Arsenic Risk Assessment

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In this commentary, we respond to the conclusions of recent publications by Hopenhayn-Rich et al. (1) and Smith et al. (2) regarding issues of arsenic risk assessment. Although Hopenhayn-Rich et al. was not published in Environmental Health Perspectives, we believe that it is important to examine these studies and their relevance to risk assessment together.

In 1988 the Risk Assessment Forum of the U.S. Environmental Protection Agency developed a cancer slope factor (CSF; the U.S. EPA estimate of carcinogenic potency) for arsenic based on an ecological epidemiology study relating skin cancer to arsenic ingestion in Taiwan. Several important questions have been raised about this CSF. One issue with this CSF is that it assumes a linear dose–response relationship for cancer, and thus it does not reflect increasing evidence indicating either a threshold or a sublinear dose–response relationship for low doses of arsenic (3,4).

Saturation of the methylation detoxification pathway has been proposed as one explanation for the sublinear dose–response relationship for arsenic (5). Another issue is whether ingestion of arsenic is associated with cancers other than skin cancer.

EPA is currently under a judicial mandate to evaluate whether the existing maximum contaminant level (MCL) should be revised (the current MCL is 50 µg/L). In evaluating the existing MCL and the possible need for a revised MCL, EPA will likely consider recent publications regarding the issues of the methylation threshold and internal cancers. Two recent publications [Hopenhayn-Rich et al. (1) and Smith et al. (2)] are seemingly pertinent to these issues; however, as described below, we found that these publications have deficiencies that limit their applicability to these regulatory questions. The studies used by Hopenhayn-Rich et al. were not designed appropriately to address the methylation threshold issue. The paper by Smith et al. failed to address a variety of significant uncertainties that call into question their risk assessment model.

Hopenhayn-Rich et al.

Methylation is generally accepted as a metabolic detoxification mechanism for low doses of inorganic arsenic (5). Hopenhayn-Rich et al., however, question the conclusion of the EPA Science Advisory Board that “at dose levels below 200 to 250 µg As3−/person/day [where metabolic saturation begins] there is a possible detoxification mechanism (methylation) that may substantially reduce cancer risk from the levels EPA has calculated” (5). Using data from previously published studies, Hopenhayn-Rich et al. used percent inorganic arsenic in urine as a measure of non-detoxified arsenic and total urinary arsenic concentration as a measure of arsenic dose and applied simple linear regression to determine whether the percentage of inorganic arsenic increases with increasing dose. Their results failed to show a correlation between percent inorganic arsenic and urinary arsenic concentration and, on that basis, the authors concluded that there is no consistent evidence to support the methylation threshold hypothesis in humans.

The Hopenhayn-Rich et al. evaluation does not, however, demonstrate the absence of a methylation threshold for the following reasons:

- The average arsenic exposures in almost all of the studies analyzed were too low to observe methylation saturation. Evidence from the study by Buchet et al. (6) suggests that methylation would be completely saturated at exposures greater than 500 µg/day, with corresponding total urinary arsenic output of approximately 290 µg/day at steady state. If average daily urine output is 1.5 l/day (1), this is equivalent to an average urinary arsenic concentration of about 190 µg/L. Among the 28 populations analyzed by Hopenhayn-Rich, only two populations (7,8) had average urinary arsenic concentrations at or above 190 µg/L (238 and 245 µg/L, respectively); a regression analysis on the individual data within the Yamauchi et al. (7) population was borderline significant at p = 0.10 [individual data were not available for the Farmer and Johnson population (8)].

- The authors used urinary arsenic concentrations from grab samples as the basis for evaluating methylation capacity. However, the proportion of inorganic arsenic excreted in the urine varies substantially over time; thus, an individual grab sample is not representative of the degree of methylation that is occurring. Studies by Buchet et al. (6) show that after ingestion of inorganic arsenic, the proportion of arsenic in the urine that is inorganic arsenic is high soon after exposure (0–12 hr), but much lower later on (>12 hr). The appropriate measurement with which to examine metabolism and elimination of arsenic is the total mass of inorganic arsenic and its metabolites eliminated over a 24- to 48-hr time period; using mass per time rather than concentration would control not only for variability in the proportions of the metabolites over the course of a day, but also for variability in urine volume. A recent 7-day diet study in Japan found that the intake and excretion of total arsenic were balanced when averaged over a week but not over 1 day (9).

Smith et al.

Currently, the CSF for ingested arsenic is based on the incidence of nonmelanoma skin cancers associated with exposure to high levels of arsenic in drinking water in Taiwan; however, Smith et al. have suggested that arsenic could be an important risk factor not only for skin cancer, but also for several internal cancers including lung, liver, bladder, and kidney. Smith et al. used the data from another epidemiological study in Taiwan (10) to examine...
whether there might be an association between ingested arsenic and internal cancers [these data are described in greater detail in a more recent epidemiological study in Taiwan (11)]. The authors applied simple linear regression to data from the Taiwanese study and found a linear relationship between well water concentrations of arsenic and mortality rates for liver, lung, kidney, and bladder cancer. The U.S. lifetime risk of cancer due to consuming 1 l/day of drinking water containing 50 μg/l arsenic was estimated by Smith et al. to be 13/1000 (2: Table 5). This risk may be converted to a CSF of 18 (mg/kg-day)−1 for administered dose, which is approximately 10 fold higher than the current CSF of 1.75 (mg/kg-day)−1.

We noted the following deficiencies in the analysis of Smith et al., particularly in relation to risks in U.S. populations:

- In deriving risk estimates associated with arsenic exposure using linear regression, Smith et al. assumed that the arsenic intake of the control population was zero. This assumption is unrealistic given other sources of arsenic in the diet and would inflate the CSF by artificially increasing the slope of the exposure–response curve.

- Smith et al. did not discuss the implications of detoxification in estimating potential risks from low-level exposures typical of the U.S. population (an estimate of typical U.S. background exposure is about 22 μg/day). The estimated exposure level of 22 μg/day for the U.S. population is substantially lower than an estimated 2130 μg/day as the Taiwan study population (based on a concentration of 0.47 mg/l As in drinking water (12,13) and assuming a water consumption rate of 4.5 l/day and 18 μg/g As in food, using the most current EPA arsenic intake estimates for Taiwan (14)). As noted above, the EPA Science Advisory Board recommends that arsenic detoxification be considered in the risk assessment of exposures below 200–250 μg/day (5). This recommendation represents a level below which methylation is not compromised. According to Buchet et al. (6), saturation of methylation begins at this level and is complete at levels greater than 500 μg/day.

- Smith et al. did not consider key uncertainties in the use of the Taiwan data in their analysis. For example, blackfoot disease and bladder cancers are associated with fluorescent humic acids found in the Taiwanese drinking water (15,16). The potential role of humic acids in bladder cancer etiology (or other cancer types) makes conclusions regarding any quantitative association between arsenic and cancer uncertain. In addition, it may render the extrapolation from Taiwanese exposure–response data to risks from arsenic in drinking water in the U.S. questionable. This may be an important consideration not only for evaluating the paper of Smith et al., but possibly for evaluating the validity of the present CSF.

- Smith et al. did not address (nor does the current CSF) the differences between the Taiwanese and U.S. populations that would reduce the accuracy of using exposure–response data from Taiwan for U.S. populations. For example, the average protein intake (which would influence the extent of detoxification of arsenic) in the blackfoot disease endemic area was only 65% of the current average U.S. protein intake, potentially compromising the detoxification of arsenic and invalidating the CSF for use in U.S. populations. Average protein intake in the blackfoot disease endemic area in 1975 was 44.1 g/day in women and 65.3 g/day in men (17; Guo H-R, personal communication); average U.S. protein intake is 65–70 g/day in women and 90–110 g/day in men (18). Additionally, the intake of methionine (an amino acid necessary for arsenic methylation) (10) plus cystine was very low in the endemic area [1.2 g/day (19)] compared to the average U.S. intake [2.3–2.5 g/day in women and 3.2–3.9 g/day in men (16)]. In fact, the intake of methionine alone was deficient; the average intake was 70% of the recommended daily minimum (17; Guo H-R, personal communication).

The exposure parameters for the Taiwan study that were used by Smith et al. may have biased the cancer risk estimate. EPA recently approved a reference dose (RFD) for arsenic (using the Taiwanese data) that uses a water-consumption rate for males and females combined of 4.5 l/day (14), as compared to the values of 3.5 and 2 l/day for males and females, respectively, used by Smith et al. In addition, the RFD derivation assumed a background dietary arsenic intake of 2 μg/day (18), based on estimates from Taiwan of 30 μg As/kg in rice and a daily rice consumption of 0.225 kg, and the assumption (from an FDA survey) that 35% of arsenic in rice was inorganic. In contrast, Smith et al. assumed that the background intake in Taiwan was zero. Consequently, CSFs calculated using the revised EPA exposure parameters would be significantly lower than those calculated by Smith et al. We also note that use of the revised exposure parameters would also decrease EPA’s present CSF for skin cancer (19).

In summary, the Smith et al. and Hopenhayn-Rich et al. analyses are flawed. Hopenhayn-Rich et al. do not provide a basis for dismissing the methylation threshold hypothesis as the basis for the apparent lack of carcinogenicity of arsenic at low levels. We recommend that arsenic regulation should not consider any dose–response relationship between arsenic and internal cancers based on the Smith et al. analysis because of the deficiencies discussed above. Mechanistic or more refined epidemiological studies are needed to assess the possible relationship between internal cancers and arsenic ingestion. An example of such a study is provided by a recent epidemiological study conducted in Taiwan which found no consistent association between the arsenic level in well water and urinary cancer incidence with arsenic levels less than 0.32 ppm and a statistically significant association between arsenic and bladder cancer at levels greater than 0.64 ppm, thus indicating a possible nonlinear dose–response relationship between arsenic exposure and urinary cancer (20). In addition, a similar association was also observed for transitional cell renal cancer, but not renal cell renal cancer. It should be noted that this study involved approximately 11 million individuals residing in 243 towns and used 10 exposure groups. This contrasts with the study used by EPA to derive the current CSF, which involved approximately 40,000 individuals in 37 villages, using only 3 exposure groups (12,13). Furthermore, we recommend that future risk assessments for arsenic consider evidence for a sublinear arsenic-induced cancer dose–response relationship, as recognized by the EPA’s Science Advisory Board (10).

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