

IRIS STEP 6 INTERAGENCY COMMENTS (OMB)

OMB Staff Working Comments on EPA's Final Agency/Interagency Science Discussion draft Toxicological Review of Tetrachloroethylene (PCE) PBPK revisions (sent to OMB sept 20, 2011)

Sept 28, 2011

We were provided a redline version of pages 3-31 through 3-48, pages 5-20 through 5-21, pages 5-29 through 5-35, and 5 pages of appendix A relating to section A.6. OMB focused only on EPA's response to the PBPK 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.

EPA did not provide any responses to public comments that may have been related to PBPK modeling.

General Science Comments:

- It is not clear that EPA has fully captured the peer reviewer comments and has provided responses to all of them. A few examples are provided below. We recommend that EPA make appropriate revisions to respond to all the comments.
 - In describing peer review comments on question A.6.1, EPA provides some quotes from two reviewers that are positive, but does not provide other comments that are negative. For instance Dr. Byczkowski (at peer review report page 3) notes that the model “is not clearly and transparently described in the reviewed document”. Similarly we did not find text from Dr. Byczkowski stating that EPA appeared to be “adequately responsive” as EPA states in section A.6.1.
 - In response to A.6.2, EPA states that they have added documentation to how the AUC was calculated to Tables 3-2 to 3-5. In looking at the redlines provided, we could not find any edits that clarified this.
 - In response to A.6.2, Dr. Byczkowski strongly suggested that PA follow documentation in the 2006 EPA PBPK Approaches document, especially section 3.6.3. In the EPA response to this comment, EPA notes that documentation regarding uncertainty factors is already provided and that no additional documentation has been provided. As section 3.6.3 relates to model documentation, in the chapter on “evaluation of predictive capacity”, it's not clear how EPA has responded to the peer reviewer comment.
 - In response to A.6.2, Dr. Mumtaz states, regarding blood brain barrier assumptions: “Those assumptions would be most unlikely and certainly could result in an unrealistically conservative RfC.” It is not clear that EPA has captured this comment and provided a response. EPA states that any uncertainties would not impact route-to-route extrapolation, however EPA does not address the likelihood of the assumption that blood levels throughout the body would also be similar in the brain.