

## **OMB Staff Comments on Carbon Tetrachloride Final draft Tox Review and Final Draft IRIS Summary**

### **General Comments:**

OMB staff focused this review on EPA's responsiveness 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 A-25, in discussing question C1, EPA mentions that one reviewer commented on the certainty related to the pheochromocytoma relevance to humans. The section quotes a comment from Dr. Byczkowski. We note that Dr. Kamendulis also commented on this (see peer review report page 85). Dr Kamendulis agreed with the sentence that was on page 216 of the external review draft which stated that "the finding of pheochromocytomas...may present a less certain human cancer risk than does the finding of liver tumors in experimental animals." EPA may want to mention this in the comment. In addition, in the response, EPA provides some language from the cancer guidelines discussing how site concordance is not always presumed. While we agree with this statement, in light of comments from 4 peer reviewers (Dr. Lash also questions the relevance of these tumors in humans, see page 104 of the peer review report, and Dr. Soni (see page 115) also comments on the species specificity of these tumors and states that "linear modeling may not be appropriate") questioning the relevance of these tumors, it would be helpful for EPA to further explain the scientific basis for including these tumors in their evaluation.
- Page A-26 through A-28, EPA's description of the comment accurately captures that three reviewers questioned a MOA (mode of action) that included genotoxicity at low doses. EPA's response is that there is insufficient data to determine whether or not carbon tetrachloride is genotoxic at low exposures, and EPA is thus using the default assumption that linear modeling is appropriate. We note that the description of the comments does not seem to capture the expert reviewers concern with the MOA and their judgment regarding the likelihood of there being a genotoxic MOA at low doses. For instance, Dr. Byczkowski states (page 15 of the peer review report) that "the genotoxicity at low exposures is not a very plausible mode of CCl<sub>4</sub> action."; Dr. Kamendulis (at page 86) states that "in light of this biological response, the potential for carbon tetrachloride to exhibit genotoxicity at low exposures is unlikely."; and Dr. Soni (at page 114) states, in referring to a non-genotoxic mode of action, "the available evidence supporting this second mode of action is more convincing and well presented in the review, but both modes appear to contribute." It would be helpful if EPA addressed these comments more directly in their determination that genotoxicity at low doses cannot be excluded.
- .Page A-29, in response to the question regarding whether linear or non-linear modeling is preferred, EPA states that three reviewers agreed with the presentation of both. EPA's response is that both approaches are maintained. Two reviewers also suggested that EPA provide a judgment as to the relative strength of both approaches. EPA's response is that "EPA does not believe that providing judgments as to the relative strength of the two approaches is scientifically supported". However we note that the IRIS summary presents

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only the results from the linear modeling, thus making it appear that EPA has in fact made a judgement call. The scientific basis for this judgment is unclear. If we look at the peer review comments regarding which approach is more scientifically sound, it appears that 3 of the 6 reviewers supported non-linear modeling for liver cancer as preferred over a linear approach (see Dr Byczkowski comments at p, 17 & 19, Dr. Kamendulis comments at p.87 and Dr. Soni comments at p. 115). If EPA does not believe it appropriate to make a judgment call, EPA should state that both approaches are scientifically sound and supported by expert reviewers and both approaches should be presented as scientifically plausible approaches for cancer assessment in the IRIS summary.

- Page A-31 through A-32, in describing the comments relating to whether the pheochromocytomas should be quantified and if so quantified by a linear approach, EPA states that two reviewers agreed with the approach (acknowledging that one of these two suggested that EPA present the results excluding these tumors), three reviewers did not agree with the EPA approach, and one reviewer did not directly address the question. In looking at the description of the response from this latter reviewer, it looks like this is the comment of Dr. Byczkowski, who stated that the relevance of these tumors is “highly uncertain.” In response to charge questions C5 and C6, it is clear that Dr. Byczkowski finds the linear approach, to “result in exaggerated risk estimates in comparison to the alternative approach” and (see page 19) he further states that “the data for the mouse pheochromocytomas with an uncertain human relevance should not be used in the derivation of cancer risk value.” Thus it seems that Dr. Byczkowski also does not support EPA’s linear modeling approach for pheochromocytomas. EPA states that it disagrees with reviewers who considered the use of the pheochromocytoma data to be unsupported. We are concerned that the assessment thus appears to be based on a linear modeling approach that is not supported by 4 of the 6 peer reviewers. In addition, EPA does not fully address the concerns relating to the linear modeling and quantification of these tumors. It would be helpful if EPA could further describe the scientific basis for the linear modeling of these tumors in light of the peer reviewer comments. EPA should also consider making changes to the assessment that are consistent with the majority of the expert reviewer opinions.
- Page A-34, In response to the charge question specifically inquiring about the nonlinear approach, for liver cancer, EPA clearly states that the majority of reviewers (4/6) supported nonlinear modeling as the more scientifically defensible approach. Thus it is unclear why in the response, the tox review, and IRIS summary, EPA presents the nonlinear modeling as an alternative approach and relies on the cancer guidelines use of linear modeling as the default approach. The majority of expert reviewers were very clear that the science justifies non-linear modeling, thus it is unclear why EPA is defaulting to a linear approach. EPA is setting the bar very high and looking for perfect information before moving away from the default. It was our understanding that with the new, 2005, cancer guidelines, EPA would consider the science first and then if it was inadequate, EPA would invoke the default approaches. EPA has taken the choice of modeling approach to their expert reviewers and the clear majority stated that the science supports nonlinear modeling. Thus it is unclear why EPA is defaulting to the linear default. The peer review comments do not support a finding of “insufficient evidence to establish a mode of action”, they appear to support a majority opinion of non-linear modeling as being supported by the scientific data. The scientific peer review process

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should be used to inform EPA's use of default approaches and thus we suggest that EPA follow the majority opinion of the expert reviewers and therefore present non-linear modeling as the preferred approach.

- Perhaps since EPA is making a finding of “insufficient evidence to establish mode of action”, EPA may want to go back to the peer reviewers and ask them if they agree with this finding. Unfortunately, the charge the peer reviewers responded to asked them to comment on what EPA considered to be two plausible mode of action approaches. It did not give the option of insufficient evidence. Since most of the reviewers supported a non-linear modeling approach, the scientific justification for determining that “insufficient evidence exists” is unclear.
- Page A-35, in the first comment/response to question C 6 regarding the scientific plausibility of linear extrapolation, it is clear that 4 of the 6 reviewers do not support linear modeling as the preferred approach (2 say it should be an alternative, 1 says don't use it at all, and 1 says its difficult to defend). Thus, as per comments above, it is unclear why EPA is selecting linear extrapolation as the default approach and we suggest appropriate revisions or consideration of further peer review.
- Page A-41 through A-42, as per comments above, and in response to question C8 regarding EPAs selection of liner low-dose extrapolation due to uncertainty in understanding the cancer MOA as well as other bioassay evidence, EPA's scientific justification for continuing to use a linear modeling approach, in light of the majority of expert reviewers not supporting this approach, is unclear. While EPA never asked the expert reviewers if they found the evidence “insufficient to establish the MOA”, it is clear that the majority believe that non-linear modeling is most appropriate. This implies that there is enough scientific information available to make a credible, scientifically sound determination as to the most appropriate MOA. It is unclear why EPA has taken the approach throughout appendix A, and in the tox review, of stating that there is insufficient information on the MOA and thus the default linear modeling is needed. This approach seems to negate all that was learned during the expert peer review process.

### **Scientific Comments on the Tox Review:**

- Page xvii, under “reviewers”, Suggest simply stating the document is “circulated for review by EPA scientists and interagency reviewers from other federal agencies” rather than stating that it “has been reviewed”. Since they are all now publicly available, it may also be useful to provide a link here to where there interagency and comments can be found.
- Page 1, EPA has edited the text to say that the oral slope factor and inhalation unit risk values represent “a plausible upper bound.” The addition of “a plausible” does not appear to be consistent with the definitions in the IRIS glossary. Is there a citation that EPA can cite that represents official Agency position which determined that these are indeed “plausible” upper bounds?

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- Page 2, states that the literature was reviewed through February 2009. Considering that 10 months have passed, EPA may want to consider conducting a quick review to see if there are any new studies which can be considered.
- Sections 4, 5, and 6: suggest making changes consistent with comments above regarding peer review comments on the mode of action (non-linear vs linear modeling) and relevance of pheochromocytomas.
- Page 167, in discussing the mode of action for the pheochromocytomas, EPA states that the mode of action is unknown. As per comments above, it is unclear that the majority of peer reviewers support this finding.
- Page 244, considering that the majority of peer reviewers questioned the relevance of the pheochromocytomas in humans, it is surprising to see that the inhalation unit risk value is derived from these tumors. EPA states: “This data set was judged to be applicable, scientifically sound, and yielded the highest estimate of risk.” Considering the expert comments received, it would be useful for EPA to provide a stronger scientific basis for relying on these tumors for quantification. In addition, as suggested by a reviewer, it would be useful for EPA to provide what the risk value would be if these tumors were excluded so that the risk managers can see the impact of their inclusion.

### **Scientific Comments on the IRIS Summary:**

- The IRIS summary (and the tox review) should have a section which provides a link to, and information on, where readers can go to see the public docket (including interagency and public comments) related to the assessment.
- As per comments on Appendix A, it is unclear why EPA is presenting only the linear modeling approach for the cancer risk values. If EPA determines that changes in the tox review, to reflect external reviewer comments are appropriate, then the IRIS summary should present the non-linear modeling results as recommended for cancer risk evaluations. If EPA is not making a judgment as to which is better, then the IRIS summary should present both approaches as equally scientifically plausible approaches.

### **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 EPA 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.