

**Comments from Members of the Chartered SAB on *SAB's Review Comments on EPA's draft Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the IRIS (5-13-10 Draft)***

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## Comments from lead reviewers

### Comments from Dr. Jeffrey Griffiths

Review by Jeffrey K. Griffiths of the SAB's review of the "Toxicological Review of Inorganic Arsenic in Support of the Summary Information on the Integrated Risk Information System (IRIS)"

In my opinion, the original charge questions were adequately addressed; no technical errors or omissions exist; the report is admirably clear and logical; and the suggestions, conclusions, and recommendations are supported by the body of the report.

**The draft letter to the Administrator is admirably short. My suggestion is to make it even more admirably short**, by placing the most important paragraph, e.g. what the SAB recommends in response to the charge questions relating to arsenic, at the beginning of the letter. The letter could begin:

"Dear Administrator Jackson:

The EPA has asked the SAB to review the implementation of the 2007 SAB recommendations regarding arsenic toxicology. [skip to next to last paragraph of the cover letter:] The SAB recommends that , as the EPA proceeds with its revisions of the 2010 draft IRIS assessment, that more detailed information be included.... It is especially important that this IRIS assessment explain the rationale for critical choices in EPAs' cancer risk calculations...."

The history of the review and assessment process since the NRC panel report from 1999 and 2001 could be shortened or contained in the Background section of the report.

The EPA has asked the SAB to address questions relating to the 2007 SAB recommendations relating to:

- Evaluation of the epidemiological literature;
- Dose-response modeling approaches for human health outcomes; and
- The sensitivity of the risk analysis to the exposure assumptions used in the risk assessment.

In this Lead Reviewer assessment I will in general not word-smith but rather assess the coherence, validity, and soundness of the recommendations by the arsenic working group.

### **Charge 1.**

By way of background, in 2003 the US EPA decided to update the Integrated Risk Information System (IRIS) assessment for arsenic, in response to a National Research Council (NRC) panel

report in 2001. In the 2001 NRC report, it was recommended that the assessment of cancer risks associated with arsenic exposure be focused on lung and bladder cancer rather than skin cancers. It is well accepted that inorganic arsenic exposure is linked to lung, bladder, and skin neoplasms as well as to vascular, hematologic, neurologic, and developmental disorders (IARC, 2004).<sup>1</sup> Some recent literature has also shown a relationship to metabolic diseases such as type 2 diabetes. This discussion is linked to the determination of 'cancerogenic' risk. During the period 2003 to 2005 the US EPA developed an update on arsenic and cancer risk. The draft Toxicological Review of Inorganic Arsenic dating to 2005 was then reviewed by the SAB, which issued a report to the EPA Administrator in June of 2007. Based upon that report, the IRIS was further refined and a 2010 draft was prepared for SAB review.

The first charge to the SAB was,

**Please comment on the EPA's response to the recommendations and the conclusions of the SAB (2007) Arsenic panel regarding the evaluation of the epidemiological literature.**

Overall, the SAB working group found that the EPA was responsive to the SAB recommendations. I concur.

The SAB discussed:

- The selection of critical studies for determination of carcinogenic risk. The work group agreed with the EPA that the most appropriate dataset remains the Taiwanese information developed by Wu 1989, Chen et al 1988, and Chen et al 1992. The work group found that the limitations of these studies, as well as their strengths, were "well presented."
- A Review and Evaluation of available human studies. The 2007 SAB report requested that a group of 8 issues be addressed in any review and evaluation (exposure misclassification, temporal variability in assigning prior arsenic levels from recent measurements, imputed exposure levels, the number of exposed persons at various estimated levels of waterborne arsenic, response / participation rates, estimated exposure variability, control selection in case-control studies, and the influences of these factors of the magnitude and statistical stability of cancer risk estimates). The SAB work group found that the draft 2010 IRIS document is responsive to these issues and that the EPA had done a thorough job of describing the strength and limitations of the literature.
- Evaluation of other published epidemiology studies using a uniform set of criteria. The work group found the EPA to have been responsive, however that additional clarification and documentation on how various study design factors were considered and weighted. It was noted that aspects of studies discussed in the part 4.1 narrative were not included in the summary table of Appendix B. The work group recommended that the review of the literature "needs to more clearly state the set of criteria that were used in evaluating the studies.....and that the table of studies (Appendix B) be reformatted to present the study summaries more clearly and in a more consistent fashion including pulling any essential information from references into text for clarity." **It would be my recommendation that since the Wu (1989), and two Chen et al studies (1988, 1992) remain the studies**

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<sup>1</sup> IARC. 2004. Some Drinking-Water Disinfectants and Contaminants, Including Arsenic. IARC Monog Eval Carcinog Risks Hum 84:39-270.

**considered the best available for carcinogenic risk assessment, the summary table of Appendix B should make it quite clear what the evaluation criteria are so that the strengths and weaknesses of the other published studies are transparently and clearly visible to the readers.**

- Study power. The work group noted that many studies have limited power to detect associations between exposure and disease if one exists. A "negative" study may reflect limited study power rather than the absence of a relationship. This is particularly pertinent given the judgment that the Taiwanese studies remain important ones given their large population sizes and the large number of person-years of follow-up, which improve study power. The study group recommended that study power be commented upon in section 4.1 of the report as well as Appendix B, which makes eminent sense.
- Bias towards the null due to study limitations regarding exposure and confounders. The study group noted that different forms of bias in epidemiological studies can lead to an underestimation or overestimation of risk. For example, exposure misclassification tends to bias studies towards an underestimation of risk. They recommended the potential for underestimation or overestimation of risk be expanded in the discussion of the draft IRIS document. **It would be my recommendation that when possible, the potential for underestimation or overestimation of risk be included in the summaries of the other epidemiological studies reviewed in the 2010 IRIS document. This may improve transparency.**
- Consideration of epidemiology studies published after 2007. The working group recommended that the EPA consider including an appendix summarizing major new studies published since 2007. The charge to the working group regarded the assessment of studies work up to 2007 but not after. While this is a sensible recommendation which also improves transparency, and would display the responsiveness of the US EPA to new epidemiological data, **it would be my recommendation to pursue this on a parallel track rather than delay finalizing the draft 2010 IRIS assessment.**

## **Charge 2.**

The working group was asked,

**Please comment on the EPA's response to the SAB recommendations and conclusions regarding the approach to modeling inorganic arsenic cancer risks and the corresponding sensitivity analyses.**

In response, the working group determined that the sensitivity analysis was response to the prior SAB review. I concur.

The draft panel report notes the specific models which were recommended and the presence of these models in the draft 2010 IRIS document. They panel recommended graphic presentations to improve the interpretation of the results, and agreed with the EPA that "none of the alternative models materially changed the estimated risk levels versus use of a linear model." Other sensitivity issues were dealt with (potential bias by the high-end exposures, exclusion of a reference population) in a scientifically sound fashion. The working group

recommended that the rationale from a 2005 review of the use of a reference population be included in the IRIS review along with a description of the reference population.

Consistent with the latter recommendation, the arsenic working group recommended a more detailed description of the underlying Taiwanese datasets, a discussion of the well water arsenic measurements and their variability, and the inclusion of additional information on how the variability of water arsenic measurement affects the risk assessment. Furthermore, the working group requested that the modeling data and parameters, and that additional sensitivity analyses regarding the reference population be considered. **In general, all of these recommendations relate to transparency and clarity and are reasonable.**

Finally, the issues of mode of action; a linear versus non-linear approach; and risk calculation were addressed. The panel concurred that given the current state of knowledge, a linear approach should be accepted. It suggested that the results of the IRIS analysis should be interpreted in light of existing population-wide information regarding lung and bladder cancer risk. **These recommendations are reasonable.**

The point was made that a discussion regarding the risk attributable to drinking water may not be appropriate for the IRIS (which includes multiple routes of exposure) and may belong in a document specific to that issue. (For example, see Smith et al 2009, which suggests that increased lung cancer risks are similar whether arsenic is ingested or inhaled).<sup>2</sup> **While there is intense interest regarding the risk from inorganic arsenic in drinking water, on reflection this recommendation is reasonable given the role of an IRIS.**

**Charge 3.** The working group was asked, **Please comment on EPA's sensitivity analyses and choice of the exposure assumptions use in modeling cancer risk as recommended by the SAB (2007) Arsenic panel.**

The working group felt that the EPA was partially responsive, and gave a detailed set of recommendations and examples to improve transparency of the exposure assumptions, and the rigor and transparency of the sensitivity analysis. **I concurred with this assessment of partial responsiveness and found the list of examples and recommendations to be comprehensive.** This list (in summary) relates to

- Better explanations regarding the results of the sensitivity analyses;
- Justifications for the drinking water consumption rate assumptions;
- A sensitivity analysis relating to gender specific water consumption;
- Water arsenic concentration assumptions;
- Water consumption by susceptible groups;
- More complete and graphical analyses; and
- The conduct of selected analyses where more than one exposure assumption is varied.

To this discussion I would note that the examples on how water intake may vary did not include ones relating to physical labor.

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<sup>2</sup> Smith AH, et al J Exposure Science and Environ Epidemiology 19:343-348.

As to the exposure assumptions, the working group noted that in face-to-face meetings with the EPA, "much of the documentation addressing the scientific basis of the exposure assumptions was provided through separate documents which could be incorporated into the draft IRIS, and then listed several examples of issues which could be addressed and connected via this incorporation. **These examples were logical and reasonable ones, and the suggestion of incorporation of the "scientific basis of exposure assumptions" made sense.**

Final comments regarding a justification for limiting non-water exposure to consumption was requested. The EPA's assumption that only ingestion of food and water are important may at times be appropriate but other routes of exposure should be discussed. In the Smith et al reference provided above, for example, an occupational inhalation exposure was compared to an ingestion route of exposure. If indeed the suggestion is to be made that the IRIS document is one that relates to all relevant exposures, then this IRIS may be missing the boat when other routes of exposure exist.

## Comments from Dr. Steve Heeringa

The SAB workgroup has done an excellent job in its review of the EPA document. Each of the charge questions is addressed thoroughly. The SAB report is clear when it supports the major positions of the IRIS document (e.g. the Taiwanese data of Wu (1989) and Chen et al. (1988,1992) as the best available data for determining population risk). The report is concise in making recommendations for additions to the report (graphical analyses), clarification of assumptions and weighting of criteria for assessment and transparency in exposition. In terms of the discussion of statistical methodology, I found no major technical errors in the report. Many of the recommendations made in the report for additional sensitivity analyses of clarification of data evaluation criteria are completely consistent with the original findings from the 2005 review. There are a few minor issues that I have with the wording of the report but these do not rise to the level of technical error.

As noted above, the report is clearly written. The justification in support of positions taking by EPA in the IRIS document and the argument for additional work or clarification of the report wording are logically presented.

The conclusions and recommendations in the committee's report are consistently defined and supported in the body of the report.

I had just a few minor points where the report might benefit from rewording or clarification. On Page 4, the first section opens with a request that EPA attempt to present power calculations for the many epidemiological studies that were reviewed ( case/control and prospective cohort designs) . Post hoc, an assessment of the potential power to detect true differences in cancer incidence in the population may be difficult. Nevertheless, the recommendation of the subcommittee still has value since if the post hoc assessment suggests power to detect true population differences are all extremely low (e.g  $<.5$ ) it suggests that on a case-by-case basis, null results from the epidemiological studies may be attributable to insufficient sample size. In the recommendation (Paragraph 2 on page 4), the report refers to a "...quantitative presentation or discussion of *relative* power". I recommend that the report drop the adjective "relative" since it implies that power of  $(1-\beta_1)=.5$  for study 1 vs.  $(1-\beta_2)=.25$  is an advantage for Study 1 when it fact Study 1 still provides at best an even chance of accepting the null when the alternative is true.

Page 4, the recommendation for additional discussion of bias. This recommendation could be made more specific. As written it invites a lengthy review of bias and confounding in case-control and cohort study designs. In the recent February 2010 FIFRA SAP review of epidemiological research and its role in risk assessment, "Draft Framework and Case Studies on Atrazine, Human Incidents, and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment", charge questions pertaining to misclassification and confounding generated a "textbook" response. The EPA might actually borrow a discussion from that report. Rather than incorporate a lengthy discussion, the SAB report might suggest that the IRIS document include a simple table that identifies potential biases (misclassification of exposure, misclassification of disease, omitting confounders, etc.) and the potential magnitude and direction of bias in inferences that are draw from the study data. A

simple summary could then relate these sources of bias to their potential in the data and methods used in the IRIS assessment.

Page 6, Recommendation re variability of well water arsenic concentrations. The fifth sentence might be rewritten to read “.. the variability of measurements *both within and across wells* within a given village ...” . This minor change would communicate a recommendation for estimation of the relative magnitude of the between and within well components of variance. As suggested in the remainder of this paragraph, this would lend some insight into the stability of well concentrations over time and the impact of assuming that a resident of a village always consumed water from the same well.

Page 7, paragraph 3, line 8 – Minor terminological issue. The term parameter variations is used to refer to non-water intake value ( a parameter of the model) and the reference population ( a source of data). Suggest separating out the reference population choice as in “.. parameter variations and choice of a reference population...”

Page 12, para 1, line 7. This is probably only my personal preference but the phrase “...EPA does a reasonable job...” is not specific in terms of evaluating their work. I suggest, dropping “Although EPA does a reasonable job of discussing these reports,” and just pick up with “ The current report lacks specific rationale...”.

## Comments from Dr. Jonathan Samet

### General Comments

In general, the draft SAB comments are satisfactory and thoughtfully and comprehensively address the charge questions from EPA. The Administrator will be provided with a clear assessment of the Agency's responsiveness to the prior comments from the SAB. My specific comments below, largely relate to portions of the draft dealing with methodological issues specific to the epidemiological aspects of the comments.

*Page 2, "The limitations of the studies are well presented, particularly regarding the ecologic study design, ..."*

Studies described as "ecological" are often considered to be inherently weaker than individual-level studies. It is correct that the study by Chen et al. is of ecological design; that is, exposure has been assigned at the population (village) level. However, exposure, i.e., concentration of As in drinking water is the same for all persons within a particular village, although dose varies among individuals.

*Page 4, first paragraph:*

This paragraph needs conceptual "tightening" in discussing considerations of power. The first sentence should be rewritten as follows: "The power of an epidemiological study is the probability of detecting an association of a specified strength between exposure and disease if one exists." Additionally, the term "negative study" should be avoided; I assume that "negative" means not achieving statistical significance.

*Page 4, second paragraph:*

Emphasis should be given to assessing the width of confidence intervals. It would be reasonable for the report to include a set of power curves for various sample sizes and effect sizes, but necessarily to calculate power for completed studies. Power calculations require an a priori assumption of effect size; do we know what effect to expect?

*Page 4, fourth paragraph (Recommendation)*

Emphasis should be given to estimating the quantitative consequences of any bias. While the existence of bias can usually be proposed with some certainty, the key issue is whether the quantitative consequences of bias are of sufficient magnitude to be of concern. Methods are available for this purpose (see, for example: Lash, Fox, and Fink: *Applying Quantitative Bias Analysis to Epidemiological Data*, Springer, 2009).

*Page 5, Recommendation*

Of course, there are always new studies, but guidance should be given as to what makes a study "major" and potentially pivotal, e.g., large sample size or effect estimate substantially different from that estimated by Chen et al.

*Page 8, bottom of page*

These considerations are quite general. The Agency should have a reasonable and standardized approach to describing the basis for assumptions.

## Comments from Dr. Paige Tolbert

The following comments are provided in my role as discussant/quality reviewer of the SAB Inorganic Arsenic Cancer Review Work Group's Review Comments on EPA's Draft Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System.

In reviewing the report by the SAB Work Group, the discussants are asked to respond to the following Chartered SAB quality review questions:

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

### **Quality Review Question #1: whether the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed.**

#### **Response:**

The SAB Work Group has adequately addressed the original charge questions posed to them by EPA.

The following questions constitute the original charge questions to the SAB Work Group:

Work Group Charge Question #1. Please comment on EPA's response to the recommendations and the conclusions of the SAB (2007) Arsenic panel regarding the evaluation of the epidemiological literature.

Work Group Charge Question #2. Please comment on EPA's response to the SAB's recommendations and conclusions regarding the approach to modeling inorganic arsenic cancer risks and the corresponding sensitivity analyses.

Work Group Charge Question #3. Please comment on EPA's sensitivity analyses and choice of the exposure assumptions used in modeling cancer risk as recommended by the SAB (2007) Arsenic panel.

I will comment on the adequacy of the Work Group's response to each of these charge questions in turn.

Regarding Work Group Charge Question #1, the Work Group concluded that the EPA had been responsive to the SAB 2007 recommendations in evaluating the published epidemiology studies, and concurred with the choice of the Taiwanese dataset as the most appropriate data to use in the risk assessment. Further, the Work Group expressed some concern regarding EPA's presentation

of the review of the epidemiologic studies and provided specific recommendations regarding how the evaluation could be improved. The Work Group adequately addressed Charge Question #1. It is well-justified in finding that the EPA was responsive to the original SAB recommendations regarding review of the epidemiologic literature and in finding that the Taiwanese data continues to provide an appropriate basis for the risk models. The Work Group found that the draft IRIS report presents a comprehensive overview of the epidemiologic literature, and is responsive to the 2007 SAB recommendation that a specific set of issues (the eight items listed on page 3 of the Work Group draft report) be reviewed in evaluating the studies. Moreover, the Work Group is on target in indicating that the review of the epidemiologic literature needs additional work. As pointed out by the Work Group, EPA needs to more clearly state the criteria used in evaluating studies and present the review in a more systematic and synthetic way; this will make EPA's choices regarding data used in the risk models more transparent and compelling. While it is always difficult to extract a uniform set of descriptors from the various studies comprising the body of literature on a topic, the Work Group is correct in pointing out that Table B-1 needs further work. It does not consistently convey the most important information about each study, such as sample size (for each exposure grouping if available), the estimate of effect (e.g., RR) and associated estimate of stability of the estimate, and expected biases. Furthermore, the text evaluating the literature in Chapters 4 and 5 of the IRIS report needs additional synthesis summarizing the relative merits of the studies to increase transparency regarding the ultimate decision to rely on the Taiwan data. For instance, a qualitative judgment of the relative bias to the null resulting from lack of individual exposure estimates across different studies could be provided (e.g., might this be expected to be a greater bias where people drink more bottled water and have higher residential mobility?) Overall, this reviewer concurs with Work Group assessment in response to Work Group Charge Question #1, although several minor clarifications to the Work Group report are suggested in my response to Quality Review Question #2.

Regarding Work Group Charge Question #2, the Work Group found that EPA was responsive to the 2007 SAB review in performing requested sensitivity analyses of the dose-response modeling and concurred with the EPA rationale for choosing a linear low-dose extrapolation risk assessment approach. The Work Group agreed with EPA's assessment that for the most part the various sensitivity analyses performed did not materially change the estimated risk levels. For the one case where the sensitivity analyses yielded materially different risk estimates, i.e., the sensitivity analysis incorporating a reference population, the Work Group requested that additional information be incorporated into the IRIS report from the relevant 2005 issue paper and the Work Group suggested further analysis of this issue. The Work Group further requested additional description of the Taiwan data to make the IRIS report self-standing, and publishing the data and parameter tables used in its modeling analysis for greater transparency in the presentation. This reviewer finds that the Work Group response to Charge Question #2 is adequate. The reviewer agrees with the Work Group's assessment that EPA was responsive in performing sensitivity analyses and that EPA was justified in its use of a linear low-dose extrapolation in its risk assessment. As the Work Group emphasized, the linear model is the prudent choice given lack of compelling evidence of a threshold or other dose-response form. The Work Group request for further work and expansion of the IRIS report as described above is also well justified.

Regarding Work Group Charge Question #3, the Work Group found the EPA Draft IRIS report was partially responsive to the 2007 SAB review. With respect to the sensitivity analysis of the impact of drinking water consumption and non-water arsenic intake assumptions on the estimated cancer potency, the Work Group found the approach to be minimally adequate, and recommended that EPA expand its treatment of this issue with more explanation of the observed sensitivity to the non-water intake assumption, better justification of the default assumptions regarding drinking water consumption and non-water arsenic intake rates, more description of how village well measurements were used in the water concentration assumptions, more complete presentation of sensitivity results, possible consideration of sensitivity to selected sets of exposure assumptions, and explanation of the rationale for not including some of the analyses suggested by the 2007 SAB review. This reviewer finds the Work Group response to Charge Question #3 adequate. The Work Group provides the basis for the finding that the EPA report is minimally responsive, and provides detailed suggestions for how the EPA report could be improved to be more responsive to the original SAB input and to increase transparency.

**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:**

This reviewer did not find technical errors, omissions or issues that are inadequately dealt with in the report. However, I suggest the following clarifications to improve the Work Group report:

- The Work Group report, as written, appears to recommend that power calculations for each study be added if possible (p. 4). While the relative power of the various studies is important to convey, this should not be done by presenting power calculations. Power calculations are useful in planning a study, but after the study is completed, the most informative presentation of epidemiologic findings that combines both the observed results and reflects the power of the study is the relative risk point estimates for a specified exposure comparison and the associated confidence intervals. Furthermore, systematic presentation of numbers of individuals in each exposure stratum provides the reader with a sense of relevant sample size within strata and the robustness of the exposure contrast. For instance, the required sample size will be larger for a smaller exposure range (e.g., the U.S. studies), since the expected magnitude of the RR for low-level exposure is lower. The recommendation regarding presentation of power should be refined and clarified in the Work Group report.
- p.2 of the Work Group report, add "Taiwan" to sentence: "The limitations of the *Taiwan* studies are well presented, particularly the ecologic study design..." to clarify that the Work Group is referring to the Taiwan studies here, not the entire body of literature, referred to in the immediately preceding text.
- Delete "toward the null" in the heading "Bias *toward the null* due to study limitations regarding exposure and confounders" (p.4) – while exposure error generally leads to a bias to the null, uncontrolled confounding can bias results upward or downward.

- This reviewer has some concern about the Work Group recommendation to summarize major studies since 2007 (p.5). To make the judgment that selected studies are major and have a potential impact on the risk assessment would require careful deliberation of the body of new studies, which could lead to a substantial delay. A quick review highlighting important developments could be helpful, but doing this in a cursory way could lead to the process becoming mired in debate. The Work Group may want to revise the language regarding this suggestion to give EPA wide latitude in determining whether to pursue this option.

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

**Response:**

As described above, this reviewer finds that the Work Group's report is clear and logical. Other than the minor clarifications outlined in response to Quality Review Question #2, above, the report effectively communicates the Work Group's assessment of the draft IRIS report with respect to EPA's charge questions.

**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 Work Group's report. As described in response to Quality Review Question #1, the Work Group provides ample rationale for its recommendations. Overall, the Work Group's conclusions and recommendations are scientifically sound and well-justified.

**Comments from other SAB Members**

**Comments from Dr. Otto Doering**

I believe that the charge questions were adequately addressed - the responses were highly specific to the questions asked.

I did not find technical omissions, but this is not my field.

I found it clear and logical.

I believe the recommendations given and questions asked by the review committee are well supported.

**Comments from Dr. David Dzombak**

1. Were the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed?

Yes.

2. Were there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report?

No

3. Is the Committee's report clear and logical?

For the most part, the report is clear and logical. There is one response from the committee to Charge Question 2, in the recommendation pertaining to the last subsection on "Explanation of the risk calculation" (top of page 8), which contains some contradictory statements. After making some recommendations in the beginning of the recommendation for additional analysis of some specific aspects of water contamination with inorganic arsenic, the section concludes with the statement that "this discussion is probably better suited for inclusion in other risk assessments and characterization documents developed by the Agency."

4. Were the conclusions drawn or recommendations provided supported by the body of the Committee's report?

The conclusions and recommendations are well supported by the body of the Committee's report. The conclusions are summarized perhaps too briefly in the letter to the Administrator, i.e., in one paragraph at the end of the two-page letter. The preceding material in the letter is a long explanation of the history of the process to re-examine the EPA toxicological review of inorganic arsenic. The amount of space devoted in the letter to background information seems excessive compared to the very concise statement of findings and recommendations.

### **Comments from Dr. Rogene Henderson**

Comments on SAB's Review Comments on EPA's draft Toxicological Review of Inorganic Arsenic

Rogene F. Henderson

1. The charge questions were adequately addressed.
2. I found no technical errors.
3. I thought the writing was exceptionally clear. Good job!
4. The conclusions were supported by the text.

There were some typos. The pages are not numbered, but I will try to indicate where corrections are needed.

First page of letter, next to last line: Dimethylarsinic acid should not be capitalized in the middle of the sentence. It should be written dimethylarsinic acid.

Second page of letter, last line of last large paragraph: "theses" should be "these"

Page 3 of report: There is an extra period about midway in the next to last paragraph.

Page 4 of report, middle of page: The phrase, "this flaw possibly lead to the underestimation of risk" should be "this flaw possibly led to an underestimation of risk."

#### REVISION ON 6/18/10

After hearing the public comments on this document on June 16, 2010, I am concerned that the subcommittee was not given broad enough charge questions to review the EPA draft document adequately. I do not think the SAB should approve the review of the document until this issue is examined in more detail.

**Comments from Dr. Bernd Khan**

The report addresses the charge questions but is difficult to review by one who does not know the subject in detail. Specifically, it would be helpful if the SAB report stated the pertinent information at the appropriate points of discussion. This might include some, but not all, of the following: the relation of As concentrations in lung and bladder relative to the steady-state As intake rate; the relation of lung and bladder cancer incidence to As concentration; the contribution of As in drinking water to total daily intake; the expected retention of inorganic As relative to various forms of organic As; and the expected magnitudes of these various organic forms relative to the inorganic form and the extent to which they transform in nature

The report is well written, with the following minor typos,

- p. i, 3rd line from bottom: delete skipped line
- p. ii, par. 2, last line: don't forget to insert date.
- p. ii, par. 3, l. 8: Insert 'as' after 'such'.
- p.3, par. 3, l. Delete second period.
- p.4, par. 3, l. 5: 'lead' should be 'leads'.

## **Comments from Dr. Cecil Lue-Hing**

SAB. CLH Homework Review Notes. Inorganic Arsenic For June 15-16/2010 Meeting

Review of SAB's Work Group Report on EPA's draft assessment "Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRS)" (EPA/635/R-10/001).

### **General Comments**

The Genesis of the report under review dates back to 2005 when the SAB was first asked to review some EPA material on inorganic arsenic relative to, metabolism, mode of action, dose-response, and human relevance. The SAB submitted its review and recommendations to EPA in 2007 and has now been charged to determine how well EPA has responded to the 2007 SAB comments and recommendations.

The SAB has been asked to respond specifically to three charge questions – literature review, modeling generally, and sensitivity analyses regarding certain model assumptions.

### **Specific Comments**

The SAB finds that the EPA has been generally responsive to the 2007 comments and recommendations on literature review, but found some deficiencies and offered recommendations to correct them.

As expected the most extensive discussions were directed at modeling and modeling assumptions.

One important issue in this debate was the EPA's choice of using a linear approach for arsenic associated cancer risks. The SAB took the EPA to task, the EPA defended and the SAB accepted the linear approach.

The next extensive discussion was directed at the selection, use, and impact of default assumptions on modeling outcomes.

Here the SAB acknowledged that EPA tried to be responsive to earlier (2007) recommendations, but there still remained several deficiencies including the need for better justified default assumptions in the risk assessment process.

### **Summary**

The SAB has responded appropriately to the three charge questions posed by EPA, and has provided additional comments and recommendations to remedy deficiencies in the EPA document. Because risk assessment procedures are as much art as science, it is possible that this portion of the Arsenic document could require one more round of review.

I am very satisfied with the performance of the SAB's Work Group and support the submittal of their review work product.

**Comments from Dr. L.D. Mc Mullen**

I want to commend the committee for developing an excellent report. I found it easy to read and it was organized in a very logical style. I feel the original charge questions were adequately addressed and I did not find any technical errors or omissions. The recommendations followed the discussion contained in the body of the report.

I do believe that we may want to change the cover letter a little. The length seems to be correct; however, three-fourths of the letter is history and that we had a meeting. Only one paragraph gives the Administrator a summary of our recommendations. It seems to me that we could reduce the history to one paragraph and leave a page and a half for a summary of our recommendations.

## Comments from Dr. Judith Meyer

### Meyer Quality Review of Arsenic Advisory

1. whether the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed;

YES

2. whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report;

No errors that I could detect.

- a. The absence of an Executive Summary is a significant omission. The Letter is almost entirely a history of the questions with only one short paragraph of what the committee recommended. The Letter definitely does not have the kind of information one would find in an Executive Summary. This report needs an Executive Summary!
- b. p. 5 recommendation at top: Can the committee provide a list of key references that EPA should be considering here? The recommendation seems very broad and could inappropriately delay this IRIS assessment. Are there some particularly relevant studies that have appeared since 2007 that the committee could cite?
- c. p. 13: I think the committee should be more forceful in its recommendation on distinguishing between organic and inorganic forms of arsenic. I think that is more than "helpful"; I would argue that it is essential, particularly when dealing with dietary intake.

3. whether the Committee's report is clear and logical;

Generally YES. HOWEVER the absence of line numbers in the document make it more difficult to provide specific comments.

- a. p. 1, paragraph 2 last sentence: move the parenthetical phrase after "The charge questions" so it is clear that this is in what is in the Attachment.
- b. p. 2, Response: It was not clear whether the comments on the strengths and limitations referred to the Taiwanese dataset or the other studies reviewed. Clarification needed.
- c. p. 4, first paragraph under Bias – Is one supposed to conclude that all the other studies suffered from the same flaw as the Chen study? The point that the committee is trying to make with this paragraph needs to be clarified.
- d. p. 8, first recommendation: Does the committee mean "Because there is tremendous interest in the contamination of water by iAs"? If so, change the sentence to that. I'm not sure what iA's water contamination means. Is the committee recommending that any of this discussion be in the IRIS document – or should all be in other documents?
- e. p. 10: I am unclear about what was not done for susceptible groups (children and pregnant women). Did they just not use different water consumption numbers for these populations? Or did they not do any analyses for these groups? If it is the latter, that seems to be a significant deficiency in the analysis that the committee should comment on.

4. whether the conclusions drawn or recommendations provided are supported by the body of the Committee's report.

YES

### **Comments from Dr. Amanda Rodewald**

The Committee clearly addressed the charge questions. The use of bulleted recommendations made the report especially easy to read. The report was clear and logical, and I did not notice any technical errors or omissions. The body of the report nicely elaborated on and supported the overarching recommendations made by the Committee.

**Comments from Dr. James Sanders**

Were the original charge questions to SAB Committee adequately addressed?

Yes, the committee did a very good job of clearly and completely addressing the three charge questions.

Were there any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report?

No.

Was the Committee's report clear and logical?

Yes. The report is brief and to the point, but easy to understand.

Were the conclusions drawn or recommendations provided supported by the body of the Committee's report?

Yes. While brief, the responses to each charge question were clear, documented, and logical. The committee is to be commended for their clarity.