

March 23, 2010

Mr. Anthony F. Maciorowski
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Dr. Sue Shallal
Designated Federal Officer (DFO)
EPA Science Advisory Board (1400F)
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Re: Notification of SAB Workgroup Public Meeting for the Toxicological Review of Inorganic Arsenic

Dear Mr. Maciorowski and Dr. Shallal:

I am writing on behalf of the undersigned entities to request that the Science Advisory Board (SAB) expand the scope of the charge questions to be addressed at the public meeting of the SAB work group to conduct a review of the draft document entitled “Toxicological Review of Inorganic Arsenic: In Support of the Summary Information on the Integrated Risk Information System (IRIS)” (EPA/635/R-10/001). This meeting is scheduled for April 6 and 7, 2010. Due to the proximity of the meeting and the importance that the SAB have complete information on important questions before it as it evaluates the pre-meeting material, I request that you email this letter and the attachment to the Work Group members as promptly as possible.

The contents of the draft U.S. Environmental Protection Agency (EPA) document to be reviewed are a matter of vital interest to the signers of this letter, as well as to state regulatory officials and to EPA and other federal offices tasked with implementing the final decision in regulatory decision-making and in risk management decisions, as well as communicating the decision to the US public at large.

The scope of the current charge questions being presented to the workgroup are exceptionally narrow and fail to fully address the advice the SAB provided to EPA in 2007 (Advisory on EPA’s Assessment of Carcinogenic Effects of Organic and Inorganic Arsenic¹, from the US EPA Science Advisory Board, hereafter 2007 Panel). The 2007 Panel made clear that it “did not conduct its own arsenic risk assessment. To do so would have required an updated literature search and exploration and resolution of many issues that are discussed throughout this report.”² The Panel left “the larger activity of completing a full risk assessment of all relevant health endpoints associated with arsenic, and arsenic containing compounds, to the Agency itself when it conducts its final arsenic assessments.”³

¹ June 28, 2007, Letter from Science Advisory Board to Mr. S. Johnson, with Advisory report (EPA-SAB-07-008); available at: <http://www.epa.gov/science1/pdf/sab-07-008.pdf> (hereinafter, “Advisory Report”).

² Advisory Report at 1

³ Advisory Report at 1.

In this letter we briefly summarize the conclusions of the 2007 Panel, to illustrate some of the reasons that reliance solely on the current charge questions would result in an incomplete review that would not provide an adequate basis for decision making. In the attachment to this letter, additional charge questions are presented that will provide for a more robust review by the workgroup. We respectfully request that the questions in the attachment be added to the charge of the present workgroup for discussion in their April 6-7 meeting

Brief Summary of 2007 Panel Conclusions

It is important that the 2010 SAB Work Group focusing on the inorganic arsenic cancer hazard assessment focus on the complete report from the 2007 SAB Panel. The eight page summary document provided by EPA fails to fully identify the scope of the SAB's advice in 2007 but is essential for full understanding.

The 2007 Panel stated that its advice "is intended to assist the Agency's continued efforts to complete its assessments on various arsenicals. There are many specific conclusions and recommendations on specific issues associated with each charge question, as well as recommendations for sensitivity analyses and additional research to answer many of the remaining questions on arsenic risk."⁴ The Panel carefully considered the extensive amount of new research conducted on inorganic arsenic, including a large number of new epidemiologic studies, and recognized that there are many questions still to be answered. It did not attempt to answer the questions but to provide advice on areas it deemed important for the Agency to take into account in response to the charge questions, including that the Agency needs to clearly and transparently identify limitations and uncertainties in its analysis. The following is a brief summary of the 2007 Panel's advice to EPA.

Mode of Action

The Panel advised EPA that inorganic arsenic and its metabolites are not direct genotoxicants. The Panel went on to conclude that available indirect genotoxicity data "strongly suggest the possibility of a threshold for arsenic carcinogenicity." The Report continues, "[h]owever, the studies discussed herein do not show where such a threshold might be, nor do they show the shape of the dose-response curve at these low levels."⁵ The Panel acknowledged the significant ongoing research in this area, and identified the critical need to better understand the mode of action in order to fully assess the carcinogenic potential.

Reliance Upon SW Taiwanese Dataset

The Agency asked the Panel to comment on whether the recommendation from NRC 2001 to use the Southwest Taiwanese dataset for estimating cancer risk remained the most appropriate choice. The Panel did not dispute the 2001 NRC recommendation, but also

⁴ Advisory Report at 2.

⁵ Advisory Report at 6.

identified limitations in the dataset, including misclassification of exposure, background exposure concentrations, and impact of nutritional factors. The Panel recommended EPA perform sensitivity analyses and a full and transparent review of all available information. The Panel called upon EPA to conduct a complete review of the extensive body of new studies that have been published since NRC 2001. The Panel went on to recommend “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. Several of these studies had the advantage of data with excellent exposure assessment. In addition, some populations likely differed from the Taiwanese population with regard to their socioeconomic and nutritional conditions. The accuracy and precision of exposure assessment is a major issue in all environmental epidemiologic studies, and in particular, in studies of arsenic in drinking water. Misclassification of exposure in such studies (when non-differential) can have a profound effect in attenuating the magnitude of the observed risk.”⁶

The Panel further advised the Agency to evaluate “low level” exposure studies (those with water concentrations below 100 ppb) somewhat differently than those from “high level” exposures. The Panel advised EPA to “determine the potential utility of these studies in exploring overall concordance of the cancer risk estimates derived from their data with risk estimates obtained from extrapolation of the Taiwan data,”⁷ recommending analyses that integrate results from a number of studies to improve statistical power and precision of estimates. The Panel recommended the Agency evaluate studies from outside Southwest Taiwan in a clear, transparent and comparative manner, to determine concordance with the Taiwanese dataset and to better understand the impact of the many identified factors.

Use of Linear Model for Cancer Risk

The question of low-dose extrapolation for modeling cancer risk from inorganic arsenic was extensively considered by the 2007 Panel. Recognizing the potential for a complex mode of action and the lack of clear and conclusive information, the Panel concluded “there is not a sufficient justification for the choice of a specific nonlinear form of the dose-response relationship.”⁸ Because EPA instructed the 2007 Panel that a linear extrapolation must be used unless a single mode of action has been established, the Panel had limited opportunity to suggest a specific approach. It is important to note that the Panel did not conclude that the dose response relationship of inorganic arsenic is linear. Rather, the Panel recommended that EPA conduct sensitivity analyses to address uncertainties and to consider other options beyond linear extrapolation, particularly at lower dose levels. The Panel stated that evidence exists from both human studies and mode of action studies which supports a nonlinear response at exposures below 100 ppb. However, the Panel did not believe it could adequately characterize the shape of the dose response curve based on the data presented to it. In fact, the Report states:

⁶ Advisory Report at 8.

⁷ Advisory Report at 38-39.

⁸ Advisory Report at 43

“Although the EPA has chosen a linear model for the arsenic dose component of the hazard model for lung and bladder cancer, the Panel encourages the Agency to test the sensitivity of the assumption of linearity by comparing its corresponding estimate of excess life risk to an alternative hazard model that has a dose contribution that is multiplicative and nonlinear in form.”⁹

It is important to note that the Panel’s consideration of non-linear approaches was limited by EPA’s instructions regarding the 2005 EPA Guidelines for Cancer Risk Assessment. We believe that a fair reading of the Guidelines allows for a fuller and more robust assessment of a non-linear dose response at levels of concern to US populations, which are well below the levels at which the Panel suggested a nonlinear response may be present.

A Full and Complete Review of the Current Draft Assessment is Essential

The importance of a full and careful review of all aspects of this assessment cannot be underestimated. The potential implications of the proposed cancer risk factor, if determined to be scientifically valid and reasonable, are staggering, particularly when one considers the normal dietary daily intake of naturally occurring arsenic from food and drinking water. For example,

- The EPA Maximum Containment Level (MCL) for drinking water would have to be reduced from 10 ppb to 0.1 ppb for minimal compliance with the upper limit of EPA’s target risk range (i.e., 1 in 10,000). This may not be achievable except at enormous cost.
- For many Americans, normal intake of arsenic from diet and water likely would greatly exceed EPA’s risk management range.
- Certain certain types of seafood, grains and other crops, such as grapes and other fruits, as well as food products containing these commodities would have to be considered as presenting unacceptable risks.
- Nearly all United States soils would exceed EPA’s target risk range.
- The continued use of many industrial materials, fertilizers or other routinely used commercial products may be unnecessarily and severely constrained.
- Various phosphate and micronutrient fertilizers contain small amounts of naturally occurring arsenic as they are mined materials, and some residual “non-nutritive” elements carry with the fertilizer. If the revised CSF value is finalized in its current form, it may inaccurately cause a significant percentage of phosphate and micronutrient fertilizers to be considered hazardous.
- Discharges from many sewage treatment plants or other facilities will no longer meet regulatory limits for arsenic if they are lowered as a result of the revised cancer slope factor. Plants would need to obtain discharge variances or treat their effluent at unrealistic costs.

Because the results of such a change in the cancer slope factor are so great, it is crucial that the slope factor is derived using a reasonable, scientifically valid basis. Thus, a clear understanding of the basis for the much higher cancer potency value in the current draft

⁹ Advisory Report at 44

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assessment is needed, including a full discussion of the factors that led EPA/NCEA to settle on the apparently final slope of 25.7, and how those factors differ from the considerations that could be used to calculate a slope in the 2005 draft of 5.67 and the prior value of 3.36 used by EPA's Office of Water. EPA/NCEA has clearly identified that the current draft responds to comments from NRC in 2001. That review, based on a document developed in 1999 and relying upon data collected in Taiwan over 30 years ago, is now quite dated. The scientific advancements that have taken place since then, which are identified in the SAB (2007) report, as well as other information made available since 2005, are not properly reflected in a meaningful way in the current draft.

As the 2010 SAB workgroup begins its deliberations, we believe that it is essential that it consider whether the current draft assessment fully addresses both the spirit and intent of the conclusions of the 2007 Panel, and recognize that a full scientific peer review of the draft assessment has not been performed. We do not believe that the current charge questions before the SAB workgroup are adequate to do so. Indeed, during a meeting on February 26, ORD Assistant Administrator Anastas commented that the charge questions do not limit what the SAB should address. We believe that this SAB Work Group should consider all relevant issues identified by the 2007 Panel. To assist in that effort, we have prepared the attached additional questions that arise out of the 2007 Panel report. We request that the additional charge questions as well as this letter be distributed to the workgroup prior to their deliberations.

We are confident that both written and oral comments being provided to the SAB workgroup by a broad range of interested stakeholders will further inform the workgroup on issues of high relevance. We urge the workgroup to take the necessary time to provide the full extent of scientific advice to EPA on this important topic.

Respectfully,

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Attachment 1.

Additional Proposed Charge Questions for the April 6-7, 2010 Science Advisory Panel Inorganic Arsenic Work Group

1. The SAB recommendations in 2007 called on EPA to conduct an integrated analysis of low-dose epidemiological studies from Australia, Northern Europe, South America and the United States. The 2007 Panel also recommended that all the epidemiological studies should be “judged by the same criteria” (p. 39). Please comment on whether criteria were clearly and sufficiently enumerated and explained, whether all available studies, including the studies conducted in SE Taiwan, were indeed judged by the same criteria, whether the rationale and justification for the final decision as to which study (or studies) should be used for cancer risk assessment was sufficiently explained in view of the evaluation and use of the *a priori* criteria, whether EPA adequately considered the uncertainties of exposure analysis, and whether a meta-analysis should have been performed with studies of low doses to appropriately characterize the cancer risk factor for US populations.
2. The 2007 Panel concluded that direct genotoxicity should be ruled out for inorganic arsenic, and that mechanistic studies are critically important (p. 27-28). The Panel also stated that “[w]hile mechanistic studies suggest that there should be a threshold for iAs bladder cancer, available data from epidemiological studies are lacking or problematic with regard to low-dose effects” (p. 33). The Panel suggested that this critically important issue should be the subject of additional mechanistic and epidemiologic research, and that “[r]esearch should also further illuminate the shape of the dose response curve at low doses for the biological effects of arsenic.” Please comment on the shape of the dose-response curve at low doses, in view of extensive additional information and published literature published available since that time, and in light of full consideration of EPA’s 2005 cancer guidance regarding weight of evidence.
3. The draft IRIS assessment proposes an increase in the oral cancer slope factor (CSF) for inorganic arsenic from the existing CSF (3.67 per mg/kg/day, used to set the Safe Drinking Water Act MCL of 10 ppb) to a new CSF of 25.7 mg/kg/day. Please comment on the assumptions, inputs, analytical approaches and decision logic used by EPA to derive the new CSF, including the choice of the Poisson analysis and the choice of the reference population, and whether the new slope, based on high exposure levels in Taiwan, is reasonable from an exposure perspective for U.S. populations and in consideration of alternative CSF values and approaches to dose-response modeling, including margin-of-exposure assessments.