

Risk and Revisionism in Arsenic Cancer Risk Assessment

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The topic of arsenic cancer risk assessment, particularly for environmental oral exposures to inorganic, carcinogenic arsenic has recently become the subject of considerable interest and some controversy in both the regulatory and public health communities. For example, the U.S. Environmental Protection Agency (EPA) has indicated its intent under court direction to reevaluate the current drinking water standard for arsenic (1), with some likelihood of a downward revision of the permissible arsenic concentration. This expected EPA action, in turn, is due at least in part to recent findings (2–5) of the association of ingested arsenic to internal cancers (i.e., cancers of the bladder, kidney, liver and lung), in a Taiwanese agrarian population and others in which such exposures have produced skin cancer and noncancer effects as reported in a large number of studies (6–9). The findings of internal cancers with their more grave consequences for mortality compared to skin cancer have greatly heightened concerns about health impacts and the need for more stringent permissible exposures.

The Taiwanese population noted above, who were exposed to geochemical inorganic arsenic in well water, also makes up the principal epidemiological database for cancer risk assessment of ingested inorganic arsenic by such regulatory agencies as EPA. Effects of such exposures were first described comprehensively by Tseng et al. in 1968 (6). Various lingering scientific issues about ingested arsenic and its various adverse health effects, including discussion of the Taiwanese data set, have recently been presented (10). More pointed skepticism and criticisms, mainly directed to the global application of the Taiwanese results with respect to cancer risk estimates, have appeared (11–15). These concerns and criticisms appear to collectively support a revisionist position that cancer risk estimates derived from the high inorganic arsenic exposures in Taiwan are probably too high for non-Taiwanese populations for a variety of reasons and that any regulatory decisions based on these data are apt to be unnecessarily stringent.

The topic of risk and revision in arsenic cancer risk assessment has been debated recently in *EHP* (14–16). Carlson-Lynch et al. (14) presented critical commentary on use of the Taiwanese data set for risk assessment at low doses in areas other than

Taiwan. This commentary took particular aim at the report of Smith et al. (4), which estimated rather high internal cancer risk rates using linear dose–response extrapolation from the Taiwan data set, and the review of Hopenhayn-Rich et al. (17), which showed that detoxification of inorganic arsenic in humans via biomethylation is efficient up to rather high intakes, suggesting that impaired biomethylation and detoxification among the exposed Taiwanese was not necessarily a factor in their cancer rates. A subject of debate, as noted below, is the extent to which methylation/detoxification attenuates cancer risk. Smith et al. (16) rebutted some of the criticisms of Carlson-Lynch et al. (14) which produced, in turn, further discussion by Beck et al. (15).

Critical comments by Carlson-Lynch et al. (14), Beck et al. (15), and others regarding relevance of the Taiwanese data for arsenic risk assessments in non-Taiwanese exposures are problematic and require technical evaluation. We present such an evaluation here. Our evaluation brings into question a number of the criticisms leveled against current cancer risk estimates for ingested inorganic arsenic. Responses to these criticisms are organized under specific headings that address some underlying questions: Were the Taiwanese inorganic arsenic exposures adequately quantified in those published reports that drive the cancer risk assessments? Are there metabolically determined thresholds to cancer risk via inorganic arsenic detoxification? Were there host factors specific to the Taiwanese that limit use of these data for global cancer risk assessments?

Additional (Dietary) Intakes of Inorganic Arsenic in Exposed Taiwanese Populations

Beck et al. (15) refer to a conference paper by Yost et al. (18) which claimed that dietary intake of inorganic arsenic by exposed Taiwanese would have ranged up to 290 µg/day and that these figures were not included by EPA in cancer risk estimates for inorganic arsenic in well water. When added to inorganic arsenic intake from water, inorganic arsenic in the diet was estimated by Yost et al. (18) to result in a shift in EPA's arsenic cancer slope factor (CSF) from 1.75 to as low as 0.13 (mg/kg-day)⁻¹.

Yost et al. (18) noted that the analytical

Oral exposures of nonoccupational populations to environmental inorganic arsenic are associated with skin and internal cancers as well as various noncarcinogenic effects. Cancer risk assessments have been based largely on epidemiological studies of a large population exposed to inorganic arsenic in well water in Taiwan. Criticisms and skepticism of the use of the Taiwanese data for estimating arsenic cancer risks outside of Taiwan, including potential use by the U.S. Environmental Protection Agency for regulatory purposes, have been expressed on various grounds. The nature and extent of such criticisms have sharpened with recent findings in the exposed Taiwanese of increased incidence of internal cancers (bladder, kidney, liver, and lung), in addition to already-observed skin cancer, coupled with a good likelihood that these findings will produce more stringent arsenic regulation in the United States and elsewhere. These criticisms collectively posit a revisionist view that: 1) cancer incidence among the Taiwanese was amplified by a number of host and environmental factors not applicable elsewhere, 2) the cancer dose–response curve may not be linear at the lower exposures elsewhere, and 3) there is a toxicokinetic and metabolic threshold to cancer risk that was exceeded by the Taiwanese. However, a number of the arguments against wide use of the Taiwanese data are flawed and subject to challenge. We explore some of these arguments and their critical evaluation, particularly as they concern certain exposure, metabolic, and nutritional determinants of the cancer risk of inorganic arsenic in the Taiwanese. *Key words:* arsenic, arsenic epidemiology, cancer risk. *Environ Health Perspect* 103:684–689 (1995)

methodology used for speciating arsenic content in Taiwanese dietary samples required chemically forcing conditions, particularly strong acid treatment, to produce satisfactory recoveries of total arsenic. Particularly troubling is the artifactual generation of inorganic arsenic as a consequence of the methodology, inasmuch as the reported fraction of total arsenic that was inorganic arsenic appeared to be contradicted by two reports (19,20) showing that the fraction of total arsenic that is inorganic arsenic in food crops relevant to the Taiwanese diet was much smaller than reported. The studies are noted below.

Pyles and Woolson (19) found that the great majority of arsenic in various crops grown in inorganic arsenic-treated test soils was present as one or more complex organoarsenic compounds. These were

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classified as aqueous-soluble (water-methanol mixture) organoarsenicals or nonpolar, lipophilic organoarsenical material. The one exception to this finding was attributed to contamination by inorganic arsenic in soil. Potato flesh showed inorganic arsenic to compose only 8% of total arsenic.

The Ontario, Canada, Ministry of the Environment included arsenic speciation data for some representative market samples in its draft document on arsenic (20,21). These data are tabulated in Appendix E of EPA's 1988 document on arsenic (22). The total arsenic content of potatoes consisted of 10% inorganic arsenic; the balance was organoarsenical(s). Rice samples contained 35% inorganic arsenic; the balance was organoarsenical(s). Although the sample size was small, the results for rice and potatoes are consistent with the overall findings of Pyles and Woolson (19).

These data raise questions about what chemical forms of arsenic are present in food crops, particularly in rice and sweet potatoes, the two staples of the Taiwanese diet. Rice was shown to have 35% inorganic arsenic (20–22), and sweet potato (yam) levels of inorganic arsenic should parallel those in potatoes, about 10% (19–22). It is generally accepted that the arsenic in seafood consists of one or more complex chemical forms that are relatively nontoxic and do not substantially figure in dose–response assessments (23–26). The apparent presence of complex organic forms of arsenic in food crops similarly indicates that such arsenic may well have bioactivity different from inorganic arsenic. Therefore, one cannot simply assume that analytically isolable forms of arsenic are toxicologically the same as the original forms or forms that are generated *in vivo* after ingestion. It is also quite possible that the chemical forcing conditions to recover all of the arsenic content in the Yost et al. (18) analyses are in fact required because of organic arsenic forms in those samples.

A second point in the matter of added inorganic arsenic from diet is what its effect would be on the slope of the dose–response curve. In the case of a linear dose–response relationship and with both a relatively fixed dietary arsenic intake from foods having biochemically incorporated arsenic but variable water inorganic arsenic intake, one would expect that the CSF value would not change, but the intercept would. That is, the curve would retain its slope but would be shifted upward with a higher intercept, representing diet arsenic-associated risk.

A third point is that while Beck et al. (15) and Yost et al. (18) focused on the role of arsenic incorporated in food-crop

components of diet, they neglected the arguably more relevant issue of arsenic introduced to diet by food preparation. Carlson-Lynch et al. (14) noted the Taiwanese consumed 225 g of rice daily. Assuming the standard cooking water-to-rice volume ratio of just over 2:1, about 450–550 mL of arsenic-containing well water would be used for cooked rice preparation. This volume is ~25% of the EPA generic drinking water intake of 2 L/day and ~10% of the 4.5 L/day figure used by EPA in its current Integrated Risk Information System (IRIS) computer file for estimating the cancer risks of inorganic arsenic (IRIS, January 1995 version, National Technical Information Service, Springfield, Virginia). This indirect inorganic arsenic intake from water would reduce the CSF a maximum of 25–30%, a reduction relatively modest compared to the overall uncertainty and variability entering into the exposure assessment and risk characterization process, and much less than the many-fold reduction referred to by Beck et al. (15).

A fourth question is how tea preparation and consumption from arsenic-contaminated water relates to either reported total inorganic arsenic intakes or total water volume intakes. However, as discussed below, the fractional input of tea to total water intake volume and tea inorganic arsenic to overall daily intake of inorganic arsenic would be accounted for within typical total water intake volumes noted in the literature. That is, inorganic arsenic intake from tea would be subsumed within the category of total water inorganic arsenic intake rather than being additive to it.

Given the above questions, it is certainly premature and inappropriate to use alternative estimates of CSFs to that in EPA's current IRIS file for ingested inorganic arsenic where the alternatives are based on such data as the analytically measured inorganic arsenic levels of Yost et al. (18).

Daily Drinking Water Consumption Rates in Agrarian Taiwanese Populations

Beck et al. (15) support EPA's use of a high average daily drinking water intake of 4.5 L/day for the arsenic-exposed Taiwanese in the current arsenic cancer risk data in the IRIS file. The consumption rate of arsenic-contaminated drinking water is an important parameter in estimating total arsenic intakes. Arsenic intakes, in turn, are important to deriving the CSF value.

The present EPA intake estimate and an earlier EPA figure of 3.5 L/day are both arbitrary, as observed by Smith et al. (16). EPA's current and past intake values do not appear to be based on any hard data from intake surveys, studies on intake ver-

sus behavior, or physiological requirement estimates using all water sources, mathematical modeling, or metabolic balance calculations. Selection of the intake figures was seemingly based on a qualitative judgment that the exposed Taiwanese were doing manual labor in a hot climate and some anecdotal data from several residents in the exposure zone. In contrast, there are a lot of published data on the topic of water intake and factors affecting such intake in human populations.

Total water needs of human populations are expressed by the following source equation:

$$W_t = W_f + W_d + W_m$$

where W_t = total water need, W_f = water intake from food (to include liquids classified in the foods category and solid foods with high water content, such as vegetables), W_d = drinking water ingested directly, and W_m = endogenous or metabolic water generated from oxidative energy production.

Only part of the human daily water requirement is derived from drinking water consumed directly, the fraction varying with age, climatology, activity patterns, and dietary habits. According to Guthrie (27), the typical adult requires a total of 1.9–2.5 L/day of water, of which 1.1 L is derived from both tap water and beverages. About 40%, or 0.4–0.5 L, is tap water. For American women of childbearing age, Ershow et al. (28) used data from the 1977–78 USDA Nationwide Food Consumption Survey to calculate that nonpregnant and nonlactating women consume 1.9 L/day of water from all sources, of which 1.16 L/day is from tapwater-based fluids; of this, 0.58 L/day is actually drinking water directly ingested as such. Galagan et al. (29) reported daily fluid and drinking water intakes for age-stratified male and female children in two California communities. Children aged 9–10 years in the two communities consumed an average of 0.8 L/day tap water.

The daily fluid requirement of adults in a hot climate, 37.8°C (100°F), is 38 mL water/kg body weight (27). For Taiwanese adult males weighing 55 kg (22) and doing moderate physical activity in a hot climate, 2.1 L of total water is required, of which about 50%, or 1 L/day, would be directly from drinking of water (based on the U.S. adult ratios). While we cannot assume that the fractions of total water intake that arise from drinking purchased beverages among Americans is comparable in the Taiwanese, given the likely lower availability of bottled and canned beverages in Taiwan, we can assume that intake volumes of tea prepared from well water in the Taiwanese would be

comparable to the intakes of purchased and home-made beverages in Americans. Tea consumption would therefore constitute total intake volumes similar to beverage intakes among Americans. That is, intake rates of tea when added to direct water intake rates would yield comparable total water intake rates. Similarly, the arsenic intake from tea would be part of the total inorganic arsenic in well water consumed daily by the exposed Taiwanese.

Taiwanese female adults weighing 50 kg and not doing hard physical outdoor work would consume 1.9 L/day, of which about 1 L/day is drinking water. With regard to the impact of humidity on water intakes in tropical climates, Adolph (30) noted that relative humidity only contributes to thermal stress and altered water intake when it exceeds 80%. Galagan et al. (29) plotted ambient temperature versus water intake for children on a body-weight basis. Children 9–10 years old would consume 1.3 L/day of water at an ambient temperature of 37.8°C.

The need for fluid intake as a function of work activity, and activity as a function of ambient temperature and humidity, has been the subject of a number of reports (30–38). Individuals who have acclimated to environmental conditions, particularly extremely hot temperatures, ingest less water than those who are not acclimated. Both acclimated and unacclimated individuals, furthermore, are commonly in a state of “voluntary dehydration.” That is, they habitually and consciously consume much less water than expected, indicating that the physiological mechanisms for fluid intake control, antidiuretic hormone (ADH, vasopressin) and the thirst mechanisms, are either blunted or ignored, producing a lower fluid intake.

Furthermore, a number of studies have shown that adults (30–38) and children (39) in hot climates will commonly have quite severe states of voluntary dehydration, i.e., they are functioning with much less than optimal water intakes. Dehydration occurs in populations with little or moderate physical activity (31,32,39) as well as in individuals under significant physical stress, such as forced exercise regimens (30,33–37) and the extreme stresses of military units in extended combat situations (38). Kristal-Boneh et al. (31) noted that young male adults living in Israel’s Negev desert and having a typical range of physical activity had a daily water intake of 2 L/day. Voluntary water drinking in these desert residents was not enough to achieve a true hydration state. Armstrong et al. (33) found that even with prolonged exercise in the heat, voluntary dehydration would persist, depending on such factors as drinking water temperature and palatability.

Rothstein et al. (34) have observed that dehydration rates of 2–3% of body weight are common in military combat situations and rates up to 5% were observed. Acclimated troops in routine training are also commonly in a state of voluntary dehydration (38).

In summary, the available literature on drinking water intake indicates that water intake among the Taiwanese farmers in the arsenic exposure zone would hardly be a simple and arbitrary estimate, absent any actual systematic population surveys in Taiwan. The exposed Taiwanese would not receive all their daily water intake from directly drinking well water or tea made from it. Tea consumption, furthermore, would arguably be fractionally similar to overall beverage intake rates among Americans, yielding similar total (i.e., direct + beverages) water intake rates. Some fraction of water intake would be coming from food water in their diet, although this cannot be easily quantified except for water used for cooked rice. Mention has been made that part of the diet was “dried” sweet potatoes, but what this means in terms of actual residual water content is unknown. The exposed Taiwanese would have been acclimated to the thermal stresses of routine farm work and they were likely to have been in a state of voluntary dehydration for some indeterminate period of time. While the condition of voluntary dehydration appears to be chronic among populations in hot climates, there is little information on variability over the long term of fluid intake rates. That is, can individuals be in a *de facto* perpetual state of suboptimal hydration? There is therefore little current basis for selection of a large well water intake volume of 4.5 L/day in the Taiwanese or any values above EPA’s generic intake volume of 2 L/day for adults.

Saturation of Arsenic Biomethylation

Biomarkers of arsenic exposure and bio-transformation. Beck et al. (15) cite EPA’s Science Advisory Board (SAB) review (40) of the draft drinking water arsenic document as indicating that blood arsenic in one study was only elevated when drinking water arsenic was above 100 µg/L (41), suggesting nonlinear arsenic pharmacokinetics in blood. The point apparently being made by both the SAB committee (40) and Beck et al. (15) is that appearance of arsenic in blood at a rather high level of arsenic intake from water indicates an increase in arsenic retention and therefore altered arsenic toxicokinetics. However, the article cited by both reports doesn’t really show this.

First, the analytical methodologies available at the time of the Valentine et al. (41)

study and their limitations of sensitivity and specificity, coupled with the recognized complexity of blood as an analytical matrix, make it much more likely that an alleged “threshold” in water arsenic intake for blood arsenic elevation is actually an arsenic intake that produced a blood arsenic concentration above the detection limit. Valentine et al. (41) reported mean blood arsenic levels for four of their five study groups in the range of 3–5 ppb (0.3–0.5 µg arsenic/dL blood). These levels are quite low, and we suspect that mean values were outside detection limits with further lack of analytical proficiency or rigid quality control protocols. Lack of analytical sensitivity in the Valentine et al. paper is supported by the recent statistical analyses of arsenic in many water samples by Eaton (42). Even with current state-of-the-art, approved analytical methodology and analysis by 22 laboratories of a much more simple matrix (i.e., water samples), the practical quantitation level for arsenic reported by Eaton, 4 ppb (4 µg/L), was still no better than the Valentine et al. mean values, 3–5 ppb, for four of their groups.

A second and equally important argument is toxicokinetic. There is 1) a linear increase in urinary arsenic across the same water arsenic intake range but 2) no alterations in urinary arsenic profiles to correspond to this claimed relationship in blood arsenic (i.e., the relative excretion rate of arsenic would begin to decline with the onset of arsenic retention). One does not observe the latter here or in various other studies.

Blood arsenic is also a poor indicator of chronic exposure or past exposures. The major biomarker of ongoing chronic arsenic exposure in human populations is urinary arsenic, not blood arsenic. The best marker of cumulative exposure is hair arsenic, provided that such hair samples can be shown to be free of surface-contaminating arsenic. It is therefore invalid to use blood arsenic–water arsenic relationships in Valentine et al. (41) to argue existence of thresholds for toxicokinetic changes via exposure biomarkers and therefore toxic risk.

Hopenhayn-Rich et al. (17) reviewed the relationship of biomethylation of arsenic to total arsenic exposures in human populations with long-term environmental and other exposures. Their cited studies collectively show that, within a rather wide range of total arsenic exposures, the fraction of biomethylated metabolites and associated biomethylation efficiencies do not vary. These various data sets indicate that biomethylation in humans persists at a high rate up to quite high inorganic arsenic intakes. Few substantive reports have been published since that paper to quantitatively

challenge that conclusion, and some of the new data in fact further support the authors' conclusions.

Warner et al. (43) reported mean total and speciated urinary arsenic levels of 18 subjects in Nevada exposed to inorganic arsenic in well water at an average concentration of 1312 µg/L. One can calculate from the authors' Table 2 that exposed subjects had 23% inorganic arsenic (170/750), 26% monomethyl arsenic (MMA; 190/750), and 52% dimethyl arsenic (DMA; 390/750). In controls, the corresponding fractional distribution was 13% (9/68), 21% (14/68), and 65% (44/68). The two distributions, given the sample sizes and standard errors, do not differ significantly. The fractional distributions in both groups also parallel data in Hopenhayn-Rich et al. (17). The levels of arsenic in Nevada water are quite high. For comparison, the highest water level reported for the exposed Taiwanese was 1820 µg/L As (22). Two conference reports from an arsenic conference (44,45) noted changes in MMA to DMA ratios with changes in exposure. While evaluation of these latter data await peer-reviewed publication, it is not clear what these ratio changes mean. Interestingly, these same reports did not offer any clear claim that inorganic arsenic itself was fractionally increased significantly with increases in total water inorganic arsenic intake. A similar, unclear relationship as to level of significance and fractional distributions between inorganic arsenic and the combined methylated forms appears in the recent Society of Toxicology meeting report of Del Razo et al. (46), who reported that the MMA/inorganic arsenic and DMA/MMA ratios were reduced in urine of individuals exposed to 400 µg/L As when compared to controls. Comparative ratios of inorganic arsenic to the sum of MMA+DMA or of inorganic arsenic to total arsenic in terms of statistical significance were not noted in the authors' meeting abstract.

Compared to other species, humans have a higher fraction of MMA (47). Since this early observation, little hard evidence has appeared indicating that the increased fraction of MMA directly figures mechanistically in skin or internal cancers. While MMA is hepatotoxic to rabbits, it has not been shown to be carcinogenic in humans. Indirect connections of metabolite ratio changes to arsenic carcinogenesis, as have been suggested (48), remain to be elaborated. Beck et al. (15) argue that current studies must be examined for MMA/DMA ratio changes in individuals with intake changes. How one does this with the current crop of cross-sectional epidemiological studies of stable arsenic exposures is not clear. The metabolic and toxicological sig-

nificance of MMA/DMA ratios to cancer endpoints remains to be demonstrated.

Biochemical/toxicokinetic issues. Valberg et al. (49) carried out some estimates of dose-variable arsenic methylation, assuming that biomethylation of inorganic arsenic is a saturable process following simple Michaelis-Menten saturation kinetics and that half-saturation occurs at a daily intake of 700 µg/day. Such assumptions as to what would be the half-saturation point are quantitatively simplistic, given that the S-adenosylmethionine-requiring methyltransferases in liver and other tissues have not been fully characterized in terms of inorganic arsenic or MMA as methyl acceptors. We do not have definitive evidence as to whether arsenic biomethylation is a "piggy back" process, biochemically usurping a process or processes intended for other physiological roles, or whether there is a unique methylation process for arsenic. We also do not have a good knowledge of the organellar sites of biomethylation in liver of intact organisms; a few *in vitro* studies have used cytosolic or mitochondrial preparations as well as liver slices.

Involvement of a liver microsomal methylase could well be that of thiol methyl transferase (TMT; E.C. 2.1.1.9), a broad-acceptor methyltransferase (50) functioning via one of the proposed dithiolic-arsenic intermediates (48) as the methyl acceptor. Cytoplasmic enzyme(s) could be either *O*-methylases or *N*-methylases. On the other hand, a recent meeting report by Styblo et al. (51) described preliminary findings with rat liver cytosol that there may also be a unique enzymatic methylation system for inorganic arsenic and MMA.

TMT in human liver microsomes shows biphasic kinetics (52) and appears to be quite close enzymologically to the erythrocyte TMT. Erythrocyte TMT has been reported to show genetic polymorphism: a fivefold spread in activities was found in a study of 231 first-degree relatives in 47 families (53). Activities of both the *O*-methyl and *N*-methyl transferases are also genetically controlled (54). Valberg et al. (49) also do not take account of potential adaptation mechanisms operating with chronic exposures. Vahter and Marafante (55) noted that tissue arsenic concentrations of experimental animals decline over time with continued arsenic dosing. This may indicate induction of a detoxifying methylase system. Vahter and Marafante (55) also note the purported tolerance to inorganic arsenic among the arsenic eaters of 19th century Styria, Austria. Whether this practice as historically reported offers any toxicokinetic support for an adaptive mechanism is not known. This tolerance

may simply represent ingestion of arsenic within a matrix yielding low arsenic bioavailability.

The earlier study of Buchet et al. (56), which involved single volunteers ingesting arsenic at one of four dose levels (125, 250, 500, 1000 µg/day) has been offered by Carlson-Lynch et al. (14) and others as support for a methylating threshold. This study is meaningless in mechanistic and biostatistical terms for assessing biomethylating efficiencies in entire populations. Furthermore, the results of Buchet et al. would actually suggest that humans have a high biomethylating capacity. The 1000 µg/day dose showed reductions of 7 and 10% in the total methyl (MMA+DMA) metabolite fraction, versus the 500 and 125 µg/day doses (74 versus 81%; 74 versus 84%). Such changes are small enough to be explained by sampling and measurement errors as well as interindividual variability. Beck et al. (15) cite an acute inorganic arsenic dosing study of mice (57) to show saturation of biomethylation. Again, such data have marginal relevance for chronic environmental arsenic exposures in human populations.

Taiwanese Nutritional Status

The report of Engel and Receveur (58) showed that the Taiwanese had intakes of protein and methionine that were above recommended levels, and these nutrients are important to the issue of inorganic arsenic detoxification. Furthermore, the relevance of animal studies of reduced biomethylation with diets restricted in amino acid or protein content to the Taiwanese or other exposed human populations is debatable, due to the actual size of reductions in the methylation-associated diet components compared to Taiwanese intakes. In a study in rabbits by Vahter and Marafante (59), the methionine-restricted diet contained only about 15% of this amino acid compared to the standard diet. The choline-deficient diet had no added choline versus 1 g/kg choline in the standard formulation, while the low-protein diet was 50% of the standard diet in protein.

Beck et al. (15) argue that, while the exposed Taiwanese may have had sufficient methionine plus cystine intakes, the dietary guidelines do not take into account xenobiotic methylation. Since a principal xenobiotic for the exposed Taiwanese in terms of detoxifying biomethylation is inorganic arsenic, one can estimate the molar (millimolar) fraction of daily methyl-source intake allocated to arsenic methylation. The highest concentration of arsenic in well water in the Taiwan endemic zone was 1.82 ppm (22). If one uses the 4.5 L/day water intake value of EPA, this is 8.2 mg/day, or 0.11 mmol As/day. Assuming

mainly dimethylation, 0.22 mmol or somewhat less of methyl source is required daily. One can calculate from the Engel and Receveur (58) nutrient estimates for these Taiwanese that the methionine + cystine average intake, based on a 55 kg male body weight, was 2.2 g/day. The millimolar equivalent, expressed as methionine, is 15 mmol. This indicates that no more than about 1.5% of the daily dietary intake of methyl source was used for arsenic biomethylation in the exposed Taiwanese for the highest recorded well level. If one takes EPA's weighted average from the Tseng data of 0.8 ppm water inorganic arsenic in the highest exposure group [i.e., >0.6 ppm As (22)], then the average demand on daily donor methyl availability is <1% (-0.7%).

Humic Acid and Related Substances

Beck et al. (15) note that humic acid, when complexed with arsenic, may play a role in carcinogenicity based on a single peer-reviewed report on altered hepatic enzyme activities (60). This is a variation on the long-held argument by some that Blackfoot disease, a dry-gangrene vasculopathy occurring in the arsenic-exposed Taiwanese, was due to the vasoactive properties of fluorescent agents, including humic acids. The arguments for and against any humic acid factor have been summarized and critiqued (10). The conclusion can be offered that it is arsenic, not humic acid, which is a constant in the various stages of this type of vasculopathy. A similar argument can be offered that the one constant for precancer lesions, notably keratoses (that often give rise to invasive carcinomas), is arsenic exposure (22) and that arsenic-linked skin and internal cancers have been seen in patients treated with Fowler's solution (arsenite) (5,22), where humic acid complexes were not relevant.

Conclusions and Overview

We have presented a number of the criticisms against use of the Taiwanese data set for quantitative cancer risk assessments and critiqued them on various grounds. There are a number of other, more fundamental questions that can be raised (10) that were not presented here; for example, how could any putative roles for arsenic essentiality in humans be reconciled with linear, very low-dose extrapolations for skin and internal cancer risks from ingested inorganic arsenic? This article is not intended as a defense of the Taiwanese data per se, but rather as a set of arguments against the use of poorly informed, inconclusive, or otherwise flawed reasoning and information by individuals or committees in identifying alleged problems with these data.

Arguments have been made that levels of carcinogenic arsenic in diet can be sig-

nificant and must be taken into account, rather than using drinking water arsenic alone. We have attempted to show, however, that the quantitative role of dietary inorganic arsenic in generation of a CSF is far from established and may not even be significant, given the overall uncertainty and variability in the cancer risk characterizations reported for inorganic arsenic. We note that there are questions about the form of arsenic in foodstuffs and their relative carcinogenic potency, questions about how dietary arsenic intakes would affect CSF values, and the matter of a likely modest effect of added arsenic ingested from foods prepared with arsenic-contaminated water.

Arguments have been made that there have been underestimates of water intake by arsenic-exposed Taiwanese in the past and that EPA's current use of an intake volume of 4.5 L/day, a value over twice that of the generic figure of 2 L/day, is appropriate. However, that higher volume selection appears to be quite arbitrary, given what we know and what was presented here about fluid intakes in various human populations. We particularly noted that any argument for a high daily intake volume of water in the Taiwanese is no more well grounded than is use of a generic/default value of 2 L/day used by EPA in many of its other risk assessments.

Arguments have been advanced that carcinogenic risk from inorganic arsenic is quantitatively linked to biomethylation/detoxification of inorganic arsenic in humans and that the exposed Taiwanese were in the reduced methylation/detoxification portion of the dose curve. However, some of the arguments advanced to show reduced biomethylation with increasing arsenic intake are not credible. Ongoing studies attempting to quantify this relationship and define a threshold for methylation efficiency have produced a mixed picture. In one study of Nevada residents ingesting arsenic-laced well water at a high average concentration, the fractional distribution of urinary arsenic among forms did not vary compared to lower total arsenic intakes. In other studies, the relative proportion of inorganic arsenic compared to the two combined methylated forms or to total arsenic does not appear to define a clean dose-response relationship or a threshold for methylating efficiency.

One of the more common arguments against use of Taiwanese data in risk assessment is rooted in the claim of alleged nutritional deficiencies in the Taiwanese, with implications for the efficiency of arsenic biomethylation relative to, say, North American populations. However, the report of nutrient intakes among the exposed Taiwanese cited here (58) indi-

cates that the nutritional status of the exposed Taiwanese, particularly in terms of nutrients associated with single carbon (methyl) metabolism, was sufficient to accommodate the body stores of methyl groups needed for arsenic biomethylation. At the highest arsenic level reported, the biomethylation process requires only a percent or so of reported total daily methyl intake, hardly a convincing methyl deficiency situation. A second difficulty with the nutrition argument is a demographic, socioeconomic one; i.e., the assumption that all North American populations exposed to arsenic are composed only of individuals whose nutritional status is superior to that of the arsenic-exposed Taiwanese. Where has this been quantitatively demonstrated? In the absence of data to the contrary, if individuals in the Taiwan endemic zone were at added risk for arsenic effects by virtue of poor nutritional status, then individuals anywhere with this risk factor are of concern, including exposed subjects in northern Mexico and some areas in the United States.

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