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Subject: Comments on Draft SAB Report, *Advisory on EPA’s Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic*

Dear Dr. Nugent:

The MethaneArsonic Acid (MAA) Research Task Force (Task Force)\(^1\) appreciates the opportunity to comment on the U.S. Environmental Protection Agency (EPA) Science Advisory Board (SAB) Arsenic Review Panel’s (ARP) draft report, *Advisory on EPA’s Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic: An Advisory Report of the US EPA Science Advisory Board (Draft Report)*, dated September 15, 2006. Attached is a copy of our comments. Briefly, these comments demonstrate that a non-linear margin-of-exposure (MOE) analysis for inorganic arsenic is supported by current understanding of inorganic arsenic’s mode of action(s) and is consistent with EPA’s 2005 Guidelines for Carcinogen Risk Assessment. Use of an MOE analysis, will allow for a fuller, more transparent presentation of the uncertainties in inorganic arsenic risk assessment.

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\(^1\) The Task Force is comprised of registrants of the pesticide active ingredients monosodium methanearsonate (MSMA), disodium methanearsonate (DSMA), calcium acid methanearsonate (CAMA), and dimethane arsinic acid (DMA, or cacodylic acid), (collectively, the organic arsenical herbicides), and consists of APC Holdings Company/Drexel Chemical Company, KMG-Bernuth Inc., and Luxembourg-Pamol, Inc.
We also note the following:

- Recent literature on inorganic arsenic dose-response that was provided to the SAB is not mentioned. The meta-analysis conducted by Dr. Pamela Mink of Exponent regarding bladder cancer in US populations, which demonstrated a lack of evidence for increased cancer risk in the low dose region in US studies is not included, and particularly of concern is the failure to include the 2006 analysis by Lamm and coworkers, published in Environmental Health Perspectives. This publication demonstrates in the southwest Taiwan population (the population recommended by SAB for EPA's quantification of risk) that dose-dependent increases in risk were observed only in three townships out of six that were studied. This analysis of the epidemiological data concluded that the data were consistent with no increased risk of carcinogenicity to individuals exposed to arsenic in drinking water at levels that are below 151 ug/L.

- The recommendation to conduct a linear dose response model for inorganic arsenic, while still postulating a non-linear dose response model is confusing, particularly given that (as noted in the attached technical comments) EPA guidance allows for a non-linear model in such circumstances as an alternative to (or in addition to) linear models. In addition, use of an MOE approach could be an important tool in risk communication to the public.

The Task Force thanks the SAB Panel for considering these comments.

Sincerely,

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1 Introduction

These comments on the September 15, 2006 Science Advisory Board (SAB) Panel draft report, "Advisory on US EPA’s Assessments of Carcinogenic Effects of Organic and Inorganic Arsenic: An Advisory Report of the US EPA Science Advisory Board" (Draft Report) (US EPA, 2006) are submitted on behalf of the MAA Research Task Force (Task Force). The Task Force’s comments focus on the SAB Panel's recommendation that "…linear extrapolation below the point of departure is the method to be used" (p 49) to describe the dose-response relationship for the carcinogenicity of inorganic arsenic (InAs) at low doses.

In the Draft Report, the SAB Panel presented compelling evidence of nonlinearity for the dose-response of InAs carcinogenicity, yet ultimately decided to recommend linear extrapolation at low doses. This decision does not accurately reflect the current scientific understanding of InAs dose-response. Given the strong scientific evidence for a nonlinear dose-response, the SAB should recommend a nonlinear dose-response model. This recommendation would be in accordance with the U.S. Environmental Protection Agency (EPA) 2005 Guidelines for Carcinogen Risk Assessment (Cancer Guidelines) (US EPA, 2005a). In particular, a Margin-of-Exposure (MOE) approach should be used for the quantitative assessment of InAs carcinogenicity risk.

Furthermore, the SAB Panel proposes that a fuller characterization of potential InAs risk would be achieved through the (1) reliance on information from additional epidemiological studies to supplement the data from Taiwan (NRC, 1999; Wu et al., 1989), (2) consideration of the potential susceptibility of the Taiwanese population to InAs-induced health effects due to differences in diet and genetics, and (3) characterization of the effects of exposure misclassification in the Taiwanese data. Consideration of these issues would provide further evidence that the approach proposed by the SAB Panel overestimates the carcinogenic potency of InAs.
2 The Use of a Nonlinear Extrapolation Model for Inorganic Arsenic is Consistent with US EPA Cancer Guidelines

The Cancer Guidelines recommend that risk assessments consider all of the available scientific information. Specifically, in defining appropriate dose-response approaches, risk evaluations should take into account information on the mode of action. In general, the Cancer Guidelines recommend consideration of all biologically plausible alternatives to characterize more fully the range of possible risks:

"Where alternative approaches have significant biological support, and no scientific consensus favors a single approach, an assessment may present results using alternative approaches. A nonlinear approach can be used to develop a reference dose or a reference concentration" (US EPA, 2005a; Section 1.3.4, p. 1-15).

This statement unambiguously states that a nonlinear approach can be used when there are several alternative approaches that are biologically feasible, even when the mode of action is not clearly defined.

2.1 Analysis of Biologically Plausible Alternatives

The Cancer Guidelines repeatedly recommend that, when the science is uncertain, all biologically plausible alternatives be used to provide risk managers and decision-makers with information about the degree of uncertainty and about the upper and lower bounds of the risk estimates. For example:

"When risk assessments are performed using only one set of procedures, it may be difficult for risk managers to determine how much health protectiveness is built into a particular hazard determination or risk characterization. When there are alternative procedures having significant biological support, the Agency encourages assessments to be performed using these alternative procedures, if feasible, in order to shed light on the uncertainties in the assessment" (Section 1.3.1, p. 1-8).
"If critical analysis of agent-specific information is consistent with one or more biologically based models as well as with the default option, the alternative models and the default option are both carried through the assessment and characterized for the risk manager" (Section 1.3.1, p. 1-9).

"… Extrapolation is based on extension of a biologically based model if supported by substantial data …Otherwise, default approaches can be applied that are consistent with current understanding of mode(s) of action of the agent, including approaches that assume linearity or nonlinearity of the dose-response relationship…." (Section 1.3.4, p. 1-14).

"Both linear and nonlinear approaches are available … when multiple estimates can be developed, the strengths and weaknesses of each are presented" (Section 3, p. 3-1).

"An assessment that omits or underestimates uncertainty can leave decision makers with a false sense of confidence in estimates of risk.… Model uncertainty is expressed through comparison of separate analyses from each model, coupled with a subjective probability statement, where feasible and appropriate, of the likelihood that each model might be correct…. Some aspects of model uncertainty that should be addressed in an assessment include …the use of effects observed at high doses as an indicator of the potential for effects at lower doses, [and] the effect of using linear or nonlinear extrapolation to estimate risks" (Section 3.6, p. 3-29).

"… [I]n situations where there are alternative models [for analysis of dose-response data] with significant biological support, the decision maker can be informed by the presentation of these alternatives along with their strengths and uncertainties" (Section 3.2.3, p. 3-15; repeated at Section 5.1, p. 5-3).

2.2 Selection of a Dose-Response Model

The Cancer Guidelines clearly recommend selection of a nonlinear dose-response model when supported by the mode of action:

"Where alternative approaches have significant biological support, and no scientific consensus favors a single approach, an assessment may present results using alternative approaches. A nonlinear approach can be used to develop a reference dose or a reference concentration" (US EPA 2005; Section 1.3.4, p. 1-15).

"A nonlinear approach should be selected when there are sufficient data to ascertain the mode of action and conclude that it is not linear at low doses and the
agent does not demonstrate mutagenic or other activity consistent with linearity at low doses" (US EPA, 2005; Section 3.3.1, p. 3-22).

"A nonlinear extrapolation method can be used for cases with sufficient data to ascertain the mode of action and to conclude that it is not linear at low doses but with not enough data to support a toxicodynamic model...” (US EPA, 2005; Section 3.3.4, p. 3-23).

"Nonlinear extrapolation having a significant biological support may be presented in addition to a linear approach when the available data and a weight of evidence evaluation support a nonlinear approach, but the data are not strong enough to ascertain the mode of action applying the Agency’s mode of action framework" (US EPA, 2005; Section 3.3.4, p. 3-23).

To be consistent with the Cancer Guidelines, when the data support a nonlinear dose-response relationship, an MOE approach should be used as an alternative choice for evaluating risk.

3 Scientific Evidence Supports a Nonlinear Dose-Response and MOE Approach

There is strong scientific evidence that the dose-response relationship for InAs carcinogenicity has a threshold. Several scientific reviews of InAs carcinogenicity have suggested that the dose-response for InAs is likely nonlinear, and that linear extrapolation from high-dose data sets, such as those from Taiwan (NRC, 1999; Wu et al., 1989), may overestimate risks at lower exposures (US EPA, 2001; ERG, 1997). For example, according to the 2001 "National primary drinking water regulations; Arsenic and clarifications to compliance and new source contaminants monitoring (Final rule)," which is the assessment for revision to the InAs maximum contaminant level (MCL):

"Independent scientific panels who have considered the Taiwan study have suggested that using the Taiwan study to estimate US risk at lower levels may result in an overly conservative estimation of US risk. The independent panels have all said that, below the observed range of the high level of contamination in Taiwan, the shape of the dose-response relationship is likely to be sublinear.
Thus, an assumption that the effects seen per dose increment remain the same from high to low levels of dose may overstate the US risk” (US EPA, 2001).

Studies conducted outside the United States have repeatedly and convincingly demonstrated that InAs-induced cancers are not observed in populations exposed to drinking water concentrations below 150 µg/L. For example, in a separate study in Taiwan, Guo et al. (2001) showed a consistent increase in skin cancer (basal cell carcinoma) only in males, and only in the highest dose group that was exposed to InAs drinking water concentrations higher than 640 µg/L. In another study, Guo (2004) observed elevated lung cancer in a population in Taiwan only at InAs drinking water levels higher than 640 µg/L. In a case-control study of a population from Argentina, Bates et al. (2004) did not find association between InAs ingestion and bladder cancer, even at the highest study exposure category of >200 µg/L.

While recognizing the uncertainties in the data from the Taiwanese study by Wu et al. (1989), the SAB Panel did not consider more refined analyses of the same dataset. Such analyses are presented in the publications by Lamm et al. (2003), Lamm and Kruse (2005), and Lamm et al. (2006). These publications demonstrate that a different analysis of the same data set leads to a conclusion that there is a threshold for arsenic carcinogenicity. The most recent of these studies, Lamm et al. (2006), re-analyzed the extensive Taiwanese dataset (NRC, 1999; Wu et al., 1989) by townships, and demonstrated that geographically-related risk factors for bladder and lung cancer may have confounded the results of the previous analyses of these data. Analysis of the data by township showed that a dose-response relationship between InAs exposure and cancer existed only in 3 out of 6 townships (Figure 1).
Figure 1. Reproduced from Lamm et al. (2006)

Figure 1 (reproduced from the Lamm et al. (2006) publication) shows the relationship between InAs drinking water concentrations and standard mortality ratios (SMRs). It is obvious from this figure that the data from townships 2, 4, and 6 have a very different dose-response relationship than the data from townships 1, 3, and 5. In townships 1, 3, and 5 there is no statistically significant relationship (p=0.3) between exposure to InAs and incidence of bladder and lung cancer (see dotted line in Figure 1). Cancer risk is high even when the arsenic concentration is close to zero, and it does not significantly increase at higher levels of exposure. These townships are located in areas of high incidence of Blackfoot disease, suggesting that the exposures that cause high rates of bladder and lung cancer (in the absence of InAs exposure) may be the same as those leading to the unique symptoms associated with Blackfoot disease, or that the Blackfoot disease is the etiological factor.

The analysis by Lamm et al. (2006) reveals that a significant relationship between exposure to InAs and incidence of cancer exists only in a subset of the data (i.e., the data from townships 2, 4, and 6). For these townships, the dose-response for InAs-related bladder and lung cancer has an apparent threshold, with bladder and lung cancer risk significantly increased only
at drinking water concentrations above 150 μg/L (0.013 mg/kg per day).\(^1\) Above the threshold, the dose-response relationship is linear with a slope of 0.7 (μg/L)\(^1\). Only this subset of the data should be used for the assessment of InAs risk.

The threshold at 150 μg/L, is consistent with studies of InAs conducted in the United States, which do not show an increased cancer risk even in populations exposed to InAs in drinking water at mean concentrations up to 190 μg/L (Steinmaus et al., 2003; Moore et al., 2002; Lewis et al., 1999; Bates et al., 1995; for review see Schoen et al., 2004). For example, a large-scale study in Utah was sponsored and directed by EPA to determine whether elevated InAs concentrations in drinking water were associated with disease (Lewis et al., 1999). This study found no effects (cancer or noncancer) at average InAs concentrations in drinking water up to 191 μg/L (with InAs drinking water concentrations ranging from 3.5 to 620 μg/L). Most recently, another EPA study conducted in Fallon, NV has further demonstrated that there is no association between InAs drinking water concentrations of about 100 μg/L and multiple cancer types (Calderon et al., 2006; Riley, 2005). At the September 12-13, 2005 SAB InAs review panel meeting, Dr. Pamela Mink presented the results of a rigorous meta-analysis demonstrating that "low level" exposure to InAs in drinking water (i.e., drinking water in the range of 100-200 μg/L) is not associated with increased risk of bladder cancer (Mink, 2005; Exponent, 2005).

Observations from epidemiological studies are supported by the plausible carcinogenic mechanisms of InAs. These mechanisms include inhibition of DNA repair, perturbation of DNA methylation patterns, modulation of signal transduction pathways (leading to changes in transcriptional controls and the over-stimulation of growth factors), and generation of oxidative stress (see, for example, Schoen et al., 2004; Rossman, 2003; Snow et al., 2005; Germolec et al., 1998). All these proposed mechanisms have been reviewed extensively and none of these mechanisms has a linear dose-response relationship. Moreover, there are convincing data, that arsenic is not a direct acting genotoxic agent (see, for example, Rossman, 2003; Kligerman et al., 2003). The SAB Panel recognizes this and specifically states:

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\(^1\) Calculated assuming consumption of 3.5 L/day of drinking water, 1 L/day cooking water, and 50 μg/day of InAs in diet by a 55 kg Taiwanese individual (US EPA, 2005b).
"Inorganic arsenic (iAs\textsuperscript{III}) and its metabolites are not direct genotoxicants because these compounds do not react with DNA" (US EPA, 2006; p. 6).

"\textsuperscript{III}iAs and some of its metabolites can exhibit indirect genotoxicity, induce aneuploidy, cause changes in DNA methylation, and alter signaling and hormone action. In addition, iAs can act as a transplacental carcinogen and a cocarcinogen. Arsenic essentiality and the possibility of hormetic effects are in need of additional research to determine if they are relevant to arsenic’s role in inducing cancers and to clarify their significance in assessing arsenic risk. " (US EPA, 2006; p. 6).

Furthermore, as recognized by the SAB Panel, InAs may have hormetic effects (\textit{i.e.}, exposures to low doses of InAs may grant some beneficial health effect (US EPA, 2006; p. 36). Support for hormetic effects of InAs comes from both \textit{in vitro} and \textit{in vivo} studies. \textit{In vitro} studies demonstrate that exposures to low levels of InAs elicit different cellular responses than higher doses, and can be protective against other toxic insults (Snow \textit{et al.}, 2005; Calabrese and Baldwin, 2003). Snow \textit{et al.} (2005) demonstrated that low-level exposure to InAs (0.5 \textmu M) reduced the amount of reactive oxygen species constitutively generated in keratinocytes and fibroblasts. Additionally, these authors showed that InAs reduced the amount of reactive oxygen species in these cell types when they were challenged with the oxidizing agent menadione.

Hormetic effects have been observed in mice, rats, hamsters, minipigs, goats, and chickens. For example, Snow \textit{et al.} (2003) demonstrated that mice exposed to 0.2-2 \textmu g/L arsenate in drinking water were protected against skin tumors induced by dimethylbenzanthrazene (DMBA)/phorbol 12-tetradecanoate 13-acetate (TPA). Uthus and Davis (2005) demonstrated that rats fed 0.5 \textmu g/g of InAs had lower levels of aberrant crypt foci in colon cells compared to rats fed either 0 or 50 \textmu g/g InAs. Uthus (2003) has noted that the beneficial effects of low-level InAs may be related to the methyl recycling of DNA, with both InAs deprivation and excessive supplementation disrupting DNA methylation patterns (Uthus, 2003). It is unknown, however, if it is the modulation of DNA methylation or other mechanisms that are responsible for beneficial effects noted in these animal studies (Uthus, 1992). While a
horneric effect of InAs has not been confirmed, these observations strongly support the findings of nonlinearity for the InAs dose-response relationship.

4 The SAB Panel's Analysis of the Mode of Action of Inorganic Arsenic Supports the Use of Nonlinear Extrapolation Models

The SAB Panel (US EPA, 2006) has carefully evaluated the available information on InAs's mode of action and agreed that although multiple modes of action may operate in InAs carcinogenesis, the postulated modes of action for InAs carcinogenicity are nonlinear and do not involve a mutagenic mode of action:

"The mechanistic studies suggest that there should be a threshold dose-response" (US EPA, 2006; p. 37).

"At present the experimental evidence on mode of action of inorganic arsenic supports a possible nonlinear dose-response at low exposure levels" (US EPA, 2006; p. 49).

"In examining the dose-response relationships of arsenicals in inducing direct or indirect mutagenic responses (including effects thought to be clastogenic in nature), it is clear that effects are only seen at doses that induce cytotoxicity. This implies a threshold" (US EPA, 2006; p. 49).

Nonetheless, the Draft Report ultimately recommends the use of linear extrapolation models, a conclusion that does not flow from, and cannot be supported by, data and scientific analyses set forth in the Draft Report.

The SAB Panel has recommended 1) sensitivity analyses addressing uncertainty in exposure in the Taiwanese population and 2) the inclusion of additional epidemiological data sets. Through these recommendations, the SAB Panel has acknowledged the uncertainty in arsenic risk assessment. By incorporating this variability and uncertainty into the overall analysis, a more complete picture of potential arsenic risks will become apparent. Additionally,
the use of a nonlinear dose-response with a risk assessment based on an MOE approach will allow for a fuller (and more scientifically correct) characterization of risks from InAs.

5 Conclusion

The SAB Panel (US EPA, 2006) concluded that because "there is insufficient justification for the choice of a specific nonlinear form of the dose-response relationship, the US EPA’s 2005 Guidelines for Cancer Risk Assessment are clear that linear extrapolation below the point of departure is the method to be used" (p.49). This conclusion is not supported by the Cancer Guidelines or by the SAB Draft Report itself. The Cancer Guidelines do not require that a single mode of action be clearly established and explicitly allow for the use of a nonlinear approach if all the plausible mode of actions are nonlinear, and linear mode of actions are ruled out (US EPA, 2005a). It is inconsistent and scientifically unsupportable for the SAB Panel to acknowledge a nonlinear dose-response, and yet recommend linear dose-response modeling. Based on the scientific literature, and the Cancer Guidelines, and the SAB Panel's own conclusions, an MOE analysis is the most appropriate way to characterize cancer risks from InAs.
References

Bates, MN; Rey, OA; Biggs, ML; Hopenhayn, C; Moore, LE; Kalman, D; Steinmaus, C; Smith, AH. 2004. "Case-control study of bladder cancer and exposure to arsenic in Argentina." *Am. J. Epidemiol.* 159(4):381-389.


