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Arsenic and Bladder Cancer Mortality

To the Editor:

As in the Taiwan study of Chen *et al*,[1] the ecologic data of Hopenhayn-Rich *et al*[2] from Argentina are highly aggregated across a wide range of exposures.[3] In Taiwan,[4] the smallest observational unit is the "village," whereas, in Cordoba, it is the "county." In both studies, the aggregated data are sufficient to conclude that there is, generally, a dose-response relation, but they are inadequate for estimating the magnitude of risk at specific inorganic arsenic (In-As) concentrations.

Nevertheless (despite frequent caveats about the crudeness of the exposure estimates, and lack of data on what they classify *a priori* as low- and medium-exposure groups), Hopenhayn-Rich *et al* estimate the risk of bladder cancer in Cordoba at specific In-As concentrations and compare the outcomes with the Taiwan study. To do so, however, they incorrectly assume that the standardized mortality rate (SMR) for a subpopulation distributed over a wide range of In-As concentrations is the SMR at the average concentration. For example, for males in the high-exposure category, it is assumed that the SMR is 2.14 at 178 μg per liter. In fact, the In-As concentrations were reported to range from 40 μg per liter to more than 2,000 μg per liter, so one knows neither the SMR at 178 μg per liter nor the In-As concentration at which the SMR is 2.14. A similar error is made with regard to interpretation of the Taiwan study, where mortality risk ratios of 5.1 and 12.1 are assumed to apply at the "weighted arsenic levels" of 170 and 470 μg per liter (these values were actually taken from the U.S. Environmental Protection Agency analysis[5] on skin cancer prevalence and are incorrect for the Chen *et al* study[6]). Attempts to estimate the risk at any specific In-As concentration, in either study, and to make comparisons are potentially misleading.

The article also concludes that the Cordoba results provide support for a lack of relevance of nutritional status (affecting methylating ability), ethnic and genetic differences, and co-contaminants, such as humic acids, in the drinking water in Taiwan, on the dose-response relation for In-As. Given the limitations of the exposure data, such a conclusion is unwarranted. Moreover, the issue is not whether the above factors completely confound the relation between In-As in water and cancer (that is, are the sole cause), but the extent to which they may modify risk. Several lines of evidence support their possible relevance as modifiers of arsenic toxicity.[7,8] In particular, nutritional status and impaired arsenic-methylating ability warrant further investigation. For example, studies from Mexico indicate that, in a population with high In-As in water, those individuals exhibiting cutaneous signs of arsenicism had reduced methylating ability, as reflected by altered ratios of arsenic metabolites in urine.[9] A study in rabbits[10] demonstrated that a 25% reduction of methyl donor compounds in food was sufficient to impair arsenic-detoxifying ability. Thus, modifiers of arsenic potency must still be considered, particularly when using the results from one population to estimate potential risk in another population.

Any effect of risk modification would be on susceptibility, manifested by alteration of cancer latency period, the "threshold" level at which one becomes susceptible (if such a threshold exists), or the magnitude of risk (the SMR). These are all relevant issues for extrapolation of risk to low In-As concentrations (for example, <50 μg per liter, the current standard in the United States). Hopenhayn-Rich *et al* do not provide estimates of risk at low In-As concentrations, however, much less evidence of the presence or absence of risk modification. The study does affirm the association of high concentrations of inorganic arsenic in drinking water with increased mortality from bladder cancer, in this instance among the ethnically mixed Cordoba population, in the absence of nutritional deficiency or evidence of other substances such as humic acid or fluorescent substances.

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The Authors Reply:

Brown and Beck have surprisingly accused us of errors that we did not make. We agree with them that the studies in Taiwan[1] and Argentina[2] have limitations that are inherent to ecologic studies, and, as they noted, we took care in pointing them out: the purpose of our "frequent caveats" was to alert the reader of the inherent weaknesses in the assumptions made in our discussion. We could not agree more that studies with individual-based exposure are needed to define clearly the dose-response relation between arsenic ingestion and cancer risks. Meanwhile, one cannot ignore nor dismiss the findings of ecologic studies.

In our study, we found a standardized mortality rate (SMR) of 2.14 for males in the highest-exposure group, and, on the basis of available data, we calculated a crude mean arsenic level in drinking water of 178 μg per liter only for concentrations above the detection limit of 40 μg per liter. We also estimated that about 20% of the population in that exposure group may have been exposed to levels ≥40 μg per liter, corresponding then to an estimated SMR of 5.7 (Brown and Beck seem to have misunderstood that 178 μg per liter was the average for the entire high-exposure group; we never stated that an SMR of 2.14 corresponded to 178 μg per liter). We agree that one cannot conclude with certainty that a specific SMR corresponds to a specific arsenic level, and we clearly stated that exposure was not uniform within counties. In our study, the correspondence of an SMR with an estimated water arsenic average was used, under the assumptions given, to compare our results with those of Taiwan, where similar exposure assumptions were made.

Brown and Beck state that we made a similar "error" in a risk assessment[3] based on EPA's weighted average arsenic water concentrations.[4] These are referred to as "incorrect for the Chen study," but no supportive evidence is given for such bold statements. It is worth noting that another risk assessment based on similar data but using different methodology arrived at similar estimates.[5]

With respect to nutrition and ethnicity, we did not state that these factors would confound the arsenic-cancer association, or that nutrition was not relevant; we indicated that, overall, the findings were similar in two populations with different dietary and ethnic characteristics. These findings are important since nutritional insufficiencies have been repeatedly suggested to increase cancer susceptibility among the arsenic-exposed Taiwanese in general, based on an assumed decreased methylation ability.[6–9] At the end of their letter, Brown and Beck do seem to agree with us regarding our findings in the absence of nutritional deficiency.

Brown and Beck misleadingly cite a Mexican study, suggesting that individuals with cutaneous arsenical signs may have reduced methylating ability due to dietary factors. First, they cite a reference that does not mention cutaneous signs.[10] Second, in another publication of the same study,[11] it was reported that within the exposed group, those with skin alterations had lower methylation ability than those without them, but no mention of nutritional differences was made. It is more likely that genetic factors or dose differences may account for variations in the second methylation step, rather than dietary differences among a seemingly homogeneous population.

We agree with our critics' final assertions: we did not provide estimates of risk at low inorganic arsenic concentrations, and we did not analyze individual level effects of possible risk modifiers—those were not our objectives. We did find an association between elevated arsenic levels in drinking water and bladder cancer risk, providing additional evidence of this relation, and we are now conducting a case-control study in the area to establish individual-based dose-response relations.

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Epidemiology Differs from Public Health Practice

To the Editor:

Taubes,[1] Neutra,[2] and others confuse epidemiology with public health practice. Epidemiology is the scientific method of