

## Reviewer's report

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

**Version:** 1 **Date:** 28 September 2007

**Reviewer:** sylvaine Cordier

### Reviewer's report:

#### General

This paper relies on birth certificates corresponding to a subsample of Taiwanese births for the ascertainment of associations between a selected number of birth defect types and exposure to disinfection by-products.

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

There are many approximations or unsupported assertions and this manuscript appears somewhat unfinished. Several times, justifications are given several pages after the reader expects to find them.

#### Study population:

Almost half of the births occurring in Taiwan between 2001 and 2003 have been excluded for "insufficient information on disinfection practice in the municipality". It appears from the following sentence and later in Table 2, that these births were probably excluded because the region where they occurred was served by more than "one type of waterworks". What does "one type of waterworks" mean is unclear: does it refer to networks? To water treatment?

The five water regions selected appear to include roughly half of the Taiwanese births and characteristics of births included and excluded are presented in Table 2, but some general description of the area under study compared to the whole country is necessary already at this stage.

#### Health outcomes:

What is the reliability of birth defect reporting on birth certificates in Taiwan? A detailed answer is given in the discussion, but precisions should be given in this section on the reporting process (actors, timing, validation ...).

The strategy followed for the choice of the birth defects under study is not clearly justified. The decision made by the authors to study single defects rather one type of "organ groups" is debatable especially when considering the small numbers involved (Table 3). Chromosomal anomalies are not mentioned. Depending on the importance of prenatal diagnosis in Taiwan, the pertinence of studying anencephalus at birth must be discussed. Among neural tube defects, spina bifida is much more frequent than anencephalus but not studied. In the

background statements, the authors point at obstructive urinary tract defects as candidate health effects as assessed in the Norwegian study they plan to reproduce, but they choose not to study them. Reliability of reporting of hypospadias has been discussed by specialists of birth defect registries and the study of this birth defect based on birth records may not be valid. A list of birth defects “excluded” is given (bottom of page 5): the reason is not clear since the list of included defects is already defined. Are multiple anomalies included?

#### Exposure assessment

Authors mention using mother’s place of residence during pregnancy: is this information available on birth certificate? Place of residence at birth is not always the relevant address (beginning of pregnancy). What is the likely importance of this problem (changes in residence during pregnancy) in Taiwan? this should be discussed.

It is not clear how individual TTHM levels were estimated and on which period (date of conception? whole pregnancy?).

#### Covariates

What is the rationale for including “high fever” after delivery among the covariates since the risk period for the birth defects studied is early pregnancy ?

#### Statistical methods

Justifications must be given for the choice of the reference category for TTHM levels

(0-4 #g/l) and of exposure categories. The number of measurements available, their distribution, range etc...must be described. All these details should be added to the Exposure Assessment section.

The last sentence of page 7 is not clear: how will a stratified analysis “evaluate the potential role of residual confounding”?

No method is described (or used) for the study of dose-response relationship.

The strategy for the meta-analysis is described at this point as including the present study and “the other available Norwegian study”. In fact several other studies were included in the meta-analysis presented in Table 5...

#### Results

No test for trend is presented in the study of the association between TTHMs levels and prevalence of birth defects.

Exclusively estimates relative to the high exposure category are underlined, even in the presence of high imprecision (renal agenesis & dysgenesis). Several inconsistent findings (many estimates in the low category of exposure are elevated, including a significantly increased risk for “any birth defect”) or inverse associations (hypospadias) are not underlined. Cleft palate cases are much more prevalent than cleft lip which is unusual, even among Asian populations.

For some categories of defects (atrial septal defects, tetralogy of Fallot), numbers are very small and analyses using four categories of exposure are not very informative (Table 3).

Whereas at least nine previous studies have been referenced in the background information, only four are presented in Table 4 (one only was announced in the Statistical analysis paragraph).

Summary estimates (Table 5) and their interpretation are highly conditioned by the choice of studies included in the meta-analysis (see above) and the exclusion of others. This point should be carefully described and justified in the methods section.

Only one reference is given for two studies by Shaw mentioned in California.

#### Discussion

In several instances, the potential misclassification errors in birth registration are discussed (page 11; line 8 and 23) and presented as “likely to be random”. However on page 12, lines 10-11, adjustment for population density is presented as a way to “eliminate partly underreporting bias between regions”. As can be seen in Table 1, regions with high TTHM levels appear to be more rural. I suggest to substantiate the issue of potential confounding by population density and to present somewhere (Table 2?) the prevalence of birth defects according to population density.

The discrepancy between the number of studies discussed in the section “Synthesis with previous knowledge” page 13, and the number of studies included in the pooled analysis should be clearly explained. For example, why four available studies when discussing neural tube defects (line 8) whereas eight studies are mentioned? This probably relates to the choice to study only individual defects instead of organ groups. I therefore suggest that the authors perform the meta-analysis of broader organ groups including the corresponding studies, in addition to the individual defects they have chosen. This is needed for a proper assessment of the associations found.

In Europe, urinary tract defects such as obstructive defects, are not considered as rare. What is the prevalence in Taiwan (page 14, line 6)?

The discussion on biological mechanisms includes only THMs whereas they should only be considered as markers of the whole mixture of disinfection by-products, also when discussing hazards. This discussion also includes a presentation of a genetic mechanism alternative to teratogenicity, affecting maternal gametes. If the authors consider this hypothesis as a serious alternative, they should substantiate it and: 1) study genetically determined birth defects; 2) assess preconceptional exposures.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Take out all Chi Square values from tables 1-2.

Include in Table 4 reference numbers for the studies selected

Table 5 should indicate more clearly which studies are included in the summary estimates.

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Discretionary Revisions (which the author can choose to ignore)

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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

**Quality of written English:** Acceptable

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