

**Comments from Members of the Chartered SAB on the SAB Draft Report:
SAB Review of the EPA’s Draft Toxicological Review of Ammonia (5/1/2015)**
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Comments from Lead Reviewers

Comments from Dr. George Daston

We were asked to address four specific questions as part of the quality review.

1. whether the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed;
2. whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report;
3. whether the Committee's report is clear and logical; and
4. whether the conclusions drawn or recommendations provided are supported by the body of the Committee's report.

General Comment: I was a lead reviewer on this draft report and the draft report on the IRIS assessment for trimethylbenzenes. Both reports had the same four general charge questions, requesting feedback on how well the new IRIS format has complied with the NRC recommendations stemming from its 2011 formaldehyde review. Given that the charge questions are the same, the SAB should consider combining the responses from both reports into one set of consistent recommendations.

Question 1: I believe that the charge questions were adequately addressed. The review is thorough and provides a number of constructive recommendations for each charge question. As noted in my general comments, the SAB should consider combining the responses to the general charge questions with those from the trimethylbenzenes draft report to ensure consistency.

Question 2: I found the report to be comprehensive. There were a couple of places where I would like to see greater clarity, however. First, while the report supports the choice of Holness et al. as the critical study for establishing the inhalation RfC, they urge EPA to contact the authors of the study to request individual exposure data to determine whether an alternate point of departure could be calculated (i.e., could the conservative estimate be replaced with data). If these data are not forthcoming (which is a distinct possibility for a study published more than 25 years ago), does the committee's support for Holness as the critical study change? Another recommendation is to more explicitly consider the Holness study in a weight-of-evidence context with other studies that had better exposure control to determine the consistency of the entire data set. If the individual data for Holness are unavailable, does the committee feel that its relative importance changes in the weight-of-evidence?

Second, the committee asks for more discussion on endogenous sources and concentrations of ammonia. The committee should provide more guidance to EPA as to why this is important. I.e., is it because exogenous ammonia would be expected to be additive to endogenous, or is it to ground truth the RfC vs levels of endogenous ammonia that are associated (or not) with pathological conditions?

Question 3: The report was logical and the recommendations are clear and comprehensive. The executive summary is concise and readable.

Question 4: The conclusions and recommendations are supported by the body of the report. I also thought that the cover letter did a good job of distilling a long report, with many recommendations, into a few very important points.

Comments from Dr. Elizabeth Matsui

1) Were the charge questions adequately addressed?

YES

2) Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

- For toxicology- and risk assessment-related content, I will defer to the reviewers with toxicology and risk assessment expertise
- With respect to the discussions about the effect of ammonia on lung function, the report expresses a concern that the degree of lung function decrement associated with ammonia exposure is not clinically relevant. This magnitude of effect (i.e. 200ml reduction in FEV1) may be clinically relevant in several instances:
 - Whether a 200ml reduction in FEV1 is associated with clinical symptomatology (cough, wheeze, etc.), depends on the individual's baseline FEV1. An individual's starting FEV1 may be low because he/she is a child, or he/she has underlying lung disease such as asthma or COPD, and a drop in FEV1 of 200mls in these individuals may be associated with clinical symptoms of lower respiratory tract involvement.
 - It is noteworthy that a 200ml increase in FEV1 following bronchodilator administration is considered evidence of bronchodilator responsiveness, so that this magnitude of change in FEV1 (increase, in this instance) is clinically relevant in this test that is used to evaluate people for lung disease.
 - It is also noteworthy that, on average, the decline in FEV1 for non-smoking adults is 25mls/year. Although this magnitude of decline is considered "normal", a 200ml decrease is equivalent to the decline that would be observed over 8 years in a non-smoking adult. Although it is reassuring that the lung function decrements that were observed apparently were reversible overnight between shifts, it would be helpful to understand if longer-term chronic exposure is associated with any irreversible loss of lung function.
 - Adults often have decreases in lung function before they report symptoms or exhibit physical exam findings of lung disease or an exacerbation of underlying lung disease. Thus, the assumption that because a change in lung function is not associated with clinical manifestations, it is not relevant or important, is flawed.
- The report also expresses some concern about studies that used self-reported respiratory symptoms as an outcome, but self-reported respiratory symptoms are a well-accepted outcome measure (and sometimes the primary outcome of clinical

trials), and in many cases valid, depending on the instrument used.

3) Is the draft report report clear and logical?

Overall, the draft report is very clear and logical.

- The report recommends that the literature search be updated since there has been a lapse of ~18 months since the literature search was completed. Since technical documents take a long time to write, this will be a recurring issue. Perhaps there should be a recommendation that, in addition to a systematic review approach to literature searches, that a standard approach be developed to address the fact that new, relevant scientific literature will likely emerge between the time that the literature search has been completed and the document is ready to be finalized.
- On page 50, line 30, there is a section heading titled, “Additional Studies on Neurotoxic Effects from Inhalation Exposure to Ammonia.” This section of the report, however, is almost entirely a discussion about non-inhalation exposure, and it appears that this is the case because the report is drawing on data about non-inhalation routes of exposure to make the case that it is possible that there are neurologic effects of inhalation exposure. If this is the case, this point could be made more clearly in this section.

4) Are the conclusions drawn or recommendations provided supported by body of draft report?

YES

Comments from Dr. Paige Tolbert

The following comments are provided in my role as discussant/quality reviewer of the advisory report, dated May 1, 2015, by the SAB Chemical Assessment Advisory Committee Augmented for the Review of the Draft IRIS Ammonia Assessment (EPA Draft Assessment, August 2013).

Quality Review Question #1: whether the original charge questions to SAB Committee were adequately addressed.

Response:

The SAB Committee has done an excellent job addressing the original charge questions posed by EPA. The Committee has provided a thoughtful and rigorous response to each charge question and a number of helpful suggestions.

Quality Review Question #2: whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee’s report

Response:

I did not find major technical errors, omissions or issues that are inadequately dealt with in the report.

A couple of minor technical errors are noted here:

The study by Mirabelli et al, 2007, is characterized as a controlled human exposure study, but it is not. (p. 4, line 21)

Reversibility is referred to as a confounder; this is incorrect. (p. 4, lines 26-28)

Quality Review Question #3: whether the Committee's report is clear and logical

Response:

Overall, I found the Committee's report to be clear and logical. The report is well-written and scientifically sound. The report effectively communicates the Committee's guidance with respect to EPA's charge questions. One general exception regarding clarity: the report was not always clear regarding its recommendations for action. In many instances, it is not clear whether the recommendation is to alter the current assessment or to encourage implementing certain approaches in future IRIS assessments. While the committee acknowledges that the EPA is in the process of phased implementation of the NRC recommended changes to IRIS assessment methods, it would be helpful to be clear regarding whether a particular recommendation is to change the current document or not. For example, in section 3.1.3. Process for Evaluating Critical Studies, the following is listed as a recommendation (p.5, Lines 5-6): "While in some circumstances professional expert judgment is needed, a systematic approach should be adopted to provide more transparency and clarity." Is the committee making this recommendation as a future goal as the agency proceeds into the next phase of implementation of the NRC recommendations or as a modification to the current assessment?

Similarly, regarding the literature search strategy, the following statement appears (p. 9, lines 8-9): "the SAB encourages EPA to reconsider the inclusion of publications beyond the March 2013 deadline (e.g., Hovland et al., 2014)." It is not clear what is being suggested here. First, I think the committee means "exclusion" not "inclusion." Second, while a similar statement appears in the Executive Summary suggesting that the committee felt strongly about this point, it does not rise to the level of being listed as a recommendation in this section. Third, the committee needs to be clear about whether it is suggesting a change in the deadline or a different level of review (e.g., triage) of the most recent literature. It is impractical for the EPA to conduct a thorough, systematic review of all publications through the present; the document would be in an endless cycle of real-time updating and review. Perhaps it might be reasonable to recommend that the deadline apply to the systematic review but that publications beyond the deadline be considered if they have clear potential to meaningfully affect the conclusions of the report (i.e., game-changers). Is the publication referred to in this statement (Hovland et al 2014) a key publication that would change the conclusions of the present report? The issue of how much updating should be done as drafts go through stages of approval has come up in previous SAB reviews of EPA assessments of other chemicals.

The committee also recommended that additional databases (OECD's HPV database, the Registry of Toxic Effects of Chemical Substances, and others) be incorporated into the search strategy. Does the committee feel major publications were missed? How strongly are you recommending this?

The committee suggests that since the generic Preamble is to be included in all IRIS assessments it may warrant separate review by the SAB. In the meantime, given that this Preamble appears in a second assessment (trimethylbenzenes) currently being reviewed by the SAB, it might be helpful to suggest that EPA look at the feedback on the Preamble offered by both review committees and revise the Preamble for both assessments accordingly (e.g., mention this in the cover letter?)

Additional editorial comments:

p. 9 line 33: “presents” should read “present”

p. 10, line 32: “casual” should read “causal”

p. 15, lines 40-44: paragraph at bottom of page appears to be out of place as it relates to Charge Question D1 not D2.

Quality Review Question #4: whether the conclusions drawn or recommendations provided are supported by the body of the Committee’s report

Response:

The conclusions drawn and recommendations provided are supported by the body of the Committee’s report. Overall, the Committee’s conclusions and recommendations are scientifically sound and well-justified. The Committee did an excellent job.

Comments from other SAB Members

Comments from Dr. Joseph Arvai

1. Were the charge questions adequately addressed?

Yes.

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

Not to my knowledge.

3. Is the draft report clear and logical?

Yes.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes.

Comments from Dr. Sylvie M. Brouder

Q1) Charge questions adequately addressed?

Yes. In general, I found the charge questions to all be addressed in fairly meticulous detail especially in regards to the science of ammonia toxicology. In comparison, I found the responses to the charge questions concerning methodology to be a bit less specific and detailed. The SAB review clearly notes methodological shortcomings at a very high level (for examples, notes lack of clarity in EPA's literature search strategy) but seems to avoid making some very specific recommendations regarding articulating a search strategy and implementation of inclusion/exclusion criteria such that selection of articles would be reproducible by others.

Q2) Technical errors or omissions / issues not adequately addressed?

Yes with the exception of the text on "weighting of evidence." It was unclear to me whether this comment was intended to highlight qualitative, quantitative or both aspects of integration/syntheses of studies. Is the concern that effect variances within specific studies were not adequately handled during synthesis versus or that more qualitative aspects of syntheses were not adequately prepared (such as qualitatively including some study quality criteria the relative weighting of a particular study contribution to the syntheses)?

Q3) Draft report clear and logical?

Yes, the report logically and systematically addressed the charge questions and the narrative is easy to follow.

Q4) Conclusions drawn / recommendations provided supported by body of draft report?

Yes. Perhaps there is opportunity to make stronger (or more specific recommendations) to move EPA toward a more rigorous, systematic review protocol. The full and rapid implementation of SR as a standard protocol is certainly desirable from multiple perspectives (rigor, lack of bias, comprehensiveness, efficiency (especially if appropriate infrastructure is enabled for cumulative SR on a given topic)). Based on this assessment effort, are there any more specific recommendations that SAB can provide to EPA on most important next steps for SR protocol implementation? Note, I am just raising this point for reflection so that the opportunity is not missed if something more specific can be offered. Also, can/should the Executive Summary be more specific on important next steps to realizing routine use of SRs as envisioned by the NRC. Note, the recommendation to secure the original data from a 1989 foundational study is well intentioned but is it really a reasonable suggestion/recommendation give years elapsed?

Comments from Dr. Costel Denson

General Comments.

The report is judged to be complete and thorough. Nonetheless, the Executive Summary in its present form is quite lengthy and is thought to capture more than the essential points. In addition, as reflected in the index, the page numbering is confusing as one moves from the Executive Summary to the main body of the report,

1. Were the charge questions adequately addressed?

There are an inordinate number of charge questions, but they are judged to be adequately addressed.

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

None. This reviewer was unable to identify any

3. Is the draft report clear and logical?

Yes

4. Are the conclusions drawn or recommendations provided supported by the body of the report?

Yes

Comments from Dr. Robert J. Johnston

1) Were the charge questions to the committee adequately addressed?

Yes, the report has adequately addressed the charge questions.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

There are no technical errors or omissions that are not adequately addressed by the draft report.

One issue that warrants additional emphasis in the SAB report, in my opinion, is the lack of a clear and formal set of systematic review protocols underlying EPA's toxicological literature review, and the potential consequences of this omission. This includes a lack of a comparable measure of precision in effect sizes. The SAB addresses this issue in sections 3.1.3. Process for Evaluating Critical Studies and 3.2.2. Literature Search Strategy/Study Selection and Evaluation. The SAB review correctly notes that "adoption of past and more recent recommendations [for systematic reviews] by the NRC (NRC, 2014) is an evolving process" and is "thus not yet reflected in the current ammonia assessment." The SAB review recognizes that "realizes that standard protocols for IRIS-specific systematic review of the literature have not yet been developed." It also highlights (again, correctly) various ambiguities in the literature search and study selection process for EPA's toxicological review. However, the SAB review does not note the risk of selection biases that can affect results of data syntheses and meta-analyses that are not subject to such rigorous systematic review processes. Without clear systematic review protocols, it is possible to draw incorrect conclusions from reviews of the literature, e.g., due to systematic selection and publication biases in the literature under study. This has been shown across different areas of the scientific literature. This concern does not appear to be recognized sufficiently in the *Draft IRIS Toxicological Review of Ammonia* or the SAB review. While I agree with the SAB review that the Agency is to be commended for its progress thus far, I believe that more emphasis should be given to the need for systematic review protocols.

3) Is the draft report clear and logical?

Yes, the draft report is clear and logical

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes. However, as noted above, there should be additional emphasis on the need to move quickly towards the application of formal and transparent systematic review processes.

Comments from Dr. Nancy K. Kim

General Comment

The report was well written easy to follow.

1. Were the charge questions to the committee adequately addressed?

Yes.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

Not that I noticed.

3. Is the draft report clear and logical?

Yes, for the most part.

1. The report should clarify if Appendices B and C are consensus comments from the committee or if they are comments for EPA's consideration.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes.

Minor comments

1. Page 9, line 33. Remove s from presents.

Comments from Dr. Lois Lehman-McKeeman

The charge questions have been adequately addressed, and the report is well-organized. The comments provided are very clear and presented logically, including the recommendation for additional data, particularly on sources of endogenous ammonium. All of the conclusions drawn are supported within the body of the draft report. There do not appear to be any technical errors in the document,

The SAB has provided constructive comments on the organization of the IRIS toxicological assessment. These recommendations should be helpful in streamlining these assessment documents, and the EPA is encouraged to carefully consider these comments.

The SAB also provided additional suggestions for additional scientific details concerning sources of endogenous ammonium (Section 3.2.8). The additional information provided is scientifically accurate and definitely far more complete than that provided. Inclusion of this additional detail should be included in the final document as it will improve the overall scientific completeness of the assessment.

Comments from Dr. James R. Mihelcic

1. Were the charge questions adequately addressed?

yes

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

None that I identified

3. Is the draft report clear and logical?

Yes, in addition, the recommendations provided to each of the charge questions are clear.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes

Other issue

regarding the footnote on bottom of page 6 (page 21 of pdf document), is the pKa for dissociation of NH_4^+ 9.3 and not 9.2 as written?

Comments from Dr. James Opaluch

1) Were the charge questions to the committee adequately addressed?

Yes

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

Not that I am aware of.

3) Is the draft report clear and logical?

I found a few parts of the report to be unclear, and recommend the following.

- I found the following sentence to be difficult to read. (Page 2 Section 3.1.1, lines 14-16) “It must be made clear that this is a brief description of the policies and procedures already adopted by EPA and that the original guidance documents are controlling, not the abbreviated description in the Preamble.”

I recommend combining this with the next sentence to read:

“It must be made clear that the Preamble does not establish new policy. The Preamble is intended to be a brief summary of policies and procedures previously adopted by EPA, and original guidance documents are controlling, not the summary embodied in the Preamble.” The Preamble should also contain an explicit reference to the original guidance documents.

- I’m confused by the sentence (page 2, lines 30-31): “EPA should clearly state that the Preamble is generic and not necessarily applicable to the

ammonia assessment.”

Presumably the Preamble *is* applicable to all chemical assessments, including the ammonia assessment. Perhaps the report intends to say “... the Preamble is *not specific* to the ammonia assessment ...” or maybe “... some elements of the Preamble may not be applicable to the ammonia assessment ...”

- Recommendation 2 (Page 4, line 1-2) does not provide sufficient guidance on what should be done. Since this is a *recommendation*, the report should clearly indicate a suggested action. My reading is the report intends to say that summaries “...are informative, but perhaps a bit too concise”. The report should be explicit about whether more detail is needed in the text, or whether it is sufficient to include a carefully constructed set of hyperlinks in the electronic version. In my opinion, we cannot expect everyone to be reading from the electronic version.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

The Recommendations on page 5 are not motivated by the text above. The text says “EPA has adequately and appropriately addressed the scientific issues raised by public commenters.” But then there are Recommendations for expanding upon the response to comments, which seems contradictory. The text might say “In general, EPA has adequately and appropriately addressed the scientific issues raised by public commenters, although the response to some comments should be expanded upon, as indicated below.”

Comments from Dr. Amanda D. Rodewald

1) Were the charge questions to the committee adequately addressed?

Yes. The draft report was thorough and provided useful feedback to the Agency.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

No. However, I recognize the topic is outside of my area of expertise.

3) Is the draft report clear and logical?

Yes.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes.

Comments from Dr. Daniel O. Stram

1. Were the charge questions adequately addressed?

Overall the answers to the charge questions seem very complete, both regarding adherence to the guidelines and recommendations of the 2011 NRC review regarding ISIS reports in general, and the specific questions that relate to the toxicological review of ammonia.

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

None that I could detect

3. Is the draft report clear and logical?

The report is written clearly and should be easily intelligible to the EPA authors of the Ammonia Toxicological Review, and more generally by the interested public and stakeholders.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes each recommendation is covered with care.

Comments from Dr. Charles Werth

1) Were the charge questions to the committee adequately addressed?

Yes, they were adequately addressed.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

I did not find any technical errors or omissions.

3) Is the draft report clear and logical?

Overall it was very well written, clear and logical. A few minor suggestions are provided for clarity.

i) Page 3, lines 32-34: Perhaps it's obvious, but should it specify that gastrointestinal endpoints are related to ingestion and not inhalation as inferred by the proceeding sentence?

ii) Page 4, line 21: Studies (plural) is used here, but only one study is cited. Is a citation missing?

iii) Page 4, lines 10-14: The charge refers to the new IRIS document structure, whereas this

recommendation drills down to the specific dataset used for the ammonia report (not as an example of some aspect of the structure, but as a specific recommendation). This seems off topic for the response to this charge.

iv) Page 16, line 2: On page 15, line 43 the impact of ammonia on brain function is specifically mentioned. Should this impact on RfD be mentioned in the recommendations, as the focus of the recommendations has been on gastrointestinal impacts?

v) Page 18, line 42: Are there any recommendations to be listed for the response to Charge Question E3?

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes, the conclusions and recommendations are supported by the body of the draft report.

Comments from Dr. Dawn J. Wright

1. Were the charge questions adequately addressed? Yes, very much so, as far as I could tell.
2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report? Not that I am aware.
3. Is the draft report clear and logical? Yes
4. Are the conclusions drawn or recommendations provided supported by the body of the draft report? Yes