Office of Management and Budget (OMB) Comments on the Interagency Science Discussion Draft IRIS Toxicological Review of Trichloroacetic Acid (dated July 2011)

OMB Staff Working Comments on EPA's Final Agency/Interagency Science Discussion draft Toxicological Review of Trichloroacetic Acid (TCA) and draft IRIS Summary (dated July 2011)

August 12, 2011

Due to 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.
    - In 2009 ORD/NCEA signed a Memorandum of Understanding with CalEPA/OEHHA to cooperate on the development of risk assessment methods and toxicological assessments. It thus seems a bit awkward that one of the expert reviewers is from the OEHHA office. We wonder if this reviewer can truly provide an independent assessment of EPAs work as the two offices are collaborating on the development of toxicological assessments.

- In certain cases, in preparing Appendix A, EPA seems to overlook some important comments from the peer reviewers. To improve transparency, it would we helpful if EPA acknowledged these comments and responded to them directly. A few examples are provided below:
    - Page 10 of the external peer review report: Dr. Fenner-Crisp notes that the MOA

discussion is “non-compliant with the Agency’s own framework described in the 2005 cancer guidelines.”

- Page 27 of the external peer review report: Dr. Stern notes that “the rationale presented for the selection of a BMR or 10% for continuous data is not valid.”
- Page 29 of the external peer review report: Dr. Pereira notes that “Also, the use of 10x the UF for human variation needs to be better justified…”
- As per comments below, it is not clear that EPA has appropriately portrayed peer reviewer comments regarding the cancer classification (see external peer review report pages 34-38).

- In light of the external peer review comments, it does not seem appropriate for EPA to continue to use the “likely to be carcinogenic” descriptor as EPA has presented it. In looking at the peer reviewer comments 6 of the 9 reviewers are very clear that as presented it is not an appropriate descriptor. In reviewing the comments (see external peer review report pages 34-38), it does not appear that any of the reviewers explicitly support EPAs determination and presentation. As per expert reviewer comments, we suggest that EPA reconsider their choice of descriptor. If EPA retains the descriptor (which is not our preferred choice as the majority of expert reviewers clearly rejected this classification), at a minimum, chapter 5 and 6 of the tox review and the IRIS summary should be explicit that the evidence is at the low end of the spectrum.
  - Of the 6 explicitly negative reviewers, it seems that Dr. Gaylor would be satisfied if EPA clarified that the characterization is appropriate to high doses only. Additionally, another reviewer (Melnick) would likely be satisfied if EPA clarified that the evidence for this descriptor was very weak and that it was at the low end of the scale compared to other chemicals with this descriptor. We do not see any of this suggested clarifying language in the revised tox review or IRIS summary.
  - Of the remaining three reviewers, Dr. Moore states that the conclusion is based on a lack of evidence, but does not comment on whether or not it is correct.
  - Dr. Rusyn states that the agency did a good job presenting their justification but does not comment on whether or not he agrees with it.
  - Dr. Salmon (from CalEPA) is the only reviewer to state that he thinks the data meet the criteria. Notably, Dr. Salmon also notes that “It is worth pointing out that current guidelines do not limit the characterization to this simple categorization, but also require provision of a narrative statement of the overall context of the finding, including comparison of the strength of the evidence and the degree of “likeliness” or “possibility” of an identified carcinogenic risk to humans.” On page A-12, EPA notes

that the data is at the low end of the spectrum, however we do not see this language incorporated appropriately into the tox review or the IRIS summary.

- EPA received some very critical comments on the mode of action discussion and the application of the EPA mode of action framework (see external peer review report pages 39-45). To address these comments, EPA appears to have made some minor revisions and edits to the text, including some clarifying text. However, it is not clear that the changes are sufficient to make the section consistent with EPAs guidance provided in the mode of action framework. In addition, multiple reviewers suggested the addition of tables, including tables that provide dose information, and EPA did not appear to add these tables. It is apparent that some of the expert reviewers were likely put on the panel because of their expertise and knowledge associated with the mode of action framework, thus it is not clear why EPA is not revising the document as suggested by these expert reviewers. We recommend that EPA revise the section as suggested and incorporate the recommended tables.

- Last month, 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." 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.

Specific Comments on Appendix A:

- Page A-1, in response to reviewer comments that the document was not concise, EPA states "the toxicological review was revised as much as possible to streamline the document and reduce redundancy." In reviewing the redline, it was not clear exactly what revisions were made to streamline and reduce redundancy. More clarity on the changes would be helpful.

- Page A-7, notes that the justification for the selection of the 10% BMR was reconsidered. However, it seems that EPA is using the same approach as in the proposal and retaining

the 10% BMR. Thus it is unclear what is meant by "reconsidered". Appendix A should provide a clear justification from EPA regarding rejection or acceptance of peer reviewer comments.

- Page A-8, in responding to the peer reviewer comment, EPA should explain why EPA has retained the determination that the data do not support a determination that TCA induces hepatocellular effects solely by peroxisomal proliferation. The reviewer also notes that the effects are not relevant to humans, however, EPA on page A-8 does not explain why the agency thinks they are relevant.

- Page A-11 through A-13, as per comments in the section above, EPA should revise the characterization of the reviewer comments regarding the cancer description, as well as the response.

- Page A-15, as per comments in the section above, EPA should make changes in the tox review to improve compliance with the EPA mode of action framework and should describe the changes in the appendix A response.

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.