

SAB Comments on the Draft Acrylamide Panel Report

1. Dr. Meryl Karol

a) *Are the original charge questions to the SAB Panel adequately addressed in the draft report?*

The draft report does an excellent job of addressing the 26 charge questions in a clear and concise manner. In addition, the cover letter provides an excellent bulleted summary of the panel's key points and recommendations, and the Executive Summary clearly states the most important findings and recommendations.

b) *Is the draft report clear and logical?*

The report is clear and logical. Especially helpful was the list of 35 abbreviations. The occasional lengthy sentences require editing, specifically:

p. 10 lines 6-9

p. 11 lines 19-22

p. 15 lines 1-5

p. 20 lines 1-5

p. 25 line 1, it is unclear what "they" refers to

p. 46 line 18 is unclear

c) *Are the conclusions drawn, and/or the recommendations made supported by information in the body of the report?*

Yes.

d) *Errors/omissions*

Grammar: the occasional misuse of which/that should be corrected.

p. 8 line 26 delete "also"

p. 9 line 2 delete "yet"

p.10 line 16 replace "in" with "of"

p. 45 line 20 move "bioassays" to precede "studies"

p.45 line 23 change line toproblematic. ~~and~~ The strengths and

p.45 line 26 delete "should"

p.46 lines 7-9 add commas as follows ... modeling, is that eachof cancer, is

p.50 line 1 correct spelling of "pharmacokinetics"

2. Dr. Steve Roberts

The Panel should be commended on an excellent job responding to numerous charge questions on the draft Toxicological Review of Acrylamide. It is clear from the comments that the panel members were conscientious in their review of the report and in crafting comments and recommendations. The report is well organized and, in general, the responses to the questions and rationale are clearly articulated. There are a few areas in which the comments could be improved, in my opinion. These are outlined in the points below:

- a) pg 15, lines 6-9, “It should be noted that future studies may demonstrate effects of acrylamide exposure on male reproductive function ... at even lower doses than those currently associated with neurotoxicity ...” This should be accompanied by an explanation of the basis for the comment.
- b) pg 15, lines 16 – 17, “The heritable germ cell effects are very worrisome and deserve even more consideration, including perhaps the use of this endpoint to generate an independent RfD.” The recommendation of perhaps generating an RfD for heritable germ cells effects appears to be contrary to the conclusion expressed in the cover letter (third bullet): “... the Panel supported the Agency’s conclusions that the available data on heritable gene mutations are not adequate to conduct a robust assessment of this endpoint at this time.”
- c) pg 17, lines 9-12. It is unclear to me how or why the MOA discussion should be presented in the context of Hill criteria.
- d) pg 19, Charge Question 4 asks for comment on derivation of the final RfD value using only data from the Johnson study. The response that follows doesn’t explicitly address this issue.
- e) pg 24, Charge Question 7 asks for other comments on the derivation of the RfD and uncertainties associated with it. The response recommends a cumulative risk assessment for acrylamide, which doesn’t seem germane to question asked.
- f) pg 30, lines 7-8, “Therefore the choice of acrylamide in blood as the dose metric may need to be revisited as this question is clarified.” The question to be clarified is not apparent. In fact, it’s not clear from reading this section exactly where the Panel stood on the question posed whether the AUC for acrylamide in blood is the best choice as the dose metric. The response to Charge Question 8 is somewhat long, but contains good discussion. It could benefit from some concise statements up front or at the end summarizing the Panel’s response to the specific questions.
- g) pg 32, lines 16-19, “The Panel agrees that the use of internal dose metrics ... combined with a fairly robust understanding of the mechanisms of action and thus the critical dose metric replaces the use of the default interspecies factor for toxicokinetic differences (i.e., $10^{1/2}$).” It’s not clear [to me] from the response to Charge Question 8 that we have a robust understanding of the critical dose metric. Perhaps with some clarification in the response to Charge Question 8, and a stronger endorsement of the dose metric chosen, this would be resolved.
- h) pg 40, lines 17-29: In describing why the cancer designation chosen for acrylamide is appropriate, this section refers to the IARC and NTP classification schemes, but makes no mention of why the definition fits according to EPA guidelines, which are presumably the most relevant.
- i) pg 44, Charge Question 20: This question asks specifically for comments on support for hormonal pathway disruption as a possible MOA. Nothing in the response that follows addresses this. The subject is covered, however, in the response to the previous charge question. That text should be moved to the response to this charge question. Alternatively, a reference to that

text (a “shout out”, in the parlance of aspirants to high office) could be placed here.

- j) pg 49, Charge Question 24, “The response to this question is nearly identical to the response to charge question #11.” It’s too identical. This question is in regard to the IUR, while the response talks about the RfC and air concentration comparisons. Part of the first paragraph and all of the second paragraph need to be revised to address the IUR.

Minor edits:

Panel Report

- a) pg 7, line 9: “... a PBTk model, and the derivation ...”
- b) pg 8, line 9: replace PBPK with PBTk
- c) pg 9, lines 13-16: This sentence is awkward and too long.
- d) pg 9, line 23, “... have been proposed ...”: By whom? Need citations or more information.
- e) pg 10, lines 5-9: This sentence is much too long and convoluted.
- f) pg 11, line 11, “Consideration of additional human data ...”: A little vague. An example would help.
- g) pg 11, line 16, “As with the RfC ...”: The topic of this section is the RfC, not the IUR. The best fix is probably to just delete this sentence. Also, the last two sentences of this paragraph are partially redundant.
- h) pg 11, line 26: A new heading on age-dependent adjustment factors is needed here.
- i) pg 13, line 9: Delete “(s)” after Review – the sentence is referring specifically to the review on acrylamide.
- j) pg 15, line 30: These references should be moved to the reference section.
- k) pg 16, line 28: Suggest “... visible axonal degeneration seen with light microscopy ...”
- l) pg 17, lines 28 and 28: I believe that convention is to spell out these numbers, e.g., “... five heritable translocation studies, two specific locus studies ...”.
- m) pg 18, lines 9: “... these observations ...” ?
- n) pg 19, lines 3 and 4: 6% and 0.05% what? What is the endpoint?
- o) pg 23, line 11: “... inclusion of an UF ...” The meaning of this sentence isn’t clear to me. Perhaps just end the sentence at “... database.”
- p) pg 24, lines 7-11: The NOAELs are “essentially the same” but the “difference could potentially be driven by dose spacing ...” This seems contradictory. I suggest replacing “but” with “and” [and maybe describing as the “small difference”].
- q) pg 26, line 18, “Three major modifications ...”: Were there three modifications to each of the three parameters (partition coefficients for glycidamide, etc.) of just modifications to the three parameters? It’s not clear the way the sentence is structured.
- r) pg 26, line 21: Delete “and”

- s) pg 26, line 23: Delete “However” and remove the comma after “model”
- t) pg 29, line 23: Replace PBPK with PBTK
- u) pg 29, line 29: Replace “fact” with “belief” or “opinion”. The topic (best choice) is inherently subjective.
- v) pg 30, lines 21 and 30: Replace PBPK with PBTK
- w) pg 34, line 15: Replace “which” with “that”
- x) pg 36, line 7: Comma after “methods”
- y) pg 40, line 5: “motors”
- z) pg 40, line 17: Replace “has” with “have”
- aa) pg 42, line 9: Replace “mode of action” with “MOA”
- bb) pg 43, line 26: Replace “the” with “they” and put period at the end of the sentence.

Letter to the Administrator

- a) First bullet, second line: Suggest “... neurotoxicity appears to be ...”
- b) Second bullet, second line: Delete “deemed”
- c) Third bullet, third line: Replace “In addition” with “However”
- d) Sixth and seventh bullets: Both cover the use of PBTK and should be combined.

3. Dr. James Sanders

Are the charge questions adequately addressed?

Yes, the Panel clearly and carefully addressed each charge question. Given the number of questions, the Panel is to be commended for their responses, and for the layout of the report.

Is the report clear and logical?

Yes. While the report is very specific and provides detail about many of the charge questions, the end result is a readable report for the general reader, as well as for the expert.

Are the conclusions supported?

The report provides back up and support for its comments and recommendations. The Panel has done a very good job of ensuring that their recommendations can be evaluated in their context.

4. Dr. Thomas Wallsten

I have read the three draft reviews. It appeared to me that all three adequately addressed the charge questions, were logically laid out, and provided supporting information for their conclusions and recommendations. I have three comments on the reports:

- a) The review of the White Paper on "Aquatic Life Criteria for Contaminants of Concern" mentioned the use of expert panels to provide professional judgment during criteria development (Section 4.1.6). I

concur that such panels can be very useful. My question is whether EPA has, or has not considered, guidelines for how such panels should operate to assure careful, unbiased judgmental extrapolations from available data to end points of concern?

- b) The same white paper urges that attention be paid to the possible effects of mixtures of contaminants, not just contaminants acting alone. This point would seem to apply to the "SAB Advisory on EPA's Third Drinking Contaminant Candidate List," yet I did not see it mentioned there (although I may have missed it).
- c) Finally, only the review of "Toxicological Review of Acrylamide" included a list of abbreviations. While some acronyms are common (e.g., LOEL, NOEL, DNA), others may be unique to specific fields or topics (e.g., CEC, ROPC, WBDO). It would be helpful for all reports to have a list of acronyms.

5. Dr. Terry Daniel

The original charge questions to the SAB Panel are adequately addressed in the draft report, the report is clear and logical, and the conclusions and recommendations are supported by the information in the body of the report.

Both the initial document and the SAB Panel review appeared very thorough and carefully considered. Given my level of expertise relevant to the substantive issues addressed, it seems most prudent in this case for me to vote "present."

6. Dr. Rogene Henderson

I found this to be a thorough, well-thought-out and clearly stated discussion of the draft IRIS assessment for acrylamide. It was a job well done! The charge questions were answered in detail. Responses were logical and well-supported by the text. I had only one small editorial note. I agree with the use of the term "toxicokinetic" instead of "pharmacokinetic" in discussing the kinetics of a toxin rather than a pharmaceutical agent. However I think we need to be consistent. I suggest changing "PBPK" on page 8, line 9 to "PBTk." On page 11, line 12, I suggest changing "pharmacokinetics" to "toxicokinetics."

I like having possible modes of action described in an Appendix.

7. Dr. David Allen

-Page 10, line 2: A discussion of the range of panel views on the range of UF that might be recommended due to data deficiencies would be useful; I could not find this discussion in the subsequent sections of the report.

8. Dr. John Balbus

a) Are the original charge questions to the SAB Panel adequately addressed in the draft report?

Yes; the report is well organized according to the original charge questions, and the text does address the questions.

b) Is the draft report is clear and logical?

Yes; the report is well organized and understandable.

c) Are the conclusions drawn, and/or recommendations made, supported by information in the body of the report?

Yes; the body of the report supports the conclusions and recommendations.

9. Dr. Duncan Patten

General Comment. In all three cases, the SAB review committees have offered excellent review and advice to EPA. The reviews are comprehensive and in sufficient detail to allow EPA staff to reconsider their positions on topics of concern and to rewrite or rework the materials presented in the white papers.

Specifically on Acrylamide: This is an area that is very distant from the experiences. However, the committee's response to the use of non-cancer endpoints seems appropriate as long as it continues to point out the continued use and importance of the cancer descriptor. The recommendation of continued use of pharmacological models also seems appropriate.

Other than these general comments, I find I am not expert enough to fully understand the commentary of the committee and therefore may make inappropriate comments or recommendations.

10. Dr. Bernd Kahn:

I have read the three draft Reviews and consider them to be well written. I have the following two minor questions concerning the Toxicological Review of Acrylamide:

p.4, l. 12 and 18: what is the distinction between "SAB Members" and "Other SAB Members"?

p.12, l.5: Should not "uncertainty" be inserted before "factor"? In subsequent discussions of the UF, use of UF every time would clarify the discussions.

11. Dr. Agnes Kane:

The SAB review panel's assessment of the "Toxicologic Review of Acrylamide" is outstanding. The panel members had significant expertise on this topic and provided appropriate, up-to-date feedback on various technical aspects of this report. Appendix B and the updated references provided an excellent discussion of possible modes of action for acrylamide that serves as a model for future IRIS assessments. Congratulations to the panel members for their hard work!

12. Dr. McMullen:

I have read the documents and have found them to be well organized and easy to follow. I believe they answer the charge questions that were provided to the

committee. These documents are not in my area of expertise and as such I have little to add on there technical merit.

13. Dr. Timothy Buckley:

This looks to me to be very well done. I identified just a couple of issues for your consideration:

- a) On page 11: The document, on lines 1-5 states: “The use of the Weibull-in-time multistage-in-dose analysis is a reasonable and scientifically justifiable way to take into account the early mortality in the high dose group in the male study. The decision not to employ this analysis, in the case of the female because mortality across treatment and control groups did not differ and the overall survival appears to be fairly good, is also reasonable.” **This underlined sentence seems to be cumbersome and unclear.**
- b) On page 13: Lines 12-14 state: “The SAB was asked to comment on (1) whether the document is logical, clear and concise, (2) if the discussion is objectively and transparently represented, and (3) if it presents an accurate synthesis of the scientific evidence for non-cancer and cancer hazard. **I don’t see a response to these questions. There may be a need to include a paragraph up front in the ES to address these global issues.**
- c) On page 20-21, Lines 1-2 state: “In the end, the Panel suggested that EPA undergo the exercise of generating an RfD from the Calleman study for purposes of comparison with the RfD derived based on the animal data. **This strikes me as an important recommendation that should be captured in the Executive Summary.**

14. Dr.