

OMB Staff Comments on Cerium Final draft Tox Review and Final Draft IRIS Summary

General Comments:

OMB staff focused this review on EPA's responsiveness to the 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 98, in discussing the response to B1, it would be helpful if EPA mentioned the reviewers' response to EPA's decision to not derive an RfD. Similarly, in discussion of C1 and elsewhere, EPA mentions where there is dissent, but does not discuss reviewer agreement.
- Page 100, and elsewhere (particularly on page 110), instead of referring to "several reviewers", it would be helpful to clarify the number of reviewers who had a comment as then the readers will have a better understanding of which opinions were held by the majority or minority of the review group.
- It appears that 4 of the 5 reviewers disagreed with EPA's final choice of lymphoid hyperplasia for the point of departure. After a 2nd and 3rd round of review of the revised document, the majority of reviewers continued to disagree with EPA's final choice.
 - We note that this is a bit confusing as after the first round of review EPA did make a change to be consistent with reviewer recommendations. For instance in the July 2008 peer review report (at page 6) a reviewer states: "the alveolar response is much more defensible as relevant to progressive adverse effects." EPA made revisions to the tox review based on the majority of expert reviewer recommendations. EPA then sent the document back to peer reviewers for review and received endorsement, from all peer reviewers, for this change in October 2008. This is not clear in the discussion on page 108. While one reviewer did ask for more clarity, it seems that all the reviewers agreed with EPA's approach to use alveolar epithelial hyperplasia as they thought this was more consistent with the mode of action information.
 - However, after this point in time (after the October 2008 review), EPA then reverted back to the original choice of lymphoid hyperplasia. Further scientific rationale for why EPA does not agree with the suggestion of using alveolar epithelial hyperplasia would be helpful in this section and in section C2.
 - In a final email to reviewers (dated 4/24/09) EPA states that this endpoint was chosen because it "represents the most sensitive endpoint occurring at the lowest dose that was indicative of lung and lymphoreticular system toxicity." The panel members recommended the use of epithelial hyperplasia, over the lymphoid hyperplasia, based on an understanding of the hypothesized mode of action. It would be helpful to have further discussion of this issue (mode of action) specifically.
 - In addition, in the tox review and IRIS summary EPA should be clear about whether or not the chosen critical effect represents an adverse effect or is a precursor to an adverse effect. This is important information for risk managers and thus more clarity in the IRIS summary would be useful. Currently the endpoint is called a 'critical effect' and whether or not it is considered adverse is not clear.

IRIS STEP 6 INTERAGENCY COMMENTS (OMB)

Comments on the Tox Review:

- Page 2, EPA states “The relevant literature was reviewed through June 2007”. EPA may want to consider updating the literature review to ensure that the science is not outdated before release (which will hopefully be in the fall of 2009).