

11/01/14 Preliminary substantive comments for review and deliberations by the CAAC Committee Augmented for the Review of the EPA’s Draft IRIS Trimethylbenzenes Assessment. Do not Cite or Quote. These preliminary comments are draft and a work in progress, They do not reflect consensus advice or recommendations, have not been reviewed or approved by the chartered SAB and do not represent EPA policy.

**CAAC TMB Panel Preliminary Comments on the October 9, 2014
Draft SAB Review of the IRIS Trimethylbenzenes Toxicological Review
November 1, 2014**

(Comments Received as of October 30, 2014)

Table of Contents

Comments from Dr. Beland.....	2
Comments from Dr. Cohen.....	2
Comments from Dr. Cory-Slechta	2
Comments from Dr. Ginsburg	3
Comments from Dr. Goeden.....	4
Comments from Dr. Hays.....	6
Comments from Dr. Lash	7
Comments from Dr. Roberts.....	7
Comments from Dr. York.....	8

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Comments from Dr. Beland

Harris letter, page 2, lines 40-42: I strongly disagree with this. Nothing is known about sensitive life stages and vulnerable populations with regard to TMBs. It would simply be an exercise in hand waving. Perhaps it could be rephrased to state that some SAB members felt this should be included, but others felt that there was insufficient information available to make a knowledgeable statement.

Page 2, line 44 and page 3, lines 4-7: Again, I do not think there are sufficient data available to support the recommendation about life stages.

Page 5, lines 39-40: Again, I do not think there are sufficient data available to support the recommendation about life stages.

Page 38, section 3.3.1: Again this strikes me as too speculative: there are no data.

Comments from Dr. Cohen

The only scientific writing issue is in the RfD sections, I.e., if we just spent a lot verbiage criticizing extrapolation of the RfC for the 1,3,5 from the other two isomers, does it now make a lot of sense to propose to get RfDs for the 1,2,4 and 1,2,3 forms based on the 1,3,5-TMB? Bit of a head-scratcher.

Lastly, much of the material in sections 3.2.8, 3.2.9, and 3.2.10 seems repetitive. So, is there any way edits can be made a la what was done in the earlier revisions so it is a clearer easier final read?

Comments from Dr. Cory-Slechta

In general, this version is better integrated and more concise than prior iterations, and I have only one comment:

p. 36, lines 22-24. It is not my recollection that the Panel collectively or uniformly dismissed the concerns about the Koch Industry study in terms of its use for an oral RfD; therefore this statement needs to be qualified if indeed there were differing points of view of the Panel.

p. 36 lines 39-42 suggest that an uncertainty factor be used to account for the lack of neurotoxicity endpoints in the Koch study and states that this is a commonly utilized approach. In this reviewer's experience, it is not commonly utilized, and there is no data to substantiate that an uncertainty factor approach would essentially be sufficient for such a purpose.

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Comments from Dr. Ginsburg

C-9 Fraction

Page 18 – The preamble section referred to is with regard to assessing chemical mixtures. However, in this case, the SAB is reviewing an IRIS assessment of individual TMB isomers which can and sometimes do appear at waste sites as single analytes. Therefore it is inappropriate for this SAB committee to conclude with the statement in these lines – that the C-9 and white spirit studies should be further considered on the basis that they represent the toxicology of a relevant mixture. Our charge is to evaluate how well USEPA has characterized the hazard associated with individual isomers not a mixture of TMBs with other aromatics. Therefore, I request consideration that the reference to the preamble be removed and that the C9 and white spirit studies be mentioned as being relevant to TMB isomer toxicology to the extent that they can represent the types of effects and dose response for effects possible for individual isomers. We should also acknowledge that this may be limited given that the content of any single TMB isomer is less than 50%, that the combination of TMBs represent less than 60% of the mixture and that the nature of interaction between individual TMB isomers and other components if the mixture has not been studied. Therefore, the SAB believes that USEPA should take a cautious approach in using these studies to fill TMB isomer data gaps and the main body of the toxicological review should provide a clearer assessment of the extent to which the mixtures studies add to the overall hazard evaluation of each isomer. A discussion of the mixtures studies could appear in the “Literature Evaluated” section and the mixtures studies themselves could appear in the body of the report under each endpoint evaluated according to the type of C9 study that is available. At that point it may be useful for USEPA to compare and contrast the mixture study result with other available data on that endpoint. For example, the Douglas et al. 1993 study of the C9 mixture failed to show any substantive neurotoxicity in spite of the fact that it exposed rats to high concentrations (up to 1500 ppm). The lack of neurotoxicity at such concentrations is in stark contrast to other studies of TMB isomers alone or of C9 mixtures in which similarly high exposures were employed and did show neurotoxicity (e.g., McKee et al. 1990 showed extensive neurotoxicity in rat reproduction C9 study and the series of pain response studies showed neurotoxicity for individual TMB isomers – e.g., Korsak and Rydzynski, 1996)]. A similar issue exists with regards to the Lehotsky developmental neurotoxicity study in which there were no neurotoxic effects reported in spite of high concentrations of C9 mixture.

Page 18 – These lines are too optimistic with respect to what the mixtures studies can tell us about the toxicology of the individual isomers, especially with respect to negative studies. We have seen several cases where 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 effects may negate or mask the underlying toxicity of a specific isomer present as a minority of the C9 mixture. Therefore, this paragraph should be removed or greatly tempered. USEPA's conclusions on the limited applicability of the negative C9 mixture studies (Appendix E, pages 8-9) is well stated and should be endorsed by this SAB committee. Essentially it says that in the face of clearly adverse effects from TMB isomer studies, the utility of negative studies from a mixture of uncertain relevance to individual isomers is of much lower weight. Further, the text appears to miss the point that TMB isomers can appear as individual constituents at waste sites and that USEPA is attempting to construct valid RfDs and RfCs for individual isomers, not for a mixture of TMBs or mixture of gasoline-related alkyl aromatics.

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Page 18 – Lines 35-41: Douglas et al. 1993 is used to indicate a lack of persistent neurotoxicity. However, Douglas et al 1993 failed to find neurotoxicity at all (except for some very minor perturbations that were asserted to be not dose related or compound related). The implication here is that Douglas et al. 1993 could inform the issue of whether TMBs cause slowly reversing or irreversible neurotoxic effects as suggested by the pain response studies. The lack of neurotoxicity in the Douglas studies may indicate some insensitivity of methodology or a lack of effect of the mixture relative to the single TMB isomer. However, it should not be used to imply a lack of persistent neurotoxicity. In fact, the Douglas et al. 1993 study did not employ a recovery period to determine if there is persistence (which of course there wouldn't be since they found no effects to start with) and Douglas et al. 1993 did not employ the type of sensitive sensory stimuli testing used in Korsak and Rydzynski, 1996. Therefore, I recommend that these lines be removed and that instead Douglas et al. 1993 is used to show the difficulty with using and interpreting mixtures studies in the current IRIS assessment.

Uncertainty

Pages 28-29, UF-S and UF-D: Both of these uncertainty factors could range from 3 to 10 fold. There is reason to believe that a slowly reversing or irreversible neurological effect could be cumulative thus causing the chronic dose response (if such data were available) to be substantially more sensitive than the subchronic effect. For TMBs this would be on the basis of cumulative toxicodynamic or damage effect, not cumulative body burden. Whether that increase in potency is minor vs 3x vs 10x remains to be seen. However, the default position has traditionally been 10x and mitigating factors such as the toxic effect is minimal, rapidly reversing and unlikely to proceed to more severe effects or lower dose effects can be used along with TK considerations to lower to 1 or 3x. In this case, a persistent neurological effect should not qualify as an effect which is easily moved from the 10x default. I would prefer that this section be written that the committee believes that UFS could lie between 3 and 10x and that additional information that may be learned from other alkylbenzene neurotoxicity be used to inform the subchronic to chronic extrapolation. Similarly, UFD is in the 3-10 fold range as developmental neurotoxicity is a potentially more sensitive endpoint that is untested for the TMB isomers. As described on Page 39 of our draft report, the Lehotsky et al. 1985 study is not very useful in spite of its prenatal exposure paradigm in rats. The early life vulnerability discussion on Page 39 should be tied into the UFD discussion to better describe the concern over the developmental neurotoxicity data gap and the potential utility of using DNT data from related alkylbenzenes (e.g., the toluene Win Shwe 2010, 2012 studies) to inform the decision of whether 3 or 10 fold is more appropriate for UFD .

Comments from Dr. Goeden

Letter to Administrator

Page 2

Line 27. This comment was not specific to oral toxicological studies. Delete toxicological Comments by Dr. Miller and others came up during the discussion of the repro/develop inhalation study by Saillenfait et al. Dr. Miller stated there were differences in chemical properties (e.g., Henry's Law constant, etc) and half-life of elimination could lead to different toxicokinetics for 1,3,5-TMB than 1,2,4. According to my notes the majority of the panel members were okay with using the same RfC for all

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three isomers since the RfCs were going to be based on the neurological effects not reproductive/developmental effects. However it was suggested that Section 1.1.7 not only focus on the similarities between the isomers but also discuss the differences and potential impact of these differences on toxicokinetics, i.e., the PBPK modeling. Other than the single oral gavage studies by Tomas et al I don't believe there were other oral studies on 1,2,4-TMB. In the single dose Tomas studies the toxicological effects were similar between 1,2,4 & 1,3,5.

Line 34. This sounds like we are suggesting that the RfD for 1,3,5-TMB be based on the available oral study which is not the case. We do want them to drive a candidate RfD based on the oral study and compare it to the RfD based on route-to-route extrapolation. This comparison will inform the selection of the most appropriate value for protection of potential neurological effects - which could be the route-to-route based RfD.

Executive Summary

Page 2

Line 19 There is one oral study on 1,3,5-TMB, that can be used for possible derivation of an RfD. Repeat dosing oral studies do not exist for the other isomers so we cannot state that the oral toxicological properties differ across the isomers. Several panel members did note that the chemical properties (e.g., Henry's Law constant) and elimination half-life differ from 1,2,4-TMB and that discussion of how these differences could impact the PBPK extrapolation should be expanded in the document.

Line 24-26. The rationale for selecting one candidate RfD over the other should be clearly stated.

Response to Charge

Page 4 Line 20. Had previously suggested deleting the word chronic since some of the toxicity values are based on non-chronic effects such as developmental effects.

Page 32 Line 2-9. It would not be appropriate to use the same combined UFs as those applied to the neurotox study. It would be appropriate to increase the UFD to 10 to address the lack of neurotox evaluation in the Saillenfait et al study.

Page 35 Line 23-40.

1) Concerns were expressed that 1,3,5-TMB is sufficiently different from 1,2,4- and 1,2,3-TMB that extrapolation across these isomers should be done with caution. It does not make sense to treat 1,2,3-TMB (i.e., consider extrapolating from 1,3,5-TMB oral study) differently than 1,2,4-TMB. The approach for derivation of oral RfDs for 1,2,4- (3.2.8) and 1,2,3-TMB (3.2.9) should be the same - i.e. extrapolation across exposure routes. Section 3.2.9 should be virtually identical to Section 3.2.8

2) The discussion presented here regarding the oral subchronic gavage study of 1,3,5-TMB should be moved to Section 3.2.10. NOTE: Koch Industries 1995 and Adenuga et al 2014 are not two separate studies. The presentation by ACC at the Panel meeting clearly states that Adenuga et al 2014 is a publication of the unpublished Koch Industries 1995 study. There is only 1 study.

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Page 36 Line 21-26. This study was not published in the peer review literature at the time at the time the TMB Assessment was drafted. The results of this study were published as Adenuga et al in 2014.

Page 39 line25 Should this be vulnerability rather than variability?

Comments from Dr. Hays

General Comments

1. The discussion of the use of the PBPK modeling is awkward, and in some cases incorrect. We need to be clear how the PBPK model was used and where we have concerns. The PBPK model was used for;
 - a. Species extrapolation for derivation of the RfCs for 123 and 124.
 - b. Dose-route extrapolation to derive the RfDs for 123 and 124 (extrapolating from the RfCs).
 - c. Comments are inserted throughout the attached pdf where there is inconsistencies and errors.
2. If the panel recommends the inclusion of C9 studies for derivation of RfCs and RfDs, we are in essence saying that the TMBs operate as a mixture from a tox standpoint. By saying this, we are also implying that the RfC and RfD should be set for all TMBs, not single isomers. Thus, a cumulative risk assessment is warranted (i.e., the RfC of ____ mg/m³ is appropriate for the exposure to the sum of all TMBs).
 - a. We do need to be consistent on whether to recommend
3. The write up for section 3.2.7 (RfC for 135) is all over the place. It needs to be cleaned up and made more coherent.

Letter to the Administrator

Page 2

Line 14 - No need to state this. PBPK is not used instead of chemical specific studies. It was used for route-to-route extrapolation because of the lack of chemical specific studies by the needed route of exposure (oral in this case).

Line 27 - EPA didn't use PBPK for 135. Rather, they just adopted the RfC and RfD for one of the other isomers. The issue is that for 135 there was an oral dosing study (whereas there were none for the other isomers). The panel recommended that EPA derive an RfD using the available study (Koch) as a comparison to the RfD derived by dose-route extrapolation from the RfC.

Executive summary

Page 2

Line 9 Again, not 'rather than specific studies for the TMBs'. For the RfCs, the PBPK model was used for species extrapolation because there were no human tox studies appropriate for derivation of an RfC. It was also used for dose-route extrapolation because no oral tox studies (for neurotox) were available.

Line 15 Be specific here. The PBPK model was used for species extrapolation to derive the RfC for 124 and 123 and dose route extrapolation for both.

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Page 23

Line 30 Delete the latter part of this sentence. the recommendations are to EITHER adjust the PBPK model OR conduct BMD modeling on air concentration first to derive the POD and then use the PBPK model at the POD to calculate blood concentration (this is at an air concentration at which the model was more reliable).

Comments from Dr. Lash

The only issue I see that requires comment is that regarding the inconsistency in presentation of the RfD for the three isomers in sections 3.2.8, 3.2.9, and 3.2.10. The latter two sections seem consistent with one another in that they both make the following statement and recommendation: "EPA chose not to use the Koch et al. (1995) study for derivation of a RfD, because it did not assess the potential for neurological effects. EPA should consider deriving RfD(s) for endpoints developed in the Koch et al. (1995) and Adenuga et al. (2014) study, such as liver and kidney weight changes, which were not seen in inhalation studies." In contrast, section 3.2.8 notes that the studies of Koch et al. (1995) are of potential utility but are not superior to PBPK models.

The consensus reached at the meeting in June, 2014 was that all three isomers of TMB should be treated the same because of the known similarities in chemical properties. Hence, the statements in section 3.2.8 regarding potential use of the Koch et al. (1995) studies should be the same as those made in the latter two sections.

Comments from Dr. Roberts

1. When the Chartered SAB reviews our report, one of the questions each member will be asked is whether we answered each charge question. In the current draft report, many of our responses discuss the topic of the charge question without providing a clear, direct answer. In my experience, the best way to make sure that there is no ambiguity is to begin each response with a short (one or two sentence) answer to the question as posed, followed by supporting discussion. Some responses already do this, but we should apply this consistently in the document. This will leave no doubt among readers (and reviewers) that we have addressed each charge question.

2. In the convention of these reports, there are recommendations and there are suggestions. Recommendations from the panel carry great weight. They deal with aspects that must be corrected, in the opinion of the panel, in order for the analysis and report to be credible, accurate, and sound. They are carried forward in the Executive Summary and often in the letter to the Administrator. Suggestions are advice for improvement of the report or analysis, but don't rise to the level of importance as a recommendation. They are "should do" or "would be nice to do" but not "must do." [Note: Suggestions don't always need to be labeled as such, and can be put forth as "The report would be improved by ..." etc.] Individual suggestions may or may not be carried forward to the Executive Summary, and seldom appear in the letter to the Administrator (other than saying something like "A number of suggestions for

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improving the analysis are offered ...”). Making a distinction between recommendations and suggestions helps the agency prioritize their efforts in responding to our advice.

In looking over our report, I think that some of our recommendations are really suggestions, and perhaps some suggestions are really recommendations. We need to examine these individually and determine our intent in terms of priority and word them accordingly.

3. The role of the C9 mixture studies in this toxicological review is touched upon in a number of places with seemingly inconsistent views expressed. While we acknowledge that there are differences of opinion among the panel on this topic, expressing different views in different sections of the report is not the best way to handle this. In my opinion, this issue should be dealt with once in the report with the contrasting views briefly explained. If the issue is germane to a charge question response elsewhere in the document, a simple reference to the section with this discussion should be sufficient.

4. There is also some inconsistency in our discussion of the decrease in pain sensitivity as a valid endpoint for RfC derivation. In the response to the specific charge question on this topic (Section 3.2.5), the panel expresses the opinion that this endpoint is appropriate and valid. However, this response is undermined by the response to the charge question on synthesis of evidence (pg 19, lines 11-15), where the functional and human significance of the neurological effect data are questioned. As with the C9 mixture issue, if there are differences of opinion, they should be dealt with directly, in one place in the report, with contrasting views briefly articulated. If there is consensus, then the report should reflect that.

5. On the same theme, there were differences of opinion as to evidence that effects of 1,2,4-TMB are reversible and the practical significance if they are. These show up in sentences scattered throughout the report, without the benefit of a coherent discussion of the issue.

6. I don't understand our response to the first charge question in 3.2.7. In the first paragraph, we recommend that the agency conduct additional evaluation of the Saillenfait et al. study before relying on the 1,2,4-TMB data to extrapolate the RfC but do not indicate what that evaluation should consist of or what outcome would lead to the use of an RfC derived from this study over the 1,2,4-TMB RfC for the 1,3,5-TMB RfC. The remainder of the response points to strengths and weaknesses of the Saillenfait et al. study, the possibility of using it to derive a subchronic RfC, and the correct interpretation of the NOAEL from this study, none of which address the question being asked as far as I can see.

7. I find Sections 3.2.8, 3.2.9 and 3.2.10 to be confusing. Apparently the answer to the series of charge questions is that the panel agrees that the oral databases for 1,2,4-TMB and 1,2,3-TMB are inadequate to develop their respective oral RfDs, but the Koch et al. (1995) study could be used to derive an oral RfD for 1,3,5-TMB, which could be extrapolated to 1,2,3- and 1,2,4-TMB. Our thoughts on how these RfDs would be used (versus those from extrapolation from RfCs for these TMBs) isn't clear (at least to me).

Comments from Dr. York

Sections 3.2.8, 3.2.9 and 3.2.10 were conceptually the same, however, given that each of these sections were written by different committee members, the wording was different. The one thing I did not like is

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how often the draft refers to the Koch Industries study report (1995) and the Adenuga et al. 2014 manuscript as if they are two subchronic studies, instead of a recent manuscript of the old 1995 study conducted by Koch Industries. For example:

Section 3.2.8. Line 43, p.33 and line 5, p.34 both refer to the Koch Industries 'studies' instead of 'study'.

Section 3.2.9. Line 23, p. 35 actually refers to 'two' subchronic gavage toxicology study of 1,3,5-TMB. This gives the impression that there were two subchronic studies, instead of a recent manuscript (Adenuga et al., 2014) of an old (Koch Industries, 1995) study.

Section 3.2.10. Line 27, p.36 makes the same mistake - "These subchronic gavage toxicology studies of 1,3,5-TMB..." when there was really only one subchronic study. Further down the paragraph (line 36) it reads as if EPA should derive RfDs for endpoints in the Koch et al (1995) and Adenuga et al. (2014), when in fact there is only one oral subchronic 1,3,5-TMB study. In lines 42 and 43, it appears that EPA should compare the RfDs generated from the Koch et al (1995) and Adenuga et al (2014) as if different ones would be derived from the same data set.