model and an associated cancer slope factor for the most sensitive end-point are presented (see Response to NAS Comments, Table 5-1, p. 5-94).

Oral Slope Factors

EPA calculated potential oral slope factors using animal data by extrapolating from a point of departure (POD) using a linear non-threshold dose response model. We feel that the approach EPA used to estimate cancer risk including the use of tumor modeling based on animal studies is scientifically justified and clearly described. EPA estimated a range of candidate TCDD OSFs from animal data. They modeled five chronic rodent bioassays using whole blood concentrations and derived benchmark dose lower confidence bound human equivalent dose

($BMDL_{HED}$) values for 28 species/sex/endpoint data sets individually (see Response to NAS Comments, Table 5-16, p.104) and for seven species/sex combined tumor data sets (see Response to NAS Comments, Table 5-17, p.105). This analysis provides credible values for $BMDL_{HED}$ derived from the animal studies that is in the range of 3.1×10^{-2} and 1.1×10^{-2} ng/kg-day which corresponds to oral slope factor values of $3.2 \times 10^{+5}$ and $9.4 \times 10^{+6}$ per mg/kg-day, respectively (see Response to NAS Comments, p. 5-44).

Selection of the Cheng 2006 Study for Deriving the Oral Slope Factor

EPA selected the Cheng et al. 2006 paper as the critical study for deriving the oral slope factor (OSF) for TCDD cancer risk. This study was chosen primarily because it considers time-integrated elimination of TCDD rather than first-order kinetics, which the agency feels is more realistic despite the attendant uncertainties in this model (Response to NAS Comments, p. 5-76). However, the primary basis for this selection is not well defined by the agency. EPA could improve its explanation of why it feels the use of the time-integrated elimination model provides a more "realistic" estimate of body burden compared to the first order kinetics model. There is some discussion of the strengths of the concentration- and age-dependent elimination model (CADM) (Response to NAS Comments, p. 5-30), but these factors are not presented in support of the decision to use this study to derive the OSF. The strengths of this relatively new model and other factors should be explicitly presented in the section where the agency explains its decision to use this study to derive the OSF. The agency needs to improve the clarity and transparency of its choice of the Cheng paper to derive an OSF for TCDD.

The Cheng paper analyzed all cancer mortality as the basis for the OSF. This is a departure from the use of cancer incidence data which is what EPA typically uses to calculate cancer slope factors. Using mortality data instead of incidence data tends to bias the slope factor downward. This would result in a lower cancer risk estimate than would result from deriving an OSF based on cancer incidence data. EPA argued that the high case mortality rates associated with lung cancer during the period of cohort evaluation (e.g., that the 5-year relative survival rates for lung cancer were less than 10% before 1973 and less than 15% before 1995), may result in a slope factor estimated using cancer mortality data that might not be much lower than that calculated using cancer incidence data (Response to NAS Comments, p. 5-86).

As EPA further describes in their report, whether this comment proves to be reasonably accurate depends on whether the cancer mortality is independent of occupational TCDD exposures levels. Unfortunately, this assumption cannot be verified due to the lack of data on relative survival and age-specific cancer risks in the exposed population compared to the NIOSH cohort (Response to NAS Comments, p. 5-86). Consequently, there is significant uncertainty about whether the cancer risk derived from an OSF using mortality data provides a reasonably accurate estimate of the risk of developing cancer from exposure to TCDD. It is likely that using cancer mortality data in place of cancer incidence data produces an underestimate of the actually cancer risks posed by exposure to TCDD. Since this method is significantly different from the cancer risk method used to derive the OSF in the 2003 draft reassessment report, EPA should more explicitly discuss this difference in the final reassessment document and make it

clear that by using cancer mortality instead of the cancer incidence data, the estimated cancer risk from exposure to TCDD may be an underestimate of the actual risks.

The Emond PBPK model

The use of the Emond human physiologically based pharmacokinetic (PBPK) model to derive the OSF is presented in significant detail and its use is scientifically justified by EPA (see Response to NAS Comments, pp. 5-31- 50 5-33). The agency provides a transparent step-by-step explanation that clearly shows how the OSF is derived beginning with a POD determined in the Cheng paper, with conversion to oral intake using the Emond human PBPK model. These steps included 1) estimating background mortality risk; 2) calculating total cancer mortality risks in the exposed group associated with a specified (extra) risk level of fatal cancer; 3) calculating incremental cancer mortality risk in the exposed population based on a given extra cancer risk; 4) calculating cumulative TCDD concentration in the fat compartment for a given extra risk; and 5) calculating the continuous daily TCDD intake associated with a given extra risk (see Response to NAS Comments, p. 5-31 to 5-32). This detailed description along with a simplified summary table (see Response to NAS Comments, Table ES-1. p. lv), make it clear how the agency derived its OSF.

Due to nonlinearities in the Emond PBPK model (specifically pertaining to the relationship between exposure and internal dose) EPA calculated a series of risk-specific oral slope factors. EPA's rationale for and presentation of these slope factors is clear and transparent. EPA did not, however, fully explain its decision to extrapolate below the background TCDD exposure levels experienced by the NIOSH cohort. The agency only states that it assumes that "the slope is the same below the NIOSH cohort background exposure level (approximately 5 ppt/yr TCDD fat concentration)" (Response to NAS Comments, p. 5-31). The agency could provide more detail for why they feel this assumption is reasonable and justifiable.

Uncertainties in the Derivation of the Oral Slope Factor

We feel comfortable that the EPA has clearly described the major qualitative uncertainties in the derivation of the oral slope factor (OSF) for the carcinogenicity of TCDD. The major uncertainties are described in detail in the report (see Response to NAS Comments, pp. 5-77 to 5-87). The uncertainties discussed include uncertainty in exposure estimates in the epidemiological studies; uncertainty in the shape of the dose response curve; uncertainty in extrapolating risks below exposure levels in the reference population; uncertainty in cancer risk estimates arising from background dioxin-like compounds (DLC) exposure; uncertainty in cancer risk estimates arising from occupational co-exposures to DLCs; and other sources of uncertainty in risk estimates from the epidemiological studies including the use of cancer mortality data rather than cancer incidence data, possible influences of intervariability in the TCDD kinetics, and exposures to other occupational carcinogens. This robust discussion of uncertainty provides a clear overview of the limitations inherent in the lack of specific information and understanding of key elements of the process for estimating an OSF for the carcinogenicity of TCDD.

Exposure to Dioxin-Like Compounds

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 into 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. We agree that it would be very difficult to establish the background cancer risk for TCDD for the worker exposed to TCDD occupationally. EPA does present a formula with clearly defined components for estimating background doses in the NTP animal study which measured background exposures to TCDD and other DLCs (see Response to NAS Comments, p. 5-88). However, EPA concludes that there is very little quantitative impact on the cancer dose-response modeling for the NTP study (Response to NAS Comments, p. 5-89). Data presented in Tables 5-23 and 5-24 support this conclusion. EPA further concludes that the expected impact of exposure to background TCDD and DLCs on the human studies would be similar to the impact estimated to occur in the animal studies, which is to decrease the estimated unit risk (Response to NAS Comments, p. 5-90). This conclusion may be correct, but there is no data or analyses to support it. Despite this, we agree with EPA that it would be very difficult to establish the background cancer risk for TCDD for the worker exposed to TCDD occupationally.

Use of Nonlinear Approaches for Assessing the Carcinogenicity of TCDD

EPA describes in detail the limitations of two illustrative examples of RfDs derived using a nonlinear dose response model. These examples are based on hypothesized key events in TCDD's mode of action for liver and lung tumors that are presented and discussed in the Response to NAS Comments (see Response to NAS Comments, pp. 5-72 to 5-74). The detailed descriptions of these limitations present a clear and transparent discussion of what is known and what is not known about the mode of action for the two tumor types discussed in these illustrative examples. It is clear from this discussion that the sequence of key events following the binding of TCDD to the AhR that ultimately lead to the development of cancer in both examples is unknown. Furthermore, no detailed hypothesized mode of action information exists for either of the two tumor types presented in the illustrative examples. Without information on the mode of action following AhR binding leading to the development of cancer, we agree with EPA's decision to follow its 2005 cancer guidelines which calls for the use of a linear extrapolation at low doses as an appropriate scientific baseline inference ("default") for carcinogen risk assessment (Response to NAS Comments, p. 5-63). We further agree that it is appropriate for EPA to take a public health protective default position regarding the interpretation of toxicological and epidemiological data, especially when there is no information on the mode of action following the binding of TCDD to the AhR that ultimately leads to the development of cancer. We strongly support the EPA's decision to follow its 2005 cancer guidelines that calls for the use of a linear no threshold model for extrapolating to low doses when calculating the cancer risk for TCDD.

EPA also presents a discussion from a workshop on low dose extrapolation that provides further insight into the limitations of a non-linear extrapolation model. This discussion makes a distinction between the likelihood that thresholds exist for an individual versus for a population. "At the human population level, however, biological and statistical attributes tend to smooth and linearize the dose-response relationship, obscuring thresholds that might exist for individuals" (Response to NAS Comments, p. 5-63). This is an important point that is discussed at length by EPA in support of its decision to use a linear no threshold model for extrapolating to low doses when calculating the cancer risk for TCDD (see Response to NAS Comments, pp. 5-54 to 5-65).

III. Reference Dose Derivation

EPA chose to derive a reference dose (RfD) for TCDD based on co-critical effects - male reproductive effects (Mocarelli et al. 2008) and changes in neonatal thyroid hormone levels (Baccarelli et al. 2008). We feel that the rationale for the selection of these critical effects is clearly described and scientifically justified (see Response to NAS Comments, pp. 4-22 to 4-26). EPA identified key epidemiological and animal studies as candidates for deriving a RfD. The study selection process is described in detail in Section Two of the EPA Response to the NAS Comments report. For each candidate study, EPA developed a point of departure (POD) for deriving a RfD. These values are summarized in Table 4-1 (Response to NAS Comments, p. 4-33). For each non-cancer epidemiological study selected as a key study, EPA evaluated the dose response information developed by the study authors to determine if the study provided non-cancer effects and TCDD-relevant exposure data for a toxicologically relevant endpoint (see Response to NAS Comments, pp. 4-9 to 4-13). If such data were available, EPA identified a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) as a candidate POD. The EPA then used the Emond PBPK model to estimate the continuous oral daily intake (mg/kg-day) that would lead to the relevant blood TCDD concentration associated with the candidate POD. If all this information was available, the result was included as candidate POD (Response to NAS Comments, p. xxxvi). We feel that this transparent process adequately provides the scientific basis for how EPA derived candidate POD values for calculating a RfD.

The agency also goes into significant detail discussing its strategy for evaluating animal bioassay data for assessing TCDD dose-response (see Response to NAS Comments, pp. 4-13 to 4-17). For each non-cancer endpoint, EPA evaluated the toxicological relevance of each endpoint and rejected those judged not to be relevant for RfD derivation. This approach makes sense. For each relevant endpoint, EPA calculated a POD and explained why some PODs – NOAELs and Benchmark Dose Levels (BMDLs) – were rejected and why only LOAELs were used to calculate possible RfDs. In the end, EPA chose to use qualified human epidemiological studies to derive a RfD. We agreed with this decision and the rationale for making it. This decision is also consistent with recommendations of panelists at the 2009 Dioxin Workshop. We are not aware of any other study nor other endpoints that would be more appropriate for deriving a RfD for TCDD.

Exposure Pattern at Seveso, Italy

The pattern of exposure to TCDD in the Seveso, Italy cohort 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 exposures for about 20 years when adverse effects were observed (Response to NAS Comments, p. 4-28). To estimate exposure, EPA used an averaging method that differs from the typical method used for animal bioassays. EPA decided that the relevant exposure should be calculated as the mean of the pulse exposure and the 10-year critical exposure window average. This approach has several inherent uncertainties that may result in exposure estimates that may range from 3 to 10 fold (Response to NAS Comments, p. 4-28). Despite this uncertainty, we feel that EPA is justified in using the exposure estimates provided by the authors to quantify TCDD exposures for dose-response assessment.

Key Elements of Studies Used to Derive a Reference Dose

We are comfortable with EPA's designation of a 20% decrease in sperm count (and an 11% decrease in sperm motility) as a LOAEL for the Mocarelli et al. (2008) study. We recognize that a decrease in sperm concentration of 20% and an attendant decrease in sperm motility would likely not have clinical significance for an individual, but we agree with EPA that such decreases associated with exposure to TCDD could lead to shifts in the distributions of these measures in the general population. Such shifts could result in decreased fertility in men at the low end of these population distributions. Consequently, we agree that this measurement is biologically significant and an appropriate LOAEL associated with exposure to TCDD.

EPA used the reported maternal exposures from the regression model developed by Baccarelli et al. to provide an estimate of the relevant effective dose instead of extrapolating from the measured infant TCDD concentrations to maternal exposures. While there is uncertainty in this decision, we feel that it is nonetheless an appropriate exposure estimate for the Baccarelli et al. study. We agree with EPA's explanation that the maternal serum TCDD concentrations measured 10-15 years after the initial exposure are proximate to the actual pregnancies. Consequently, there is less uncertainty in the kinetic extrapolation between time of measurement and time of birth (i.e., the critical exposure window). We agree that the narrow critical window at a much later time than the initial exposure (where the TCDD elimination curve is flat) is assumed to lead to a relatively steady-state exposure over the critical time period with much less uncertainty in the magnitude of the effective dose.

We agree with EPA's designation of 5 µ-units Thyroid Stimulating Hormone (TSH) per ml blood as the LOAEL for the Baccarelli et al. (2008) study. This value was established by the World Health Organization (WHO) in 1994 as an indicator of potential iodine deficiency and potential thyroid problems in neonates (Response to NAS Comments, p. 4-24). Increases in TSH levels are indicative of decreased thyroid hormone (T4 and/or T3) levels. While the toxicological concern in the Baccarelli study is not iodine deficiency, but rather decreased T4 or T3 levels, there is ample evidence, cited by EPA that increased metabolism leads to increased clearance of T4, as evidenced by lower T4 or T3 levels in blood. Adequate levels of thyroid hormones are essential

in the newborn and young infant as this is a period of active brain development. Thyroid hormone deficiency during pregnancy and in neonatal life can also lead to neurological deficiencies. However, the exact relationship between TSH increases and adverse neurodevelopmental outcomes are not well studied. This finding is corroborated in animal studies that indicate that modest changes in thyroid hormone status for even a relatively short period of time can lead to altered brain development (Response to NAS Comments, p. 4-25). Lastly, Baccarelli also found a correlation between TSH levels and TCDD exposure at Seveso – the higher the exposure, the greater the increase in TSH (Response to NAS Comments, p. 4-25).

Uncertainty Factors

We do not fully agree with the EPA's selection and rationale for selecting the uncertainty factors (UFs) used in the derivation of RfDs. We are disappointed that EPA chose not to use an UF to address the unique susceptibility and vulnerability of children to toxic chemicals. Developing children are uniquely vulnerable to the toxic effects of chemicals due to an increased susceptibility and an increased risk of exposure; children's metabolic pathways, especially in the first months after birth, are immature; their ability to metabolize, detoxify, and excrete many toxicants differs from that of adults; they are less well able to deal with a number of toxic chemicals such as dioxin. In addition, children can increase their exposure to chemicals through normal developmentally appropriate pica behavior – the intentional ingestion of non-food items. Pica is estimated to occur in about half of children ages one to three. Because young children's breathing zones are so much closer to the ground, their exposure to contaminated soil via inhalation is more likely. The President's Executive Order of 1997 specifically requires the EPA to "make it a high priority to identify and assess environmental health risks and safety risks that may disproportionately affect children … [and to] … ensure that its policies, programs, activities, and standards address disproportionate risks to children that result from environmental health risks or safety risks." Certainly the dioxin reassessment and the development of a RfD for TCDD would be subject to this order. At a minimum, EPA must explain why they did not include a specific uncertainty factor to account for the unique susceptibility and vulnerability of children in the derivation of a RfD for TCDD.

In the derivation of the final selected RfD based on the co-critical papers (Mocarelli and Baccarelli), a total UF of 30 was used that takes into account the lack of a NOAEL (UF=10) and human interindividual variability (UF=3) (Response to NAS Comments, p. 4-28). As stated above, the unique susceptibility and vulnerability of children is not considered in this calculation. It is also not clear why the human interindividual variability is only 3, instead of 10. EPA needs to address why it did not include an UF to account for the unique susceptibility and vulnerability of children and why it chose to use an UF of 3 to account for human interindividual variability.

We agree with the other uncertainty factors (UFs) used by EPA to derive RfDs including the use of a 10-fold interspecies UF to extrapolate from animals to humans; a 10-fold intraspecies UF to account for interindividual variability when a NOAEL is used as the POD; an UF of 10 to account for use of a LOAEL instead of a NOAEL; a 3-fold UF to account for sensitive populations; and an UF of 3 to account for the toxicodynamic component of the interspecies extrapolation factor.

Biochemical Endpoints for the Derivation of the RfD

We feel that the EPA's decision not to consider biochemical endpoints (such as CYP induction, oxidative stress, etc.) as potential critical effects for derivation of the RfD for TCDD is clearly described and scientifically justified. The agency chose not to consider this type of endpoints because of uncertainties in the qualitative determination of adversity associated with such endpoints and the quantitative determination of appropriate response levels for these types of endpoints in relation to TCDD exposure. This decision follows standard EPA guidance and is consistent with the IRIS program definition of an adverse effect. We agree that only effects that have a clear toxicological significance should be considered as a potentially relevant endpoint for the derivation of a RfD.

Qualitative Discussion of Uncertainty

EPA's qualitative discussion of uncertainty in the RfD (pp. 4-28 to 4-32) is well written and clearly described. This is an important section because there are many inherent uncertainties in our knowledge and understanding of how chemicals interact with the human body leading to adverse health effects. The agency carefully discusses multiple uncertainties beginning with the exposure data from the human epidemiological studies considered in the derivation of the RfD; the lack of a completely unexposed population; the lack of complete concordance in effects observed in animal studies and humans; and limitations in animal bioassays. The discussion of these and other uncertainties support the decisions made by EPA in deriving a RfD for TCDD.

In closing, we want to once again urge EPA to complete its response to the comments it received from the NAS in 2006, to update the reassessment as appropriate and as quickly as possible, and to finally release the reassessment report to the public. After more than 20 years, the American public deserves to know what the risks of exposure to dioxin are and what steps the agency plans to take to protect the health of the American people.

Thank you for your attention to this critical environmental health and environmental justice issue. We appreciate the opportunity to comment on this important matter.

Respectfully submitted,

Stephen Lester
Science Director
Center for Health, Environment & Justice
PO Box 6806
Falls Church, VA 22040
703-237-2249
slester@chej.org
www.chej.org