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Letter to the Editor

Inorganic Arsenic in Drinking Water and Bladder Cancer: A Meta-Analysis for Dose-Response Assessment

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This article concludes that there is "a positive dose-response relationship between exposure to arsenic in drinking water and bladder cancer" and goes so far as to estimate a lifetime excess probability of bladder cancer associated with arsenic at a very low concentration [10µg/L]. While it is well-established that chronic arsenic exposure at several-fold that concentration is associated with and likely causes, bladder cancer, the analysis of this article provides little support for its own conclusions. For example, the 95% confidence intervals for absolute risk in Table 3 all include zero. That means that a hypothesis that the true value is actually zero would not be rejected at the usual 5% level of significance. Furthermore, that is true for all the arsenic concentrations shown in Table 3 (1 ppb to 50ppb).

In addition to interpretation of the analysis there are several troubling aspects concerning methodology.

Study Selection

One source for study selection, among others, was being referenced in one or more prominent documents such as a USEPA document [1] or the two reports of the NRC (National Research Council) [2, 3]. Being referenced in a report, however, such as one of the NRC reports for example, does not constitute endorsement of the study for use in dose-response analysis; to the contrary in some cases, or with noted study limitations. With one exception, this doesn't seem to be taken into account in the study selection, nor is there any indication that the authors vetted the studies otherwise for suitability in dose-response analysis or for extrapolation to lifetime risk. The inclusion of the study by Moore et al. is baffling [4]. It is about P53 alterations in bladder cancer, not incidence or mortality.

"Dose-response" Methodology

Fitting a straight-line through the data indicates trend, not dose-response. For example, two separate sets of data, one suggesting a convex dose-response shape and the other a concave shape, would both indicate an upper trend when fit with a straight line, but interpretation as a dose-response curve would be misleading in both cases. Any proposed model for dose-response, straight-line or otherwise, unless biologically justified, needs to be evaluated with the usual procedures of a statistical measure of fit to the data, examination of residuals, etc., to be creditably interpreted as a dose-response curve. Minimally, this could have been for at least one study, but it wasn't done at all. Simply assuming that a dose-response curve is linear or any other shape, obviously doesn't make it correct and it may not even be approximate. (The reference to fitting a straight line in the discussion above refers to the use of lnRR as response. Their equation (5) is required for conversion to absolute risk.)

Lifetime Risk

Extrapolation of results from the case-control and cohort-studies is, simply put, a leap-of-faith. Lifetime risk is presumably for life-time exposure, in which duration of exposure, as well as arsenic concentration, needs to be considered. According to Table 1, all but one (possibly two) of the studies adjusted for age, but only one adjusted for exposure duration as well. No mention of exposure duration was found in the article. The analysis is limited to arsenic concentration in the various studies. The significance of exposure duration, as well as concentration, is apparent from the quantitative analyses in the NRC reports which focused on a study with lifetime exposure and evaluated several possible interactions of concentration and duration.

In summary, the article has some fundamental shortcomings that undermine its usefulness. Some shortcomings are acknowledged in the final paragraph (but not in the abstract). Of course, all risk assessments, and meta-analyses, contain some uncertainties, but if inappropriate or poorly conducted, they have as much potential to mislead as to inform. The authors extol the virtues of meta-analysis if appropriately applied, but then fall short of that objective.

References

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Response to the Letter

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Ken's comments are all strictly correct. Our paper forces the analysis into a regulatory risk framework with a default linearity assumption and then development of confidence intervals on the slope factor (which is not the same as hypothesis testing, the issue he raises). But I think he raises important points people need to bear in mind with respect to our paper.