

IRIS STEP 6 INTERAGENCY COMMENTS (OMB)

OMB Staff Working Comments on EPA's Final Agency/Interagency Science Discussion draft Toxicological Review of Dichloromethane (DCM) and draft IRIS Summary (dated June 2011)

Aug 12, 2011

Due to the limited time provided for interagency science consultation, OMB focused only 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, for future assessments 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.
 - In 2009 ORD/NCEA signed a Memorandum of Understanding with CalEPA/OEHHA to cooperate on the development of risk assessment methods and toxicological assessments. It thus seems a bit awkward that one of the expert reviewers is from the OEHHA office. We wonder if this reviewer can truly provide an independent assessment of EPA's work as the two offices are collaborating on the development of toxicological assessments.
- We applaud EPA for having very specific questions regarding the pharmacokinetic modeling and for having multiple reviewers with this expertise. In fact, the expert panel has some of the US's best modelers. It is therefore surprising to see that in many cases EPA rejects their comments. Some specific cases are noted in the details below. It may be helpful for EPA to take a second look at the expert reviewer comments to see if they can be more receptive to their scientific suggestions.
- Similar to the comments above, we recognize that Dr. Kamendulis was likely on the panel due to her expertise in hepatotoxicity. We note that she had significant concern with EPA's choice of study and endpoint for the RfD, but stated that "However, this reviewer would be satisfied if the limitations and deficiencies of this study and endpoint were sufficiently documented in the draft document."
 - EPA stated that such information was added to section 5.2.1 however we did not see this information in the redline provided. We suggest adding such a discussion and carrying it through to Section 6 as well as the IRIS summary.
 - Dr. Kamendulis (peer review report page 31) also noted that EPA "does not describe whether there is any biological significance for this endpoint." From her comments, it appears that she thinks it does not have a correlate to human exposure. EPA states that they have addressed this comment, but we note that section 5.2.1 states that "Hepatocyte vacuolation was considered a toxicologically relevant effect since the effect was characterized as correlating with fatty change (Burek et al., 1984) or as a vacuolation of

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lipids in the hepatocyte (Nitschke et al., 1988a). It is not clear what is meant by ‘toxicologically relevant’. Does EPA mean this is adverse or perhaps just a precursor to other effects? EPA notes that this could lead to more serious effects, thus it seems as though it is a precursor effect. Therefore, EPA should clarify in the toxicological review and IRIS summary that the endpoint used for the RfD is not an adverse effect but is a precursor effect. Such a change would likely move EPA in a direction that is more responsive to Dr. Kamendulis’ comments on this topic.

- In light of these expert reviewer comments, we also suggest that EPA re-evaluate the confidence in the RfD derivation.
- Dr. Kamendulis also had concerns with the derivation of the Oral Slope Factor (OSF).
 - Regarding the OSF, Dr. Kamendulis stated: “The EPA’s reanalysis used a different statistical approach and control groups than used by the authors, which lead to a very marginal statistical significant increase in the highest dose group. I do not agree with this approach and agree with the original interpretation by the authors who concluded that dichloromethane was negative for carcinogenicity by the oral route of exposure. Therefore, this study is inappropriate to use for the derivation of an OSF for dichloromethane.” It is not clear that EPA has sufficiently addressed this concern and explained why EPA’s different approach was taken. Although only Dr. Kamendulis and Dr. Bruckner opposed EPA’s approach, considering their expertise, further rationale is needed for why EPA has not made changes they suggested.
- Dr. Moore, in responding to the majority of questions (those relating to PBPK modeling, the RfD derivation and the RfC derivation) simply commented that the question was “outside my specific expertise.” Dr. Moore is an expert in genotoxicity and that is likely why she was added to the panel. Of all the reviewers, she is the most qualified to answer the question regarding whether or not DCM induces cancer through a mutagenic mode of action. In response to this question (C2) she clearly states, after providing much background information: “Therefore, I do not believe that there is sufficient data to prove a mutagenic MOA for DCM. In looking at the alternative MOAs, there appears to be no evidence to strongly conclude that the MOA has a nonmutagenic MOA. So, unfortunately, one must conclude that while there is evidence to indicate that the MOA for DCM might be a mutagenic MOA, it is not possible to conclusively define a MOA for tumor induction. One then has to conclude that the MOA for DCM induced tumors is unknown.”
 - It is surprising that EPA has not changed the conclusion based on this expert’s opinion and notes that “EPA disagrees with one reviewer’s determination.” Rather than place this reviewer in the minority, we suggest that EPA, considering this reviewer’s expertise and reason for being on the panel, consider revising its conclusions regarding a mutagenic mode of action.
- In certain cases, in preparing Appendix A, EPA seems to overlook some important comments from the peer reviewers. It would be helpful if EPA acknowledged these comments, responded to them directly in Appendix A, and made appropriate changes in the tox review and IRIS summary. A few examples are provided below:
 - Page 9 of the external peer review report: Dr. Bruckner states: “The accounts of relevant scientific investigations are presented objectively, yet the summary sections and

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rationales for decisions do not provide balanced overviews for the reader to consider in assessing the weight of scientific evidence on particular questions or subjects. Only findings/evidence in support of EPA's judgements and courses of action are presented."

- Page 12 of the external peer review report: Dr. Krishnan states, "Based on the arguments and simulations presented, it would appear that the model version D is the best. Such a conclusion should preferably be based on comparative simulations of dose metrics as well as some assessment of quantitative fitting analysis. In this regard, there does not appear to be a priori strategy of model averaging or a quantitative method for choosing the best model, it seems." He also states (page 13): "Whereas it is likely that some models in peer-reviewed literature just do not meet the requirements of an assessment, there has to be a strong case to significantly rework the model (or re-parameterize) during the evaluation and use in risk assessment, as is the case here."
- Page 14 of the external peer review report: Dr. Mehendale states, "No matter how sophisticated the PBTK model is for DCM, it is fraught with daunting errors, unless the inhibition of CYP2E1 by CO is fully taken into account."
- Page 20 of the external peer review report, Dr. Krishnan, in reiterating his comment that the scaling factor is not justified, provides two citations from the literature for supporting his argument. It is not clear where EPA discusses the studies he points to.
- Page 21 of the external peer review report, Dr. Krishnan states: "While it is clear that that intent is to derive toxicity values that are protective of the most sensitive populations, it appears that the estimates may be overly conservative..... At least in the case of the RfD derivations, using the 1st percentile provides a HED value that is well below (~7-fold) that which would be derived if an uncertainty factor of 10 was applied (1.51 versus 0.216)."
- Page 26 of the external peer review report, Dr. Bruckner states, in referring to BMD modeling and PBPK modeling, "This approach and several assumptions result in a quite conservative RfD." (emphasis added by Dr. Bruckner)
- Page 35 of the external peer review report, Dr. Bruckner states, "I do not believe, however, that they have given a full account of pertinent information for and against their rationale for deriving an OSF, so readers are not given a balanced perspective." (emphasis added by Dr. Bruckner) At page 36, he states "Sound scientific judgment should be utilized in classifying potential human carcinogens and conducting cancer risk assessment, rather than consistently making worst case assumptions and reaching decisions based on entrenched policy. In light of knowledge available from the extensive human and animal database on DCM, I think it is a big "stretch" to classify DCM as a likely human carcinogen. Possible human carcinogen is much more appropriate for a chemical with limited evidence of animal carcinogenicity and largely negative epidemiology data." (emphasis added by Dr. Bruckner)

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- Page 42 of the external peer review report, Dr. Moore states, in referring to mode of action “This MOA analysis framework should look at both “genotoxic” and nongenotoxic endpoints such as cell proliferation. Once this is done, issues of temporality and dose response concordance can be evaluated to assess the proposed and other possible MOAs. I would strongly encourage the authors to do this sort of MOA framework analysis in their revision.”
- Page 44 of the external peer review report, Dr. Bruckner states: “The linear multistage extrapolation approach utilized here is based on a series of conservative assumptions. The net result (the cancer risk estimate) is much more health protective than necessary for DCM. This approach ignores protection and repair systems known to be operative in cells and organ systems, as well as the likelihood of minimal or negligible GST-mediated metabolism in humans at low/trace exposure levels.”
- Page 46 of the external peer review report, Dr. Bruckner states: “Nevertheless, the use of such high vapor concentrations by NTP is troubling, considering the shift from the CYP to the GST pathway under such exposure conditions. This artificial experimental design certainly calls into question the validity of extrapolations to very low human vapor exposures in environmental settings.”
- Page 48 of the external peer review report, Dr. Kishnan states: “Clarification is needed as to the validity and adequacy of this approach in light of the use of a probabilistic PBPK model that already accounts for the population distribution of parameters of relevance. Why is the slope factor determined for the most sensitive subpopulation and not for the entire population that also consists of this subpopulation (which would be more realistic)?..... Similarly, since the distributions of parameters representative of children of various ages are used in the PBPK model, the need to use additional adjustment factor for early life exposures should be more clearly presented.”
- The majority of expert reviewers who commented on the database uncertainty factor for the RfD, suggested that a 3x factor was too high. Dr. Bruckner supported this with scientific information and Dr. Kamendulis referred to the extensive body of scientific literature when making his comment. Considering this feedback from the expert reviewers, it is surprising that EPA is not revising the uncertainty factor.
 - We additionally note that Dr. Krishnan provided a comment on EPA's confidence in the RfD (see external peer review report page 28) and noted that it is high. He noted that this seemed “somewhat inconsistent” considering the uncertainty factors applied. Appendix A should address the comment and appropriate changes in the toxicological review and IRIS summary should be made.
- Regarding the cancer classification, expert reviewers were split regarding whether or not it was appropriate (see external peer review report pages 35-39). The reviewers that did not support the classification provided very compelling discussion that shows they evaluated all the available information and the weight of the evidence. EPA's response to these comments does not seem to address their concerns but instead cites some default approaches (eg, EPA considers mouse liver tumors to be relevant to humans) and does not provide a clear

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explanation, based on the weight of evidence, regarding why the Agency disagrees with these reviewers. It would be helpful if EPA provided a response, including scientific rationale, to each of the critical reviewers comments.

- Last month, EPA announced improvements to the IRIS assessments that would lead to: “reducing volume and redundancy of assessments; fuller discussion of methods and concise statements of criteria used in studies for hazard evaluation; clearer articulation of the rationale and criteria for screening studies; implementing uniform approaches for choosing studies and evaluating their findings; and describing the determinants of weight that were used in synthesizing the evidence.” Although we understand that such improvements will take time to implement and may not be possible for all the assessments currently underway, considering the importance of this assessment it would be helpful for EPA to transparently describe the changes that have been made to achieve the goals mentioned in the EPA announcement.

Specific Comments on Appendix A:

- Page A-2, EPA states: “Three reviewers supported the chosen model for rat PBPK toxicokinetics, and noted the clear presentation and discussion of the model assumptions, parameters, and uncertainties.” However it is not clear from the external peer review report if this statement is supported by the peer reviewers’ comments. Dr. Bruckner did make a similar positive statement, however we don’t see any other positive reviewer comments. Dr. Salmon does not explicitly state support for the model although he does list some positive attributes as well as some concerns regarding uncertainties in the 2E1 pathway. Dr. Kamendulis states that the model “appears to have been applied appropriately” but recommends more information be added regarding justification for the many changes made, and requests more information on variability. Dr. Krishnan, stated that the model “would appear to be deficient,” and Dr. Mehendale provides detailed questions and comments expressing concern.
- Page A-4, considering Dr. Mehendale’s expertise, and his strong comments regarding the need to consider the inhibitory effect of CO on 2E1 metabolism, it is rather surprising that EPA states that the “toxicological review was not revised to include a discussion of this issue.” Even if EPA disagrees with a reviewer’s expertise, shouldn’t the issue be raised and EPA’s rationale for not incorporating changes be incorporated into the toxicological review, considering its importance to the expert reviewer? If nothing else, it would clarify for readers why EPA did not consider the inhibitory effects of CO.
- Page A-7, EPA states: “Four reviewers noted agreement with the choice of the dose metric, and one reviewer did not comment directly on these questions.” EPA should note that Dr. Krishnan noted that it “has been justified in a limited manner.”
- Page A-7, EPA states: “An alternative derivation using an UF = 3 instead of the scaling factor is not presented because it is not a procedure that is supported by the available data.” It seems the reviewer was suggesting the use of a default UF, rather than a scaling factor. It is unclear why EPA is saying that this is a procedure not supported by the data.

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The reviewer (Dr. Kamendulis) also noted that the document lacked discussion of why such a scaling factor was used. In addition, Dr. Krishnan, also noted that the document did not clearly provide scientific support to justify the scaling factor. EPA should respond to these comments and add the appropriate discussion to the toxicological review.

- Page A-13, EPA states “Consistent with EPA’s Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a), the cancer assessment for dichloromethane is based on tumor data from the most sensitive species.” We could not find any language in the Cancer Guideline which state that the assessment should be derived from tumor data of the most sensitive species. We suggest revising this sentence to track with language from the cancer guidelines. We believe that relevance and mode of action information would also help to inform the appropriate species for use in a cancer assessment.
- Page A-16, in response to a reviewers suggestion for adding a exposure-response array, EPA states that this was not done because data cannot be generated for all the endpoints. Acknowledging this, wouldn’t it still be helpful to provide the recommended figure for those endpoints where data could be generated?
- Page A-23, the description of comments on B7 should also note that one reviewer thought it was a “conservative approach”.
- Page A-26, EPA’s characterization of the comments by reviewers who have concerns with EPAs cancer classification does not appear to capture the extent or significance of the comments. We suggest revising, perhaps by using direct quotes rather than paraphrasing concerns.
- Page A-30, EPA should acknowledge and respond to Dr. Bruckners comment which states: “It is also noteworthy that the tumor incidences in these DCM-treated mice and the F-344 rats were of marginal statistical significance.”

Specific Comments on the IRIS summary:

- The IRIS summary should provide a link to the interagency comments associated with this final document. 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. We understand that EPA is working on this and we hope this change can be made in time for posting of this assessment.