

Reviewer's report

Title: Arsenic in drinking water and cerebrovascular disease, chronic airways obstruction, diabetes mellitus, and kidney disease in Michigan: a standardized mortality ratio analysis

Version: 1 Date: 16 October 2006

Reviewer: Michael Kosnett

Reviewer's report:

General

The authors present an ecological study of disease specific mortality in one of the larger geographic areas of the United States subject to elevated concentrations of arsenic in drinking water. Although certain questions and suggestions may be posed to the authors, the study overall will make a meritorious contribution to the literature on this important topic.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The following comments, suggestions, and questions are offered for the authors' and editors' consideration:

1. Consideration should be given to rephrasing the second sentence of the first paragraph of the "Background" section, as the current wording appears to imply that the NRC Subcommittee on Arsenic in Drinking Water did not recommend that EPA reduce the maximum contaminant level for arsenic in drinking water. On the contrary, the 1999 Subcommittee report stated, "...it is the subcommittee's consensus that the current EPA MCL for arsenic in drinking water of 50 µg/L does not achieve EPA's goal for public health protection and, therefore, requires downward revision as promptly as possible." (See 1999 NRC report on page 9). In this context, the authors might also make note of the opinions and recommendations presented in the 2001 Update on Arsenic in Drinking Water by the NRC subcommittee. That report noted, "...even if the curve is sublinear at some point (e.g. if a threshold exists) the available data showing cellular effects at arsenic concentrations in the range of those measured in U.S. populations suggest that any hypothetical threshold would likely occur below concentrations that are relevant to U.S. populations." (See 2001 NRC report on page 6).
2. In subsequent paragraphs in the Background section of the manuscript that briefly review associations between arsenic in drinking water and adverse health effects in several studies, the authors state, "Most of these studies, however, examined arsenic concentrations of 300 µg/L and above, providing little insight into health effects from low-to-moderate concentrations (10 – 100 µg/L) which are more commonly found in sources of drinking water in the US and Europe." It is suggested that the authors expand their discussion of epidemiological studies (including some they have cited) that have in fact reported dose-response relationships extending below 300 µg/L. For example, with respect to cancer endpoints, the authors might specifically note the extent to which the epidemiological studies by Chen CL et al (JAMA 292:2984-2990; 2004), Steinmaus et al (Am J Epid 158:1193-1201; 2003; reference 25 in the authors' manuscript) Chiou HY et al (Am J Epid 153:411-18; 2001), Ferreccio C et al (Epidemiology 11:673-679; 2000; reference 3 in the authors' manuscript), and Hopenhayn-Rich et al (Epidemiology 1996; 7:117-124; reference 5 in the authors' manuscript) have reported positive relationships associated with arsenic drinking water concentrations less than 300 µg/L.
3. Can the authors comment on the extent to which misclassification bias, specifically lack of exposure to elevated levels of arsenic in the study area, might have resulted in an underestimation of the risk of adverse effects associated with consumption of arsenic in drinking water? The authors note that approximately 32% of the study area population was served by municipal surface water from the Great Lakes. It was noted that the arsenic concentration was > 10 µg/L in 50% of the water samples analyzed in the study area, and that most samples analyzed by the MDEQ came from private wells. There is no indication that the wells tested for arsenic represent a scientific sampling of the exposure pattern in the study area. Presumably, data on exposure to arsenic in drinking water is available for the portion of the population in the study area that has been served by water from municipal wells. Using such data, could the authors estimate the percentage of the population in the study area unlikely to be exposed to an elevated concentration of arsenic? If less than

half of the study area population were likely to have been exposed to elevated levels of arsenic in drinking water, what would this suggest about the magnitude of health risk among those who were truly exposed?

4. In the sixth paragraph of the Discussion section, the authors state, "The lack of significantly elevated rates for cancers of the bladder, kidney, lung, and skin in our study might suggest that arsenic levels in groundwater of southeastern Michigan are below the threshold for cancer induction, or that there may be moderating factors that were not considered here." [emphasis added]. Can the authors comment on the limited power of their study to detect the magnitude of the increase in cancer mortality that other analyses suggest might be associated with consumption of arsenic in drinking water at concentrations on the order of 10 µg/L? For example, the 2001 Update report by the NRC Subcommittee on Arsenic in Drinking water suggested that the lifetime excess in lung cancer incidence for men associated with consumption of drinking water with an arsenic concentration of 10 µg/L may be 18 per 10,000 (or 0.18 per 100). Assuming 90% mortality, this corresponds to a lifetime excess lung cancer mortality of approximately 0.16 per 100. Given a lifetime lung cancer mortality risk for men in Michigan on the order of 5 per 100, consumption of water with an arsenic concentration of 10 µg/L would increase this to 5.16 per 100, yielding a relative risk of approximately 1.03. Is this value inconsistent with authors' findings of a male lung cancer SMR of 1.02 (99% CI 0.98, 1.06) in study area? It is suggested that the authors interpret their cancer mortality findings in light of the 2001 NRC report conclusion, "Therefore, although the subcommittee's risk estimates are of public-health concern, they are not high enough to be easily detected in U.S. populations by comparing geographical differences in the rates of specific cancers with geographical differences in the concentration of arsenic in drinking water" (2001 NRC report, page 223).

5. In the eighth paragraph of the Discussion section, the authors note that the study area has higher rates of high blood pressure than the rest of Michigan, and implicitly suggest that this might be a confounding factor for the observed increase in cerebrovascular mortality. In the context of this discussion, the authors might note that high blood pressure may possibly be considered an intermediary variable, given that arsenic exposure has been associated with hypertension in some epidemiological studies, including the pilot study conducted in Huron County, Michigan that was published in 1982 (cf authors' reference 26, and the 1999 and 2001 NRC reports).

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

6. In the second sentence of the discussion section, it is suggested that "risk of diabetes" be changed to "the risk of mortality from diabetes", because the cited study by Lewis et was a mortality study.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.