

December 23, 2010

Via E-Mail

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US Environmental Protection Agency  
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EPA Science Advisory Board  
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**Re: Clarification of Record of November 22, 2010 SAB Quality Review Teleconference**

Dear Drs. Swackhamer and Nugent:

This letter seeks to correct the record of the November 22, 2010, Science Advisory Board (SAB) Quality Review Teleconference on EPA's Draft Toxicological Review of Inorganic Arsenic, a public meeting subject to the Federal Advisory Committee Act (FACA). During the teleconference, it appeared there was some confusion or misunderstanding among one or more members of the SAB as to an important point in the scientific evidence and, further, with regard to what the public commenters meant in making their comments. There was no opportunity for commenters to offer clarification or explanation in response to the SAB members' remarks during the teleconference, and even though it may be unusual, we therefore urge you to share this clarification with the members of the SAB. To aid in an accurate understanding of the call, private parties arranged to have it transcribed and a copy of the transcript is attached for your reference.

During the SAB's discussion after the close of public comments, Dr. Lue-Hing questioned whether the public commenters had identified scientific evidence sufficient to meet the criteria in EPA's cancer guidelines to support non-linear dose-response modeling to estimate cancer potency for inorganic arsenic. Dr. Lue-Hing's comment was as follows: "One of my concerns is the public commenters have made specific and repeated references that oppose 2007 data, and my suspicion is if there were game-changers out there, those game-changers would have been at least mentioned today in their public comments and I didn't hear that. And I'm wondering if there really are game-changers out there among the data between 2007 and today." (Tr. at 153.) Dr. Roberts posed a similar question: "I mean, is there a study out there that would change in a fundamental way the analysis or the estimate of cancer potency?" (Tr. at 152.)

It is not the typical case that a single study or two signifies a “breakthrough,” “game-changer” or “eureka” moment, especially for a chemical like arsenic which has a relatively complex toxicological mode of action. Instead, conclusions most often must be drawn based on the weight of accumulated scientific evidence. Reflecting this reality, EPA’s cancer guidelines speak in terms of reaching a point at which “sufficient evidence” of a mode of action has been demonstrated. And yet, despite these facts, the bar in reviewing the carcinogenicity of inorganic arsenic seems repeatedly to be set much higher: a requirement both that “game-changer” studies be identified, and that, in the words of SAB Work Group Chair Dr. Faustman, the literature must “definitively describe a mode of action for all of the multiple cancer endpoints of relevance.” (Tr. at 145.) These are not the actual criteria. Moreover, the correct criteria – a demonstration of “sufficient evidence” – have been met.

While a review of the attached transcript makes clear that it may have been difficult in the time allotted for oral comments to summarize the accumulated weight of the evidence, there was no lack of statements alerting the SAB to the fact that a “tipping point” has been reached regarding inorganic arsenic’s carcinogenic mode of action. Furthermore, commenters urged the SAB to consider their written submissions, which laid out in more detail the substantiation for these conclusions. For example, Dr. Barbara Beck stated “in this case the impact of the new [post-2007] literature, specifically the dose-response mode-of-action literature and the epidemiological studies, including meta-analyses on the arsenic risk assessment, is profound.” (Tr. at 43.) Similarly, Dr. Samuel Cohen, a renowned arsenic researcher whose work formed the basis of the SAB’s 2005 recognition of a threshold for the organic arsenical, dimethylarsinic acid (DMA), presented the results of the key studies, including his most recent research, which has been submitted for publication:

The focus of my comments will be regarding considerations of mode of action and its implications for the risk assessment of inorganic arsenic levels in the drinking water. As I’ve stated in my previous comments and in my most recent written comments all of the modes of action that are being considered for inorganic arsenic toxicity and carcinogenicity are nonlinear. As has been discussed extensively, the specific mode of action for inorganic arsenic carcinogenicity has not been delineated. However, there’s extensive knowledge about the mode of action. Any mode of action involving linearity such as DNA reactivity has been excluded. Thus, it seems rather circuitous and disingenuous to argue that we should default to a linear risk assessment even though we do not definitively know the specific mode of action for inorganic arsenic.

The 2005 EPA Cancer Guidelines do not ask for definitive knowledge, but indicate that a consideration for a nonlinear risk assessment should be included if there is sufficient evidence. Clearly, there is sufficient evidence. [Tr. at 51-52.]

Likewise, Dr. Joyce Tsuji highlighted the results of a meta-analysis she co-authored that was published in 2008 and updated in her written comments submitted to the SAB. The conclusion of this research is that “studies in the past 5 years show convergence on a nonlinear mode of action for inorganic arsenic that corresponds to relevant human exposures in epidemiological studies.” (Tr. at 57.)

The recent literature that these scientists – and others, including Dr. Steven Lamm – have contributed to and cited in this review, particularly as set out in their written comments, is similar to the weight of evidence on which the SAB premised its decision that DMA carcinogenicity has a threshold; a copy of the 2007 SAB report is attached. Also attached are three recently published articles regarding inorganic arsenic’s carcinogenic mode of action, including a review article and two research studies on arsenic exposure and bladder cancer.

Another area in which clarification or correction is needed relates to Dr. Faustman’s statement that “there is not enough specific data...nor are there hypotheses to explain the role of arsenic in lung cancer.” (Tr. at 145.) This assertion is clearly at odds with Dr. Cohen’s oral and written comments, which provide evidence that recent research supports the same non-linear mode of action as has been observed for other cancer endpoints: oxidative stress and cytotoxicity. (See particularly Tr. at 54-55 and Cohen written comments at 4, drawing attention to data set forth in a manuscript on the MOA for lung cancer, which is attached to his written comments).

We have recently demonstrated that a similar cytotoxic response occurs for human bronchial epithelial cells also, again at similar concentrations. Add to that the high oxygen concentration present in the lung. One can readily understand why lung can be a target site for arsenic carcinogenicity.

The fact that human bronchial epithelial cells react in vitro in the same way as human urothelial cells and keratinocytes provides support for cytotoxicity as a mode of action also for the lung in humans.

Although it was not possible for public commenters to bring this information to the attention of the SAB during its November 22 discussion, we believe it would be a major mistake for the SAB to finalize its report without making clear that the EPA cancer guidelines do not contemplate singular “game-changing” studies or “definitive” evidence to warrant a finding of non-linearity. This is especially important, given the questions raised by at least one SAB member about the state of the science and the import of comments made before the SAB.

Sincerely,

Industrial Minerals Association - North America  
Mulch & Soil Council  
National Mining Association  
National Stone, Sand, and Gravel Association  
North American Metals Council  
Organic Arsenical Products Task Force  
Treated Wood Council  
Utility Water Act Group  
Wood Preservative Science Council

Cc: Vanessa Vu, Director of SAB Office