

Author's response to reviews

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

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Author's response to reviews: see over

Dr. Philippe Grandjean, Editor-in-Chief
Dr. David Ozonoff, Editor-in-Chief
Environmental Health: A Global Access Science Source

Dear Drs. Grandjean and Ozonoff,

Thank you for your efforts in overseeing the peer-review process for our manuscript, “**Arsenic in drinking water and cerebrovascular disease, diabetes mellitus, and kidney disease in Michigan: a standardized mortality ratio analysis**”. My co-authors and I have revised the manuscript in accordance with the reviewers’ comments. On behalf of the authors, I pledge that there are no conflicts of interest and that this material has not been published in, or submitted to another journal. All authors have read the manuscript, agree that the work is ready for publication, and accept responsibility for the manuscript's contents. This study received support from grant R01 CA96002-10 from the US National Cancer Institute.

We wish to thank the reviewers for their insights and thoughtful suggestions. The reviewers found the study to be a meaningful contribution to the important topic of risk from low-to-moderate arsenic exposure; however, a few areas for improvement were identified. In accordance with the reviewers’ suggestions, we (1) calculated population-based estimates of arsenic exposure, (2) added statistics about exposure, demographics, and migration for each county in the study area, and (3) recalculated SMRs for the six counties, Genesee County only, and the five counties other than Genesee County. Results are interpreted based on their concordance across these analyses. Deaths from cerebrovascular disease, diabetes mellitus, and kidney disease remained elevated across all analyses. Deaths from chronic airways obstruction, however, were not elevated in the five county analysis. We revised the manuscript considerably, in light of these new analyses and their results, and in accordance with suggestions from the reviewers.

Attached is an electronic copy of the revised manuscript and a detailed response to reviewers’ comments. We believe the paper to be substantially improved as a result of the reviewers’ comments and appreciate the opportunity to publish our work in *Environmental Health*.

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Respectfully,

Jaymie R. Meliker

Response to Reviewers

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

In this document we respond to the comments provided by each of 3 reviewers. We thank the reviewers for their thoughtful and detailed comments. In accordance with the reviewers' suggestions, we have (1) calculated population-based estimates of arsenic exposure, (2) added statistics about exposure, demographics, and migration for each county in the study area, and (3) recalculated SMRs for the six counties, Genesee County only, and the five counties other than Genesee County. Results are interpreted based on their concordance across these analyses. Deaths from cerebrovascular disease, diabetes mellitus, and kidney disease remained elevated across all analyses. Deaths from chronic airways obstruction, however, were not elevated in the five county analysis. We revised the manuscript considerably, in light of these new analyses and their results, and in accordance with suggestions from the reviewers. The reviewers' comments are shown below, followed by our responses in italics.

Reviewer 1: Kenneth Cantor:

The authors present an ecological analysis of 23 selected mortality outcomes with respect to arsenic levels in a six county study area in Southern Michigan. SMRs for these outcomes, by sex, in the six counties (with somewhat elevated arsenic in drinking water) were calculated, using statewide race, and age-specific rates. The report requires a more detailed description of exposure assessment, as well as addressing the issue that one county of the six (Genesee) has more than half the total study-area population. More details may be found below.

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

A. One county of the six - Genesee County - represents almost 60% of the total study population - yet the exposure figures are presented for the whole of the six county area. It is not clear from the text how representative the exposure scenario in Genesee county is of the full study area. This may or may not be a fundamental flaw in the approach and analysis. At any rate, the issue must be addressed. In addition, the demographics of Genesee County are somewhat different from the other counties, and this could influence study findings. (For example, in 2000, Genesee Co. was 75.3% white, implying that most of the non-white population in the 6 county area resided in Genesee.) The authors could address these related problems by the following:

1. Present a table showing exposure & total population statistics for each of the six counties in the study area. This could be an expansion of the current Table 1.
2. Present separate analyses for Genesee and the other five counties.

We are grateful for these suggestions and revised the manuscript accordingly. We revised Table 1 to depict exposure and total population statistics for each of the six counties in the study area. We also conducted and present separate analyses for Genesee County, and the other five counties, in addition to the full six county analysis. Interpretation is based on concordance of results across analyses.

B. Estimates of exposure need further clarification. The paper cites "9,251 analyses of water samples from the six-county area." Presumably, these analyses are the basis for the exposure estimate of an

arithmetic mean of 17.7 ug/L, with 10% of the samples exceeding 43.0 ug/L. It appears that the arithmetic mean is not a population-mean exposure (which is what is needed), and that the great majority of water sample analyses are from private wells. What is really needed - if county-wide mortality statistics are used in the analyses - are county-wide estimates of arsenic exposures, including weighted estimates of arsenic levels in public water supplies. The authors should make the best attempt possible to estimate population-wide average exposures, not only exposures from individual well water supplies.

In Table 1 we now present population-based exposure estimates, as described in the methods: "Using the MDEQ arsenic database, county-level mean and median arsenic concentrations were calculated for private wells. In addition, arsenic estimates were compiled for each public well water supply in the area from the MDEQ arsenic database [30]; those not drinking groundwater were served by municipal surface water from the Great Lakes which contains arsenic concentrations averaging 0.30 ug/L [31]. The size of the population served by private well, public well, and public surface water supplies was compiled from an MDEQ database and population-weighted estimates were tabulated."

C. A weakness of all ecologic studies is the possibility that in- or out-migration could distort the findings. Migration statistics should be presented, to assist readers in interpreting the findings.

Migration statistics are now provided for each county in the study area, for the entire six county area, and for the remainder of Michigan in Table 1. The reviewer will note that migration was relatively low in the study area, and comparable with that for the State as a whole.

Discretionary Revisions (which the author can choose to ignore)

A. The authors cite reference 17 (Lewis et al.) liberally throughout the discussion. A close look at this reference reveals a high likelihood of extensive misclassification of exposure, throwing great doubt on its findings. The authors may wish to rethink how they compare their own findings with those of Lewis et al.

We considered this suggestion carefully and reduced the degree to which we cite this reference. However, the study by Lewis et al. is one of the few studies of low-level arsenic exposure and we felt it necessary to draw comparisons with diabetes, kidney disease, and cerebrovascular disease where relevant.

B. Would it be helpful to mention which counties are in the Detroit metro area?

We believe this question stems from Dr. Cantor's awareness of our case-control study investigating arsenic and bladder cancer in the SE Michigan area. That study includes 11 counties and borders Detroit. In contrast, this study contains six counties, is limited to the counties of highest exposure, and is no closer than 50 miles from Detroit. In the revised manuscript, we describe the study area in greater detail in the methods section: "The counties involved include Genesee, Huron, Lapeer, Sanilac, Shiawassee, and Tuscola, and are located in the Michigan thumb region (Figure 1). The 2000 US Census indicates the six counties have a population of approximately 740,000 people and occupy an area of approximately 11,500 km². The majority of the population resides in Genesee County

(439,000), while the remainder is split fairly evenly among the other five counties (Table 1). Genesee County also contains the industrial city of Flint and the largest proportion of African Americans in the study area; in contrast, the other five counties are predominantly rural and white.”

C. To help avoid the possible pitfall arising from multiple comparisons, the authors used 99% CIs instead of the usual 95% CIs. In principle, this is an informal application of the Bonferroni approach to statistical significance, and quite appropriate in some settings. In my opinion, this is not necessary here, and the standard 95% CIs would be quite sufficient. This is an exploratory exercise, not a hypothesis-testing study.

We discussed the use of 99% vs. 95% CIs very thoroughly. Considering that some of our disease end points are somewhat rare, and that we are now showing results for 23 diseases, for each gender, in 3 different combinations of geographic regions (a total of 138 SMRs being reported), we felt the results would be most valuable if guided by 99% CIs.

Reviewer 2: Bruce Fowler:

This is a well-written manuscript which reports the results of an SMR analysis study over a 6 county area of Michigan to investigate possible relationships between exposures to low-moderate concentrations of arsenic in well- drinking water and the relative incidence of a variety of clinical endpoints associated with higher levels of arsenic in studies from other countries. The present studies demonstrated a number of modest but statistically significant increases in SMR values for a number of clinical endpoints. The largest of these were for diabetes mellitus and kidney diseases. Statistically significant reductions were noted for chronic liver diseases and cirrhosis. The investigators conclude that the findings of this study are the first to support an association between low- moderate exposure levels of arsenic in drinking water and a number of causes of mortality. They indicate the need for further detailed epidemiological studies on this population/

The findings of this study are important both in terms of providing actual data at the low end of the dose response curve for arsenic in drinking water and common causes of mortality and the fact that these are data from a U.S. study population which have up to this point been not available. This is a useful contribution and should be published in its present form.

This reviewer suggested no changes.

Reviewer 3: Michael Kosnett:

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 $\mu\text{g/L}$ 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).

We thank this reviewer for the close read of our manuscript. We did not intend 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. We revised this paragraph as follows: "Assessment of health risks associated with exposure to moderately elevated levels of arsenic in drinking water (10-100 $\mu\text{g/l}$) has become the subject of considerable interest and some controversy in both regulatory and public health communities. The National Research Council (NRC) subcommittee on Arsenic in Drinking Water, for instance, found that "additional epidemiological evaluations are needed to characterize the dose-response relationship for arsenic-associated cancer and noncancer end points, especially at low doses" [1, p.3] and simultaneously concluded that the guideline of "50 $\mu\text{g/L}$ does not achieve...public health protection, and therefore, requires downward revision as promptly as possible." [1, p.9]. In the end, the United States Environmental Protection Agency (USEPA) recommended a reduction in the maximum contaminant level (MCL) to 10 $\mu\text{g/l}$ for arsenic in US public drinking water supplies [2]."

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 $\mu\text{g/L}$ and above, providing little insight into health effects from low-to-moderate concentrations (10 – 100 $\mu\text{g/L}$) 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 $\mu\text{g/L}$. 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), Ferrecio 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 $\mu\text{g/L}$.

As this reviewer notes, we did cite several manuscripts that investigate low-level exposure. And we have reread the literature and agree that more data is now available in the 100-300 $\mu\text{g/L}$ range and this has been incorporated into the introduction. However, those studies that have suggested evidence at even lower concentrations tend to have inadequately small numbers of cases to draw firm conclusions. For example, in the Chen et al. study, significant results are only found above 100 $\mu\text{g/L}$; in the Chiou et al., study, only 18 cancers are observed; in the Ferrecio et al. study, only 22 cases are exposed to < 50 $\mu\text{g/L}$, with the next category of exposure being quite broad--from 50-199 $\mu\text{g/L}$. With such small N, it is difficult to infer low-level dose-response relationships. Therefore, we thought it best

to state “Most of these studies, however, examined arsenic concentrations of 100 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.” and later in the introduction “Individual-level incidence studies of low-to-moderate arsenic exposure have also generated ambiguous findings with regard to the role of arsenic in cancers of the bladder and skin [20-25]In light of this uncertainty, it is important to continue to investigate health risks from exposure to arsenic concentrations in the 10-100 µg/L range.”

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 $> 10 \mu\text{g/L}$ 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?

In light of these comments and those from Reviewer 1, we calculated population-based exposure estimates to improve the exposure assessment in the study area (see Table 1). We chose not to hypothesize about the effects of exposure misclassification, as we would also need to offer conjecture about potential bias from migration differences. This is an ecologic SMR study and we sought to let the results speak for themselves without over-interpretation. As we concluded, “further epidemiologic studies are required to confirm the results suggested by this ecologic SMR analysis.”

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 $10 \mu\text{g/L}$? 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 $10 \mu\text{g/L}$ 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 $10 \mu\text{g/L}$ 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).

This was a very helpful comment raised by this reviewer. We added this possibility to our discussion of why the cancer SMRs tended to not be significantly elevated: “However, if the excess risk for these cancers is small, it is possible that ecologic studies will be unable to detect significant risk, as was cautioned by the NRC subcommittee on Arsenic in Drinking Water [51, p.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).

We also thank the reviewer for pointing out that we were overlooking the potential for high blood pressure to be an intermediate variable. We added note of this in the discussion: “In addition, high blood pressure may not be a confounder, but rather could be an intermediate variable in cerebrovascular mortality.”

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 al. was a mortality study.

This change was made.