

AMERICAN CHEMISTRY COUNCIL

Biocides Panel Chromated Copper Arsenate Work Group

Comments on the Charge to EPA SAB Arsenic Review Panel (September 12–13, 2005) Regarding Inorganic Arsenic Carcinogenicity

EPA has requested comments and advice from the Science Advisory Board (SAB) regarding EPA's recent hazard characterization for organic arsenic herbicides and on their revised hazard and dose-response assessment/characterization of inorganic arsenic. The issues and questions for the SAB to consider are outlined in EPA's *Charge to EPA Science Advisory Board Arsenic Review Panel*. The American Chemistry Council Biocides Panel CCA Work Group provides brief comments for EPA and the Science Advisory Board Arsenic Review Panel to consider in evaluating EPA's Charge regarding inorganic arsenic.

General Comments

The Charge to the SAB as released by EPA on July 26, 2005, includes aspects of some of the key issues for revising the inorganic arsenic cancer slope but needs to request a more comprehensive examination of the important issues to take advantage of the expertise of the SAB in developing a cancer slope factor for inorganic arsenic based on the current state of the science. The Charge seeks to gain SAB input on issues primarily related to dimethylarsinic acid (DMA^V) with additional requests for the SAB to consider a few of EPA's conclusions related to inorganic arsenic. The Charge and EPA's reassessment of inorganic arsenic carcinogenicity have a relatively narrow focus with a main premise that the NRC conclusions and recommendations (NRC 1999, 2001) are reliable and should be followed despite the emergence of considerable new literature and advancement in scientific knowledge related to carcinogenicity and exposure to arsenic.

The introduction of the Charge notes that EPA has followed the recommendations of NRC (2001) in developing a linear extrapolation of inorganic arsenic cancer risk from data from the

southwest Taiwanese arseniasis-endemic region. Nevertheless, since the NRC (2001) assessment, additional studies have been published that collectively question whether the key study of this population (Morales et al. 2000) accurately reflects cancer risks in the U.S. Such studies show most fundamentally a general lack of increase in cancer risks at low doses (i.e., water concentrations less than 100–200 $\mu\text{g/L}$) from epidemiological studies in Taiwan as well as in the U.S. and South America. Moreover, additional recent studies confirm the importance of nutritional deficiencies or confounding by well type in southwest Taiwan (i.e., as a result of the presence of carcinogenic humic acids in artesian wells or by high dose versus low dose). Consistent with the epidemiological data showing a difference in the dose-response relationship between high and low exposures, the current literature indicates that all plausible mechanisms or modes of action of arsenic carcinogenicity would be sublinear. The scientific evidence thus indicates that risks at low exposures of relevance for the U.S. cannot simply be extrapolated from high dose exposures in the southwest Taiwan arseniasis-endemic area.

Consequently, the knowledge and the experience of the SAB should be tapped to conduct a full and comprehensive review of the important issues for revising the inorganic arsenic slope factor given the current scientific information.

Specific Comments

Use of Human Epidemiological Data for Inorganic Arsenic

A fundamental issue for the SAB to consider is the nature of the dose-response relationship for inorganic arsenic at lower doses of relevance for exposures in the U.S. The Charge mentions that additional epidemiological data from populations exposed in the U.S. have been published, and asks a very limited question that seeks confirmation of EPA's conclusion that the Taiwanese data set remains the most appropriate choice for evaluating cancer risk in humans. Nevertheless, NRC (2001) recommended that epidemiological studies in other geographic locations were needed and thus several studies published after the NRC (2001) review should be considered by the SAB.

The SAB should be asked to conduct a much more comprehensive evaluation of the nature of the human epidemiological evidence, beginning with a careful evaluation of each of the recent U.S. epidemiological studies (Steimaus et al. 2003; Lamm et al. 2004; Karagas et al. 2004; Tollestrup et al. 2003; commentary by Frost et al. 2002). These studies should also be considered collectively with the available database of studies prior to 2001 (e.g., Bates et al. 1995; Lewis et al. 1999). Also of relevance is the epidemiological study in Argentina by Bates et al. (2004). NRC (2001) used epidemiological studies of populations in South America (e.g., Ferreccio et al. 2000) to support the applicability of the Taiwanese cancer data to more nutritionally sufficient populations such as in South America or the U.S. The more recent study of low dose exposure by Bates et al. (2004), however, does not validate the findings in Taiwan. The SAB should be asked to consider the implications of this study.

Questions should be asked regarding uncertainties in the southwest Taiwanese data and their applicability for estimating cancer risk in U.S. populations. A recent study for the SAB to consider is that of Lamm et al. (2003), who have reevaluated the southwest Taiwanese population evaluated by Morales et al. (2000) and showed a difference in the dose-response assessment between villages that exclusively relied upon artesian wells and those that did not. The potential confounding influence of other carcinogenic or co-carcinogenic substances such as humic acids in artesian wells is apparent, and the SAB should be asked to consider the impact of these findings.

Brown and Ross (2002) note considerable uncertainty in well water concentrations that individuals were exposed to in the different villages of the Morales et al. (2000) study. Cancer mortality data were related to the village median well water concentration despite wide ranges in concentrations in individual wells for some villages. Brown and Ross (2002) further describe ways in which the impact of such uncertainties can be examined. The evaluation of the well water data presented by Brown and Ross (2002) should be considered.

Another factor that affects the relevance of the southwest Taiwanese population for populations in the U.S. is nutritional differences. NRC (2001) dismissed the importance of the nutritionally impoverished conditions for the southwest Taiwanese population studied by Morales et al. (2000), indicating that nutritional deficiency could not account for the observed cancers. The

question that should be considered is the effect of nutritional deficiencies on the dose response curve at high exposure levels. Specifically, although elevated arsenic exposure is well known to be associated with increased cancer risk, what is unclear is the degree to which nutritional deficiencies, particularly in those exposed at higher doses, might have increased the susceptibility of the southwest Taiwanese population to the toxic effects of arsenic. Such a factor may increase the apparent dose-response relationship for this population over a nutritionally sufficient population. Since NRC (2001), several additional studies have been published on the importance of nutritional deficiencies in various substances on potentiating arsenic toxicity and carcinogenicity by interfering with arsenic methylation, defenses against oxidative stress, or with DNA repair (Chen et al. 2001; Mitra et al. 2004; Spallholz et al. 2004; Schoen et al. 2004). The SAB should be asked to review the current literature on this topic and comment on the impact of this factor on the representativeness of the southwest Taiwanese data for U.S. populations.

Another issue for more detailed consideration by the SAB is the shape of the dose response curve at high versus low doses, even for Taiwanese populations. Several studies in Taiwan also indicate no significant increases in risk at low doses, including Morales et al. (2000). Chiou et al. (2001) reported for a population in Northeast Taiwan that no significant increases in bladder cancer risk occurred below 100 $\mu\text{g/L}$ water concentration. Although a trend analysis was significant, the number of bladder cancer cases at low doses was very small. Chen et al. (2004) combined both northeast and southwest Taiwanese populations and showed a similar outcome of no significant increases in lung cancer risk below 100 $\mu\text{g/L}$.

Modes of Carcinogenic Action for Inorganic Arsenic

The Charge to the SAB related to toxicology and modes of carcinogenic action for inorganic arsenic is focused on methylation and the toxicity of metabolites. The Charge makes a distinction between the formation of metabolites (MMA or DMA, either trivalent or pentavalent forms) and toxicological responses with exposure to inorganic arsenic versus with DMA^V. The Charge thus implies that methylation of ingested inorganic arsenic is a process that results in the formation of toxic intermediate compounds. However, the methylation of arsenic is more complex than this portrayal and somewhat paradoxical in that on the whole body level, rather

than *in vitro*, poor methylation capacity (either through genetics or nutritional deficiency) is associated with greater risk of arsenical health effects particularly at high exposure levels (Chen et al. 2001; Chen et al. 2003a,b; Schoen et al. 2004). Therefore, methylation of inorganic arsenic should not be viewed solely as resulting in increased toxicity.

The Charge requests that the SAB comment on the conclusion that multiple modes of action might be operating following exposure to inorganic arsenic. The preface to this request mentions only the formation of various metabolites, each with their own toxicities. Other factors in the mode of carcinogenic action likely contribute to the dose-response assessment of arsenic beyond the formation of different metabolites. Specifically, it would be helpful to request SAB input on the full nature of the modes of carcinogenic action for inorganic arsenic and its metabolites, beyond the formation of metabolites. The SAB could be asked to comment on whether the modes of action associated with inorganic arsenic and metabolites would act by direct means (e.g., point mutations on DNA) or more indirectly (e.g., oxidative stress, modulation of intracellular signal transduction pathways, alterations in methylation of DNA, sister chromatid exchanges, alterations in DNA repair). Other effects of arsenic at low doses that might affect the shape of the dose response assessment are induction of protective effects that may reduce arsenic toxicity by upregulating genes and systems related to control of oxidative stress, DNA repair, and increased levels of glutathione. The SAB should be asked to give full consideration of these mechanisms and their implications for the dose response for arsenic carcinogenicity.

Dose-Response Modeling and Low Dose Extrapolation for Inorganic Arsenic

EPA is apparently following the recommendations of NRC (2001) in using linear dose-response modeling because of “significant remaining uncertainties regarding which of the metabolites might be the ultimate carcinogenic moiety and whether or not mixtures of toxic metabolites interact and the site(s) of action.” The question to the panel therefore is whether they agree with the linear approach, particularly in light of the complex mode of action for inorganic arsenic with its metabolites.

As noted above, EPA should take advantage of the background and experience of the SAB in asking for a more thorough evaluation of the various mechanisms of action of inorganic arsenic and its metabolites and their implication for the shape of the dose-response curve, particularly at low doses. Although the ultimate carcinogenic moiety is not known and more than one mechanism of action might be operating, the SAB should be asked to consider the shape of the dose-response relationship (linear or non-linear) implicated by the plausible modes of action.

The SAB should also be asked to consider the extrapolation of the Morales et al. (2000) data to U.S. populations performed by U.S. EPA (2001) and NRC (2001), as well as comments on modeling by Brown and Ross (2002). The use of an external comparison population should also be evaluated by the SAB. U.S. EPA (2001) estimated cancer risks associated with various water concentrations based on Morales et al. (2000) without using an external comparison population. NRC (2001) and U.S. EPA (2005) extrapolate risks to U.S. populations by using the extrapolation of the Morales et al. (2000) that forces the relationship through a single data point represented by an external comparison population. Risk estimates associated with U.S. EPA (2001) and NRC (2001) are very different.

SAB should also be asked to evaluate the appropriateness of an external comparison population, particularly in light of the findings of Lamm et al. (2003) regarding the apparent effect of use of artesian wells in increasing cancer risks. Moreover, interactions between socioeconomic status and exposure to elevated arsenic in well water within the southwest Taiwanese region should be investigated. Those exposed to elevated arsenic in well water have been noted as impoverished and associations have been reported between health effects (e.g., blackfoot disease, skin cancer) and low socioeconomic status and undernourishment (Chen et al. 2001). U.S. EPA (2005) acknowledges that use of a comparison population that is not comparable to the exposed population can bias the evaluation. Use of the comparison population data point in this case also changes the fit of the data and makes the dose-response curve relatively insensitive to the shape of the data at low doses. Thus, because of the large impact of this point on the dose response modeling and questions on the relevance of an external comparison population, the SAB should review this issue.

The SAB should be asked to consider alternative modeling approaches as well, such as margin of exposure or other analyses of the dose-response relationship at low doses, including consideration of data sets other than from Southwest Taiwan.

Additional Sources of Arsenic Exposure

The Charge requests SAB review of drinking water intake and dietary arsenic intake from food. The SAB should be asked to consider the impact of all additional sources of arsenic together.

The Charge asks what arsenic intake from the diet is appropriate for the control and study population of southwestern Taiwan used in developing the cancer slope factor. The preface to this question and the workgroup issue paper conclude (based on NRC 2001) that the dose-response modeling (ED_{01}) is relatively insensitive to the effect of what dietary intake rate from food is assumed, because inorganic arsenic intake from diet is the same for the comparison population (presumably southwest Taiwanese) and the exposed population. Whether the diet is the same for the arseniasis-endemic region and the greater southwest Taiwanese area is also questionable. Moreover, a small effect on risk may be significant when considered with the other factors each of which individually may have a small effect on risk (e.g., uncertainty in water consumption). In addition, whether the type of modeling used accurately reflects the true nature of the relationship at low doses should be considered. U.S. EPA (2001) shows a noticeable effect on the risk level (5 times lower risk) when the southwest Taiwanese exposure was adjusted for $50 \mu\text{g}/\text{day}$ of inorganic arsenic from food and an additional 1 L/day from water used in cooking.

Childhood Arsenic Exposure

The Charge asks: Do these data provide adequate characterization of the impact of childhood exposure to inorganic arsenic?

We suggest that this question be clarified to state, “Do these data provide adequate characterization of the *carcinogenic potential* ~~impact~~ of childhood exposure to inorganic arsenic?” in order to avoid confusion regarding focus on noncancer effects, which is not within the Charge for this SAB. It would also be helpful to add a preface to inform that panel that the

studies of arsenic exposure and cancer risk involve populations who were exposed *in utero*, as well as in childhood and adulthood.

Conclusion

EPA has examined various issues with regard to the cancer risk of inorganic arsenic, as reflected in the Workgroup Issue Paper and the Toxicological Review of Inorganic Arsenic. These draft documents were released outside the agency at the end of July (2005). Although both documents are listed as review materials for the SAB, the Charge seeks very limited comment regarding the many important issues for updating the cancer risk assessment for inorganic arsenic. Moreover, the Issue Paper and the Charge appear to largely accept the NRC (2001) conclusions and seek little input from the SAB, despite considerable additional scientific evidence that has been published since the NRC (2001) review. A full review of the weight of scientific evidence regarding the dose-response relationship for arsenic carcinogenicity at low doses cannot be elicited by simplified questions on methylation or whether the SAB agrees that the Taiwan dataset is the best. Rather than accept EPA's review of the issues, the SAB should be asked to conduct its own comprehensive review of the issues including evaluation, for example, of each of the recent epidemiological studies and other key publications on nutritional effects and modes of action. A more comprehensive list of potential questions is listed as an attachment to illustrate the range of issues of importance on which to seek SAB input. The SAB and public comment period (albeit brief) is EPA's opportunity to obtain a full and comprehensive peer review of a regulatory value that is likely to have far-reaching implications for the risk assessment of arsenic and public health decisions.

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