OMB Staff Working Comments on EPA's Toxicological Review of 1,1,2,2-Tetrachloroethane and draft IRIS Summary (dated July 2010)

August 30, 2010

General Science Comments:

- OMB staff focused this review 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.

Scientific comments on Appendix A:

- Page 71 and elsewhere, EPA refers to results as "non-positive." It is unclear what is meant here. Please define. If EPA means results were 'negative' it is not clear why 'negative' is not used.

- Page A-3, in discussing Dr. Allen's comments regarding the NCI 1978 study and the request for more justification as to why it was not used, it is unclear why EPA, in response, has chosen to delete text in section 5.1.2.1, rather than provide the justification requested.

- Page A3, in discussing comments on questions B-2, it is not clear that EPA fully addressed the comment from Dr. Bruckner which states: "One should choose the most sensitive toxicologically-significant endpoint rather than merely the most sensitive endpoint." EPA should further discuss the toxicological significance of the endpoint chosen in this particular case. This should include discussion of any difference in significance between absolute and relative liver weight changes. It may also be helpful for EPA to discuss the basis for its supposition that the increased relative weight gain is an early effect on a continuum. EPA appears to state that evidence on this question is unavailable (page A4). If this is the case, then it is unclear why EPA did not choose other endpoints (such as changes in serum enzyme activity).

- Page A3, we also note that on page 31 of the peer review report, Dr. Bruckner reiterates that "I do not concur with the selection of increased relative liver weight as the response to model." EPA may thus want to clarify the statement on page A3 which states that "the reviewers generally agreed with the selection of increased liver weight…." as it appears that Dr. Bruckner did not agree with this choice.

Page A3, EPA does not appear to respond to Dr. Allen's comments regarding suggested improvements to figure 5-1. Please explain.

- Page A5, in discussing reviewer comments on question B4:

    - We suggest that EPA not paraphrase, or shorten, reviewers' comments. For example, Dr. Allen states: "Typically, dropping of doses is done only when issues of model fit are encountered, and even then they should have some strong justification." As Dr. Allen is

looking for strong justification, it would be helpful for EPA to provide this information in Appendix A as well as section 5.1.1.2

- In addition to his concern about dropping doses, EPA may want to also consider including his comments regarding how this leads "to some ludicrous statements in this document." EPA may also want to comment on each of the statements he discusses to provide justification or clarification.
- Similarly, the commenter also makes many suggestions for changes in Appendix B (see page 30 and 31 of the peer review report) regarding the actual benchmark dose modeling. It would be helpful for EPA to address these specific comments in Appendix A. As we did not see any redline changes in Appendix B, it would be useful for EPA to explain whether and how the expert reviewer comments have been addressed. Page A5 states that the modeling was changed, but we did not see any redline, nor any responses to the specific comments. If EPA has in fact run the comparative models (with and without dose groups dropped), EPA may want to do a quick check with the reviewers that had significant technical concerns with this section to ensure that they are comfortable with the new modeling that is presented to see if, based upon the new results provided, the reviewers concur with EPA's final choices. This could be particularly important as it appears this has led to the selection of a new critical effect.
- Unless the modeling is exactly as recommended, EPA may want to consider a quick peer review of the modeling that has been conducted. As the peer review report was completed over 6 months ago, perhaps EPA has done this already. If so, it may be helpful to mention this.

- Page A6 and A7 discuss the comment from Dr. Allen (as per page 33 of the peer review report) to use a comparative approach addressing major metabolites to help understand the uncertainty values. EPA's response is that such an evaluation is "outside of the scope". It is not clear why this is the case as such an evaluation may be very helpful in understanding the need for the uncertainty factors applied. EPA may want to add further text explaining why such an evaluation would not be useful to understanding the uncertainties in this particular risk assessment.

- Page A7, it may be helpful for EPA to explain why the information suggested by the expert reviewer, and added to Section 5.3 regarding halocarbons and their differential toxicity among species, was not considered sufficient to remove the toxicokinetic portion of the interspecies uncertainty factor. It would be very useful for EPA to present the criteria that are used to decide when full default uncertainty factors are needed and when they are not. Having this information available would be useful in this review, as well as others. It would also likely be useful to the expert reviewers as well. In this case, it is unclear why Dr. Bruckners suggestion was not adopted.

- Page A8, two reviewers expressed concerns about the "likely to be carcinogenic" classification, and it is not clear that EPA's response addresses their specific concerns regarding the weakness of the data (eg concerns with the mice liver tumor response, actual dose absorbed). More details explaining EPA's disagreement would improve clarity. Additionally, if EPA agrees that the classification is weak, this information should be provided in the text. As per EPA's cancer guidelines, text explaining the strength/weakness

of the determination would be a useful part of the discussion and this could also be carried forward to the IRIS summary (particularly in section II.A.1)

- Page A8, the response should also address the concerns stated by a reviewer regarding having the classification apply to "all routes of exposure." It is not clear where in the tox review this concern is addressed.

- Page A10/A11, in response to question D3, it is not clear that this section addresses:
  - Dr. Allen's suggestion that a UF approach be used for the cancer assessment
  - Dr. Bruckner's suggestion that the mode of action involves regenerative hyperplasia

Comments on the IRIS summary:

- Please see comments above regarding section II.A.1

Comment on the Peer Review Report:

- While we note that the peer review report is already final, we find it very helpful that the report provides short summaries of the background of the expert reviewers. The report also mentions the review panels the experts have participated in. 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.