

IRIS STEP 6 INTERAGENCY COMMENTS (OMB)

OMB Followup Comments on Inorganic Arsenic Assessment

(page numbers refer to pages in redline draft dated March 2009)

General Comments:

- We thank EPA staff for their responsiveness to our first round comments. The clarity, transparency and readability of the document is greatly improved. Our remaining comments are presented below. We are happy to work quickly with EPA to address the comments.
- We have heard that Dr. Vanessa Vu at SAB may have discussed with the previous ORD AA ways for the SAB to quickly and efficiently do a quick review of the draft assessment to ensure that SAB was satisfied with the way its comments have been addressed. Has ORD staff spoken recently to Dr. Vu about her ideas or suggestions? Considering the importance of this assessment, a quick check back with SAB would likely help strengthen this document. Can you share with us the options Dr. Vu may have and ORD's thoughts on conducting such a review for this particular assessment?
- We have received copies of 3 letters sent to EPA by different stakeholder groups regarding comments related to this assessment. We trust that staff have seen and considered these letters, but please confirm.
- Most recent assessments circulated for interagency review have contained a chapter in Section 5 entitled "uncertainties in the cancer risk values". It would be useful to have a similar section here that discusses uncertainties and implications of some of the assumptions that EPA made and the likely impact of those assumptions.
- Section 5 in multiple places mentions the Arsenic Rule. This seems inconsistent with EPA's previous approach to IRIS assessments, which separate the science from any risk management decisions. We also note that previously EPA has not presented information that comes from sources other than scientific journal articles and has referred readers generally to other sources for this type of information.
- While we do not comment specifically on the IRIS summary, we hope that EPA will make conforming changes there as you address our comments on the assessment.

Specific Comments:

- Section 5.3.1 The addition of this section is very helpful. The SAB comments are summarized in text as requesting only a further sensitivity analysis of modeling methods and choices. This approach may miss other SAB recommendations. A more complete presentation of their recommendations, in text, may be useful. For example:
 - In response to Charge C2, SAB suggested that EPA use a uniform set of evaluation criteria to assess other epidemiology studies from the U.S. and other countries exposed to lower arsenic concentrations. SAB stated that "comparative analysis could lead to further insights into the possible influence of these differences on population response to arsenic in drinking water."

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- SAB suggested that EPA: “also conduct adjunct analyses to test the robustness of results against their assumptions, determine the impact of variability in some parameters, compare the results against those from other data sets, and provide a transparent assessment of the available epidemiological data using a consistent set of criteria.”
- SAB recommended that “the other relevant epidemiologic databases from studies of arsenic-exposed populations be used to compare the unit risks at high exposure levels that emerge from the Taiwan data.”
- SAB also recommended that “results on bladder cancer risk from published epidemiology studies of U.S. and other populations chronically exposed to arsenic levels ranging from 0.5 to 160 µg/L inorganic arsenic in drinking water, be critically evaluated.”
- Table 5-1.
 - It would be useful to add the SAB 2007 review and its recommendations to the table. Otherwise it could appear as though there has been no effort since 2005, and the fact that SAB made recommendations regarding the assessment is not transparently presented. Pages 103-105 do discuss some of the implemented SAB 2007 recommendations; thus, seeing them in the table would be helpful.
 - In order for readers to fully understand how the assessments have evolved over time, after an added SAB 2007 column, it would be useful to add the parameters for this final assessment. This would greatly improve clarity and would make it easy to see all the changes over time and their implications--including the information presented in this final assessment.
 - In the endpoints calculated section, it would be useful to present the oral slope factor, unit risk and drinking water concentrations at 10^{-4} and 10^{-6} risk levels. This is consistent with section II.B.I of the IRIS summary and this would be extremely helpful here. It is unclear why one of the metrics EPA presents is incidence at 10ug/L in drinking water as this is not consistent with typical IRIS summary information.
- In the response to interagency comments on page 14 EPA states: “As discussed in revised Section 5.3.8.2,.....Adoption of more recent background U.S. mortality and cancer incidence data may have resulted in the current risk estimates being about 50% increased compared to what the would have been if older data had been used.” In section 5.3.8.2, we were unable to find transparent discussion of the impact of U.S. mortality and cancer incidence data leading to a 50% increase compared to older data. It would be useful to present these data in this section.
- Appendix B: it is helpful that EPA added front matter discussion to Appendix B describing the factors SAB asked to have considered. However, as EPA mentions, all of this information is not in the table, and when we look to section 4.1 we can not uniformly find how this information was considered. In particular, for many studies we are unable to locate:
 - a) estimates of the level of exposure misclassification;
 - b) temporal variability in assigning past arsenic levels from recent measurements;
 - c) the extent of reliance on imputed exposure levels;
 - d) the number of persons exposed at various estimated levels of waterborne arsenic;
 - e) study response/participation rates;
 - f) estimates of exposure variability;
 - g) control selection methods in case-control studies; and,
 - h) the resulting influence of these factors on the magnitude and statistical stability of cancer risk estimates.As these are the issues that SAB

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suggested EPA consider, is there a way to more clearly present this information either in the table or text of section 4.1? We note that SAB suggested a tabular format; thus, perhaps adding this information to the table may meet SAB's concern. SAB also suggested that the strengths and weaknesses be described in relation to each of the criterion above and suggested that the caveats and assumptions "be presented so that they are apparent to anyone who uses these data." Is there a way to better present this evaluation?

- Our first set of comments asked whether EPA could use a Monte Carlo approach, or distributions, rather than a point estimate for water consumption. EPA responded that it would be misleading to apply a Monte Carlo approach to only one exposure variable and not others. If EPA is clear about the approach and explains why it was done for just one variable, why would this be misleading? We note that it is not uncommon in Monte Carlo analysis to use distributions for some parameters and point estimates for others.
- We appreciate EPA's responsiveness and the new presentation for slope factors that are gender specific. Did EPA use gender specific consumption rates for males and females or did EPA use the population (both genders combined) value? This was unclear. We would recommend using gender specific values wherever possible.
- Page 107, the last paragraph discusses the NAS recommendations and mentions that SAB also reviewed the modeling. However, it does not provide the SAB recommendation. It would be useful to provide a sentence or two describing the SAB recommendation.
- Page 109, 2nd paragraph, EPA states that they have assumed that the ratios of cancer mortality to incidence for arsenic related cancers are the same for the U.S. and Taiwanese populations. Can EPA discuss the effects of this assumption to give a sense of its magnitude? If the ratio is lower in the U.S., what would the overall impact be? Are there any general data regarding cancer incidence and mortality in the U.S. vs Taiwan to help inform the effects of this assumption? Does EPA expect that changes to this assumption would have a small or large effect on the final outcome. Discussion of this would be helpful and informative.
- Page 109, 5.3.5, 2nd paragraph. EPA used 10ug/day as the non-water arsenic intake for both reference and exposed populations. EPA also states (page 110) that NRC in 1999 reported 50 ug/day in 1999 and used 30 ug/day in 2001 for exposed populations. In 2005, EPA used 0, 30 and 50 ug/day for exposed populations. It is not clear why EPA now finds 10 ug/day to be the best estimate for both populations. More clarity here would be useful. Did SAB make any suggestion for the value for the exposed population? The implications of varying this parameter should be clearly discussed in a final section on uncertainties.
- Page 115, 5.3.7.3, 2nd to last sentence, why were intakes resulting in 10^{-2} lifetime risks estimated? Why not 10^{-4} through 10^{-6} ?
- Page 116, 5.3.8.1 text and tables, please present risk for 10^{-4} to 10^{-6} as this is consistent with presentation in all IRIS summaries. It is also unclear why incidence at 10 ug/L in drinking water is presented. If EPA's intent is to tie this information to a regulation (that may change

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over time), it seems inappropriate for the IRIS tox review document (as per previous statements EPA has made regarding including this type of information).

- Page 118, 5.3.8.2, in the first paragraph, it would also be helpful to discuss why the results in this assessment are so different from those presented in the 2005 draft assessment. For both assessments internal cancers were used and the same modeling approach was used. More clarity in explaining how and why the assessment has changed since 2005 would be useful. Similar discussion in section 6.2 would also be helpful.
- Page 119, EPA states that converting mortality estimates to incidence adds uncertainty. Can EPA say anything more about the impact or direction of this uncertainty and its potential effect? Discussion of this in an uncertainty section would be useful.
- Page 122, 1st full paragraph, states that the BEIR IV more recent data likely contribute to the risk differences in table 5-6. Can EPA say anything about the impacts of the new data (e.g. percent change in value due to its use) on the final outcome?
- Page 125, now very nicely discusses the impacts of non-water intake on the final values. This discussion should be considered in an uncertainty section where EPA talks about the confidence in the assumption (e.g. 10 ug/day) chosen for exposed and reference populations.
- Page 131, EPA states: “A key assumption underlying this model is that the risk of arsenic-related cancer is a constant multiplicative function of the “background” age profile of cancer risks in the target U.S. population.” EPA should additionally discuss the implications of this assumption on the final value.

Editorial Comments:

- Page 98, 3rd full paragraph. Was the application of the cancer slope factors in the OPP RED externally peer reviewed? If so, it would be helpful to mention that here. REDs typically go through a robust public comment period, but if this was also peer reviewed, this would be good supporting information to add.
- Page 108, section 5.3.4, 1st paragraph. Did SAB also recommend using lung and bladder cancer mortality? If so, the SAB citation should be added. This paragraph also talks about mortality and we note that EPA's final estimates are for incidence, not mortality. Is the transition from mortality to incidence, and the implications of changing the endpoint, clearly discussed in the chapter? If EPA has transitioned from mortality to incidence, it would be helpful to clarify the implications of changing the endpoint.
- Page 109, 1st paragraph, last sentence. Please clarify whether or not SAB 2007 also supported linear extrapolation from the point of departure.
- Page 111, 5.3.6, 2nd paragraph. It would be useful to mention where the sensitivity analysis using different well concentrations is presented.

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- Page 113, 5.3.7.1. Where can readers find the actual modeling data as well as results from different models tested, the resulting impacts and details of the goodness of fit and parsimony criteria applied to the different models? Similarly, where are the confidence limit calculations (discussed in section 5.3.7.2) presented?
- Page 113, footnote 5 appears to be missing in the redline draft.
- Page 118 suggested edit: “the combined cancer slope factor for women (25.7 per mg/kg-day) is ~~appropriate~~ chosen for use in establishing health criteria, since, based on the available data, women appear to be the more sensitive group”
- Page 119, 1st paragraph, refers to “the Rule”. EPA should clarify what this is.
- Page 119, table 5-5, it is unclear where the values from the current analysis come from. Are the calculations presented anywhere? Are all the values in the table incidence values? This should be clarified. On page 120 EPA states that the Chen results are mortality -- thus is it appropriate to compare mortality and incidence? Are the Chen results for lung cancer also mortality? What would be the impact of adjusting them to incidence and then how would they compare with the current analysis values?
- Page 120, table 5-6 and in text, EPA should clarify why they are presenting a comparison at 10 ug/L arsenic in drinking water. This type of comparison is not typical in IRIS tox reviews.
- Page 125, line 1, suggest replacing “small or moderate” with specific numbers. Similarly in the 2nd sentence, suggest deleting “small” and simply present the value. Similar edits throughout this discussion (see also the 3rd paragraph on page 125) would be useful.
- Page 126, footnote 8, EPA talks about how the data fit less well for some models. It would be useful to provide information on the criterion EPA used for good model fit. Are these modeling data presented in the document?
- Page 127, 2nd paragraph, suggest replacing “very similar risks” with actual values.
- The introduction to Appendix A states that the summary of comments and responses is inclusive of issues raised by public commenters. Does this mean that all public comments were similar to SAB comments? We do not see any public comments specifically mentioned in this appendix.