

Proposed Discussion Topics for January 29 TMB Panel Teleconference

3.1. Enhancements to IRIS Assessments

3.1.1. Preamble

page 6. 1 27 Recommendation for future IRIS Assessment or needed for the TMB assessments (Roberts)

page 7 1. 4 Recommendation for future IRIS Assessment or needed for the TMB assessments (Roberts)

(Rhombert) P7 line 43 next page The bullets note some substantial issues that the Panel says "appear ... as not consistent with existing EPA policy". The following text only asks that the status of these policy statements be clarified, but I would like the Panel to express disapproval, especially of the notion that funding source is legitimate reason to downgrade a study, that negative studies carry less weight than positive ones, and that specificity is not a part of causal analysis. In my view, these policies not only have not been adopted by the agency, they should not be. I think this warrants discussion.

3.1.2 Presenting Assessment Steps and Outcomes

page 10, line 27 Recommendation for future IRIS Assessment or needed for the TMB assessments (Roberts)

page 11, line 34 Recommendation for future IRIS Assessment or needed for the TMB assessments (Roberts)

3.1.3 Standardized Evaluation of Critical Studies

page 12-13, line 42 Recommendation for future IRIS Assessment or needed for the TMB assessments or a suggestion to bolster the assessment (Roberts)

3.1.4 Addressing Public Commenters on the Draft TMB Assessment (May 2012)

Page 13 line 18 (Roberts) I suggest replacing "why" at the beginning of the second point with "contention that." As written, reversibility of the pain sensitivity effect appears to be fact, when much of the panel disagreed with this, as discussed elsewhere in the report.

page 13, line 39 (Roberts) Recommendation for future IRIS Assessment s or needed for the TMB assessments (needs to be consistent with Synthesis of Evidence discussion)

3.2. Toxicological Review of TMB report

3.2.1 Executive Summary

page 14, line 18 -24 Recommendation for future IRIS Assessment or needed for the TMB assessments or a suggestion to bolster the assessment? (Roberts)

3.2.2 Lit Search Study Selection

(Roberts) Page 15, lines 26-36: It is not clear to me how the absence of the specific cited studies weakens the assessment of the TMBs. Also, I'm not sure that the additional references

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suggested for inclusion at the bottom of the page are more than tangentially related to the TMB assessment. Rather than talking about these specific studies, I think that our report would be improved by providing a clearer presentation of our thoughts on exactly how information on related compounds and mixtures (such as C-9) should come into play in a toxicological review such as this. Our suggestions are that the EPA should discuss this more, but we are vague as to how it should be discussed and to what end.

page 15, line 39 Recommendation for future IRIS Assessments or needed for the TMB assessments or a suggestion to bolster the assessment?

3.2.3 Hazard ID Synthesis

(Roberts) The response to the Synthesis of Evidence charge question currently consists primarily of criticisms: 1) that the EPA did not more fully utilize information on C-9 mixtures; 2) that insufficient comparisons were made with other methyl-substituted aromatic compounds; and 3) that the neurological data used by the EPA to derive toxicity values were based upon unconventional endpoints and are of questionable relevance to humans. I don't recall any of these being consensus opinions, and in the case of neurological effect data, statements here contradict and undermine the panel response to later charge questions that specifically ask about this critical endpoint.

I propose the following revisions to this section:

The panel suggests a structural change in this and future toxicological reviews in which a section is added at the end of synthesis section for discussion of relevant toxicity data from related compounds and mixtures.

- *The objective of this section is to place information available for the topic chemical(s) in a somewhat broader context.*
- *Discussion of toxicity information in this section is necessarily at a higher level (i.e., less detailed) than the synthesis sections focusing on the topic chemical(s)*
- *Information provided could include the extent to which data for the topic chemical(s) is consistent or inconsistent with related chemicals or mixtures, and whether information from related chemicals and mixtures suggests that important data gaps might exist for the topic chemical.*

The panel suggests that for the TMB toxicological review this section include a discussion of the C-9 mixtures and other methyl-substituted aromatics.

- *There were differences of opinion among panel members on the extent to which information for the C-9 mixtures is relevant to an assessment of TMB isomers. [The different viewpoints should be briefly summarized in a balanced way in our response.]*
- *This section provides an opportunity for the EPA to articulate, for transparency purposes, its view on how the C-9 mixture data fit into the TMB assessment.*
- *Some panel members suggested information on related aromatics such as xylene and toluene that could be included in this section.*
- [Note that there are comments and suggestions related to this topic scattered throughout our report. Most of these could be collected and expressed as a coherent series of comments in this section.]

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Unless panel members object, the paragraph on neurological effect data (page 17, 39-44) should be deleted. If some panel members feel strongly that those points should be made, they belong in the responses to charge questions about the neurological endpoint as differing opinions.

(Rhombert) On p.16, lines 28-36, there is discussion of the role of solvent mixtures in the synthesis of evidence. This paragraph seems to be confusing the issue of the role of C-9 in the hazard characterization with the use of TMBs toxicity characterization to evaluate risks from mixtures, including C-9. The main question needing to be addressed is whether the rather negative toxicity findings with C-9 can be reconciled with the effects seen for TMBs in view of the fact that C-9 is over half TMBs in composition. This point is raised subsequently (on p.19, lines 7-14), but having this central point presented as an afterthought ("another important point" raised after the main discussion) tends to obscure the central issue. I think the Panel report needs to be clear that the question of using any TMB toxicity characterizations to examine the potential risks of mixtures, while worthy of discussion, is not the justification for or against using the C-9 testing results as part of the evidence on TMB hazard potential. The assessment-of-mixtures issue is actually secondary to this hazard issue -- if one is arguing that the other components of C-9 are suppressing TMB toxicity (and the arguments for why this seems to be need to be laid out, if one adopts this stance) then the application of the TMB-alone toxicity characterizations for use in mixtures assessment is problematic. On the other hand, if TMBs in mixtures are presumed to exert their effects despite the other components, then the toxicity differences of C-9 and TMBs alone need to be explained somehow.

(Ginsberg) Page 17, Line 14 – add a new sentence: “However, the SAB notes there are several examples in which the mixtures study shows lower toxicity than the individual isomer study (e.g., Douglas et al. 1993; Clark et al. 1989) which raises the possibility that competing interactions for distributional phenomena, induction of detoxification systems or other unforeseen biological phenomena may mask the underlying toxicity of a particular isomer present as a minority of the C9 mixture. In the face of well-done studies on individual isomers the C9 mixture studies deserve lower weight but should be considered as potentially useful in filling data gaps.

(Ginsberg) Page 17, Lines 15-16 the changes go in the wrong direction and should be reversed – EPA is not setting RfDs for individual isomers only for sites with mixtures and I am aware of sites with only one isomer present, not all three.

(Ginsberg) Page 17, lines 20 remove the word “persistent”. The Douglas study did not evaluate for persistence of effect.

page 17, line 5 Needed for the TMB assessments or a suggestion to bolster the assessment?

page 18, line 33 Needed for the TMB assessments or a suggestion to bolster the assessment?

(Cory Schlecta) page 27 lines 39-40 states that the neurological endpoints are ‘somewhat unconventional’; that is only true if you are not a neuroscientist.

3.2.4 PBPK

(Rhomberg) On p.19 in PBPK recommendations (comparison document p.21, line 6-8), a sentence is deleted that refers to the lack of a summary of mechanistic evidence. I am not sure why this is deleted, and I would favor its reinstatement.

(Roberts) page 21, line 18, “Results of sensitivity analyses can be used to respond to related concerns.” I don’t know what this means. I think we need to clarify this point. Also, on line 35, “... at a minimum discuss the model selection in future drafts of the assessment.” Discuss it how? Also, this should probably be rephrased to indicate the final assessment rather than future drafts.

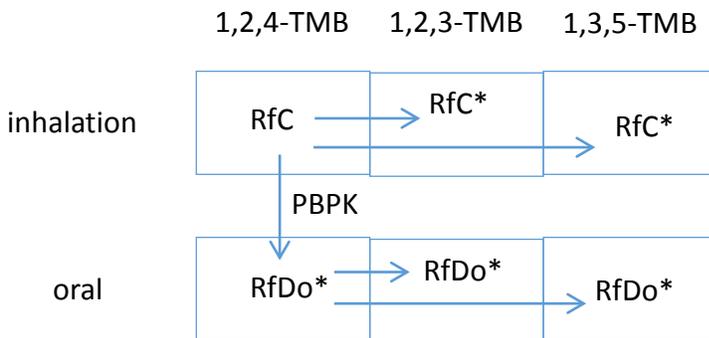
(Roberts) page 21, line 28-35 The recommendation that the EPA “evaluate the Jarnberg and Johanson model and at a minimum discuss the model selection in future drafts of the assessment.” What do we mean by evaluate the model? Do we mean that the EPA should briefly describe the model and explain why it wasn’t used? Do we mean run the model and see how extrapolation of 1,2,4-TMB data might be changed? If so, should that be included in the report? Some additional clarity on the recommendation would make it more useful to the EPA I think. [Note: I think that this might be a suggestion rather than a recommendation.]

(Rhomberg) On p.21, 38 (p.25, lines 1-23 of the compare document), a whole section on [recommendations] evaluating the PBPK is marked for elimination. I would like some discussion on why this is no longer needed. Have the recommendations changed, or is this seen as being obviated by the review of PBPK shown elsewhere? This parallels the question I raise above about p.2, lines 18-30.

RFC and RfD approach in general

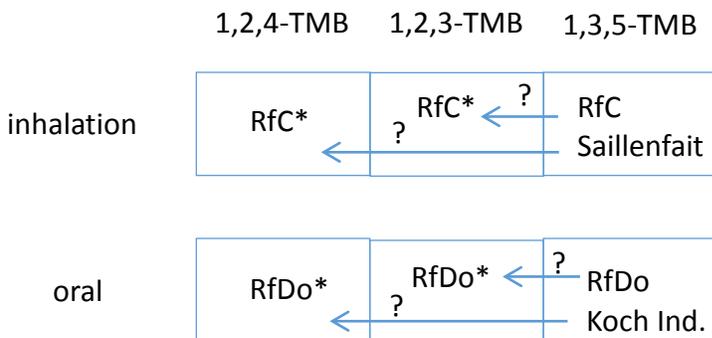
(Roberts) I think that the EPA and possible other extrapolations of toxicity values is confusing. Perhaps we should include a figure something like the one below to help the reader keep it straight.

EPA-derived RfC and RfD values based upon neurotoxicity



* extrapolated

Proposed additional RfC and RfD values based upon other endpoints



* extrapolated

3.2.5. Inhalation Reference Concentration

(Rhombert)Page 23 1 41- p24 19 I am concerned about the discussion of reversibility being added (in the comparison document on p.27, lines 32-42). First, the Panel's discussions as I remember them had significant strains of opinion that the reversibility question had not been settled, and this section seems to say that it has been. Rather than the usual approach of noting issues and recommending a deeper consideration by the agency, this section seems to be having the Panel decide and tell the agency how to address the issue. As to specifics, if one examines the Supplemental Material (p.B-110) about the Korsak and Rydzynski (1996) study, it is clear that both tested isomers have very parallel patterns of decline in effect when examined 2-weeks after exposure termination; the decline is marked as significant for 1,2,4-TMB and as (not quite) significant for 1,2,3-TMB, but the patterns are virtually identical, and it seems inaccurate to say that the issue only arises for 1,2,4-TMB. It is true that the decline in effect does not go all the way back to zero in 2-weeks, but the only testing of recovery is for the high dose group and only for the one time-point 2 weeks after exposure, so it seems unwarranted to presume that further recovery would not happen. The post-exposure declines are marked enough, the patterns similar enough across isomers, and the reversal effect notable enough in contrast to the smoothly increasing effect during the period of exposure that a real phenomenon seems to occur. There is need for discussion of what can be said about the prospects for further decline with time, should that ever be tested, and for what the pace of partial recovery says about the larger question of how reversibility plays into the question of chronic as compared to sub-chronic toxicity. But any such discussion needs to begin with a clear acknowledgement of how the evidence looks.

3.2.7 Inhalation RfC 1,3,5

(Rhombert) On p.29,lines 26-27,a sentence is deleted that says that reversibility is irrelevant since exposure is ongoing. This is sentence should definitely stay out, since the point it expresses is not valid.

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Exec Summary

(Rhomberg) On p.2, lines 18-30, the edits change the focus of the text away from the PBPK approach and toward discussion of the studies for RfC/D determination. That is, it is a change in the topic of the paragraph. I think some Panel discussion of what was intended here would be a good idea, since it is not clear why one topic is being dropped and another expanded, all via extensive text edits that leave some sentence fragments still present but with much alteration in what they are addressing.