Response to Charge Questions: Arnold Schecter; October 22, 2010

This is my third written set of comments and is meant to add to the previous comments.

Overview:

The EPA document, responses to NAS queries relating to the 2003 EPA Dioxin Reassessment, seems to me reasonable. I have some suggestions as to how it could be improved but see no reason to hold up the EPA dioxin document of 2003 further, assuming EPA staff will make the modifications and answer the questions posed at the first Washington DC meeting several months ago. EPA's Dioxin Reassessment document has been revised for many years and it is important for this government document to be available to the public as soon as possible. Some questions are not going to be resolved for many years, such as threshold or no threshold, linear or not at low doses, molecular events involved in various chemical, toxicological or clinical outcomes, and when to consider events as adverse.

The NAS updates "Veterans and Agent Orange" every two years The WHO updates their dioxin TEF estimates every five years. In a similar fashion, CDC's ATSDR plans periodic updates on their documents, including their dioxin, PCDF, and PCB documents. The NTP updates their evaluation of certain chemicals when it is deemed to be indicated. Therefore, it is reasonable to release a finalized version of the EPA Dioxin Reassessment initially written in 2003 with modifications expected based on new input this year.

I would like to see more use of TEFs, more use of veteran data such as that generated by the Ranch Hand study over several decades, and more references cited for major points, For example, two Seveso studies alone could be expanded by epidemiology toxicology data. I do not believe there are any human studies investigating TCDD only and would therefore object to excluding those that do not exclusively focus on TCDDThere is also no reason to exclude informaton derived from studies described as TCDD only.

Each year additional publications add to the literature on dioxins and dioxin like chemicals. The EPA 2003 dioxin document is already dated. I suggest finalizing it now and releasing it in the near future, noting that new scientific data is generated each year and that the document will be updated periodically.

A glossary would be helpful. Any EPA documents should be finalized with the understanding that scientists from different fields will be reading the documents. In addition, the general public, journalists, elected officials and their staff, attorneys, judges, members of environmental groups, and others will be reading EPA documents. They should be written so as to be clear and understandable by members of these groups so as to avoid misinterpretation.

Overview of the three key recommendations:

1. Improved transparency and clarity in selection of key data sets for dose-response analysis could be improved but is not deficient enough to require any major revision. More data sets could have been included. Stating why certain were excluded would be helpful.

2. Further justification of approaches to dose response modeling for cancer and noncancer endpoints, that is for health endpoints where there is consensus by the Panel or strong input from the public.

3. Improved transparency, thoroughness and clarity in quantitative uncertainty analysis should be done to the extent noted in the written summary of the earlier meeting in Washington and comments made by individual panalists in writing.

General Charge Questions

1.1 Is the draft *Response to Comments* clear and logical? Has EPA objectively and dclearly 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 noncaner and cancer health effects of TCDD?

More studies could be useful in supporting the assessments. Animal studies, epidemiology studies, and studies citing other than "pure TCDD" papers but with TEQ considerations might be helpful. Yusho, Yucheng and Ranch Hand as well as VA studies should not be excluded without stated rationale.

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 clarify in data-set selection for dose-response analysis?

2.2 Are the epidemiology and animal bioassay study criteria/consideration 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.

I believe exclusion criteria may have been applied in too stringent a fashion. Too few studies are cited. Phrases such as "standard toxicological practices" and "consistent with EPA criteria or policy" do not say anything meaningful to this reader. I believe DLCs should be included. There is strong scientific justification for this and it expands the data base.

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

I do not work with modeling so will be brief. Ideally, we would like to know the number of molecules in a target organ of interest and be able to compare it with the number of molecules causing changes which might be adverse in humans or other species. As this information is not available, we have worked with adipose tissue, milk, whole blood, serum, and plasma with blood and milk reported on a lipid basis. We do have a small literature based on autopsies of U.S. individuals from New York where chlorinated dioxins, dibenzofurans, and PCBs have been reported for some organs of the same people. There also exists animal data providing levels in various organs under certain (dosing) situations.

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 exposure 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 old 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 for 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 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.

The use of only two Seveso studies to make important conclusions could be open to criticism. Are no other epidemiology or toxicology studies available to support the conclusions?

Section 5. Cancer Assessment

The conclusion that TCDD is carcinogenic to humans is scientifically justified and clearly stated.

It is reasonable to describe how in vitro, in vivo, and human data do or do not support the conclusions.

Uncertainties in mode or mechanism of action exist but do not weaken evidence of animal and human data as to carcinogenicity of TCDD as a promoter and initiator. Lucier and Huff have repeatedly published on the consistency of animal studies with respect to TCDD and cancer in various species, organs, and genders.

This reader believes there is a tendency to overstate TCDD and understate other DLCs contributing to total TEQ and hence adverse outcomes.

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.

QUA is outside my area of expertise. No further comments.