Author's response to reviews

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

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Author's response to reviews: see over
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.

1. Study population
Page 5, line 6: it is still not clear to me what a waterwork means. Writing that water regions, which were served by only one type of waterworks seems to imply type of water treatment whereas at the bottom of page 6, the sentence before last says water regions where waterworks were served by only one type of water chlorination. So, regions are served by waterworks which are served by water chlorination. 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.
The waterwork is synonymous to mean water treatment plant. Each selected waterwork/water treatment plant applies only one type of water disinfection process: chlorination. The plants using chloramination, chlorine dioxide disinfection or ozonation were not included in the study. This has been explained in the revised version on page 6-7.

2. Health outcomes
Page 5, 3rd paragraph: the sentence “The follow-up time is from one month after conception through 7 days after birth” 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 health outcomes paragraph: what exactly is the target population for the assessment of birth defects?
The sentence has been revised” The clinical surveillance of pregnancy begins at 1 month after conception and continues through 7 days after birth.”. We have included these elements “birth defects that were diagnosed after 7 days of age, gestational age less than 20 weeks and induced abortion due to birth defects are not included in the registry.” in the health outcomes paragraph (page 5-6). We agree that this is potentially a major flaw, depending on the coverage of prenatal diagnosis and the number of medical terminations of pregnancy after prenatal diagnosis. The birth defects might be underreported such as...
anencephaly. This underreporting was likely to be nondifferential, i.e. not related to exposure. In most situations nondifferential misclassification of a binary outcome will produce bias toward the null, provided that the misclassification is independent of other errors. [Rothman KJ, Greenland S. Precision and validity in epidemiologic studies. In Rothman KJ, Greenland S: Modern epidemiology, 2nd edition, Lippincott-Raven Publishers: Philadelphia, 1998, p. 130.] We discussed this issue in the page 12.

3. 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?
We assumed that there is only one average TTHM level computed during the whole pregnancy because there is little seasonal variation in these levels in Taiwan. We agree that estimates the level of exposure for the first trimester of pregnancy is much more relevant for major cardiac and cleft defects. It could be our further study to assess the relevant exposure months of pregnancy focusing on ventricular septal defect and cleft palate.

4. Covariates
Why is high fever still included among covariates in this paragraph (page 7) and in Table 4? The answer to my previous question on this variable is not clear. (response NÂ°11).
We have excluded the high fever from this paragraph (page 7) and table 3 and 4.

5. Statistical methods
Testing a trend using Chi-square cannot apply to adjusted Ors, this is not appropriate.
We revised the trend testing approach in the page 7-8. We tested the trend in the exposure-outcome relations in logistic regression by fitting an ordinal scale exposure variable (0,1,2,3) based on the exposure categories.

6. 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 Taiwanese pregnant women up to page 12, line 4 (Cohen’s k statistics was 0.92) 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 random misclassification depending on the results to be defended: it would weaken the observed association rather
than introduce a spurious effect (page 12, lines 8-9), or alternatively the
effect estimate could be biased either towards the null or away from the null
(page 15, lines 12-13). This is not acceptable.
We excluded the section which has been mentioned in page 5 from page 11, line 21. We
have revised the statements in page 12 and 15.

7. The answer to a previous comment on reporting of hypospadias (N° 7
point by point response) is also debatable: how can the readers use
their own judgment of the validity if no figure is provided by the authors
about the validity of this reporting.
We agree that reporting on hypospadias is problematic, but may be of interest for the
readers. We have included sentences in Discussion (p. 15) which underline caution: “A
negative association was found for hypospadias. This could be explained either by chance
while unity was within the 95% confidence interval. Unfortunately the diagnosis of
hypospadias may also be compromised because it is made within the 7 days from delivery.
Therefore the results of hypospadias should be interpreted cautiously.”

8. Table 1
I think quantiles of the distributions(25,50, 75) would be more interesting
than Min and Max, since these correspond to the limits of the categories (5,
10, 20 etc..).
The quantiles of distributions have been added in the table 1.

9. 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%).
The title “Mean TTHM are announced” in the table 2 has been deleted. The numbers of
any birth defect in the last line should be 378 rather than 37.

10. Table 6:
The publication from Sweden was published in 2002, not 2000. The
reference category in this population is not None but No chlorination (Table
2 in the Cedergren paper) or 1-10 µg/L (Table 3 same paper).
This has been corrected. The reference should be “Kallen BA, Rubert E. Drinking water
chlorination and delivery outcome- a registration-based study in Sweden.
Reproductive Toxicology 2000; 14:303-309.” rather than Cedergren 2002 paper. The
exposure contrast should be chlorine dioxide vs. none in the table 6.

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.