

AMERICAN CHEMISTRY COUNCIL
Biocides Panel
Chromated Copper Arsenate Work Group

Questions for the EPA SAB Arsenic Review Panel (September 12-13, 2005) Regarding The Dose Response of Inorganic Arsenic Carcinogenicity

The American Chemistry Council Biocides Panel CCA Work Group provides brief summaries of issues for the Science Advisory Board Arsenic Review Panel to consider in evaluating EPA's proposed cancer slope factor for inorganic arsenic. These questions are intended to assist the SAB in their consideration of the underlying exposure, toxicity, and epidemiological data with the ultimate goal of a more accurate representation of those data in the cancer slope factor for inorganic arsenic.

1. Adequacy of the exposure assessment in the Taiwan data set: well type and potential for other confounding factors

Background

Morales et al. (2000) evaluated well water concentrations and bladder cancer mortality rates were evaluated in a population in southwest Taiwan. This evaluation included both villages solely using artesian wells (median village arsenic concentrations = 350-934 $\mu\text{g/L}$) and those also using non-artesian wells (median village arsenic concentrations = 10-717 $\mu\text{g/L}$).

Reanalysis of these data by Lamm et al. (2003) indicates that bladder cancer mortality rates depended on arsenic level only for villages that exclusively relied on artesian wells for their water source. No dose-response with arsenic concentration was observed for villages that did not exclusively rely on artesian wells.

Questions

- Because the non-artesian wells had lower arsenic concentrations overall, could these results be explained by the difference in arsenic carcinogenicity at high doses versus low doses?
- Given that other carcinogenic substances such as humic acids have been reported in artesian wells in this area of Taiwan, could arsenic be acting as a co-carcinogen with some other substance or characteristic of these wells?
- Wouldn't an analysis that includes villages relying solely on artesian wells misrepresent the risk characterization of arsenic, especially for low doses?

2. Adequacy of the exposure assessment in the Taiwan data set: dietary arsenic

Background

The southwest Taiwanese population, which is the study population in the research that forms the basis of the cancer slope factor in IRIS and is the focus Morales et al (2000), consumed a very impoverished diet consisting primarily of yams and rice. The yams are dried and consumed over the year. Consequently, additional water is needed to rehydrate and cook both the rice and yams. In deriving the reference dose, EPA incorporated an assumption of additional exposure to inorganic arsenic that would be accumulated in yams and rice and also assumed a higher drinking water intake rate to account for water used in rehydrating the dried yam and rice diet. In contrast, the derivation of the existing cancer slope factor in IRIS for arsenic did not include any consideration of intake of inorganic arsenic from the diet (nor from water used to rehydrate and cook foods), thereby substantially underestimating actual intakes of inorganic arsenic for this study population.

Additional studies indicate that the amount of arsenic contributed by the diet in Taiwan may be even higher than assumed in the RfD derivation. In the IRIS file, EPA indicates that the inorganic arsenic content in the Taiwanese diet was unknown and was assumed to result in an

intake of 2 µg/day. In contrast, analyses of yams and rice conducted by Schoof et al. (1998) indicated that intake from the diet may have been much higher resulting in an intake of 50 µg/day (Schoof et al. 1998, Table 6).

Questions

- What would be the effect on the slope factor if arsenic exposure in Taiwan were underestimated?
 - What are the appropriate intake values for inorganic arsenic from the diet and water consumption rates to adequately characterize arsenic intake for this population, including the additional water consumption for rehydrating and cooking?
 - Have these dietary contributions to total inorganic arsenic exposure (including food rehydration) been adequately accounted for in the derivation of the proposed slope factor?
- 3. Subsequent to the NAS review published in 2001, new epidemiological data from U.S. and foreign populations have become available. Are these data consistent with recommendations regarding arsenic cancer risk?**

Background

Since the NRC (2001) review, several additional epidemiological studies have been completed for arsenic-exposed populations in the U.S. (Steinmaus et al. 2003; Lamm et al. 2004; Karagas et al. 2001, 2004) and for those with lower arsenic exposure levels in Argentina (Bates et al. 2004). Unlike studies in Taiwan, these studies do not show a dose-response relationship for increases in cancers with exposure. Additionally, Frost et al. (2002) note that the Lewis et al. (1999) research had sufficient power to detect the cancer risks estimated by NRC (2001) yet likewise do not identify a dose-response relationship between exposure and cancers related to arsenic.

An additional study of the population in southwest Taiwan has been completed as well. Similar to bladder cancer risk at lower well water concentrations reported by Morales et al. (2000), Chen et al. (2004) likewise indicate a lack of increase in lung cancer risk at arsenic well water concentrations of 10- 100 $\mu\text{g/L}$.

Questions

- What do these studies tell us about risks to populations in the U.S.?
- Do these studies support difference conclusions for low dose exposures in the U.S. than indicated based on analyses of the Taiwanese population that include higher doses?
- Is the SAB confident that the proposed slope factor is reflective of the findings of these studies?

4. Mechanism of action for arsenic carcinogenicity, and the shape of the dose-response curve at low doses

Background

Various plausible mechanisms of action have been proposed and investigated for the carcinogenicity of arsenic (Schoen et al. 2004). The likely mechanisms do not involve direct point mutations on DNA but act indirectly through modulation of intracellular signal transduction pathways, oxidative stress, alteration of DNA methylation or impairment of systems that counteract DNA damage. Thus, the accumulation of these effects is necessary for an increased likelihood of cancer. Other actions of arsenic at low doses can induce 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.

Questions

- Wouldn't the plausible mechanisms by which arsenic may cause cancer, result in a change in the shape of the dose response curve at low doses versus at high doses such that cancer risk at low doses would be lower than extrapolated based on the cancer risk at high doses?
- Do the toxicological and epidemiological data indicate that this change in the dose-response curve would occur at environmentally relevant doses?

5. Impact of nutrition on cancer risk associated with exposure to arsenic

Background

Recent studies have continued to establish the importance of nutrition in modifying susceptibility to the toxic effects of arsenic (Chen et al. 2001; Mitra et al. 2004; Spallholz et al. 2004, Schoen et al. 2004). These studies indicate that poor nutrition results in lower potential to metabolize and excrete inorganic arsenic and repair DNA damage. This research suggests that studies of populations with extremely poor nutritional status are not representative of the relationship between cancer risk and dose for populations with more sufficient or sufficient nutrition such as the U.S. populations.

Questions

- Given the extremely poor nutritional status of the Taiwanese population evaluated by Morales et al. (1999), wouldn't this population show a greater cancer incidence at a given dose than the U.S. population?
- Wouldn't sufficient nutrition at low doses also have a protective effect such that risks at lower doses in which protective mechanisms are operating may be less than predicted based on high doses in which these mechanisms are overwhelmed?

- Is there information within studies of other arsenic-exposed populations (including both high and low doses) that are more similar to U.S. populations (in terms of nutritional status) that can be used to better characterize risks?

6. Children's susceptibility at low doses

Given that the Taiwanese population used to derive the cancer slope factor included exposure to arsenic by entire populations, including adults, children, infants and even *in utero* exposures, isn't consideration of childhood exposures already incorporated into the existing databases upon which the cancer slope factor is derived?

7. Use of a comparison population in evaluating the dose-response curve

Background

Morales et al. (2000) and NRC (2001) estimate cancer risk by forcing regressions of arsenic water concentrations and cancer incidence through one data point representing a comparison population for Taiwan or the U.S. Without this comparison population, the shape of the dose-response curve is sublinear such that there is little change in risk at lower water concentrations. The comparison populations, however, appear to have a much lower risk than predicted based on the incidence at the lower water concentration for the exposed population. Therefore, these populations may not be valid comparison populations for these data because the cancer incidence may differ due to other factors than arsenic exposure.

Questions

- Does the use of a comparison population in this way place overwhelming emphasis on one data point which has inherent uncertainty for whether it is a true comparison population for the exposed population?

- What would be a technically more rigorous method for evaluating the relationship between dose and risk from the available data?

References

Bates, M.N., O.A. Rey, M.L. Biggs, C. Hopenhayn, L.E. Moore, D. Kalman, C. Steinmaus, and A.H. Smith. 2004. Case-control study of bladder cancer and exposure to arsenic in Argentina. *Am. J. Epidemiol.* 159(4):381–389.

Chen, C-J., Y-M. Hsueh, M-P. Tseng, Y-C Lin, L-I Hsu, W-L. Chou, H-Y. Chiou, I-H. Wang, Y-L. Chou, C-H. Tseng, and S-H. Liou. 2001. Individual susceptibility to arseniasis. pp. 135–143. In: *Proc. of the Fourth Annual International Conference on Arsenic Exposure and Health Effects*. June 18–22, 2000. W.R. Chappell, C.O. Abernathy, and R.L. Calderon (eds). Elsevier Science Ltd.

Chen, C-L., L-I. Hsu, H-Y. Chiou, Y-M. Hsueh, S-Y. Chen, M-M. Wu, and C-J. Chen. 2004. Ingested arsenic, cigarette smoking, and lung cancer risk, a follow-up study in arseniasis-endemic areas in Taiwan. *JAMA* 292(24):2984–2990.

Frost, F., G. Craun, and K.G. Brown. 2002. Detection of excess arsenic-related cancer risks. *Environ. Health Perspect.* 110(1):A12–A13.

Karagas, M.R., T.D. Tosteson, J.S. Morris, E. Demidenko, L.A. Mott, J. Heaney, and A. Schned. 2004. Incidence of transitional cell carcinoma of the bladder and arsenic exposure in New Hampshire. *Cancer Causes Control* 15(5):465–472.

Lamm, S.H., D.M. Byrd, M.B. Kruse, M. Feinleib, and S.H. Lai. 2003. Bladder cancer and arsenic exposure: Differences in the two populations enrolled in a study in southwest Taiwan. *Biomed. Environ. Sci.* 16(4):355–368.

Lamm, S.H., A. Engel, M.B. Kruse, M. Feinleib, D.M. Byrd, S. Lai, and R. Wilson. 2004. Arsenic in drinking water and bladder cancer mortality in the United States: an analysis based on 133 U.S. counties and 30 years of observation. *J. Occup. Environ. Med.* 46(3):298–306.

Lewis, D.R., J.W. Southwick, R. Ouellet-Hellstrom, J. Rench, and R.L. Calderon. 1999. Drinking water arsenic in Utah: A cohort mortality study. *Environ. Health Perspect.* 107(5):359–65.

Meacher, D.M., D.B. Menzel, M.D. Dillencourt, L.F. Bic, R.A. Schoof, L.J. Yost, J.C. Eickhoff, and C.H. Farr. 2002. Estimation of multimedia inorganic arsenic intake in the U.S. population. *Hum. Ecol. Risk Assess.* 8(7):1697–1721.

Mitra, S.R., D.N. Guha Mazumder, A. Basu, G. Block, R. Haque, S. Samanta, N. Ghosh, M.M. Hira Smith, O.S. von Ehrenstein, and A.H. Smith. 2004. Nutritional factors and susceptibility to arsenic-caused skin lesions in West Bengal, India. *Environ. Health Perspect.* 112(10):1104–1109.

Morales, K.H., L. Ryan, T.L. Kuo, M.M. Wu, and C.J. Chen. 2000. Risk of internal cancers from arsenic in drinking water. *Environ. Health Perspect.* 108(7):655–661.

NRC. 2001. Arsenic in drinking water, 2001 update. National Research Council, Division of Earth and Life Studies, Board on Environmental Studies and Toxicology, Committee on Toxicology, Subcommittee to Update 1999 Arsenic in Drinking Water Report. National Academy Press, Washington, DC.

Schoen, A., B. Beck, R. Sharma, and E. Dube. 2004. Arsenic toxicity at low doses: Epidemiological and mode of action considerations. *Toxicol. Appl. Pharmacol.* 198(3):253–267.

Schoof, R.A., J. Eickhoff, L.J. Yost, E.A. Crecelius, D.W. Cragin, D.M. Meacher, and D.B. Menzel. 1999. Dietary exposure to inorganic arsenic. pp. 81–88. In: *Proc. Third International Conference on Arsenic Exposure and Health Effects*. W.R. Chappell, C.O. Abernathy, and R.L. Calderon (eds). Elsevier Science Ltd.

Spallholz, J.E., L.M. Boylan, and M.M. Rhaman. 2004. Environmental hypothesis: Is poor dietary selenium intake an underlying factor for arsenicosis and cancer in Bangladesh and West Bengal, India? *Sci. Total Environ.* 323(2004):21–32.

Steinmaus, C., Y. Yuan, M.N. Bates, and A.H. Smith. 2003. Case-control study of bladder cancer and drinking water arsenic in the western United States. *Am. J. Epidemiol.* 158(12):1193–1201.

Yost, L.J., S.-H. Tao, S.K. Egan, L.M. Barraj, K.M. Smith, J.S. Tsuji, Y.W. Lowney, R.A. Schoof, and N.J. Rachman. 2004. Estimation of dietary intake of inorganic arsenic in U.S. children. *Hum. Ecol. Risk Assess.* 10:473–483.