Office of Management and Budget (OMB) Comments on the final Agency/Interagency Science Discussion Draft IRIS Toxicological Review of Hexachloroethane (dated April 2011)

May 19, 2011

OMB staff focused 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, 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.

- EPA received the peer review report November 12, 2010. Since then, it does not appear that EPA has addressed all of the peer reviewer concerns. We note that the IRIS process (May 20 2009) states that EPA will make revisions in 60 days before beginning internal EPA review (duration 45 days).Following are a few examples of comments for which we cannot see how they were addressed:

    - Reviewers stated that the document was "repetitious", "excessive', should provide a "table up front listing all the studies EPA considered relevant", "may benefit from a clearer and more comprehensive discussion of possible modes of action", "missed opportunities to integrate and synthesize information to help the reader integrate the data", and should include a "brief executive summary" (see peer review report page 5-9). We did not see any substantive changes to address these concerns.

    - Dr. Lock strongly urges (in emphasis he added on page 11 of the peer review report) that EPA go back to the NTP 90 day study to confirm or refute the increase in α2u-globulin protein using immunochemistry. Having this information is critical to determining whether the mode of action is relevant to

humans and is critical for the relevance of tumors. EPA simply states that this is a noted data gap. Considering the time EPA has taken to revise the report, it is not clear why EPA has not made the effort to conduct this study to gather this critical information. Would this study take more than 4 months for EPA to complete? Couldn't it have been conducted once EPA knew peer reviewers found it to be relevant and important?

  - On page A-4 EPA clearly notes four instances where reviewers requested further discussion of selections and rationale relating to the choice of the Gorzinski study. When we look at section 5.1.1 which discusses the choice of the study, we see no further elaboration (eg no redline changes from the external review draft) to address these reviewer comments.

  - On Page 13 of the peer review report Dr. Haber suggested that the chronic study would have the advantage and stated that the "toxicological review should discuss these opposing considerations in choosing the principal study, rather than simply defaulting to the lowest POD." Please address this comment in Appendix A and also add relevant discussion to the Tox review in section 5.1.4. It may be helpful for EPA to provide a table showing the positive and negative attribute of each study. From the discussion on page 111 of the tox review, EPA does talk about the limitations of the Gorzinski study, but then chooses it. If this is due to a policy choice to use the lowest POD, EPA should state this very clearly in section 5 and also in the IRIS summary. It is very important that risk managers and users of IRIS assessments understand where the science may take us and where policy comes into the determination. This seems like a policy decision.

- The EPA definition of chronic exposure (see http://www.epa.gov/iris/help_gloss.htm#c) is: "Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans (more than approximately 90 days to 2 years in typically used laboratory animal species)." As the 1985 Gorzinski study is 112 days which falls into the definition of chronic as defined by EPA, it is still unclear why EPA is treating this as a subchronic study. This study clearly meets the EPA definition of 'chronic' rather than 'subchronic'. Throughout the tox review this should be defined as a chronic study, not a subchronic study.

  - It is unfortunate that EPA did not explicitly point this out to peer reviewers. As per their comments, EPA revised the uncertainty factor (UF) for

subchronic to chronic from 10 to 3. Had EPA acknowledged that the study is 'chronic' as per EPA definitions, it is possible no UF at all would have been needed here. The three reviewers that recommended 2-4 or 3 instead of 10, may likely have suggested a value of 1, as did one reviewer.

- Regarding the database uncertainty factor for the RfC, five of the reviewers provided a quantitative comment. As noted on page A-10, two agreed with an UF=10 and three suggested an UF=3. It is not clear why EPA does not follow the advice of the majority of experts who provided comments. EPA's discussion on page A-11 provides a listing of missing studies, suggesting a default, checklist type of approach to the application of the database UF; while peer review comments suggest a more holistic weight of evidence approach to the UF. More discussion is needed as to why the reviewers expertise is discounted.

- On page A-12, EPA oversimplifies the reviewer responses to question C1. EPA states that five of the reviewers support the descriptor "likely to be carcinogenic". In looking at the peer review report, we note discrepancies. Dr. Costa, says this classification is "excessive" but "appears inevitable" and notes that it falls at the "low end of this group". Dr. Haber agrees that it is appropriate but caveats it by noting that "the weight of evidence is on the low end of the spectrum for this descriptor." Dr. Lash states: "although I think calling HCE a "likely carcinogen in humans" would seem to be overstated, consideration of the U.S. EPA cancer guidelines makes this the only plausible choice, although this reviewer is not entirely satisfied with such a choice." Page A-12 should be revised to better capture the reviewers concerns. More importantly, it is unclear why EPA has not revised the tox review to clarify throughout that the data fall at the low end of the spectrum for this descriptor. The 2005 Cancer Guidelines state: "Descriptors represent points along a continuum of evidence; consequently, there are gradations and borderline cases that are clarified by the full narrative. Descriptors, as well as an introductory paragraph, are a short summary of the complete narrative that preserves the complexity that is an essential part of the hazard characterization. **Users of these cancer guidelines and of the risk assessments that result from the use of these cancer guidelines should consider the entire range of information included in the narrative rather than focusing simply on the descriptor.**" (emphasis is provided in the cancer guidelines).

    - As per the expert reviewer comments and the Cancer Guidelines, the tox review and IRIS summary should clearly reflect the majority of reviewer

concerns that the weight of evidence is on the low end of the spectrum for this descriptor. This information should be provided whenever the descriptor is mentioned.

Specific Comments on Appendix A:

- Page A-1, while EPA mentions the concern by the reviewers that the document was repetitious and needed more synthesis, EPA does not provide a response to these comments.

- Page A-2, EPA notes that one reviewer stated that the data on renal cancer is consistent with a mode of action (MOA) that is a combination of α2u-globulin nephropathy and exacerbation of chronic progressive nephropathy (CPN). EPA states that this is addressed in section 4.7.3.1. However, upon review it is not clear that EPA has made any changes to this section to reflect the reviewers comment. It would be helpful for EPA, here and throughout Appendix A, to clearly articulate changes that were made in response to reviewer comments, and where EPA believes no change was necessary. If EPA is rejecting the reviewer comment that the MOA is a combination of α2u-globulin accumulation and CPN, EPA should state this more clearly.

- Page A-3, once again EPA discusses what they have concluded, but EPA does not address why they seem to disagree with the peer reviewer conclusion that the MOA is due to a combination of CPN and α2u-globulin accumulation. More clarity regarding why EPA disagrees with the peer reviewer would be useful.

- Page A-4, as per comments above, in the response, EPA states where the topic areas of concern are discussed in the tox review. However when we look at the tox review (sections 5.1.1 and 5.1.2, we see no substantive edits to address the reviewers comments which all asked that EPA provide further discussion and rationale for the choices made.

- Page A-9, in response to the comments from Dr. Haber, “EPA states that a literature search did not identify any structure-activity relationships relevant to the neurobehavioral effects of

- HCE exposure." Despite this negative finding, it would be helpful for EPA to include in the tox review, as suggested by Dr. Haber, a discussion of the striking difference in the target between the oral and inhalation studies and what the causes may be. Can EPA also please provide details of the literature search that was conducted and yielded no relevant information? It would be helpful to make this supporting information (describing the search) available in an appendix of the tox review.

- Page A-9, in response to question B3, EPA should not state that all reviewers thought the NOAEL approach was justified. As per the peer review report (see page 29), Dr. Kodell did not think EPAs reasons were valid without qualifications. He stated: "I do not believe it has been clearly described why BMD modeling could not be done in this case."

- Page A-13, once again EPA discusses what they have concluded and where this information is discussed, but it is not clear what, if any, changes EPA has made in response to the peer reviewer concerns and comments. Despite significant reviewer comments in response to this question, we see very little redline in the relevant sections of the toxicological review.

- Page A-14, EPA's statement that five reviewers "agreed with the selection" of the NTP (1989) study is an oversimplification. It does not capture comments such as those from Dr. Haber noting that "The male rat kidney tumors are a reasonable basis for the quantitation, recognizing the uncertainties regarding human relevance." Please revise the framing to capture the nuances of the reviewers comments.

- Page 14, EPA accurately notes that one reviewer questioned the use of linear low-dose extrapolation. Please provide a response to this concern.

- Page A-14, EPA states that a reviewer recommended deriving the oral slope factor from the hepatocellular carcinomas in male mice. A response to this comment should be provided. We note that according to the peer review report, at page 39, at least two reviewers thought these were the best data for oral cancer modeling. On page 108 of the draft tox review, EPA presents the values for these tumors (table 5-6) but it is not clear why EPA does not use these data. Considering the repeatedly noted uncertainties regarding the relevance of the rat kidney data by the peer reviewers with the most expertise in this area, it is not clear why EPA did not use the male mouse data instead. Does EPA think the rat kidney data are relevant or is it a case that EPA does not have sufficient data to show that they are not relevant. This is an important

distinction which should be made. It seems as though the peer reviewers do not think they are relevant, but also acknowledge that data gaps do not allow for proving this. However, this does not make them scientifically relevant, this makes it uncertain. If it was a policy decision to use the lowest POD, regardless of confidence in the relevance, EPA should state this clearly.

Specific Comments on the toxicological review:

(In addition to comments below, please see comments above regarding general comments and Appendix A and make appropriate conforming changes in the tox review and IRIS summary)

- Page xiii, please clarify that the document was provided for interagency science discussion. The IRIS process document does not call this a review and language in the tox review should be consistent.

- Page 66 (and elsewhere) as per reviewer comments please clarify that the while HCE is classified as "likely to be carcinogenic", the data fall at the low end of the spectrum for this category.

- Page 66, considering reviewer comments regarding the relevance of pheochromocytomas in male rats (see peer review report at page 36 where Dr. Lash states: "Additionally, the relevance of pheochromocytomas is subject to considerable uncertainty as well, and this seems to be minimized by the current document."), it is not clear why EPA is including them as supporting the cancer justification.

Specific Comments on the IRIS summary:

- The IRIS summary should provide a link to the interagency comments associated with this final document. It is not clear how EPA is making interagency comments publicly available if no link from the final IRIS summary or tox review is provided. 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.

- It is not clear why the IRIS summary does not include the BMD modeling results for the male mice. Even though EPA has not chosen this endpoint, due to concerns about relevance and the role of α2u-globulin, this endpoint should be carried forward and presented, perhaps in the supporting information section, for risk managers that may choose to use it. The discussion in the IRIS summary should also include clear

discussion regarding the question of the relevance of the rat kidney tumors to humans. It is not clear that EPA has articulated the state of the science regarding the data gaps that do not allow EPA to either prove or disprove relevance. EPA needs to be clear that due to the data gaps, EPA is invoking a policy choice to consider them relevant and to use them for the point of departure.