

**OMB Staff Working Comments on EPA's Toxicological Review of Pentachlorophenol and draft IRIS Summary** (dated July 2010)

September 3, 2010

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.

**General Science Comments:**

- In a few places we are concerned about how EPA treats default assumptions and their impact on uncertainty.
  - Page A-5, in regards to the site-concordance issue, EPA states: "Therefore, the lack of site concordance between animals and humans is not considered to be a significant uncertainty in the assessment." It is not clear to us why the default of assuming relevance would negate any uncertainty in the assessment. Wouldn't it be more correct to say that because of uncertainty, EPA takes a conservative health protective approach and assumes that all tumors are relevant regardless of site concordance differences?
  - Page A-10, in response to a comment that EPA compare different cancer modeling approaches to better evaluate the sensitivity of the selected analysis, EPA appears to cite only the default approach suggested by the cancer guidelines. It is not clear how EPA has responded to the suggestion of a sensitivity analysis to inform the final outcome. While we recognize EPA's science policy approach of using the default, it is not clear why this would preclude presentation of other model outcomes in a sensitivity analysis as suggested by the expert reviewer.
  - Page A-11, EPA states that there is "insufficient data to establish significant biological support for a nonlinear approach." At least one reviewer appears to disagree (ie, does think there is sufficient biological support for the nonlinear approach). It would be helpful if EPA could clarify exactly what is missing to find the reviewers comments compelling. EPA may want to perhaps recognize that there is a difference between acknowledging significant biological support and then having enough data to actually conduct nonlinear modeling.
    - Related to this, on page A-15, EPA discusses alternative mechanisms and notes that they are not fully understood. It would be helpful for readers if EPA clarified that the cancer guidelines suggest that the guidance for presenting alternative modeling analyses is that there be "significant biological support" not "full understanding". A similar clarification would be helpful on page A-17 (line 12-17) as well as on page A-20 (line 1-5).

*Specific Comments on Appendix A:*

- Page A-5, the response regarding question A4, does not appear to capture and respond to comments from Dr. Bartell to conduct alternate dose-response modeling to inform the degree of uncertainty associated with low-dose extrapolation (as per page 13 of the peer review report). Under other questions EPA responds to questions about the choice of

*IRIS STEP 6 INTERAGENCY COMMENTS (OMB)*

BMD model chosen, but a response relating to using this information to inform the uncertainty appears to be missing in the other responses EPA cites on lines 21-22. We did not see where the responses to some of Dr. Bartells other comments were addressed. These are comments relating to: the EPA statement on page 171 of the draft tox review, assumptions used to derive equation 2, and the impact of the choice of prior distribution on uncertainty in the combined analysis. Similarly, Dr. Stayner (as page 14 of the peer review report) also suggests a sensitivity analysis be conducted and we were not clear where EPA addresses this concern in Appendix A and the body of the toxicological review.

- Page A-5, in describing comments on question B1, it was not clear that EPA has captured and responded to Dr. Stayners comment (as per page 15 of the peer review report) regarding whether EPA's choice is scientific or based on policy.
- Page A-9, regarding question D1, it seems that two reviewers had comments regarding the clarity of the descriptor and one reviewer was unable to find it. In the toxicological review, we could not find any redline changes that addressed these concerns. It seems as though the response on page A-9 reiterates some of what is in other parts of the toxicological review, but it is unclear how this provides more clarity in the main text of the toxicological review.
- Page A-11, in responding to comments regarding question D3, it would be helpful if EPA clearly responded to Dr. Williams comment regarding the fact that the mouse liver cancers are species specific and justification for their use is warranted. Such a response would be helpful in the main text of the toxicological review as well. Similarly, it is not clear that the comment regarding a mode of action including tumor promotion is responded to.
- Page A-13, in the response to question D5, it is not clear how this response addresses Dr. Bartells comments (as per page 32 of the peer review report) regarding the choice of tPCP over the EC-7 formulation.
- Page A-13, in describing comments on question D6, please confirm that four reviewers found the approach justified. Also, please respond to reviewer's comments regarding the assumption of independence. Page A-14, in responding to comments on question D6, EPA notes that there is a comparative bootstrap analysis which is not shown in the document. As an expert reviewer asked about this, can it be included in an appendix?
- Page A-20 thru A-22. In several places, the appropriate interpretation of statistical significance and how it relates to the cancer guidelines is unclear. Please clarify, perhaps with direct quotes from the guidelines. (See, e.g., p A-20, line 34-37, p A-21, lines 1-2, and p A-22, lines 15-18.)
- Page A-23, line 1-6, in addition to providing a general response, it may be helpful if EPA responds specifically to the concerns in the context of the three studies cited by the commenter.

## IRIS STEP 6 INTERAGENCY COMMENTS (OMB)

- Page A-24, line 12-14, it is not clear how this response addresses the commenters concerns regarding consistency. Shouldn't evaluation of magnitude and precision of estimates also include evaluation of statistical significance and the consistency of statistical significant findings?
- Page A-26, line 20-22, more clarity in this response would be helpful. We could not understand how this addressed the commenter's concern.

### *Specific Comments on Other Sections in the Toxicological Review:*

(page numbers refer to the pages in the redline that was provided)

- Page 27, line 13, EPA has added a statement regarding relevance of formaldehyde to lymphopoietic cancers. Is there a citation for this new clause? It is also unclear how this statement is relevant to the pentachlorophenol review.
- Page 33, line 36-38, it may be helpful for EPA to clarify the justification for assuming frequency-matching and the impact it has on the analysis.
- Page 143, line 34-35, as it is always helpful to provide readers with information regarding other assessments related to toxicity of the compound of concern (in this case pentachlorophenol), it is unclear why EPA has deleted the link to TOXNET as this information could be useful to users of the toxicological review.

### *Editorial Comment:*

- In general, we find that Appendix A seems to lump together, in paragraph style, all the comments responding to a particular question and then lumps together the response. Clarity would be much improved, and it would be easier to follow EPA's responses, if a response was provided after each specific comment relating to the particular question. Additionally, throughout Appendix A, the way the comments are presented, it often seems as though there were more than 5 reviewers. For instance on page A-1, EPA appears to refer to 6 reviewers. If EPA could clarify when multiple comments came from the same commenter this would be helpful to readers.