Reviewer's report

Title: Water Disinfection By-products and the Risk of Specific Birth Defects: A Population-based Cross-Sectional Study in Taiwan

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Reviewer: sylvaine Cordier

Reviewer's report:

The manuscript has considerably improved but there are still unanswered questions and I have a few additional ones that may be of importance.

Study population

Page 5, line 6: it is still not clear to me what a â##waterworkâ## means. Writing that â##â#¦water regions, which were served by only one type of waterworksâ## seems to imply â##type of water treatmentâ## whereas at the bottom of page 6, the sentence before last says â##â#¦water regions where waterworks were served by only one type of water chlorinationâ##. So, regions are served by waterworks which are served by water chlorinationâ#¦.

This needs to be sorted out by the editor, there is certainly a need for some language standardization.

The type(s?) of water chlorination need also to be specified.

Health outcomes

Page 5, 3rd paragraph: the sentence â##The follow-up time is from one month after conception through 7 days after birthâ## is misleading. If I understand right, it refers in fact to clinical surveillance of pregnancy, not to assessment of pregnancy outcome since, as it is specified only much later in the manuscript (top of page 12), birth defects in induced abortions are NOT included. This is potentially a major flaw, depending on the coverage of prenatal diagnosis in Taiwan and the number of medical terminations of pregnancy after prenatal diagnosis. It might have a major impact on rates of major birth defects such as anencephaly for instance.

These elements should be presented in the â##health outcomesâ## paragraph: what exactly is the target population for the assessment of birth defects?

Exposure assessment

Do I understand right in assuming that there is only ONE average TTHM level computed for the whole pregnancy? Why not estimate the level of exposure for the first trimester of pregnancy which is much more relevant for birth defects? Are there indications of seasonal variations in these levels in Taiwan?

Covariates

Why is â##high feverâ## still included among covariates in this paragraph (page

7) and in Table 5? The answer to my previous question on this variable is not clear. (response NÂ°11).

Statistical methods

Testing a trend using Chi-square cannot apply to adjusted Ors, this is not appropriate.

Discussion

Page 11, 3rd paragraph: some other studies have used several sources for assessment of birth defects. I have not checked them all, but information on pregnancy terminations is a major source of assessment which has been used in many countries where prenatal diagnosis is frequent.

The section starting on page 11, line 21 (â##Taiwanese pregnant women â#¦â##) up to page 12, line 4 (â##â#¦(Cohenâ##s k statistics was 0.92)â##) has already been included page 5, lines 19-24 and following.

The whole issue of the origin, importance and potential impact of misclassification should be more carefully discussed, in a way closer to the data the authors are presenting and not in general and academic terms as it stands now. This even leads to contradictory statements about consequences of â##random misclassificationâ## depending on the results to be defended: it â##would weaken the observed association rather than introduce a spurious effect (page 12, lines 8-9)â##, or alternatively â##the effect estimate could be biased either towards the null or away from the nullâ## (page 15, lines 12-13). This is not acceptable. The answer to a previous comment on reporting of hypospadias (NÂ°7 point by point response) is also debatable: how can the readers â##use their own judgment of the validityâ## if no figure is provided by the authors about the validity of this reporting.

Table 1

I think quantiles of the distributions(25,50, 75â#¦) would be more interesting than Min and Max, since these correspond to the limits of the categories (5, 10, 20 etc..).

Table 2 should be deleted. Mean TTHM are announced in the title but no in the table. There is a mistake in the last line (37/75528 is not equal to 0.5%).

Table 6:

The publication from Sweden was published in 2002, not 2000. The reference category in this population is not â##Noneâ## but â##No chlorinationâ## (Table 2 in the Cedergren paper) or â##1-10 Âµg/Lâ## (Table 3 same paper).

What next?: Accept after minor essential revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being

published

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