Reviewer's report

Title: Association between arsenic, cadmium, manganese, and lead levels in private wells and birth defects prevalence in North Carolina: A semi-ecologic study

Version: 1
Date: 11 June 2014
Reviewer: Jean Brender

Reviewer's report:

This paper explores the relation between the heavy metals arsenic, cadmium, manganese, and lead levels in private well water and the prevalence of selected birth defects in North Carolina during the period of January 2003 through December 2008. Per instructions of the journal, comments to the authors are divided into two sections: major compulsory revisions and minor essential revisions. This reviewer had no discretionary revisions to suggest.

Major compulsory revisions

1. In the Methods section, under Exposure Assessment, third paragraph. The authors do not indicate whether the levels of metals found in private wells correlate with the levels measured in public water supplies. Some evidence is indicated regarding the positive correlation between these two sources because it is highly likely that most women obtain their drinking water from public water supplies. If these data are not available, the authors should restrict their reporting of results to women living outside of areas supplied by public water systems. They present this restricted analysis as part of a sensitivity analysis, but it probably should be the main analysis unless data are available that show correlation between measured metals in private well water and public water supplies within the census tracts.

Minor essential revisions

1. Abstract: Since the relation between higher manganese concentrations and conotruncal defects was the only association that remained with the various sensitivity analyses, the Conclusion section of the abstract should specify conotruncal defects instead of “specific birth defects.”

2. Introduction, first paragraph: Brender et al. study did not find any significant associations (small numbers of exposed cases and controls) between arsenic, cadmium, lead, or mercury in drinking water and NTDs. Therefore this sentence should be rephrased.

3. No information is given regarding the percentage of women in childbearing years who are on private wells. Since North Carolina has participated in the National Birth Defects Prevention Study that has a water module, state-specific information is available on the percent of participants in that study who obtained
their drinking water from private wells (several of the co-authors are collaborators on that project). This percentage should be provided in the Introduction.

4. Methods, first paragraph: Clarification is needed regarding why only live births were used in this study. Other papers that include data from North Carolina Birth Defects Monitoring Program indicate that this Registry also identifies birth defect cases from stillbirths and elective terminations. While maternal demographic and residential information might not be available for terminations, these data are generally available on the fetal death certificate for stillbirths.

5. In the Methods, under Study Design and Study Population, the authors indicate in the second paragraph that metal analyses “from newly constructed private wells since July 2008 … and wells tested between 1998 and 2010 where owners requested testing of existing wells.” The second source of measurements raises the concern about potential information and selection biases and some discussion about these potential biases is indicated in the Study limitations and strengths section of the Discussion section.

6. In the Methods section, under Exposure Assessment, first paragraph, the authors indicate that 22,000+ measurements of metal concentrations were collected between 1998 and 2010. Are these measurement all from different (unique) wells or do they include multiple test results of the same metals from the same wells?

7. Results section, paragraph 1 and Table 1: Birth defects vary substantially by maternal demographic factors. Therefore, comparisons between cases and controls would be much more informative if cases were split into neural tube defects, oral clefts, congenital heart defects, gastrointestinal defects, GU defects, limb deficiencies, etc.

8. Results, fifth paragraph and general comments about tables: In several instances, one table will include the crude prevalences and another table will include the adjusted prevalences. Either the crude and adjusted prevalences should be included in the same table or eliminate the crude prevalence tables.

9. Results, eighth paragraph, Table S9 is discussed before Tables S5-S8 in the following paragraph under “Sensitivity analyses results.” Table S9 should be relabeled S8 and the supplemental tables following this table should be renumbered to keep the text in sequence with the tables.

10. Under “Sensitivity analysis results” in the Results section, to assist the reader in locating the specific results on the tables that the text refers to, recommend putting in the appropriate table in parenthesis after the prevalence ratio and confidence interval.

11. In the Discussion section, under the heading “Arsenic levels were modestly associated with birth defects prevalence”: while the OR for NTDs was elevated in relation to higher concentrations of arsenic in drinking water in one of the studies cited (reference 22, Brender et al.), the 95% confidence intervals were consistent with the null. It is recommended that this sentence is rephrased to reflect the positive associations that were significant and non-significant.

12. In the Discussion section, under “Arsenic-by-manganese interaction”, some
discussion is indicated of this study's findings in relation to the work done by Toccalino et al. on mixtures of contaminants in drinking water by Toccalino et al. (Toccalino PL, Normal JE, Scott JC. Chemical mixtures in untreated water from public-supply wells in the U.S.—occurrence, composition, and potential toxicity. Sci Total Environ. 2012; 431:262–270).

13. Table 2, recommend adding percentages by the numbers of each of the specific defects as done for all the cases and controls.

14. Tables 2 and 3, in addition to the chemical name, it would be helpful to have the actual concentrations that correspond to the 90th percentile for each chemical.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.