OMB Staff Working Comments on EPA's Final Agency/Interagency Science Discussion draft Toxicological Review of Tetrachloroethylene (PCE) and draft IRIS Summary (dated June 2011)

Sept 1, 2011

While we recognize that EPA has made important and likely very substantive changes throughout the document, considering its size (just over 1000 pages) and the limited time provided for interagency science consultation, OMB focused only on EPA's response to the NAS peer review. Where EPA agrees with the comments, we suggest that appropriate conforming changes be made in the main text of the toxicological review and the IRIS summary.

General Science Comments:

- Last week, EPA provided the interagency reviewers with a new peer review report specific to the PBPK modeling. EPA plans to address these comments in Appendix A, but has not done so yet. Consistent with Step 6b of the IRIS Process (see: http://www.epa.gov/iris/pdfs/2009_IRIS_PROCESS_FINAL_05_19_09.PDF), interagency reviewers should be provided with "the opportunity to review the final draft of the IRIS Summary and Toxicological Review and appendix describing disposition of peer review and public comments." To be consistent with the IRIS process, we suggest that EPA incorporate responses to this peer review into appendix A and the tox review and *then* provide the final documents to interagency reviewers as per Step 6b. We applaud EPA for conducting this review as it appears that significant changes to the model have been made. We look forward to seeing EPA's responses to the peer reviewer comments.

- The structure and approach to Appendix A is not clear. It is not clear how EPA is numbering the sections and how that tracks with the NRC report (the external peer review report). We recommend that this be clarified. In addition, it is not clear how EPA is choosing what comments to respond to. EPA states that the major peer review comments are below and are quoted verbatim from the NRC report, from the Summary section. It is unclear what summary section EPA refers to as there is an overall summary and then a summary and clear recommendations for each chapter of the NRC report.
  - To ensure that EPA is responsive to all the major NRC recommendations, it would be helpful to reorganize the response to comment by chapter of the NRC report and then provide the summary recommendations from each chapter verbatim (along with the page number citation), and then provide the EPA response. Otherwise, there is a concern that EPA may be missing some major recommendations. More thorough responses to the NRC recommendations may also be needed. For instance in the summary of chapter 8, NRC clearly states (at page 80): "The majority of the committee finds that EPA has not adequately justified the use of MCL data over the evidence for liver or kidney cancer in its cancer risk assessment. Evidence of tetrachloroethylene-induced leukemia from epidemiologic studies is limited and inconsistent. The NTP (1986) and JISA (1993) study results of increased MCL incidences in F344 rats given tetrachloroethylene by inhalation are also questionable because of the high background rates of MCL in control animals. More thorough statistical evaluation of the data, such as the life-table analysis proposed by Thomas et al. (2007), could provide a stronger basis for drawing conclusions. However, MCL resulting from tetrachloroethylene exposure has not been observed in other strains of rats or other animal species, and no definitive evidence is available to support a hypothesized MOA by which tetrachloroethylene

increases MCL in F344 rats. Those are all sources of uncertainty surrounding the relevance of MCL to human cancer risk."

These appear to be important and major comments yet we do not see them presented or responded to in Appendix A. This example is particularly important since EPA is continuing to rely on the MCL endpoint for the cancer modeling and we did not see the recommended life-table analysis presented or described, nor did we see an explanation from EPA regarding why the recommended analysis was not provided.

- For the non-cancer endpoints, NRC specifically recommended five studies (see NRC page 41). For the RfC and RfD, EPA relies on three studies; however two of these studies were recommended by NRC and one was not. In appendix A, EPA explains why they rejected two of the NRC recommendations (because they were acute studies) but it is not clear that EPA has adequately explained why, despite NRC comments, the Seeber study is found to be acceptable. NRC states (at page 87): "The committee also found, however, that the draft sometimes failed to consider weaknesses in study methods or inconsistencies in results, two factors that should carry great weight in selecting key studies for calculating an RfC. For example, test outcomes (neurologic signs, emotional lability, choice reaction time, cancellation d2, and digit symbol) in a study by Seeber (1989) were worse in the low-exposure group compared with the high-exposure group. EPA's discussion of the study (Section 4.6.1.2.2) did not mention that discrepancy." On page 5-12 of the tox review, EPA describes the Seeber study, but does not mention these NRC concerns. Nor are these concerns described or responded to in Appendix A. Because this is a key study for the RfD and RfC determination we recommend that EPA respond to this concern and further explain their decision to use this study.

- Regarding the database uncertainty factor used for the RfD and RfC, as EPA notes, NRC (page 92 and elsewhere) states: "The committee recommends that EPA revisit and defend more clearly its decision to apply a factor of 3 for database deficiencies in light of new data and the committee's findings in Chapter 3. New studies include, for example, recent papers from researchers in EPA's National Health and Environmental Effects Research Laboratory provide excellent data from well-designed studies using controlled, acute exposures that link deficits in visual function and signal detection with atmospheric tetrachlorethylene concentrations and instantaneous concentrations in the brain. This includes papers by Oshiro et al. (2008) and Boyes et al. (2009) investigating function and by Shafer et al. (2005) on mechanisms, which is described in the IRIS document but not fully integrated." On page A-6, EPA states "EPA accepts these NRC recommendations. Based on concerns raised by the NRC, EPA re-examined the adequacy of the database and increased the UFD from 3 to 10 (Sections 5.1.3 and 5.2.3). However, EPA does not provide a scientific justification. We have looked at 5.1.3 and 5.2.3 and it does not mention any of the studies NRC mentions. In order to respond to the NRC concern, we suggest that EPA evaluate the studies NRC mentions and look at what point of departure would be derived from them. If these values are above the values used in the RfC and RfD derivation, then it would seem that increasing the UF would not be justified as the RfC and RfD points of departure would be sufficiently protective. In addition, it is not clear why EPA has not integrated these newer studies into the toxicological review and considered them for the non-cancer derivation. Such an evaluation may allow EPA to better justify their use of whichever uncertainty factor they determine is

appropriate. We note that NRC never recommends a 10x factor but only suggests that EPA 'revisit and defend more clearly' the decision. Considering the robustness of the database on PCE, it is unclear why a 10x factor is needed.

- In addition, EPA may want to consider going back to the expert reviewers to see if the EPA evaluation and changes have sufficiently addressed the reviewer comments. We note that other interagency reviewers, including the National Toxicology Program (NTP) also question whether or not a full 10x factor is needed. The NTP comments state: "In our opinion, the uncertainty factor of 3 is more appropriate for derivation of RfD." We also note that ATSDR used similar studies to EPA, and their uncertainty factor is only 100 not 1000 (see ATSDR 1997 as well as ATSDR comments).

· On page A-1, EPA notes the NRC concern (NRC Page 4) which states: "However, the committee has identified concerns about some of the approaches that EPA used to evaluate the data on tetrachloroethylene and subjects about which inadequate information or rationales are used to support its risk assessment—factors that call into question the soundness and reliability of EPA's proposed reference values and cancer risk estimates for tetrachloroethylene. One of the overarching weaknesses of the draft assessment was a lack of critical analysis of the data on which EPA relied in evaluating methodologic strengths and weaknesses." EPA states that the assessment has been significantly revised to address these concerns, however it is not clear where these changes can be found. Thus we are not sure whether this important NRC comment has been adequately addressed. It would be helpful if EPA in their response could provide some specific examples of the types of changes that have been made (in particular those that present studies providing a critical analysis of strengths and weaknesses, something the NRC found to be missing) and the pages where these can be found in the toxicological review.

  Similarly, NRC on page 85 states: "EPA should provide a clearer discussion of criteria used to identify studies of merit and a more balanced critique to strengthen the draft IRIS assessment. EPA acknowledges this comment on page A-11, however it is not apparent where we can find a discussion of the criteria used and where this evaluation is presented.

· On page A-9, EPA notes the NRC request for a revision that includes: "…(2) characterization of maternal toxicity (e.g., mild or severe) associated with the studies listed in Table 4-10 and use of consistent nomenclature (ppm or mg/m3) for listing tetrachloroethylene concentrations;". In response to this EPA states: "With respect to recommendation (2), it is difficult to determine the relationship between maternal and developmental toxicity in a developmental or reproductive toxicity study." It is not clear to us that EPA is responding to the NRC concern. NRC is not asking about the relationship between maternal and developmental toxicity per se, but is also asking that EPA (as per the 1991 EPA guidance which NRC cites on page 44), evaluate the range of maternal-toxicity data (mild to severe effects). Thus it is not clear whether EPA has conducted the analysis NRC recommended.

· The NRC report stated (page 10 and elsewhere) "The majority of the members judged that the uncertainties associated with MCL (particularly the high background incidence, uncertainty about the dose-response relationship, and poor understanding of mode of action)

were too great to support using MCL data rather than data on hepatic or renal cancer for determining quantitative estimates of risk." It is not clear why EPA is continuing to use the MCL endpoint as the critical endpoint for the cancer quantification, despite this majority statement. On quick skim, it seems that this choice is almost two orders of magnitude different from the value obtained using hepatic or renal endpoints. Thus the impact is quite large. On page 5-94 of the tox review, EPA states: "The choice of data set for best representing an upper bound estimate of human carcinogenic potency involves a number of factors, including the magnitude and robustness of the response, the role of metabolism, the carcinogenic MOAs, the dose-response model fit, and the resulting low-dose extrapolation predictions." It is not clear how these factors were evaluated, particularly with respect to the NRC concerns and it is surprising, in light of the NRC report and discussion of this endpoint, to see section 5.4.4.2 of the tox review, giving greatest weight to the MCL endpoint.

On page A-16 EPA states: "Based on the remaining factors, and recognizing the differences in opinion among the NRC panel members regarding the use of the MCL data for cancer quantification, the rat MCL data were selected for deriving the upper bound estimate of carcinogenic potency because of the magnitude of the observed response (similar to the other endpoints); the additional dose response modeling was able to fit the dataset's supralinearity, as well as estimate a BMDL (similar to the other endpoints); and it is the largest unit risk estimate, which is the preferred science policy choice of EPA." This justification does not appear to fully address the NRC concerns. We suggest that EPA reconsider the NRC majority comments and the chosen cancer endpoint. At a minimum, EPA should respond directly to the scientific concerns raised by NRC, particularly the concerns noted regarding high background incidence, uncertainty about the dose-response relationship, and poor understanding of mode of action, when comparing the MCL endpoint to the renal and hepatic endpoints.

- In regards to the MCL endpoint, NRC further states (page 10 and elsewhere): "Those members judged that the use of the MCL data could be justified only if it is EPA's policy to choose the most conservative unit risk when considering options but that such justification should be distinguished as a policy decision, not a scientific one." While EPA notes, in Appendix A, that the higher IUR is the preferred science policy choice of EPA, if EPA continues to rely on the MCL endpoint, the tox review (at Sections 5 and 6) and the IRIS summary should note this policy choice as well. It would additionally be helpful to provide users of the IRIS files with the alternative numbers that are derived using the hepatic and renal endpoints.

Specific Comments on the IRIS summary:

- The IRIS summary should provide a link to the interagency comments associated with this final document. If an outsider were to go to IRIS to find an IRIS summary, they would have no way of knowing there were interagency comments available. We understand that EPA is working on this and we hope this change can be made in time for posting of this assessment.