



November 15, 2010

Dr. Angela Nugent, Designated Federal Officer
US EPA Science Advisory Board (1400R)
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Comments to the US EPA Science Advisory Board Regarding Unresolved Scientific Issues in the 2010 Draft IRIS Arsenic Assessment

Dear Dr. Nugent:

In 2005, a United States Environmental Protection Agency (US EPA) Science Advisory Board (SAB) Arsenic Panel was convened to review the report, "Toxicological Review of Inorganic Arsenic," which focused on evaluating arsenic carcinogenicity for the Integrated Risk Information System (IRIS) (2005 IRIS Arsenic Assessment) (US EPA, 2005). The review was in response to specific charge questions that covered a range of key scientific issues. In 2007, the SAB released a report providing specific recommendations for improving the assessment, including further considerations relating to mode of action (MOA) data, the interpretation of epidemiological investigations, and dose-response modeling (SAB, 2007).

A revised version of the 2005 IRIS Arsenic Assessment was released by the US EPA in 2010, specifically by the National Center for Environmental Assessment (NCEA) and the Office of Water (OW) (US EPA, 2010). Although this draft maintains that it has comprehensively addressed SAB's comments (See Appendix A of the 2010 report), many of the comments were not addressed or only partly addressed, with a number of critical scientific issues remaining unresolved. After the release of the 2010 IRIS Arsenic Assessment, an SAB Workgroup was convened to answer three questions presented to them by NCEA. These charge questions focused on the adequacy of the 2010 IRIS Arsenic Assessment's response to certain 2007 SAB's recommendations (SAB, 2010a).

The attached table (Table 1) provides a summary of the SAB review of the IRIS assessment of arsenic. The table is arranged by the charge questions presented to the 2005 SAB Arsenic Panel:

- Columns 1-2 list the original 2005 charge questions to the SAB that were relevant to inorganic arsenic;
- Column 3 is a summary of SAB's 2007 recommendations (SAB, 2007);
- Column 4 summarizes the implementation of the recommendations in the 2010 IRIS Arsenic Assessment (US EPA, 2010);
- Column 5 presents US EPA's charge questions to the 2010 SAB Workgroup;
- Column 6 is an overview of the 2010 SAB Workgroup comments on the 2010 IRIS Arsenic Assessment (SAB, 2010a); and
- Column 7 presents unresolved scientific issues.

Overall, the table demonstrates that the SAB Workgroup was never asked to conduct a review of the full IRIS assessment of inorganic arsenic, both in terms of the adequacy of the report in responding to the SAB (2007) comments and addressing outstanding scientific issues.

The specific mandate of the 2010 SAB Workgroup was to "evaluate and comment on the agency's implementation of the SAB 2007 recommendations regarding EPA's revision of the cancer assessment of inorganic arsenic" (SAB, 2010a). However, because the Workgroup did not review issues beyond the very narrow charge questions, the 2010 IRIS Arsenic Assessment did not undergo an adequate review. The full breadth of the prior SAB comments were not considered as part of the SAB workgroup review, leaving important scientific issues inadequately addressed (Table 1).

In particular, issues related to the synthesis of MOA information and nonlinear dose-response modeling were not addressed in any substantive manner. For example, although based on information that was available at the time, the 2007 SAB decided that there was not enough definitive information on arsenic's MOA to depart from the linearity assumption; nonetheless, the SAB concluded that all of arsenic's MOAs are likely nonlinear and that understanding the dose response relationship at low doses was an extremely important area of research. They also noted that hormesis should be considered in an evaluation of a possible threshold for arsenic. Since 2005, significant new literature regarding arsenic's MOA provides further evidence that arsenic's dose response is likely nonlinear. While the 2010 IRIS Arsenic Assessment reviewed some new MOA literature, the review contained only literature published through August 2007. Moreover, the review was incomplete (*i.e.*, the literature review prior to 2007 was incomplete) and there was no meaningful synthesis with respect to the issues addressed by SAB.

Similarly, while the 2010 IRIS Arsenic Assessment included additional epidemiological literature, the synthesis of the literature was incomplete and fell short of SAB's specific request in 2007 to conduct an integrative analysis of low dose studies to test concordance with the Taiwanese results. Several other issues, including issues related to testing the assumption of linearity for the Taiwan data, were also not adequately addressed in the 2010 IRIS Arsenic Assessment. These issues are presented in more detail in Table 1.

The narrow approach of the Workgroup review is clear. One Workgroup member stated: "the Workgroup did go beyond the charge in discussing research needed to fill critical data needs, but that the group generally wanted to stay within the charge" (SAB, 2010b). Additionally, the selected Workgroup did not have the full expertise to sufficiently evaluate the scientific merit of the final draft. As acknowledged by a Workgroup member, "the Work Group was constituted to address a narrow charge" and "the expertise of the group was not appropriate for a full review of EPA's Toxicological Assessment" (SAB, 2010b). The Workgroup's choice not to go beyond the narrow charge and the lack of technical expertise to address outstanding scientific issues is problematic. After the meeting, Rogene Henderson, a member of the SAB stated:

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. (Rogene Henderson, in SAB, 2010c, p. 16)

Overall, there are several outstanding issues in the 2010 draft IRIS document that can have a substantial impact on evaluation of arsenic risk assessment. Some of these concerns were raised by the 2007 SAB Panel, and remain as significant scientific issues for the 2010 IRIS Arsenic Assessment. The Workgroup that was convened in April 2010 had neither the charge nor the sufficient expertise to address several of these outstanding concerns and, thus, the 2010 IRIS Arsenic Assessment does not adequately incorporate the best available science and has not been given an adequate peer review.

The above comments are my own, prepared with the support of Organic Arsenical Products Task Force.

Sincerely,

Barbara D. Beck, Ph.D., DABT, FATS, ERT
Principal

Table 1
Integrated Risk Information System (IRIS) Assessment of Inorganic Arsenic (InAs) Carcinogenicity:
Unresolved Scientific Issues in the 2010 Report

Charge Question	Original Charge Question Issue	Recommendations of the SAB 2005 Science Panel in 2007 SAB Report¹	Implementation of Recommendations in NCEA/OW's 2010 Report	NCEA/OW's Charge Question to 2010 SAB Workgroup	SAB 2010 Workgroup Response	Unresolved Scientific Issues
A1	Consideration of pharmacokinetic data for arsenic cancer risk assessment	The Panel strongly encouraged the Agency to proceed with physiologically based, pharmacokinetic (PBPK) model development to support risk assessment efforts.	Despite new PBPK information, NCEA concluded that none of the current models has "sufficiently addressed the complex nature of the kinetics associated with InAs carcinogenesis; therefore, this is an ongoing effort along with BBDR [biologically based dose response] modeling."	There was no related follow-up question, although work on PBPK and BBDR models has produced significant new insights regarding arsenic carcinogenicity.	The focused 2010 charge questions did not address this issue and the Workgroup did not go beyond the charge questions presented by NCEA.	Recent insights from studies where large amounts of dose-response information have been synthesized provide important information about the shape of the dose-response curve at low doses. This information, in combination with recently developed PBPK models, should be included in any assessment of arsenic carcinogenicity. A complete BBDR model is expected soon and is critical to a current assessment of arsenic carcinogenicity.
A2	Dimethyl arsenic acid (DMA): Not relevant to the assessment of InAs.					
B1	DMA: Not relevant to the assessment of InAs.					
B2	DMA: Not relevant to the assessment of InAs.					

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B3	Modes of Action (MOAs) involved in the carcinogenicity of inorganic arsenic	The Panel noted that characterizing the shape of the curve at low doses is an "extremely important area for research attention." Because none of the plausible MOAs for InAs involve direct genotoxicity and there is evidence of hormesis, the Panel recommended consideration of a threshold, when a departure point is defined.	NCEA concurred that InAs had multiple MOAs and presented substantial information supporting a nonlinear MOA. Nevertheless, NCEA did not sufficiently integrate this information to draw conclusions about the shape of the dose-response curve at low doses. ²	Although there was substantial new MOA information, there was no charge question related to the existence or relevance of this new information.	The focused 2010 charge questions did not address this issue. Although the 2010 Workgroup did not provide a robust discussion of arsenic carcinogenic MOA, the Workgroup did state that cell death and compensatory proliferation is a reasonable hypothesis for bladder carcinogenesis, but that there are not enough data to confirm this MOA.	Existing and extensive data published since the SAB 2007 report provide convincing evidence that arsenic has a nonlinear dose response. NCEA's failure to include all of the current information on arsenic's MOA in an integrative analysis makes the current arsenic assessment incomplete.
C1	DMA: Not relevant to the assessment of InAs.					

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C2	Use of the database from Taiwan	The Panel suggested that NCEA integrate information from low-dose arsenic studies and document uncertainty in Taiwanese dataset.	NCEA did not perform an integrative analysis of the existing low dose studies, as recommended. ²	Comment was requested on whether it was appropriate to use the Taiwan data as the sole basis for quantitative estimates of arsenic carcinogenicity, given the robust available epidemiological data.	In addressing this question, the 2010 Workgroup did not adequately analyze the outstanding scientific issues; it mainly suggested revisions to improve clarity and transparency. Also, the Workgroup suggested that key epidemiological studies published after 2007 be included in a revised analysis.	There is a large database of epidemiological studies that, overall, are consistent with a threshold for arsenic carcinogenicity. Based on the extensive data that are available, there is a need to incorporate information from existing meta-analyses or perform <i>de novo</i> integrative analysis on low-dose arsenic studies.
D1	DMA: Not relevant to the assessment of InAs.					

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D2	Linear vs. nonlinear extrapolation for InAs carcinogenicity	The Panel noted the available evidence indicated that plausible MOAs for InAs are nonlinear with a possible threshold, but that there is no clear indication of the shape of the curve in the low-dose region. In the absence of a definitive MOA, the Panel recommended linear extrapolation until the departure point is defined, but recommended that nonlinear models also be explored.	NCEA used linear extrapolation in the principal analysis; explored some aspects of nonlinearity, but only in models that included an outside comparison population.	Comments requested on the linearity assumption and additional analyses to test the sensitivity of the linearity assumption.	Workgroup agreed with default linear approach and stated that NCEA adequately explored nonlinear models. Workgroup also noted that cell death and compensatory proliferation is a reasonable hypothesis for bladder carcinogenesis, but there are not enough data to confirm.	The 2007 SAB report was clear that nonlinear models should be explored. Although the data were modeled using a nonlinear model, the analysis was restricted to a limited set of assumptions that resulted in restricted outcomes. For example, the nonlinear model was not evaluated without a comparison population. Evaluating the model without an outside comparison population is critical for testing the possibility of nonlinearity at low doses.

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D3	Adequacy of modeling program to calculate InAs risks	The Panel recommended further exploration into the measurements of exposure in the study from Taiwan, and, specifically, the effect of using the median well concentrations in villages with multiple wells. The Panel recommended testing the sensitivity of the model to comparison population, nonlinear models, dietary arsenic in the comparison population, and different age groupings to estimate baseline risk.	Made some technical adjustments to model; adjusted background incidence and mortality data; performed analysis showing how results varied with differing assumptions regarding arsenic well concentrations, low-dose extrapolation, choice of comparison population and dietary intake in comparison population. However, because each assumption was assessed in isolation and not in combination, the full range of uncertainty in the risk estimated was not quantified.	Comment requested on adequacy of modeling and related sensitivity analyses.	In general, thought NCEA's sensitivity analyses were responsive to SAB's requests; suggested that "EPA might consider whether any combinations of these parameter variations should be examined." This would allow for a more complete view of uncertainty associated with the assessment. Also indicated that nonlinear models had been adequately explored.	An explicit element of the recommendation in the SAB 2007 report was to contrast "results for the linear dose model employed in this program to alternative hazard models that are multiplicative and nonlinear in form," as well as test how different assumptions about the comparison population may change risk estimates. It is important that these assumptions be tested in combination so the shape of the dose-response curve can be evaluated without a comparison population. Also, the impact of using the median well concentration in village with multiple wells was not addressed in a meaningful way, <i>e.g.</i> , there was no analysis comparing results from villages with more robust <i>versus</i> less robust measurements.

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D4	Appropriate drinking water intake value in US and SW Taiwan populations	No specific value recommended; Panel suggested that variability in drinking water rates for SW Taiwan population should be incorporated into analysis and explored in a sensitivity analysis.	Underestimated drinking water intake in SW Taiwan populations by using a baseline value of 3.5 L/day for males and 3.0 L/day for females. Underestimating water intake will inflate cancer potency estimates.	Comment requested on NCEA's sensitivity analyses and choice of the exposure assumptions as recommended in the 2007 SAB Panel report.	Commented that NCEA should provide more justification for values selected and explain what the values represent (high-end, mean, <i>etc.</i>); also made a recommendation to examine the effects of gender differences of consumption.	Assumptions about drinking water intake in the SW Taiwan population can have a substantial impact on cancer potency estimate. In the NCEA assessment, justification for selected drinking water intake values was vague; a high-end consumer was not evaluated; and NCEA's 2010 report did not appropriately account from water from food preparation.

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D5	Appropriate background dietary intake of InAs for both the control and study population of SW Taiwan	The Panel did not put forth a specific value, but suggested a value $\geq 50 \mu\text{g InAs/day}$ was well-supported and that values up to $200 \mu\text{g InAs/day}$ be evaluated in a sensitivity analysis; also commented that the control population should not be assumed to have zero exposure.	Assumed a baseline intake of $10 \mu\text{g InAs/day}$ for exposed and control population; performed sensitivity analysis where non-water background exposures were 0, 30, and $50 \mu\text{g InAs/day}$ in control and background population; evaluated $100 \mu\text{g InAs/day}$ and $200 \mu\text{g InAs/day}$ compared to $10 \mu\text{g InAs/day}$ in control population. ²	Comment requested on NCEA's sensitivity analyses and choice of the exposure assumptions as recommended by the SAB (2007) Arsenic panel.	Recommended more justification for selected values (<i>e.g.</i> , it was not clear why $10 \mu\text{g InAs/day}$ was chosen as the baseline background exposure).	Assumptions about food intake are less influential than assumptions about water intake, but, nonetheless, can affect cancer potency estimates. The baseline value selected by NCEA of $10 \mu\text{g/day}$ is arbitrary and without foundation. An intake level of 30 to $60 \mu\text{g/day}$ for the SW Taiwan population is better supported by the literature and should be used as the baseline assumption.

Notes:

* The SAB Scientific Panel for Inorganic Arsenic (InAs) was nominated in 2005 and issued its report in 2007. Thus the "2007 Report" refers to the report of the 2005 Panel.

1) As presented in the 2007 report, "Advisory on EPA's Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic: A Report of the US EPA Science Advisory Board."

2) Recently, members of the original 2007 SAB panel submitted a letter to the public docket and the SAB identifying areas where the NCEA/OW (2010) report failed to address SAB (2007) recommendations. The SAB (2010) letter specifically identified a deficiency in NCEA/OW's response to this issue (US EPA, 2010).

References

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