Additional papers on water disinfection by-products and congenital anomalies

Introduction

1. The Committee has previously provided advice on the findings of epidemiological studies on chlorinated drinking water and reproductive outcomes and published a Statement in 2004. At the February 2008 meeting, members were presented with the findings of a new (phase 2) epidemiological study by SAHSU on chlorinated drinking water and congenital anomalies, together with additional epidemiological studies relevant to congenital anomalies and other adverse reproductive outcomes (TOX/2008/06).

2. Members considered that SAHSU study was well conducted and agreed with the conclusions. Members agreed that the additional data did not show a consistent relationship between chlorinated drinking-water and adverse pregnancy outcomes including congenital anomalies. A draft statement was considered at the April meeting and is attached at Annex 1. However, since April, two additional studies have been published, one of which (Hwang, 2008) has received some press interest. These studies are presented here for members’ consideration and to decide whether the statement should be amended to include them.

Hwang et al, 2008

3. Hwang et al (2008) reports increased risks for a number of specific congenital anomalies associated with concentrations of total trihalomethanes (TTHMs) in chlorinated drinking water (see Annex 2). Briefly, a population based cross-sectional study was conducted in Taiwan. The source population consisted of all 721,289 births registered by the Taiwanese Birth Registry from 2001 to 2003. The final study population consisted of 396,049 infants after excluding 325,240 newborns due to insufficient information regarding exposure.

4. The risk of any congenital anomaly, and of the eleven most common specific congenital anomalies according to ICD-9, were compared in three exposure categories (>20, 10 -19, and 5 - 9 micrograms/litre TTHMs) with a reference category of 0 – 4 micrograms/litre TTHMs. The following covariates were included in the analyses: gender of infant, maternal age, plurality, maternal health status and population density in the municipality of birth. No measure of socioeconomic status appears to have been included.

5. The study focused on 5 water regions in Taiwan where the process of disinfection was chlorination, rather than chloramination, chlorine dioxide disinfection or ozonation.
One or more water treatment plants serve each municipality and the standard sampling frequency for TTHMs was a minimum of four samples per year for each plant.

6. Among the 396,049 newborns, 2,148 births (0.5%) were identified with one or more congenital anomalies “of interest”. The overall risk of congenital anomalies was not associated with TTHM concentration. The authors report increases in the risk of anencephalus (odds ratio (OR) 1.96, 95% CI 0.94 – 4.07), ventricular septal defects (OR 1.81, 95% 0.98 – 3.35), and cleft palate (OR 1.56, 95% 1.00 – 2.41) in the high exposure category compared with the reference category but a dose-related increase was only seen for cleft palate.

7. The authors also conducted a meta-analysis of the 5 studies on water chlorination byproducts and congenital anomalies published since 2001. This includes the recent SAHSU study. Only the summary ORs for ventricular septal defects showed consistent evidence of an increased risk (summary adjusted OR 1.59, 95% CI 1.21 – 2.07 according to Table 7 in Annex 2; OR 1.25, 95% CI 1.08 – 1.46 according to the text). The summary OR for cleft palate showed consistent evidence of no effect. A sensitivity analysis revealed that heterogeneity was due to the SAHSU study. After exclusion of this study, the summary OR was homogeneous and elevated (fixed-effects model: 1.43, 95% CI 0.97-2.10). Similarly, after exclusion of a study by Shaw et al (2003) from California, the effect estimate for anencephalus was elevated (fixed-effects model: 1.73, 95% CI 1.01-2.96).

Comments

8. This study is far smaller than the SAHSU study, which included 22,828 cases with congenital anomalies. It should also be noted that the concentrations of TTHMs used in this study were lower than those used in the SAHSU study:

<table>
<thead>
<tr>
<th>Concentration (µg/l)</th>
<th>Hwang et al</th>
<th>SAHSU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referent</td>
<td>0-4</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Low</td>
<td>5-9</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>10-19</td>
<td>30-&lt;60</td>
</tr>
<tr>
<td>High</td>
<td>20+</td>
<td>60+</td>
</tr>
</tbody>
</table>

In the SAHSU study, there was an increased risk of ventricular septal defects (OR 1.43, 95% CI 1.00 – 2.04) in the highest TTHMs exposure category compared with the referent exposure and a slightly decreased risk in the medium concentration category (exact figures not provided). Referring to the concentration differences, Professor Elliott, author of the SAHSU study has commented “biological plausibility … is reduced and it does not make sense to combine the results with our study as the exposure levels are so different” (Elliott, personal communication). With respect to the meta-analysis, it
should also be noted that the study in Norway by Hwang et al (2002) used colour and the use of chlorination as an indirect measure of exposure.

9. Professor Elliott has made other comments on this study (which he refers to as the Jaakkola study) as follows:

- “Jaakkola et al carried out many tests (3 levels vs reference x 15 endpoints), therefore 95% CIs etc need to be viewed with caution as there will be an expected 2-3 "false positives" (ie 2-3 findings where lower bound of CI exceeds one are expected by chance).
- The meta-analysis compares the top category in each study with the reference category. This is bound to accentuate the findings for VSD as we had a (borderline) significant excess in the top category. The meta-analysis will mostly reflect our finding, and then the Norwegian study, as the numbers are so much larger (again "apples" and pears" are being compared between Jaakkola and Nieuwenhuijsen et al because of the big differences in exposure levels between the two studies…. By the way I don't understand the p-values in table 7 and they don't match those in the text.
- We make the point in our study that for none of the anomalies (including VSD) was the trend across categories significant -- this weakens interpretation of the borderline significant finding in the top category for VSD (especially in the context of multiple endpoints, etc, tested in Nieuwenhuijsen et al).
- Jaakkola findings have been over-interpreted in my opinion. However, it could be argued that the VSD finding from meta-analysis, reflecting mainly significant finding for "high" vs "low" colour in the Norwegian study (not sure what that means in terms of THM exposure?), and our own borderline significant finding, could be worthy of further consideration elsewhere.”


10. A further paper published since April by Luben et al (2008) (appended at annex 3) investigated the relationship between maternal exposure (between 6 and 16 weeks gestation) to chlorine disinfection by-products and the risk of hypospadias. The population-based case-control study was conducted in Arkansas using birth records from 1998 – 2002. Birth certificate and congenital anomaly registry data were used to identify 647 cases and 1,246 randomly selected controls. Quarterly monitoring data for TTHMs and haloacetic acids (HAA5s) from 263 water utilities were used in the exposure assessment. Using concentrations of disinfection byproducts in the water as a measure of exposure and a referent category of ≤ 33.5 μg/l, adjusted odds ratios were calculated for hypospadias and exposure to the TTHM categories of >33.5 – 49.6 μg/l (OR 0.93, 95% CI 0.70 – 1.24) and >49.6 μg/l (OR 1.16, 95% CI 0.88 – 1.51). ORs were also calculated for the sum of the five most common haloacetic acids (HAA5) and six individual species of HAAs. These showed no statistically significant increased risks when the highest exposure tertile was compared to the lowest.

11. Additional analyses were conducted for estimates of exposure from ingestion, and metrics incorporating consumption, showering and bathing. Where data were
available on individual ingestion, there were increased incidences of hypospadias for both TTHMs and HAA5 in both intermediate and high exposure groups compared to the referent groups but only one increase was statistically significant and there was no dose-relationship. The risk estimates for these analyses were imprecise. For TTHMs only, exposure was also estimated from ingestion, inhalation and dermal routes, using two sets of metrics and uptake factors. Increases in incidence of hypospadias were seen at both exposure levels, compared with the referent group, in all cases although none was statistically significant. The authors conclude that the results provide little evidence for a positive relationship between DBP exposure during gestation and an increased risk of hypospadias but emphasise the necessity of including individual-level data when assessing exposure to DBPs.

COT Opinion

11. The committee is asked for its views on the two new studies and whether it would wish to amend its draft statement?

Secretariat

June 2008

References

Elliott PE. Personal communication to J Fawell and S Pennison, 4 June 2008.


COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Revised Draft COT Statement on a SAHSU Study on Chlorination Disinfection By-Products and Risk of Congenital Anomalies in England and Wales

Introduction

1. The Committee considered the issue of chlorinated drinking water and adverse reproductive outcomes in 1999 and 2001. The most recent statement was published in 2004 [1]. In light of a new, large study by the Small Area Health Statistics Unit (SAHSU), which investigated potential associations between chlorination disinfection by-products and the risk of congenital anomalies, and additional studies on other reproductive outcomes published since 2004, we were asked to consider whether we wished to revise our earlier advice.

Background

Chlorination and disinfection by-products (DBPS)

2. Disinfection of drinking water is an important public health measure and UK public water suppliers are required to disinfect the water supply. Chlorination is the most commonly used method of disinfection in the UK and is intended to protect human health from microbial contaminants. Disinfection of drinking water is fundamental to preventing the spread of waterborne diseases, such as cholera.

3. In addition to disinfecting drinking water, chlorination can also produce a range of disinfection by-products (DBPs) by reaction between chlorine and natural organic matter (NOM) present in surface waters. In most supplies, the main DBPs are the four chlorinated and brominated trihalomethanes (THMs): chloroform, bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform. Haloacetic acids (HAAs), haloacetonitriles (HANs), halophenols, haloaldehydes and haloketones can also be formed.

4. The sum of the four THMs is termed Total THMs (TTHMs). DBPs are currently regulated in the UK by specifying a maximum concentration of 100 micrograms/litre for TTHMs, measured at the consumers’ taps (concentrations of DBPs may increase within the distribution system due to the continued reaction of residual chlorine with NOM). HAAs and other DBPs are not regulated directly. TTHM concentrations are often regarded as a marker for total DBPs. Removal of precursor organic compounds before chlorination is commonly practised in the UK to reduce TTHM concentrations, and this is
also considered to reduce the formation of HAAs and other DBPs, which are therefore limited indirectly.

**Previous COT advice on chlorinated drinking water and reproductive outcomes**

5. During 1998 and 1999, the COT considered the available epidemiological information on the association between chlorination by-products in drinking-water and a range of adverse reproductive outcomes. Animal reproductive toxicity studies with some individual chlorination by-products were also considered. After evaluation of the data, the COT concluded the following:

- “We consider that there is insufficient evidence to conclude that the presence of chlorination by-products in tapwater increases the risk of adverse reproductive outcomes.
- We recommend, however, that the claimed associations between patterns of drinking water-intake and the incidence of adverse reproductive outcomes be investigated further, since any causal association would be of significant public health concern.
- We therefore consider that efforts to minimise exposure to chlorination by-products by individuals and water authorities remain appropriate, providing that they do not compromise the efficiency of disinfection of drinking water” [2].

The COT considered the issue again in 2001 and reaffirmed its 1999 conclusions [3].

**SAHSU (first phase) study on adverse reproductive outcomes and chlorination disinfection by-products and 2004 evaluation**

6. In 2004, the COT considered a first phase study by SAHSU that investigated chlorinated drinking water and adverse reproductive outcomes using routinely collected THM measurements in drinking water (as an index of exposure to chlorination by-products) and available health statistics on stillbirths and birthweight [4].

7. In the 2004 SAHSU study, modelled estimates of quarterly THM concentrations in water zones from 3 water companies in England (Northumbrian, Severn Trent Water and United Utilities) were linked to about 1 million routine birthweight and stillbirth records based on location of maternal residence at the time of birth. THM estimates corresponding to the final three months of pregnancy were used. Three TTHM exposure categories were defined: low (below 30 micrograms/litre), medium (30 – 60 micrograms/litre) and high (above 60 micrograms/litre). In its evaluation the COT noted that in the North West (United Utilities) THM exposure showed an inverse association with mean birth weight, a direct association with prevalence of low and very low birthweight, and a direct association with the prevalence of stillbirths. However, there was evidence of confounding by social deprivation, adjustment for which may not have
been complete. In the Severn Trent region, in contrast, the prevalence of very low birthweight decreased with increasing TTHM exposure, and there was no association with low birthweight or stillbirth rate. In the Northumbrian region, there was no evidence of associations between TTHM levels and any of the pregnancy outcomes, but the number of births included in the study was relatively small.

8. In its 2004 evaluation, the COT also considered data from thirteen other epidemiological studies published after the 1998 evaluation, which investigated associations between chlorinated drinking-water and pregnancy outcomes (other than congenital malformations) [1].

9. Overall, the committee concluded that the data that it had evaluated did not show a causal relationship between chlorinated drinking-water and pregnancy outcomes, namely: low birth weight, very low birthweight, stillbirth, spontaneous abortion, perinatal death, infant death, low Apgar score, infant’s head circumference at birth, infant’s body length, pre-term delivery, length of gestation, neonatal jaundice and neonatal hypothyroidism [1]. Data on congenital malformations were not assessed. Further research to reduce the uncertainties in the interpretation of the reported associations between intake of drinking-water and the incidence of adverse reproductive outcomes was recommended. The COT added that while research to determine the effects of chlorinated water continued, efforts by water companies to minimise consumers’ exposure to chlorination by-products would remain appropriate provided that the efficiency of disinfection was not compromised.

SAHSU (second phase) study on chlorination disinfection by-products and risk of congenital anomalies in England and Wales

10. SAHSU has now completed phase 2 of its research, on congenital anomalies [5]. This study is the largest of its type so far. The study examined the relationship between THM levels in the public water supply and risk of congenital anomalies in England and Wales. The primary analysis focused on TTHM (as a marker for disinfection by-products) and broad categories of congenital anomalies. A secondary analysis focused on restricted subsets of anomalies and specific THM groups including bromoform and brominated THMs.

11. THM data were taken from twelve water companies, where water samples were routinely taken from consumers’ taps in each water supply zone (each zone covered a population of up to 50,000). The raw THM data were modelled to give more robust estimates of the mean THM concentration in each zone.

12. Individual records of congenital anomalies by postcode distribution were obtained from the National Congenital Anomalies System (NCAS), the regional congenital anomaly registries via the British Isles Network of Congenital Anomaly Registers (BINOCAR), and the national terminations registry.
13. The broad categories of congenital anomalies in the primary analysis included: cleft lip/palate; diaphragmatic hernia and abdominal defects; major cardiac defects; neural tube defects; urinary tract defects; and respiratory defects.

14. Further analyses were conducted using restricted groups of congenital anomalies with better ascertainment that were considered likely to share the same causes. These included: abdominal wall defects, major cardiac defects, specific urinary tract defects, and respiratory defects. The relevant ICD-10 codes are given in the publication. Additionally, separate analyses were conducted for cleft palate, cleft lip with and without cleft palate, exomphalos, gastrochisis, hypoplastic left heart syndrome, ventricular septal defects, congenital anomalies of the oesophagus and two subsets of urinary tract defects comprising intrinsic kidney disease and urinary obstruction. Further analyses were conducted excluding cases with anomalies that were found to be part of a chromosomal syndrome, as well as examining cases with isolated anomalies only.

15. There were in total 22,828 cases with congenital anomalies: 1,641 (7.2 %) of these had a chromosomal defect, 2,249 (9.9%) were classified as having multiple (non-chromosomal) anomalies and 18,938 (83.0%) were classified as having isolated anomalies only.

16. The study period was defined according to the first possible date on which THM data for the first trimester were available (i.e. 15 October 1993 for United Utilities & Severn Trent; 15 October 1997 for Northumbrian; and 15 October 1998 for all other water regions) until 31 December 2001.

17. A postcode to water zone link was created using a Geographical Information System (GIS). The postcode of the maternal residence at the time of birth was used to identify the water zone of interest and the appropriate modelled exposure in the first trimester for each birth record.

18. The weighted average THM estimate associated with each birth record was categorised into one of three pre-defined exposure categories for each of three metrics: concentrations of TTHMs (< 30, 30 - < 60 and 60 + micrograms/litre), total brominated THMs (< 10, 10 - < 20 and 20 + micrograms/litre), and bromoform (< 2, 2 - < 4 and 4 + micrograms/litre).

19. Statistical analysis adjusted for potential confounders including sex, maternal age, and socio-economic status. Also, interactions between THM exposure and potential confounding variables were tested.

20. Mean TTHM concentrations ranged from 16.4 micrograms/litre in the lowest exposure category, to 72.2 micrograms/litre in the highest. The highest correlations were seen between total brominated THMs and dibromochloromethane (0.93), and between TTHM and chloroform (0.90).

21. There was a higher prevalence of each anomaly in the most deprived compared to the most affluent areas. Prevalence of anomalies was similar in males and females.
except for cleft lip/palate and urinary defects, where prevalence was 50 – 100% higher in males. There were U-shaped relationships between prevalence of congenital anomalies and maternal age, except for neural tube defects where the prevalence decreased with increasing age. The reported prevalence of each anomaly was substantially higher in the regional registries than in the NCAS reflecting better ascertainment.

22. Unadjusted and adjusted analyses showed similar risk estimates. There were no statistically significant trends across the three exposure categories for TTHMs, total brominated THMs or bromoform, for either the broadly defined or restricted groups of anomalies.

23. The only significant association (p< 0.05) within the broadly defined groups of anomalies was an excess risk of major cardiac defects in the medium (but not high) exposure category of total brominated THMs (OR 1.12, 95% CI 1.01 – 1.23). For the restricted set of isolated anomalies, there was a statistically significant excess risk of ventricular septal defects (OR 1.43, 95% CI 1.00 – 2.04) associated with exposure to TTHM in the highest category, and for congenital anomalies of the oesophagus (OR 1.66, 95% CI 1.12 – 2.45) in the medium (but not high) category of TTHM exposure.

24. For bromoform, there was a significant excess of both major cardiac defects and gastroschisis (OR 1.18, 95% CI 1.00 – 1.39 and OR 1.38, 95% CI 1.00 – 1.92, respectively) in the high exposure category.

25. The authors concluded that this large national study found little evidence for a relationship between THM concentrations in drinking water and risk of congenital anomalies. There were no significant interactions between TTHM exposure and any of the potential confounders. The authors noted that the significant positive associations may have been due to chance as there is little toxicological evidence for reproductive or teratogenic effects for bromoform or other DBPs, and the bromoform concentrations in the study were low. It was also noted that careful selection of subsets of major cardiac defects, ventricular septal defects and gastroschisis as isolated anomalies may have increased accuracy of case definition (and reduced misclassification).

26. We note that the SAHSU study focussed on the main DBPs in chlorinated drinking-water, namely THMs, and did not consider other DBPs such as HAAs.

27. We also note that studies of this type, which use a group level exposure assessment, do not consider variations in individual exposure: for example, movement of women between exposure zones during pregnancy, variation in individual water consumption and additional exposure from other sources such as showering, bathing and swimming were not taken into account. The lack of individual exposure data limits the interpretation of the results and might obscure the detection of an association.

28. Nevertheless, we consider that this was a large and well designed study and that it did not indicate a relationship between THMs and congenital anomalies.
Additional data

29. To date, THMs have been the most widely measured individual DBPs in epidemiological studies. However, THMs may not be a good marker of other DBPs. A preliminary study measuring the next largest group of DBPs, namely HAAs, in the UK drinking water found a high correlation between TTHMs and HAAs in two of three study regions, but no correlation in the third region. A total of five HAAs were detected at relatively high levels, with the means ranging from around 35 to 95 micrograms/L for the three regions investigated [6]. THMs and HAAs are present in by far the greatest concentrations, with other DBPs considered to be present at much smaller concentrations, usually less than 1 microgram/L [7].

Additional epidemiological studies on congenital malformations/birth defects

30. In addition to the SAHSU study, ten other epidemiological studies were identified which investigated associations between drinking water chlorination and congenital anomalies [8-17]. The studies are described in the discussion paper considered at our February 2008 meeting [18]. The search strategy is appended in Annex 1.

31. No UK-based studies were identified. Most studies were conducted in the USA, Canada, Norway and Sweden. The retrieved studies were smaller in size than the SAHSU study, and most had limitations such as inadequacies in exposure assessment and a main focus on outcomes other than congenital anomalies. The additional studies investigated various categories of anomalies, including all congenital anomalies, cardiac defects, nervous system anomalies, urinary tract defects, respiratory defects and oral clefts. Overall, the additional epidemiological evidence is inconsistent and does not suggest an association between drinking water chlorination DBPs and congenital anomalies.

Additional epidemiological studies on adverse pregnancy outcomes since the 2004 consideration

32. The COT previously reviewed the literature on DBPs in drinking water and other adverse birth outcomes (other than congenital anomalies) when it considered the phase 1 study by SAHSU in 2004. Five additional epidemiological studies were identified for the present review [19-23]. These studies are described in the Committee discussion paper [18]. The search strategy is appended in Annex 1.

33. None of these studies was conducted in the UK. Some evaluated associations between total and individual HAAs in addition to THMs (e.g. monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, monobromoacetic acid, and dibromoacetic acid), and a number of outcomes were considered including measures of growth retardation (such as intrauterine growth retardation, small for gestational age, and low term birth weight), pregnancy loss or pre-term delivery. These studies do not show a consistent relationship between drinking water DBPs and adverse pregnancy outcomes.
Animal data

34. Animal data on DBPs and adverse birth outcomes were previously considered by the COT in 1998 and 2004. In 1998, the committee concluded that the available reproductive toxicity studies conducted with individual chlorination by-products indicated that the levels of exposure to these substances in drinking water were about 10,000 times lower than levels at which adverse effects occur in animals[1].

35. A recent weight of evidence review [24] considered reproductive and developmental animal studies on a number of individual DBPs, including both THMs and HAAs, and described more recent toxicological studies including studies on congenital anomalies. Studies published between 2001 and 2006 were considered. The updated review found little indication of previously unreported reproductive or developmental toxicity. It concluded that the NOAELs and LOAELs in animals are much higher than known levels of human exposure, and that there are limited data that explore modes of action for reproductive toxicity. The authors noted that in a few instances, mild adverse reactions were reported in fetuses of dams treated at doses that produced maternal toxicity, and were generally considered secondary to maternal toxicity.

36. The review data confirm our previous view that, in animal studies, reproductive/developmental effects have mainly been seen with DBPs at high doses often associated with maternal toxicity. The fact that positive findings are seen in animal studies under these conditions does not provide corroboration for positive associations observed in epidemiological studies.

Overall conclusions

37. We conclude that in human studies there is no consistent relationship between chlorinated drinking-water and adverse pregnancy outcomes, including low birth weight, pregnancy loss, pre-term delivery and congenital malformations. In animal studies, effects have largely been seen at high doses associated with maternal toxicity and these are not considered to be predictive of effects in humans exposed to far lower levels of DBPs.
References


ANNEX 1A

Search strategy for additional epidemiological studies on congenital malformations/birth defects

- The search was carried out on the databases PubMed and Toxline and was limited to papers reporting on studies on humans published between 1 January 2004 and 31 August 2007, inclusive.
- The search terms used were:
  - chlorinat* by-product* AND congenital malformation*
  - chlorinat* by-product* AND congenital defect*
  - drinking water AND congenital malformation*
  - drinking water AND congenital defect*
  - trihalomethanes AND congenital malformation*
  - trihalomethanes AND congenital defect*
  - disinfection by-product* AND congenital malformation*
  - disinfection by-product* AND congenital defect*
  - dbp* AND congenital malformation*
  - dbp* AND congenital defect*

Search strategy for additional epidemiological studies on adverse pregnancy outcomes since the 2004 consideration

- The search was carried out on the databases PubMed and Toxline and was limited to papers reporting studies on humans published between 1 January 2004 until 31 August 2007, inclusive.
- The search terms used were:
  - chlorinat* by-product* AND pregnancy outcome*
  - drinking water AND pregnancy outcome*
  - trihalomethanes AND pregnancy outcome*
  - disinfection by-product* AND pregnancy outcome*
  - dbp* AND pregnancy outcome
  - all above terms combined with birth weight (birthweight), preterm delivery, premature*, still birth

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