

OMB Staff Comments on 1,2,3-Trichloropropane Final draft Tox Review and Final Draft IRIS Summary

General Comments:

OMB staff focused this review on EPA's responsiveness to the peer review comments, thus many of our comments are on Appendix A (the summary of peer review and public comments). As EPA considers these comments we presume that any appropriate changes and conforming changes would be made in the main text of the toxicological review and in the IRIS summary, as appropriate.

Scientific Comments on the draft final Tox Review:

(page numbers refer to June 2009 draft redline)

Specific concerns regarding forestomach tumors:

- In discussing site concordance, in multiple places EPA states that the cancer guidelines "state that site concordance is not always assumed between animals and humans". EPA relies on this as the justification for including tumors in organs that have no direct human homolog. In discussing the site concordance issue the cancer guidelines also state (page 3-30): "Site concordance of tumor effects between animals and humans should be considered in each case." We would like to see EPA more fully consider this particular case (eg the forestomach tumors) before generally assuming site concordance. EPA's charge (cancer Q4) specifically asked reviewers to comment on the inclusion of forestomach tumors.
- Of the 7 reviewers, 5 responded to EPA's direct charge questions about whether EPA should include forestomach tumors in the quantitative cancer values. Bruckner, Kodell, Mehendale, and Zarbl all expressed concerns about including these lesions: 3 said they should not be included and 1 reviewer expressed a reservation about inclusion. Only Zeise said they should be included. Specifically, the majority of reviewers (4 reviewers of the 5 that responded) argue (in detail in their comments) against the inclusion, based on the dosing method (gavage) and level, the vehicle, the mutations, and the mode of action. EPA, however, does include these tumors. EPA's rationale seems to be based on the reference to the cancer guidelines; however, it is not clear that EPA has given this the case-by-case consideration that the cancer guidelines suggest, and it is also not clear how EPA has fully considered the details provided in the reviewers comments.
- In addition, EPA combines this endpoint with other alimentary system tumors in a way that the implications of inclusion are not clear to the readers. A reviewer, who finds the inclusion of these tumors to be "not justified", explicitly states that "the effect of including these lesions should be quantified and discussed for comparison". It would be extremely useful to know what the slope factors would be if these tumors were excluded. If EPA continues to include these tumors (which is not recommended based upon the majority of peer reviewer comments), the presentation should be improved. In discussions of uncertainties and relevance to humans, the quantitative impact of including these tumors should be presented clearly.

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- Page 126 states: “Linear extrapolation is, generally, considered to be a health-protective approach; however, linear extrapolation neither underestimates nor overestimates cancer risk when the linear extrapolation is appropriate for an agent’s mode of action (U.S. EPA, 2005).” We note that the peer reviewers comment that the forestomach tumors are likely not caused by a mutagenic mode of action (see, for example, Zarbl and Kodell comments). Thus, it is not clear that the clause regarding the over/underestimate is appropriate here for tumors being quantified that are not known to be acting through a mutagenic mode of action. It seems that for these tumors, it is a default approach and as the peer reviewers state, may lead to a large overestimate of risk.
- While there seems to be agreement from some reviewers regarding the ADAF’s, if in fact the forestomach tumors are driving the slope factor value (and we don’t know if this is true, but would like to know), is it still appropriate to apply the adjustment factors considering that the mode of action of the forestomach tumors is likely not through a mutagenic mode of action? We note that in the peer review report, page 33, Dr. Bull, mentions the uncertainty regarding “whether mutagenicity is the primary influence on the carcinogenic response in certain organs. This need not detract for the overall conclusion that 1,2,3-TCP is a mutagenic carcinogen. However, it may be a reason for selecting among different target organs for the purposes of low-dose extrapolation.”
- Zymbal gland, Hardarian gland, and preputial gland tumors also do not have a human homolog. Similar to our comments above regarding forestomach tumors, we would like EPA to give the same consideration and presentation to these tumors, such that their impact on the assessment and final slope factor is clear. EPA does state that the impact of non-alimentary tumors on the overall risk was small. However, the meaning of “small” is unclear and presentation of quantitative values would be useful. (we note that on page 9 of the peer review report, Mehendale expresses a concern about these other tumors. It is not clear where this is addressed and considered in Appendix A).

Scientific comments on Appendix A:

- In many places EPA refers to ‘several reviewers’. We find that in some cases this means 3 reviewers and in other cases it is 5 reviewers. As sometimes this represents the majority, and other times the minority, of reviewers it would be helpful throughout if EPA clearly stated the number of reviewers who had such comments.
- Page 140, a peer reviewer suggests that EPA refer to the scientific findings of IARC. EPA responds that this isn’t typical. We believe this scientific information would be useful, and in the past EPA has referred to the NIH page which provides comparison information from other respected organizations (including IARC). It would seem helpful for EPA to provide the link to such comparison information in the Tox Review.
- Page 142, EPA states that the cancer guidelines state that “target organ concordance is not a prerequisite for evaluating the implications of animal studies for humans..., and is supported by the mutagenic mode of carcinogenic action” While this may be true, as referred to above it is not clear that EPA has fully evaluated the implications of this information. It seems that

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EPA has simply incorporated the data based on assumed relevance. In addition, this seems to imply a disagreement with the peer reviewers regarding the mode of action for forestomach tumors, and it is not clear why EPA thinks the forestomach tumors represent a mutagenic mode of action (see reviewer comments on this topic).

- Page 142, EPA notes that two reviewers highlight the need for the consideration and discussion of the mouse tumor data. We note that reviewer Bull, page 31, also comments that there is a “lack of adequate dose-response data from the most sensitive species” and this was not adequately addressed. As EPA is now relying on these data (the mouse data) to derive the slope factor, it would be helpful to discuss Bulls’ concern.
- Page 143, in discussing RfD Q1:
 - EPA states that one reviewer expressed a concern about having such a large cancer risk at the RfD. We could not find these numbers and this comment in the peer review report.
 - it is not clear that Bulls’ scientific concerns regarding changes in liver and kidney weight in the absence of pathology is addressed.
 - EPA notes that another reviewer expresses a concern over deriving an RfD at doses that are carcinogenic. It would be helpful for EPA to clarify that this reviewers scientific concern had to do with the fact that the carcinogenicity led to reduced survival of animals in the non-cancer evaluation.
- Page 150, in discussing RfC Q2:
 - It would be useful to discuss the scientific comments from Bull regarding concerns about the route of exposure (with corn oil gavage) as well as Zarbl concerns regarding histology in the lymphoid tissues.
- Page 153, in discussing RfC Q3: EPA mentions that several commenters suggested BMD modeling and EPA notes that this information is now in Appendix C. However, it seems that EPA in the draft final Tox Review, is no longer using the NOAEL approach, and is relying on BMD data. This scientific change in approach should be reflected in this section of Appendix A.
- Page 154, in discussing Cancer Q2:
 - This question asked for agreement regarding the EPA proposed mode of action that it was “possible” that the chemical was acting through a mutagenic mode of action, but the data were limited. Bruckner concurs with this; Bull states that there is a mutagenic mode of action, but states that other modes of action have not been sufficiently considered; Hattis would strengthen the “very likely” conclusion; Kodell believes it is possible; Mehendale states that the conclusion is justified; Zarbl states that the data are limited; and Zeise believes the hypothesis is strongly supported by the data. It is not clear that these scientific comments come across clearly in EPA’s disposition (EPA states that the “reviewers generally indicated support..”. It seems that 3 of the reviewers would strengthen EPA’s statement, 3 agree with it, and one finds limited support for it. Considering the disparate peer review comments, and the fact that the majority of reviewers do not

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support a stronger statement, it is not clear, why based on the peer reviewers comments EPA is now finalizing an even stronger statement that it is definitively a mutagenic mode of action. Further justification for this seems needed.

- As EPA is now stating that there is a mutagenic mode of action, no longer calling it “possible”, this has implications for the ADAF application. We note that 2 reviewers commented that the ADAF’s should not be applied due to the inconclusive data regarding the mode of action. A third reviewer (Bull), as mentioned previously, expressed concerns about alternative modes of action at different target organs. A more robust discussion of the ADAF application would be useful. EPA’s discussion of this now simply refers back to the finding of a mutagenic mode of action, but doesn’t really discuss the merits of it in this particular case. Discussion of the Bull comments in this section would be helpful.

- Page 159, Cancer Q4: please see comments in above section regarding treatment of forestomach tumors.
- We note that instead of relying on rat tumor data for the slope factor as originally proposed, EPA is now relying on mouse tumor data. This is leading to an 8 fold increase in the slope factor. In reading Appendix A, it is not clear what led EPA to make such a change and thus further discussion of the scientific comments (and EPA’s response) that led to this modification would be extremely useful in understanding the scientific changes in the document. Was this change suggested by the majority of the peer reviewers? If so, it would be helpful to clarify this.

Editorial Science comments:

- Page 28: EPA refers to the non-cancer critical effect as including “right kidney weight change”
- Page 78, 87, and elsewhere (including the IRIS Summary): EPA 2000c is a draft document and does not yet represent official agency position. The fact that the document is just a draft should be made clear when EPA refers to it in text.
- Page 109-110, EPA describes table 5-6 as including “a full lifetime” exposure duration, however in the table this is not clear. EPA should clarify that this is represented by “total risk” and is the sum of the 3 rows presented.