SAHSU STUDY ON CHLORINATION DISINFECTION BY-PRODUCTS AND RISK OF CONGENITAL ANOMALIES IN ENGLAND AND WALES

Introduction

1. This paper presents a study by the Small Area Health Statistics Unit (SAHSU) which investigated potential associations between chlorination disinfection by-products and the risk of congenital anomalies. A summary of the study is presented below and the full draft SAHSU paper is provided at Annex A. Members are invited to consider the SAHSU study and comment on the public health significance of its findings.

2. Additional epidemiological and toxicological data relevant to chlorination disinfection by-products and congenital anomalies are also presented. Some background information summarising previous considerations of drinking-water chlorination and risk of adverse pregnancy outcomes by the COT is also provided below, together with summaries of more recent epidemiological studies of this type published since the COT’s last consideration of this topic in 2004.

Background

Chlorination and disinfection by-products (DBPS)

3. 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.

4. In addition to disinfecting the water, chlorination can also produce a range of disinfection by-products (DBPs), by reacting with 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.

5. DBPs are currently regulated in the UK by specifying a maximum concentration of 100 micrograms/litre for total THM5 (TTHM5 – the sum of the four THMs), 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**

6. During 1998 - 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. Additionally, available 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 increase 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 (COT 1998).

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

7. In 2004, the COT published a statement on chlorinated drinking water and reproductive outcomes (COT/04/8) (attached at Annex B). At that time the COT considered a first phase study by SAHSU, which utilised routinely collected THM measurements in drinking water (as an index of exposure to chlorination by-products) and available health statistics on stillbirths and birthweight, to examine the possibility of such effects (Toledano M et al., 2004).

8. 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 total THM exposure categories were defined: low (below 30 micrograms/litre), medium (30 – 60 micrograms/litre) and high (above 60 microgram/litre). In their evaluation the COT noted that in the NW (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 completely successful. In the Severn Trent region, in contrast, the prevalence of very low birthweight decreased with increasing total THM exposure, and there was no association with low birthweight or stillbirth rate. In the Northumbrian region, there was no evidence of associations between total THM levels and any of the pregnancy outcomes, but the number of births included in the study was relatively small.

9. In their 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).

10. Overall, the committee concluded that the data that they 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 (COT/04/8). 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 2007 study on chlorination disinfection by-products and risk of congenital anomalies in England and Wales

11. SAHSU have now completed phase 2 of their research on congenital anomalies. This study is the largest of its type so far. SAHSU examined the relationship between THM levels in the public water supply and risk of congenital anomalies across England and Wales. The primary analysis focused on total THM (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.

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

13. Individual postcoded records of congenital anomalies were obtained from the National Congenital Anomalies System (NCAS), the regional registries via the
British Isles Network of Congenital Anomaly register (BINOCAR), and the national terminations registry.

14. The broad categories of congenital anomalies in the primary analysis included: cleft lip/palate; diaphragmatic hernia and abdominal defects; major cardiac defects; neural tube defect; urinary tract defects; and respiratory defects.

15. Further analyses were conducted using restricted groups of congenital anomalies that were considered to be etiologically coherent, with better ascertainment, and included; abdominal wall defects, major cardiac defects, specific urinary tract defects, and respiratory defects. Additionally, separate analyses were conducted for cleft palate, cleft lip with and without cleft palate, exomphalos, gastroschisis, hypoplastic left heart syndrome, ventricular septal defects, two subsets of urinary tract defects including renal disease, and obstructive disease, and congenital anomalies of the oesophagus. 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.

16. There were a total of 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%) were classified as having isolated anomalies only.

17. The study population 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.

18. A postcode to water zone link was created using point-in-polygon methods within a Geographical Information System (GIS), to allocate each postcode to its water supply zone. Postcode locations were derived from a historical file developed by SAHSU. The postcode of the maternal residence at the year of birth was used to identify the water zone of interest and the appropriate modelled exposure for each birth record. This was obtained by calculating the weighted average of the modelled quarterly THM estimates for the appropriate zone for the first 93 days of the pregnancy. For cases, a gestation age was generally available and the first 93 days of pregnancy were calculated. Where gestational age was missing, an anomaly specific average gestation was assigned. The weighting was based on the proportion of the trimester falling into each quarterly period. Where the pregnancy was less than 93 days, e.g. for terminations, the whole pregnancy time period was used. For non-cases, it was assumed that the births had gone to full term in calculating the first 93 days of pregnancy.

19. The weighted average THM estimate associated with each birth record was categorised into one of three pre-defined exposure categories: 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). These were chosen with reference to the published literature on the possible association of birth outcomes with THMs and with regard to the joint distribution of numbers of births and THM concentrations across the water regions.

20. In the statistical analysis, adjustment for potential confounders included sex, maternal age, and socio-economic status. Also, interactions between THM exposure and potential confounding variable were tested.

Results

21. Mean TTHM concentrations ranged from 16.4 micrograms/litre in the lowest exposure category, to 72.2 micrograms/litre in the highest. The greatest correlations were seen between total brominated THMs and dibromochloromethane (0.93), and between TTHM and chloroform (0.9).

22. There was a higher prevalence of each anomaly in the 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.

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

24. 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 risks for TTHM in the highest exposure category of ventricular septal defects (OR = 1.43, 95% CI 1.00 – 2.04) and in the medium (but not high) exposure category for congenital anomalies of the oesophagus (OR = 1.66, 95% CI 1.12 – 2.45).

25. For bromoform, there was a significant excess in the high exposure category for 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.

26. There were no significant interactions between TTHM exposure and any of the potential confounders. Analyses of cases with multiple anomalies showed no significant association with THM concentrations but the numbers were small.
Discussion

27. 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. However, the 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).

28. Strengths of this study include its large sample size, the attention paid to case definition, and the use of modelled trimester-weighted THM exposure estimates to improve exposure classification.

29. Limitations of registry-based studies of congenital anomalies include geographically variable and incomplete ascertainment. However, the authors state that such geographical variations should not bias the study results provided that completeness of reporting is not related to exposure of interest. An isolated/multiple classification among a restricted set of anomalies was used to attempt to overcome differential reporting of minor anomalies, but it was reported that there was some indication that this may have occurred.

30. Opposing trends between the NCAS regions and BINOCAR regions were found, where ascertainment was highest in the highest exposure categories in the NCAS regions, but lowest in the highest exposure categories in the BINOCAR regions (no such trends were said to be apparent for the brominated compounds). Whether such trends reflected differences in case definition or completeness of reporting across registries, and whether these may lead to important biases, was said to be difficult to establish with any certainty.

Comments

31. Regarding small area studies such as this, there is always a concern related to the use of group level exposure data which limits the ability to measure individual exposure and so also reduces the potential to produce valid estimates of health effects for a particular exposure. It is also worth noting that women can move between exposure zones during pregnancy, there will be variation in individual water consumption and that additional exposure from other sources such as showering, bathing and swimming were not taken into account.

32. One of the project referees’ noted that the authors have attempted to improve exposure estimates and Nieuwenhuijsen and other members of the group have done some considerable work to establish a valid exposure assessment method to be used in small area studies. Keegan et al (2001) have suggested that for chloroform and BDCM, the main THMs, the between zone component of variation was greater than the within zone variation and that the use of THM data can be use in epidemiological studies at the small area level. However, the same
The author has pointed out that, in a year when the variation between zones was at its highest, a considerable proportion of total variation was within zones.

33. The study focused on the main DBPs in chlorinated drinking-water, namely THMs and did not consider other DBPs such as HAAs.

34. Members are asked for their views on this study and whether it can be considered as reliable evidence of a lack of association between congenital anomalies and chlorination disinfection by-products.

**Additional epidemiological studies on congenital anomalies and other adverse reproductive outcomes**

**Introduction**

35. Epidemiology studies that have been conducted on chlorination disinfection by-products and adverse health effects have used a range of measures to assess exposure to DBPs. For example, these have included:

- Natural organic matter content of raw water (measured as colour) and the use of chlorination in the municipality of the mother’s residence
- Levels of total and/or individual THMs (modelled or measured) from current and/or historical information
- Estimated exposure – this may be by ingestion only or include dermal and/or inhalation exposure

36. To date, THMs are 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 only a moderate correlation between THMs and HAAs in parts of the study areas. The total of five HAAs were also detected at levels higher than expected with the means ranging from around 35 to 95 micrograms/L for the three regions investigated (Malliarou et al., 2005). 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 (WHO 2000).

**Summary of epidemiological studies on congenital malformations/birth defects**

37. In addition to the SAHSU study, ten other epidemiological studies on congenital anomalies and DBPs were identified and the main findings are summarised below (see Annex C for a more detailed review of the studies, summary table, and the search strategy). Most of the additional identified epidemiological studies on congenital anomalies were smaller in size than the SAHSU study, and had limitations such as inadequacies in exposure assessment.
**All congenital defects**

38. Five studies considered total congenital anomalies. In a hospital-based case-control study in Massachusetts which focussed mainly on inorganic chemicals and chlorinated solvents, Aschengrau et al (1993) found a non-significant increased risk of major malformations (adjusted OR 1.5, 95% CI 0.7 – 2.1) for maternal residence in areas supplied with chlorinated water compared with chloraminated water via the public water supply. In a cross-sectional, population-based study in New Jersey, Bove et al (1995) investigated the risk of congenital anomalies associated with TTHMs in the local public water supply. THM levels were measured in routine tap water samples. They reported a statistically significant increased risk of total congenital anomalies associated with TTHM levels from > 80 micrograms/l to 100 micrograms/l compared to levels of < 20 micrograms/l (OR 1.75, 90% CI 1.34 – 2.25). However, for the higher exposure category of > 100 micrograms/l vs < 20 micrograms/l, the risk was lower and non-significant (OR 1.04, 90% CI 0.58 – 1.35) i.e. there was no dose response. When these levels were combined, there was a statistically increased risk (OR 1.57, 90% CI 1.23 – 1.99) for > 80 microgram/l TTHMs vs < 20 micrograms/l. The authors considered that the continuous TTHM variable supported a trend. However, the study had limitations such as relatively small number of cases, and many exposure categories.

39. In nation-wide studies in Norway, Magnus et al (1999) reported a non-statistically significant elevated association, and Hwang B et al (2002) reported a statistically significant increased association between DBPs in the public water supply and any birth defect but both these studies used a crude assessment of exposure to DBPs, involving water colour as an index. In a large Swedish population-based study, Kallen & Roberts (2000) found no association between congenital malformations and maternal residence in areas chlorinated with either sodium hypochlorite or chlorine dioxide; the control population lived in areas where there was no disinfection.

**Nervous system anomalies**

40. CNS anomalies were considered in eight of the identified studies. Bove et al (1995) reported a statistically significant association for CNS defects (OR 2.59, 90% CI 1.53 – 4.30) and for NTDs (OR 2.96, 90% CI 1.26 – 6.62) when comparing exposure to TTHM > 80 micrograms/l with exposure to the referent category of TTHM < 20 micrograms/l. There were no clear dose response relationships.

41. In a New Jersey population-based case-control study of NTDs and DBPs, Klotz & Pyrch (1999) reported a prevalence odds ratio (POR) of 2.1 (90% CI 1.1 – 4.0) for residence in areas supplied with water containing the highest tertile of TTHMs compared with the lowest (i.e. >40 micrograms/litre compared with < 5 micrograms/litre), when TTHM levels were obtained from public monitoring data. They also reported an increased risk of NTDs (POR 2.6, 95% CI 1.2 – 6.0) for
TTHMs >40 microgram's/litre compared with < 5 microgram's/litre for mothers who did not take multivitamin or folate supplements during the 3 months before pregnancy. However, a non-statistically significant increased risk was found when levels of 80+ micrograms/litre TTHMs were compared with <20 micrograms/litre (OR 2.1, 90%CI 0.8-5.3). The study made multiple comparisons and was criticised for insufficient adjustment for confounding by Graves et al (2000).

42. In one of two case-control studies by Shaw et al (2003) in California, an elevated risk of NTDs (especially spina bifida) was reported for maternal residence in areas supplied with drinking water containing levels of 1 to 24 microgram/l TTHM (compared with the referent 0 microgram/l category), but not for residence in areas supplied with water containing higher concentrations, and the authors concluded that there was no convincing evidence for a positive exposure-response relationship. In the other study, described in the same paper, Shaw et al (2003) reported that the risk of NTDs showed an inverse association with TTHM exposure (modelled as a continuous variable or a categorical exposure of TTHMs up to 75 microgram/l).

43. Aschengrau et al (1993) found ‘no increased risks’ for CNS defects when comparing residence in areas with chlorinated water to residence in areas with chloraminated water. In a retrospective cohort study in Nova Scotia, Dodds et al (1999) found ‘no significant increased risks’ for NTDs with TTHMs up to 100 micrograms/l in the public water supply. Hwang et al (2002) reported ‘no consistent association’ and Magnus et al (1999) found no statistically significant increased risk for NTDs with exposure to DBPs; however, both used a crude assessment of DBP exposure.

44. In an extension of the study by Dodds et al (1999), Dodds & King (2001) reported an increased risk of NTDs with exposure to BDCM at concentrations > 20 micrograms/l vs < 20 micrograms/l (RR 2.5, 95% CI 1.2 – 5.1), but the authors noted that the few cases in the exposure category resulted in a fairly unstable point estimate, and there was no evidence of a dose-response relationship. The same study found no association between NTDs and exposure to chloroform.

45. Overall, the findings for NTDs are inconsistent and do not appear to be convincing.

Urinary tract defects

46. Three studies reported results for urinary tract defects. Aschengrau et al (1993) reported an increased risk (OR 4.1, 95% CI 1.2 – 14.1) when comparing exposure to chlorinated water with chloraminated water. Magnus et al (1999) found a statistically significant increased risk, but suffered from using a crude measure of DBP exposure involving the use of a colour index. Hwang et al (2002) reported an elevated risk, but also used a crude index of DBP exposure involving colour. Thus, there is limited epidemiological evidence for urinary defects, but it does not appear to be convincing.
**Respiratory effects**

47. Three studies reported results for respiratory defects. Aschengrau et al (1993) reported an increased risk (OR 3.2, 95% CI 1.1 – 1.95) when comparing exposure to chlorinated water with chloraminated water. Hwang B et al (2002) reported increased risks for respiratory effects, and Magnus et al (1999) found a non-significant increased risk. However, as mentioned above, all three studies had limitations, especially regarding a crude assessment of exposure to DBPs.

**Cardiac defects**

48. Six studies considered cardiac defects. Bove et al (1995) reported a non-statistically significant increased risk for major cardiac effects (OR 1.83, 95% CI 0.97 – 3.29) for TTHMs > 80 micrograms/l vs < 20 micrograms/l. The study had limitations as mentioned above. Hwang B et al (2002) reported an elevated risk, but again this study was limited by a crude assessment of exposure to DBPs. Cedergren et al (2002), in a population-based Swedish study which specifically investigated risk of congenital cardiac defects, CBPs and nitrates in drinking water, reported an increased risk of cardiac defects at THM concentrations > 10 micrograms/l and a significant trend for increasing levels. The highest THM level measured was 41 micrograms/l. A reduced risk (OR 0.85, 95% CI 0.60 – 1.21) was reported for exposure to hypochlorite (chlorination) as a disinfection method compared with no disinfection. Magnus et al (1999) found non-significant elevated risks for exposure to DBPs, using a crude assessment of exposure.

49. Aschengrau et al (1993) reported ‘no increased risks’ for cardiac defects when comparing exposure to chlorinated water with chloraminated water. Dodds et al (1999) reported ‘no statistically increased risks’ for cardiac defects when comparing exposure up to 100 microgram/l TTHMs with a referent exposure category of 0 – 49 microgram/l. Dodds & King (2001) reported reduced risks for exposure both up to 100 microgram/l chloroform (OR 0.7, 95% 0.5 – 1.0) and up to 20 microgram/l BDCM (OR 0.3, 95% 0.2 – 0.7). Shaw et al (2003) observed ‘no associations’ for cardiac defects with exposures up to 75 microgram/l. Thus, the evidence for an association of cardiac defects with DBPs does not appear convincing.

**Oral clefts**

50. Five studies reported risks for oral clefts. Bove et al (1995) found a statistically significant elevated risk (OR 3.17, 90% CI 1.18 – 7.26) for TTHMs > 100 micrograms/l vs ≤ 20 micrograms/l. The authors also noted that there was no evidence for a trend. The study had limitations as mentioned above.

51. Dodds et al (1999) reported ‘no statistically significant increased risks’ for TTHM exposures up to > 100 micrograms/l compared to a referent exposure category of 0 – 49 microgram/l. Dodds & King (2001) found ‘no associations’ with
exposure to chloroform and BDCM up to 100 and > 20 micrograms/l respectively. Magnus et al (1999) reported a reduced risk for oral clefts with exposure to DBPs, but used a crude assessment of exposure. Shaw et al (2003) reported ‘no association’ with exposures to TTHMs up to 75 micrograms/l or for chloroform and BDCM (levels unclear). The weight of evidence does not suggest an association of DBPs and oral clefts.

52. A number of factors may have affected the lack of consistency seen in the above studies, such as differences in exposure measurements, exposure misclassification (relatively crude methods of exposure assessment), and differences in the composition of DBPs in the water supply. However, overall, there would appear to be no convincing epidemiological evidence for an association between DBPs and congenital anomalies.

Summary of new epidemiological studies on adverse pregnancy outcomes since COT’s 2004 consideration

53. The COT reviewed the literature on DBPs in drinking water and other adverse birth outcomes when it considered a phase 1 study by SAHSU in 2004 on possible associations between DBPs and low birth weight, very low birth weight, and still birth. Five additional epidemiological studies investigating associations between DBPs in drinking-water and adverse birth outcomes (other than congenital malformations) were identified since the Committee’s 2004 consideration and the main findings are summarised below (see Annex D for a more detailed review of these studies, a summary table, and the search strategy).

Please note that in the studies below that the total of five HAAs (HAA5) includes the sum of monochloroacetic acid (MCA), dichloroacetic acid (DCA), trichloroacetic acid (TCA), monobromoacetic acid (MBA), and dibromoacetic acid (DBA)].

IUGR, SGA & low term birth weight

54. Some studies reported positive associations between exposure to DBPs and some measure of growth retardation such as intrauterine growth retardation (IUGR), small for gestational age (SGA) and low term birth weight. A population-based study in Massachusetts observed significant associations between SGA and TTHMs in the public water supply (OR 1.06, 95% CI 1.02-1.10 for TTHMs >33 – 74 vs 0 – 33 micrograms/l and OR 1.13, 95% CI 1.07 – 1.20 for TTHM >74 – 163 vs 0 – 33 micrograms/l). Significant associations were also found for chloroform >26 – 63 vs 0 – 26 micrograms/l (OR 1.05, 95% CI 1.02 – 1.09) and >63 - 135 vs 0 – 26 micrograms/l (OR 1.11, 95% CI 1.04 – 1.17), and for BDCM >5 – 13 vs 0 - 5 micrograms/l (OR 1.1, 95% CI 1.07 – 1.14) and >13 – 46 vs 0 - 5 micrograms/l (OR 1.15, 95% CI 1.08 – 1.22) (Wright J et al, 2004).

55. In a prospective population-based study in 3 US states, Savitz et al (2005) reported a statistically significant association with SGA (OR 2.1, CI 1.1 – 3.8) for TTHM exposure (≥ 80 micrograms/litre compared with referent exposure). This
study made multiple comparisons and the significance of few positive associations is difficult to interpret.

56. However, in a retrospective cohort study in Arizona, Hinckley et al (2005) observed no association between IUGR and TTHMs in the public water supply (highest exposure level given as ≥ 53 micrograms/l; referent category < 40 micrograms/l) or individual THMs. In a population-based study in Maryland, Porter et al (2005) reported no consistent or dose-related association between TTHMs or individual THMs in the public water supply and IUGR (the concentrations were unclear). Also, in a hospital-based case-control study in Montreal, Infante-Rivard (2004) found no association overall between either TTHMs (up to a cut off value of 30 micrograms/l) or individual THMs exposure and IUGR. However, among newborns with the G1259C polymorphism in the CYP2E1 gene, the adjusted OR for IUGR associated with exposure to average TTHM above 29.4 microgram/l was 13.20 (95% CI 1.19 – 146.72), based on 45 cases and 37 controls.

57. Wright et al (2004) observed a significant association between TTHM exposure > 74 – 163 micrograms/l when compared with 0 – 33 micrograms/l, and a decreased birth weight (-18 g, 95% CI – 26 to – 10 g). Wright et al (2004) also reported a reduction in mean birth weight (-18g, 95% - 26 to -10g) for chloroform concentrations > 63 - 135 micrograms/l compared with 0 -26 micrograms/l, and for BDCM > 13 – 46 micrograms/l compared with 0 – 5 micrograms/l (-12g, 95% CI – 20 to – 3g). However, Hinckley et al (2005) reported ‘no association’ of low term birth weight with TTHMs levels up to 53 micrograms/l and BDCM or DBCM levels up to 18 or 16 micrograms/l, respectively.

58. For HAAs, there was inconsistent evidence for an association with some measure of growth retardation. Hinckley et al (2005) reported statistically significant increased risks of IUGR for exposure to DCA at ≥ 8 micrograms/l compared with exposure to < 6 microgram/l (OR 1.28, 95% CI 1.08 – 1.51), and similarly for exposure to TCA at ≥ 6 micrograms/l compared with exposure to < 4 microgram/l (OR 1.19, 95% CI 1.01 – 1.41). Hinckley et al (2005) also observed an increased risk of low term birth weight for DBA concentrations ≥ 5 micrograms/l compared with ≤ 4 micrograms/l (OR 1.49, 95% CI 1.09 – 2.04). ‘No associations’ were observed for HAA5 concentration up to 19 micrograms/l. Porter et al (2005) reported some potential for a slightly elevated risk for IUGR during the second and 3rd trimester for 5th quintile HAA5 exposure compared with referent exposure (OR 1.34, 95% 1.04 – 1.71), however the authors reported ‘no dose-response’ relationship.

59. Savitz et al (2005) found ‘no association’ between SGA and exposure to HAAs (exposure levels unclear). Also, Wright et al (2004) reported ‘no association’ of SGA with HAA5 up to 58 micrograms/l, DCA up to 24 microgram/l, and TCA up to 28 microgram/l. The significance of the observed small elevated risks reported above for low concentrations of total and individual HAAs are unclear.

Pregnancy loss and pre-term delivery
60. Regarding other outcomes investigated since 2004, women drinking more than 5 glasses of drinking water/day containing > 75 micrograms/l TTHMs were reported to have no higher level of pregnancy loss than ‘all other women’ (Savitz et al 2005). However, Savitz et al (2005) reported increased risks of pregnancy loss for DCBM (OR 1.6, no CIs given) and DBCM (OR 1.7, no CIs given), when exposure to upper quartile concentrations was compared with exposures to lowest three quartiles of exposure (concentrations unclear).

61. Wright et al (2004) found ‘reduced risks’ of pre-term delivery for TTHMs up to 163 micrograms/l, chloroform up to 135 microgram/l, and BDCM up to 46 micrograms/l. Savitz et al (2005) also reported inverse or no associations of pre-term birth with DBPs, including HAAs, DCBM, and chloroform (exposure levels unclear).

62. Overall, the new epidemiological studies published since the COT's 2004 consideration do not appear to suggest any consistent evidence for a causal relationship between DBPs and adverse pregnancy outcomes.

Animal data

63. 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 some of the 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 may occur in animals (COT/04/8, appended at Annex B).

64. TOX/2004/12, considered by the COT in 2004, noted that administration of high doses of some DBPs to laboratory animals has resulted in adverse effects. DBCM caused decreased litter size and viability in a 2-generation study in Swiss mice; bromoform was fetotoxic when administered to SD rats on GDs 6-15, TCA reduced pup weight and length in rats, HANs increased resorption rates, decreased the percentage of Long Evans rats delivering viable litters and decreased birth weight and BDCM induced full litter resorption (FLR) in F344 rats (IPCS, 2000). The latter effect was the subject of a number of more recent studies considered in TOX/2004/12. A maternally mediated mechanism involving decreased progesterone secretion by the corpora lutea had been proposed. However, in SD rats, BDCM did not appear to affect pregnancy outcomes. Additionally, TOX/2004/12 reported in-vitro studies (using a non-standard protocol) that suggested that effects on hormone secretion by human placental tissue might occur at tissue doses that might be relevant to human drinking water exposures.

65. After their 2004 consideration (including animal data) the COT concluded that the data that they had evaluated did not show a causal relationship between chlorinated drinking-water and adverse pregnancy outcomes. However, data on congenital malformations were not assessed.
66. As mentioned above, the Tardiff et al (2006) weight of evidence review (appended at annex E) considered toxicological reproductive and developmental studies on a number of individual DBPs, including some THMs and HAAs, and described some more recent toxicological studies including studies on congenital anomalies. Briefly, regarding the more recent animal toxicity studies on malformations, the following was noted:

- Christian et al (2001a) were reported to have investigated developmental and reproductive effects using a modern design. Rats and rabbits received doses up to 900 ppm BDCM. The maternal NOAEL was 150 ppm for rats (18.4 mg/kg/day) and rabbits (13.4 mg/kg/day). The NOAEL for developmental toxicity was 45 mg/kg/day for rats and 55 mg/kg/day for rabbits.

- Christian et al (2002) were also reported to have conducted a two-generation reproductive study in rats with DBA that produced no birth defects at the highest tested dose of 650 ppm (132 mg/kg/day), although other forms of reproductive toxicity were seen.

- A range finding study by Christian et al (2001b) with DBA (up to 1000 ppm) and BDCM (up to 1350 ppm) in drinking water for 14 days in rats and rabbits essentially found no developmental effects or reproductive effects (taste aversion reduced bodyweight gain at the highest levels).

67. Tardiff et al (2006) noted that the toxicology review articles all concluded that adverse effects in animals only occur at doses much higher than those encountered by humans and that the toxicological data did not support a dose-response relationship. They concluded that their updated review found little indication of previously unreported reproductive or developmental toxicity. They also concluded that the relevant data indicate that the NOAELs and LOAELs in animals are much higher than known levels of human exposure, and only limited data explore modes of action for reproductive toxicity. 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.

**Conclusions**

68. In animal studies, reproductive/developmental effects have mainly been seen with DBPs at high doses often associated with maternal toxicity, which are difficult to interpret in relation to low levels of human exposure. The epidemiological evidence for congenital anomalies is inconsistent but, overall, there would appear to be no convincing evidence for an association between DBPs and congenital anomalies.
69. The additional epidemiological investigations of adverse birth outcomes (excluding congenital malformations) published since 2004 did not provide consistent evidence of associations with THM levels in drinking water. Few studies have been reported on other DBPs.

**COT Opinion**

70. In considering the new SAHSU phase 2 study and the other evidence provided, members are asked to consider the following questions:

   i) Does the COT have any comments on the SAHSU study and do members agree with the conclusions?

   ii) In light of the new SASHU study and the other evidence provided, does the COT wish to change the conclusions reached in 2004 i.e. that the data do not show a causal relationship between chlorinated drinking-water and adverse pregnancy outcomes?

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**Secretariat**

**January 2008**
References

http://www.food.gov.uk/multimedia/pdfs/cot_drikwa01.pdf


COT Statement on chlorinated drinking water and reproductive outcomes (COT/04/8 - November 2004). 
http://www.advisorybodies.doh.gov.uk/cotnonfood/chlorination.htm


Graves CG, Matanoski GM, Tardiff RG (2001). Weight of evidence for an association between adverse reproductive and developmental effects and

Hinckley AF, Bachand AM, Reif JS (2005). Late pregnancy exposures to disinfection by-products and growth-related birth outcomes. Environmental Health Perspectives 113 (No. 12): 1808-1813.


