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

July 21, 2011

While we recognize that EPA has made important and likely very substantive changes throughout the document, considering its size (1393 pages of main text plus 1593 pages of technical appendices) and the limited time provided for interagency science consultation, OMB focused only on EPA's response to the external 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:

- While we note that the peer review report is already final, for future assessments it would be helpful if the peer review report provided short summaries of the background of the expert reviewers. It may also be helpful if the peer review reports were to include information discussing any monetary funding (perhaps through a grant, cooperative agreement, sole-source agreement, or competitive contract) that the expert reviewer may have received from EPA's ORD. This would be consistent with generally-accepted disclosure practices for peer reviewers, particularly for reviews with significant public policy implications.

- It was difficult to review many portions of the response to peer review comments. For instance, appendix I at page 2 states that EPA made changes to address peer review comments and those changes can be seen in Section 3.5.7.4. However in both the clean and redline version provided to the interagency group, we cannot find a Section 3.5.7.4. Similarly there is no Section 3.5.5.2. Thus in these cases, and others as well, it is not clear what changes EPA has incorporated to address the peer review concerns. Appendix I unfortunately does not provide details as to the substance of the changes made. In addition to fixing the section numbers, it would be helpful to provide a more detailed description of the changes made in Appendix I.
    - Specifically, sections that are referred to in Appendix I as containing changed language which we could not find (and therefore could not review):

3.5.7.4	4.6.1.2.2	3.5.7.3.2
3.5.5.2	4.5.6.2.1	3.5.7.4
3.5.5.3	4.5.6.3.2.5	3.5.7.5
3.5.6.3	3.3.3.2	4.5.7.4
3.5.6.2	3.5.4.3	5.2.2.1.3
3.5.6.4	3.5.6.3.3	5.2.3.3.1
3.5.7.2	3.5.7.3.1	5.2.3.3.2

- Last week, EPA announced improvements to the IRIS assessments that would lead to: "reducing volume and redundancy of assessments; fuller discussion of methods and concise statements of criteria used in studies for hazard evaluation; clearer articulation of the rationale and criteria for screening studies; implementing uniform approaches for choosing studies and evaluating their findings; and describing the determinants of weight that were

used in synthesizing the evidence." We note that in 2006 NAS made recommendations that are similar to EPAs commitment (eg, using objective criteria, performing a sensitivity analysis, etc; see NAS 2006 for a full list of recommendations). Although we understand that such improvements will take time to implement and may not be possible for all the assessments currently underway, considering the importance of this assessment it would be helpful for EPA to transparently describe the changes that have been made to achieve the goals mentioned in the EPA announcement.

- Appendix I, the response to peer review and public comments, does not provide any response to the NAS review of 2006. Since this is such an important and complex assessment (as reflected by both an NAS review in 2006 and SAB review in 2010), it would be helpful if Appendix I also addressed the major recommendations of the NAS review.

- In their comments on the Mode of Action (MOA), SAB stated (see page 2-3 and elsewhere in the SAB report: "The Panel agreed that the weight of evidence supports a mutagenic MOA for TCE-induced kidney tumors. However, the Panel concluded that the weight of evidence also supported an MOA involving cytotoxicity and compensatory cell proliferation and including these may more accurately reflect kidney tumor formation than does a mutagenic mechanism alone. The combination of cytotoxicity, proliferation and DNA damage together may be a much stronger MOA than any individual components." EPA notes this on page 14 of Appendix I, however it is not clear what analysis and changes have been made to address this comment.
    - As a non-linear model, based on cytotoxicity and compensatory cell proliferation was found to have significant biological support, it is not clear why EPA continues to present only linear modeling. The EPA cancer guidelines (2005) at page 1-8 state: "When there are alternative procedures having significant biological support, the Agency encourages assessments to be performed using these alternative procedures, if feasible, in order to shed light on the uncertainties in the assessment, recognizing that the Agency may decide to give greater weight to one set of procedures than another in a specific assessment or management decision."
    - We would like to see EPA implement the recommendation from page 1-9 of the Cancer Guidelines: "If critical analysis of agent-specific information is consistent with one or more biologically based models as well as with the default option, the alternative models and the default option are both carried through the assessment and characterized for the risk manager."

- Considering the SAB comments above regarding a plausible mode of action for kidney tumors that does not involve a mutagenic mode of action, it seems that this would create uncertainty regarding the application of the age dependent adjustment factors (ADAFs). While SAB supported the use of the ADAFs for kidney tumors, some discussion is needed regarding their application since SAB also stated that "However, the Panel concluded that the weight of evidence also supported an MOA involving cytotoxicity and compensatory cell proliferation and including these may more accurately reflect kidney tumor formation than does a mutagenic mechanism alone. The combination of cytotoxicity, proliferation and DNA damage together may be a much stronger MOA than any individual components." In light of this SAB statement, a discussion of the uncertainty associated with using the ADAFs when there is a MOA that is not mutagenic is needed.

- While EPA states that they have added the recommended sensitivity analysis (in Sections 3.5.6.4 and 3.5.7.2, both of which we could not find), it is not clear how EPA has used the results of the sensitivity analysis to inform the final determinations and the confidence in them. Some discussion of this is needed in Sections 5 and 6.

Specific Comments on Appendix I:

- It is not clear how EPA addressed SAB comments that were not in bullets. For instance, page 15 of the SAB report states, in regard to liver effects: "Less repetition and better integration of these sections would improve the readability of the document." It is not clear what changes EPA has made to address this statement, and other similar statements that are suggestions from the SAB, but are not included in a bulleted recommendation.

- In response to public comments, on page 5 of Appendix I EPA states that they have added data on TCA bioavailability to the TCA sub-model of the PBPK model. However, EPA then states that this was not incorporated into the PBPK model. Since TCA is such an important metabolite, further description of why this information was not incorporated into the model would be useful. Since EPA has the data, it would also be useful to discuss what the impacts on the final values would have been had EPA incorporated the information.

- While EPA acknowledges that SAB would like EPA to do a quantitative analysis of the relative contributions of TCA and/or DCA to TCE liver carcinogenisis, on page 13 EPA states that this analysis is precluded due to a high degree of heterogeneity. It would be helpful if EPA provided language discussing the impacts of this variability on the final determination.

- At page 21, EPA chose not to implement the SAB recommendation which stated that: "Chapter 5 should include the information on POD derivation from Table F-13 of Appendix F, including approach, selection criterion and decision points." The NAS has recently commented on the need for clear articulation of selection criteria and decisions points, and EPAs current approach to describing studies (as was done in Chapter 5 of the TCE draft) and in this case SAB specifically suggested a clearer presentation. We suggest that EPA reconsider the SAB recommendation.

- On page 37 of the SAB report, there are clear recommendations regarding the level of certainty for dose metrics and endpoints. It is not clear where this is addressed in Appendix I and how this suggestion is incorporated in the toxicological review.

- Page 24, notes that some public commenters were concerned that the PBPK model led to 'double counting' of variability. It would be helpful if EPA responded directly to this comment to address the concern.

- Page 27, we do not agree with the EPA statement that an analysis which looks at validation of the quantitative risk assessments should be beyond the scope of the assessment. It is important that EPA look to 'ground-truth' (or validate) modeled risk values whenever available data may exist.

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.