

## REVIEW

## Chlorination disinfection byproducts in water and their association with adverse reproductive outcomes: a review

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### Abstract

**Objectives and methods**—Chlorination has been the major disinfectant process for domestic drinking water for many years. Concern about the potential health effects of the byproducts of chlorination has prompted the investigation of the possible association between exposure to these byproducts and incidence of human cancer, and more recently, with adverse reproductive outcomes. This paper evaluates both the toxicological and epidemiological data involving chlorination disinfection byproducts (DBPs) and adverse reproductive outcomes, and makes recommendations for future research.

**Results and conclusions**—Relatively few toxicological and epidemiological studies have been carried out examining the effects of DBPs on reproductive health outcomes. The main outcomes of interest so far have been low birth weight, preterm delivery, spontaneous abortions, stillbirth, and birth defects—in particular central nervous system, major cardiac defects, oral cleft, and respiratory, and neural tube defects. Various toxicological and epidemiological studies point towards an association between trihalomethanes (THMs), one of the main DBPs and marker for total DBP load, and (low) birth weight, although the evidence is not conclusive. Administered doses in toxicological studies have been high and even though epidemiological studies have mostly shown excess risks, these were often not significant and the assessment of exposure was often limited. Some studies have shown associations for DBPs and other outcomes such as spontaneous abortions, stillbirth and birth defects, and although the evidence for these associations is weaker it is gaining weight. There is no evidence for an association between THMs and preterm delivery. The main limitation of most studies so far has been the relatively crude methodology, in particular for assessment of exposure.

**Recommendations**—Large, well designed epidemiological studies focusing on well defined end points taking into account rel-

evant confounders and with particular emphasis on exposure characterisation are ideally needed to confirm or refute these preliminary findings. In practice, these studies may be impracticable, partly due to the cost involved, but this is an issue that can be put right—for example, by use of subsets of the population in the design of exposure models. The studies should also reflect differences of culture and water treatment in different parts of the world. To identify the specific components that may be of aetiological concern and hence to fit the most appropriate exposure model with which to investigate human exposure to chlorinated DBPs, further detailed toxicological assessments of the mixture of byproducts commonly found in drinking water are also needed.

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Disinfection byproducts (DBPs) in drinking water have received considerable interest because of their possible association with cancer, particularly bladder and rectal cancer.<sup>1 2</sup> More recently the interest has shifted from cancer to reproductive outcomes. Little is known of the potential adverse reproductive effects of the DBPs, of which the trihalomethanes (THMs) are generally the most prevalent and are routinely measured. These are a volatile group of compounds, which comprises chloroform, bromodichloromethane (BDCM), chlorodibromomethane (CDBM), and bromoform. To establish whether there are adverse effects due to byproduct compounds in drinking water is difficult, as they exist in low concentrations and in conjunction with many other chemicals. Obtaining estimates of a person's exposure in utero to such agents is dependent not only on the type of disinfection process of the mother's residential water source, but also on the person's consumption of tap water, the level of toxicants present in the water supply during the critical exposure period, and exposure through pathways other than ingestion such as inhalation of and dermal contact with and uptake of compounds while showering, bathing, and

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swimming.<sup>3-8</sup> Furthermore, little is known about other maternal characteristics that could also be considered to be risk factors for adverse reproductive outcomes, thus making interpretation of associations with drinking water more difficult to evaluate. Here we review the toxicological and epidemiological evidence to date, evaluate the potential risk of chlorination DBPs on human reproductive health, and provide recommendations for future research.

### Formation of disinfection byproducts (DBPs)

Chlorine was introduced as a disinfectant to the urban water supply at the beginning of the 20th century to improve the hygienic quality by eliminating waterborne bacterial pathogens and the consequent transmission of water borne diseases. As such, it is considered of major importance for public health and most drinking water originating from surface water supplies is currently disinfected with chlorine. Alternative chemicals such as chloramine (chlorine reacted with ammonia), chlorine dioxide, ozone, and ultraviolet radiation have also been used as disinfectants, although to a much lesser extent.<sup>9</sup> Chlorine, which exists as hypochlorous acid and hypochlorite in water (range 0.2–1 mg/l), also reacts with natural organic compounds—such as humic and fulvic acids—to form a wide range of unwanted halogenated organic compounds including trihalomethanes, haloacetic acids (HAAs), chlorophenols, chloral hydrate, and haloacetonitriles (HANs).<sup>10</sup> Drinking water from surface waters generally contains higher concentrations of DBPs than ground water due to the higher concentrations of organic material. Chloroform is usually the most prevalent byproduct formed, although brominated THMs can occur at high concentrations when waters with high bromide concentrations are chlorinated.<sup>11</sup> After THMs the non-volatile HAAs are the most prevalent, occurring generally at about half the concentrations of the THMs.<sup>11</sup> Most other DBPs occur at trace concentrations (usually <1 µg/l). Although THMs are generally the most prevalent, they may not be the most important from a health point of view. The THMs are routinely measured in water supplies in the United Kingdom and United States for compliance with the standard, and an estimate of total THMs (TTHMs) is obtained by adding the estimated concentrations of chloroform, BDCM, CDBM and bromoform (TTHM standard 100 µg/l as a rolling 3 month average). Water supply in the United Kingdom is divided into water zones (<50 000 people per zone) and water companies are required to take at least four measurements per year per zone.

### Biological basis for the hypothesis that chlorination DBPs have deleterious effects on reproduction: toxicological evidence

Several of the halogenated byproducts have been evaluated for their potential to induce or influence adverse reproductive health outcomes,<sup>12-36</sup> but the biological mechanism by which these compounds may influence devel-

opment in utero is not well understood. The animal bioassays to date have characterised the reproductive effects as well as the embryo toxicity and teratogenicity of individual disinfection byproduct chemicals. This approach includes a wide range of adverse reproductive outcomes from developmental disability, structural congenital malformations, and growth retardation to fetal death.

Several disinfection byproduct compounds routinely found in drinking water have been found to cause reproductive and developmental toxicity in laboratory animals when given at high doses.<sup>37</sup> Most adverse effects have manifested themselves as reductions in both body weight and survival of the offspring, although some toxicants have been related to congenital malformations of the cardiovascular and neurological systems (table 1). The THMs have generally shown no direct evidence of teratogenicity, although severe maternal and fetotoxic effects have been shown at high doses, resulting in reduced fetal body weight and survival rates.<sup>14</sup> Oral administration of chloroform showed little reproductive effect, except some reduced foetal body weight at high doses,<sup>14 15</sup> and administration through inhalation also showed growth retardation and pregnancy loss.<sup>16 17</sup> Bromoform showed no effect on reproductive indices.<sup>14 18</sup> Most studies found no reproductive effects of BDCM,<sup>14 20 21</sup> but Narotsky *et al*<sup>19</sup> reported fetal resorption, although there was no effect on duration of gestation, pup survival, weight, or morphology. Klinefelter<sup>13</sup> found that exposure to BDCM can produce sperm abnormalities in male rats as indicated by decreased sperm motility. Borzelleca and Carchman<sup>22</sup> found decreased litter sizes and pup viability at very high doses of CDBM, but Ruddick *et al*<sup>14</sup> found no evidence for fetotoxic or teratogenic effects at lower doses.

Halogenated acetic acids have been found to cause testicular damage in rats with disruption of spermatogenesis and motility, with the brominated analogue being the stronger toxicant.<sup>26 27 29-32</sup> Neural tube and craniofacial defects have been found with administration of dichloroacetic or trichloroacetic acid in rats,<sup>28</sup> and cardiac malformations have been induced at high doses of dichloroacetic acid.<sup>25</sup> Hunter *et al*<sup>23</sup> found changes in neural tube development when they exposed mouse embryos to HAAs. Several chloroacetonitrile compounds have been shown to increase the rate of resorptions, reduce fetal body weight and survival,<sup>34</sup> and to result in an increase in malformations of the cardiovascular, digestive, soft tissue, and urogenital systems.<sup>35 36</sup> However, no adverse effects have been found for the brominated analogues.<sup>37</sup> 2-Chlorophenol has also been associated with subfertility and stillbirths.<sup>23</sup> As with the trihalomethanes, these adverse developmental effects have only been found at high doses in conjunction with severe fetotoxicity (table 1).

The toxicological effects of many other byproducts remain largely unknown with little evaluation of male and female fertility, conception delay, growth retardation, of specific birth

Table 1 Summary of animal toxicological assessments of reproductive effects of chlorination disinfection byproducts

Byproduct	Usual concentration in drinking water	Doses given in drinking water or gavage (mg/kg/day)	Teratogenic effects	Reference (Year)
Chloral hydrate	<20 µg/l	16 and 160 mg/kg 55 and 188 mg/kg	No adverse effects on body weight or malformations found Decreased sperm motility in male rats at highest dose only	Kallman <i>et al.</i> <sup>12</sup> (1984) Klinefelter <sup>13</sup> (1995)
Trihalomethanes: Chloroform	<100 µg/l	100–400 mg/kg orally	Reduced foetal body weight at highest dose, evidence for fetotoxic response, no teratogenic effects	Ruddick <i>et al.</i> <sup>14</sup> (1983)
Bromoform	<6 µg/l	0–126 mg/kg orally 30–300 ppm inhalation	No evidence of teratogenicity, reduced foetal weight only at highest dose Growth retardation and minor skeletal aberrations at all concentrations and minor embryo and fetotoxicity at high concentrations	Thompson <i>et al.</i> <sup>15</sup> (1974) Schwetz <i>et al.</i> <sup>16</sup> (1974)
Bromodichloromethane (BDCEM)	<50 µg/l	0–100 ppm inhalation 0–200 mg/kg	Pregnancy loss, reduced foetal body weight and crown-rump length at high dose No effect on fertility or reproduction indices, including sperm density, motility, and morphology	Murray <i>et al.</i> <sup>17</sup> (1979) Gulati <i>et al.</i> <sup>18</sup> (1989)
Chlorodibromomethane (CDBM)	<45 µg/l	100–400 mg/kg orally 50–200 mg/kg orally 25–75 mg/kg	Evidence for fetotoxic response, no effect on foetal weight, no teratogenic effects No reduction in foetal body weight, no fetotoxic response, no teratogenic effects Foetal resorption at 50 and 75 mg/kg doses. No effect on duration of gestation, pup survival, weight, and morphology	Ruddick <i>et al.</i> <sup>14</sup> (1983) Ruddick <i>et al.</i> <sup>14</sup> (1983) Narotsky <i>et al.</i> <sup>19</sup> (1997)
Chlorophenols 2-Chlorophenol (CP) 2,4-Dichlorophenol (DCP)	<1 µg/l	22 and 39 mg/kg 0–1500 ppm orally 5.8–40.3 mg/kg/day orally 50–200 mg/kg orally 0–685 mg/kg	Decreased sperm motility in male rats at highest dose only No findings related to treatment in male and female reproductive variables No reproxicological effects in males and females No foetal weight reduction, evidence of fetotoxic response, no teratogenic effect Decreased litter size, and pup viability at high dose, slight depression of foetal weight	Klinefelter <sup>13</sup> (1995) NTP <sup>20</sup> (1999) Delaney <i>et al.</i> <sup>21</sup> (1997) Ruddick <i>et al.</i> <sup>14</sup> (1983) Borzelleca <i>et al.</i> <sup>22</sup> (1982)
Halogenated acetic acids: Dichloroacetic acid (DCAA)	<100 µg/l	3–300 mg/kg 3–300 mg/kg	CP: increased conception rate and stillbirth; reduction in size of litters at highest dose only DCP: No adverse effect on reproductive performance	Exon <i>et al.</i> <sup>23</sup> (1985) Exon <i>et al.</i> <sup>24</sup> (1994)
Trichloroacetic acid (TCAA)	<100 µg/l	14–2400 mg/kg	DCAA: increased embryonic resorption = 900 mg/kg, reduction in body weight and cardiac malformations = 140 mg/kg DCAA: inhibited spermiation at highest dose, reduced epididymal sperm counts and sperm motility, sperm morphology impacted also at lower doses	Smith <i>et al.</i> <sup>25</sup> (1992) Toth <i>et al.</i> <sup>26</sup> (1992)
Monobromoacetic acid (MBAA) Dibromoacetic acid (DBAA)	<10 µg/l mostly <1 µg/l	0–3000 mg/kg/day 330–1800 mg/kg 0–100 mg/kg/day 0–270 mg/kg/day 0–1250 mg/kg/day 0–250 mg/kg	DCAA: increased embryonic resorption, reduction in body weight and increase in cardiovascular malformations at all doses. Skeletal malformations found at highest dose only MBAA: no effects DBAA: reduced epididymal sperm counts and sperm motility, morphological changes DBAA: Sperm motility and morphology effected	Linder <i>et al.</i> <sup>27</sup> (1997) Smith <i>et al.</i> <sup>28</sup> (1989) Linder <i>et al.</i> <sup>29</sup> (1994) Linder <i>et al.</i> <sup>30</sup> (1994) Linder <i>et al.</i> <sup>29</sup> (1994) Linder <i>et al.</i> <sup>31</sup> (1995)
Halogenated acetamitriles: Dichloroacetamitrile (DCAN)	<10 µg/l mostly <1 µg/l	0–250 mg/kg/day	DBAA: reduction in sperm motility and sperm count at highest dose; only, and moderate changes at lower doses DBAA: spermatid changes	Linder <i>et al.</i> <sup>32</sup> (1997)
Trichloroacetamitrile (TCAN)	<0.1 µg/l	1–55 mg/kg 1–555 mg/kg	DCAN: increased foetal resorption and reduction in foetal body weight with increasing dose. Cardiovascular, skeletal, and urogenital malformations ≥45 mg/kg. TCAN: increased foetal resorption and reduction in foetal body weight with increasing dose. Cardiovascular and urogenital malformations at ≥15 mg/kg. No skeletal defects found.	Smith <i>et al.</i> <sup>33</sup> (1987) Smith <i>et al.</i> <sup>34</sup> (1989) Smith <i>et al.</i> <sup>35</sup> (1988)
Hydroxyfuranone (MX)	<0.1 µg/l		No data	
Chlorinated acetones	<1 µg/l		No data	

defects.<sup>38,39</sup> Such outcomes are in themselves, complex end points to study, and it is difficult to determine the extent to which organic chemicals contained in the water supply may affect a developing fetus and what gestational period is most critical. The effects at high doses of the various DBPs should be interpreted with caution, in particular when extrapolating these results to humans. Also, it should be noted that most substances were given by gavage whereas humans show a different pattern of exposure, and can also be exposed by inhalation and skin contact.

### Epidemiological studies

Few epidemiological studies have been carried out to investigate the relation between DBPs in drinking water and reproductive outcomes (table 2). The focus has been on the THMs, partly because they are the most prevalent DBPs and are routinely measured. Several studies have been conducted to assess the relation between water consumption and risk of spontaneous abortion and congenital anomalies in Santa Clara County, California, but these will not be reviewed here because water contamination by an organic solvent, trichloroethane, rather than DBPs has been implicated in this area.<sup>40-44</sup> We will briefly summarise the studies of DBPs according to the type of assessment of exposure that has been used, with particular reference to the study design, case ascertainment, and assessment of exposure. Table 2 provides more detail on sample size, risk estimates, and potential confounders that were accounted for—for example, smoking, alcohol intake, socioeconomic status, and maternal age. Assessment of exposure is one of the most difficult, and so far the weakest aspects of the epidemiological studies conducted to date. Uptake of chlorination byproducts—such as the THMs—does not only occur through ingestion of tap water and food, but also through inhalation and skin absorption during showering, bathing, and swimming, with a different metabolism for the various routes and potentially large variation between people.<sup>3-8</sup> Issues such as mobility during pregnancy, the consumption of tap versus bottled water, and cold versus boiled water are also very important. The assessment of exposure, however, is made easier by having the methodological advantage of a short latency time between exposure and outcome in reproductive epidemiological studies.

#### USE OF WATER SOURCE AND WATER TREATMENT AS EXPOSURE INDEX

The crudest measures of exposure, used by Aschengrau *et al*,<sup>45</sup> Kanitz *et al*,<sup>46</sup> and Magnus *et al*<sup>47</sup> have been based on the comparison of the type of water source (ground *v* surface) or water treatment used (chlorinated *v* non-chlorinated). The main limitation of these studies was the assessment of exposure, with little information on the spatial and temporal variation in total and individual THMs and other DBPs, mobility of pregnant mothers, and the (variation in) individual uptake of THM through ingestion, inhalation, and dermal

absorption including the use of bottled water and private wells. Also other contaminants were generally not considered.

Aschengrau *et al*<sup>45</sup> carried out a case-control study in Massachusetts with routinely collected data on chemicals and metals in public water supplies and a range of pregnancy outcomes, including congenital anomalies, stillbirths, and neonatal death. Their main interest seemed to be chemicals other than chlorination byproducts, but they found a non-significant excess of stillbirth and major congenital malformations, and a fairly large significant excess of respiratory and urinary tract defects when comparing chlorinated with chloraminated surface water (table 2). There was no information on the number of cases of respiratory and urinary tract defects. Also, there were no differences in risk when comparing water source (surface *v* ground or mixed). Risk estimates for all end points other than “all congenital anomalies” were based upon small numbers, as was evident from the wide ranging confidence intervals (95% CIs).

Kanitz *et al*<sup>46</sup> conducted a retrospective cohort study in Genoa, Italy comparing somatic variables, low birth weight (<2500 g), body length ( $\leq 49.5$  cm), cranial circumference ( $\leq 35$  cm), and neonatal jaundice from hospitals records in populations where drinking water was treated with sodium hypochlorite (THM concentrations 8–16  $\mu\text{g/l}$ ), chlorine dioxide (THM concentrations 1–3  $\mu\text{g/l}$ ), both or not at all (control town). The main interest was the exposure to chlorites and chlorates as a result of disinfection with chlorine dioxide. They found large, but not significant, excess risks of low birth weight, and significant, but smaller, excess risks of small body length and small cranial circumference when comparing disinfected water (both chlorine dioxide or sodium hypochlorite) with non-disinfected water. The large excess risks for all end points (except for small cranial circumference) were similar for both the disinfection processes, which is surprising given the overall low THM concentrations and likely differences in DBP profiles. An important limitation was the few cases.

Magnus *et al*<sup>47</sup> carried out a retrospective cohort study, which included all the children born in Norway in 1993–5, as included in the Norwegian Birth Registry, and for which the water chlorination status was known in at least one waterworks and weighted mean colour number could be calculated. All births occurring after the 16th week of gestation are recorded in the birth registry. They studied birth defects, particularly neural tube, major cardiac, respiratory tract, urinary, and oral cleft defects by comparing chlorinated with non-chlorinated water with further separation in low and high colour categories. They found excess risks for all the birth defects when comparing non-chlorinated low colour water with chlorinated high colour water, but only for urinary tract defects was this significant (odds ratio (OR) 1.99 95%CI 1.10 to 3.57). The authors also reported that disinfection byproduct concentrations in Norway were generally



fairly low with an average of 9.4 µg/l for TTHM and 14.6 µg/l for HAAs.

#### USE OF ROUTINELY COLLECTED MEASUREMENTS OF THMS AS AN INDEX OF EXPOSURE

A more informative exposure profile has been used in epidemiological studies that took advantage of routinely collected measurements of THM concentrations in public water supplies. These ecological exposure estimates have been assigned to the mother's residence either at the time of birth or the aetiologically relevant periods over the pregnancy for the respective birth outcomes.<sup>48-51</sup> Such estimates enabled the actual concentrations of THMs present in the water supply to be considered as well as providing an opportunity to model fluctuations in THM concentrations over time and average any unstable exposure estimates. The main limitation was that they could not take into account variation in the person's THM uptake through ingestion, inhalation, and dermal absorption, including the use of bottled water and private wells. Also, generally only TTHM estimates were used and the other contaminants were not considered.

Kramer *et al*<sup>48</sup> carried out a population based case-control study in Iowa studying the relation between THM concentrations at the water source from a municipal water survey and low birthweight (<2500 g), prematurity (gestational age <37 weeks) and intrauterine growth retardation (baby weight for gestational age <5% percentile (table 2). Despite the exposures being low (highest exposure category ≥10 µg/l), their main findings were weakly suggestive of an increasing risk of intrauterine growth retardation with increasing exposure to both chloroform and dichlorobromomethane, and the other was an exposure-response relation for chloroform and low birthweight. A limitation of the study was the timing of the assessment of exposure. The THM data were based upon a 1987 survey, whereas the study outcomes were ascertained from the period January 1989 to June 1990. This one off survey did not consider fluctuations in THM concentrations over time or average any exposure estimates.

Bove *et al*<sup>49</sup> carried out a large retrospective cohort study in New Jersey studying the relation between monthly estimates of TTHM exposure concentrations provided by the Bureau of Safe Drinking Water (five exposure categories ≤20, >20-40, >40-60, >60-80, >80-100, >100 µg/l TTHMs) as well as other contaminants, and birth outcomes such as birth weight, low birth weight (<2500 g), preterm birth (<37 weeks), small for gestational age (baby weight for gestational age <5% percentile), and birth defects (all recorded malformations, central nervous system, neural tube, oral cleft, and major cardiac defects). Outcome data were obtained from birth certificates and the New Jersey Birth Defects Registry. The authors found that mean birth weight among term births was 70.4 g lower when comparing those exposed to concentrations >100 µg/l with the reference group (TTHM concentrations ≤20 µg/l). Excess risks

for "all surveillance birth defects", small for gestational age, central nervous system defects, neural tube defects, and all cardiac defects were shown with an increase in TTHM concentrations. Although monotonic trends were not apparent, the test for trend, and the use of TTHM categories provided support for trends for all these outcomes. There was no evidence, however, to support a trend for major cardiac defects (possibly due to the few cases in the exposure categories) and oral cleft defects, despite the finding of a threefold increase in risk (OR 3.17) for oral cleft defects at TTHM concentrations >100 µg/l compared with the reference group. No association was found between TTHM concentrations and preterm birth, very low birth weight, or foetal death. The main limitations of the study were the many exposure categories resulting in few cases for some outcomes in certain exposure categories, and other aspects of the assessment of exposure—for example, the availability of TTHM concentrations only and not for individual THMs. One of the main advantages of the study is the large number of cases for outcomes other than defects—for example, birth weight and low birth weight.

Gallagher *et al*<sup>50</sup> carried out a retrospective cohort study in Colorado with routinely collected TTHM (>75% chloroform) data and computer modelling to obtain third trimester exposure estimates (TTHM exposure categories with cut off points of 20, 40, and 60 µg/l). These were analysed for low birth weight (<2500 g), term low birth weight, and preterm delivery (<37 weeks gestation) from birth records. Out of 86 census blocks 58 with no exposure measurements were excluded from analyses. The authors found an excess risk for low birth weight, in particular term low birth weight (OR 5.9, 95% CI 2.0 to 17.0) for those exposed to >60 µg/l TTHMs compared with those in the low exposure group, but no association between preterm delivery and TTHM concentrations. The main limitations of the study seemed to be the very few cases in the high exposure group and the use of TTHM rather than the individual THMs.

Dodds *et al*<sup>51</sup> carried out a very large retrospective cohort study in the Canadian province of Nova Scotia with TTHM concentrations from public water sources, modelled by year, month and source, to obtain four exposure categories (0-49, 50-74, 75-99, ≥100 µg/l). These were analysed for small for gestational age (bottom 10% of the birth weight distribution), low birth weight (<2500 g), very low birth weight (<1500 g), preterm delivery (<37 weeks), neural tube, cleft, and major cardiac defects, stillbirth, and chromosomal abnormalities obtained from perinatal and fetal anomaly databases. The authors did not find excess risk for very low and low birthweight, preterm delivery, cleft, or major cardiac defect, but did for neural tube defects, small for gestational age, chromosomal abnormalities, and stillbirth. Only for stillbirth was this significant and it showed a trend with increased exposure. The main advantage of the study was the large number of subjects. However, rela-

Table 2 Summary of epidemiological studies on chlorinated disinfection byproducts and adverse reproductive outcomes

Author (year)	Study details (location, time, sample size)	Cases	Exposure assessment	Other risk factors included	Main positive findings OR (95% CI)
Kramer et al <sup>88</sup> (1992)	Iowa, US 151 Towns with a single water source 1989–90 Sample population: 4028	588 (Total) 159 Low birth weight 342 Preterm delivery 187 Intrauterine growth retardation, small for gestational age	Based on maternal residential address and one municipal water survey to estimate individual TTHM concentrations (2 or 3 exposure categories)	Maternal age Parity Marital status Education Smoking Prenatal care	<b>Chloroform, No v medium (1–9 µg/l) v high (≥10 µg/l):</b> <i>Low birth weight</i> <b>Chloroform, 1 v 1.1 (0.7–1.6) v 1.3 (0.8–2.2)</b> <i>Intrauterine growth retardation</i> <b>Chloroform, 1 v 1.3 (0.9–1.8) v 1.8 (1.1–2.9)</b> <i>Intrauterine growth retardation</i> <b>Dichlorobromomethane, 1 v 1.2 (0.8–1.7) v 1.7 (0.9–2.9)</b>
Aschengrau et al <sup>85</sup> (1993)	Massachusetts, USA 2 Hospitals 1977–80 Sample population: 2348	1171 (total) 1039 Major congenital malformations Urinary tract defects Respiratory tract defects 77 Stillbirths 55 Neonatal deaths	Based on maternal residential address to ascertain type of water supply, chlorination v chloramination, and ground or mixed water v surface water.	Maternal age Pregnancy history Alcohol Ethnicity Hospital payment Other water contaminants	<b>Chlorinated v chloraminated:</b> <i>Stillbirth</i> <b>2.6 (0.9 to 7.5)</b> <i>Neonatal deaths</i> <b>1.1 (95% CI not provided)</b> <i>Congenital malformations</i> <b>Major malformations 1.5 (0.7 to 2.1)</b> <b>Respiratory defects 3.2 (1.1 to 9.5)</b> <b>Urinary tract defects 4.1 (1.2 to 14.1)</b>
Bove et al <sup>89</sup> (1995)	New Jersey, USA 75 Towns with a public water supply 1985–88 Sample population: 81602	29268 (Total) <i>Live births:</i> 1853 Low birth weight 905 Very low birth weight 4082 Small for gestational age 7167 Preterm 594 Foetal deaths <i>All births: defects:</i> 669 Surveillance 118 Central nervous system defects 83 Oral cleft 56 Neural tube 108 Major cardiac	Based on maternal residential address and municipal water surveys to estimate monthly TTHM concentrations (5 or 6 exposure categories)	Maternal age Ethnicity Sex of baby Primipara Prenatal care Education Previous still or miscarriage Other contaminants	<b>TTHM concentrations &gt;100 µg/l v ≤20 µg/l:</b> <i>Low birth weight</i> <b>1.4 (50% CI 1.2 to 1.7)</b> <i>Intrauterine growth retardation or small for gestational age</i> <b>1.5 (90% CI 1.2 to 1.9)</b> <b>TTHM concentrations &gt;80 µg/l v ≤20 µg/l:</b> <i>Surveillance Register defects</i> <b>1.6 (90% CI 1.2 to 2.0)</b> <i>CNS system defects</i> <b>2.6 (90% CI 1.5 to 4.3)</b> <i>Neural tube defects</i> <b>3.0 (90% CI 1.3 to 6.6)</b> <i>Major cardiac defects</i> <b>1.8 (90% CI 1.0 to 3.3)</b> <b>TTHM concentrations &gt;100 µg/l v ≤20 µg/l:</b> <i>Oral cleft defects</i> <b>3.2 (90% CI 1.2 to 7.3)</b>
Savitz et al <sup>92</sup> (1995)	Carolina, USA 6 Hospitals 1988–91 Sample population: 1003	548 (Total) 126 Spontaneous abortion 244 Preterm 178 Low birth weight	Based on maternal residential address and quarterly municipal water surveys to estimate average TTHM concentrations. Analysis of: (a) Surface v ground water source, (b) TTHM concentrations, (3 exposure categories) (c) Consumption during pregnancy (d) Water source × amount (e) TTHM dose (concentration × amount)	Maternal age Ethnicity Hospital Education Marital status Poverty level Smoking Alcohol consumption Employment Nausea	<b>40.8–59.9 v 81.1–168.8 µg/l TTHM:</b> <i>Spontaneous abortion</i> <b>1.2 (0.6 to 2.4)</b> <b>40.8–63.3 v 82.8–168.8 µg/l TTHM:</b> <i>Low birth weight</i> <b>1.3 (0.8 to 2.1)</b> <b>Per 50 µg/l TTHM increment change:</b> <i>Spontaneous abortion</i> <b>1.7 (1.1 to 2.7)</b>

Table 2 (continued)

Author (year)	Study details (location, time, sample size)	Cases	Exposure assessment	Other risk factors included	Main positive findings OR (95% CI)
Kanitz <i>et al</i> <sup>6</sup> (1996)	Liguria, Italy 2 Hospitals 1988–1989 Sample population: 676	548 Live births in exposed area 50 Preterm 141 Caesarean section 133 Neonatal jaundice 20 Low birth weight 288 Small body length 370 Small cranial circumference	Based on maternal residential address to ascertain type of water source (chlorine dioxide or hypochlorite <i>v</i> not treated)	Maternal age Education Smoking Alcohol Sex of child	<b>Sodium hypochlorite treated (8–16 µg/l TTHMs) <i>v</i> non treated water:</b> <i>Neonatal jaundice</i> 1.1 (0.7 to 2.8) <i>Low birth weight</i> 6.0 (0.6 to 12.6) <i>Small body length</i> 2.3 (1.3 to 4.2) <i>Small cranial circumference</i> 3.5 (2.1 to 8.5)
Waller <i>et al</i> <sup>53</sup> (1998)	California, USA 3 Regions of surface, ground, and mixed drinking water 1989–1991 Sample population: 5144 pregnancies	499 Spontaneous abortions	Based on maternal residential address and quarterly municipal water surveys to estimate average TTHM and individual THM concentrations. Analysis based on: (a) THM concentrations (3 or 10 exposure categories) (b) consumption during first trimester from interview (2 exposure categories)	Maternal age Gestational age Smoking History of pregnancy loss Ethnicity Employment	<b>High TTHM dose (≥5 glasses/day + ≥75 µg/l) <i>v</i> low dose (&lt;5 glasses/day + &lt;75 µg/l):</b> <i>Spontaneous abortion</i> 1.8 (1.1 to 3.0). <b>High BDCM dose (≥5 glasses/day + ≥18 µg/l) <i>v</i> low dose (&lt;5 glasses/day + &lt;18 µg/l):</b> <i>Spontaneous abortion</i> 3.0 (1.4 to 6.6)
Gallagher <i>et al</i> <sup>60</sup> (1998)	Colorado, USA 28 Census blocks in 2 water districts 1990–1993 Sample population: 1244 live births	72 Low birth weight 29 Term low birth weight 68 Preterm delivery	Based on maternal residential address and municipal water surveys. Estimate of household TTHM concentration during last trimester based on hydraulic modelling (4 exposure categories)	Maternal age Smoking Marital status Parity Education Employment Prenatal care	<b>High TTHM concentration (≥ 61 µg/l) <i>v</i> lowest (≤20 µg/l):</b> <i>Low birth weight</i> 2.1 (1.0 to 4.8) <i>Term low birth weight</i> 5.9 (2.0 to 17.0)
Dodds <i>et al</i> <sup>51</sup> (1999)	Nova Scotia, Canada 1988–95 Sample population: 49842 births	4673 Small for gestational age 2393 Low birth weight 342 Very low birth weight 2689 Preterm delivery 77 Neural tube 82 Cleft defect 430 Major cardiac defects 197 Stillbirth 96 Chromosomal abnormalities	Based on maternal residential address and TTHM concentrations for public water facilities (3 sampling locations) modelled with linear regression on the basis of observations by year, month, and facility (4 exposure categories)	Maternal age Parity Maternal smoking Attendance prenatal classes Neighbourhood family income Sex Pregnancy and predelivery weight	<b>0–49 µg/l <i>v</i> &gt;100 µg/l TTHMs</b> <i>Still birth</i> 1.66 (1.09 to 2.52) <i>Chromosomal abnormalities</i> 1.58 (0.73 to 2.59) <i>Small for gestational age</i> 1.08 (0.99 to 1.18) <i>Neural tube defects</i> 1.18 (0.67 to 2.10)
Klotz and Pynch <sup>56</sup> (1999)	New Jersey, US 1993–4 Sample population: All births, of which 112 cases and 248 controls were selected	112 Neural tube defects	Based on residential address and public water facility TTHM data, and tap water sampling for TTHMs, HANs, and HAAs (3–5 exposure categories)	Sociodemographics Pregnancy and medical history Parental occupational Use of vitamins	<b>TTHMs public monitoring data, Known residence and isolated cases &lt;5 µg/l <i>v</i> &gt;40 µg/l</b> <i>Neural tube defects</i> 2.1 (1.1 to 4.0)
Magnus <i>et al</i> <sup>47</sup> (1999)	Norway Sample population: 141077	2608 All birth defects 62 Neural tube defects 250 Major cardiac defects 91 Respiratory defects 122 Urinary defects 143 Oral cleft	Chlorination yes <i>v</i> no Colour high <i>v</i> low (in chlorinated water average TTHMs = 9.4 µg/l, average HAAs = 14.6 µg/l)	Maternal age Parity Geographical placement Population density Industry profile	<b>No chlorination low colour <i>v</i> chlorination high colour</b> <i>All birth defects</i> 1.14 (0.99 to 1.31) <i>Urinary tract defects</i> 1.99 (1.10 to 3.57) <i>Neural tube defects</i> 1.26 (0.61 to 2.62) <i>Major cardiac defects</i> 1.05 (0.76 to 1.46) <i>Respiratory tract defects</i> 1.07 (0.52 to 2.19)

tively few people (2.7%) were exposed to concentrations  $<25 \mu\text{g/l}$ , reducing the contrast in exposure across the study region. Other studies have found positive associations within the range of the lowest exposure category (0–49  $\mu\text{g/l}$ )

#### USE OF ROUTINELY COLLECTED THM MEASUREMENTS AND ESTIMATION OF INDIVIDUAL THM INGESTION AS EXPOSURE INDEX

More detailed studies have incorporated both ecological and individual estimates in their assessment of exposure.<sup>52 53 56</sup> Routinely collected concentrations of THMs were combined with consumption and activity data, obtained from a questionnaire or interview, to estimate the person's ingested THM concentrations or showering and swimming habits or both.

Savitz *et al*<sup>52</sup> carried out a population based case control study in North Carolina to study various water indices (water source, number of glasses a day, TTHM concentration, TTHM ingested dose) relative to low birth weight ( $<2500 \text{ g}$ ), preterm delivery ( $<37 \text{ weeks}$ ), and spontaneous abortion. No information was given on how the TTHM concentrations were obtained exactly. The authors reported some underascertainment of spontaneous abortion related to social class and a sizeable fraction of non-respondents. They found a lower risk for all three outcomes with an increasing number of glasses of water consumed per day for which no clear explanation was offered. Moreover, they found a significant excess risk (OR 1.7, 95% CI 1.1 to 2.7) for spontaneous abortion with a 50  $\mu\text{g/l}$  increment in TTHMs as a continuous variable, but not with exposure categories. No consistent associations were reported between the other water indices and outcomes, although there was some indication of a non-significant excess risk of low birth weight with higher TTHM concentrations with TTHM categories, but not with the 50  $\mu\text{g/l}$  increment in TTHM or the ingested estimated dose. The main limitations of the study were the underascertainment of spontaneous abortions and the assessment of exposure. For example, only water consumption was taken into account and the potential for exposure through other routes was not explored, and there were no analyses for the individual THMs. Also, although quarterly average THM values for each area were assigned to a person thereby allowing for changes in THM concentrations over time, the questionnaire was only presented once, so no information on changes in water consumption during pregnancy were available.

Waller *et al*<sup>53</sup> carried out a prospective cohort study of spontaneous abortion (pregnancy loss at  $<20 \text{ weeks}$  gestation) in three regions of California with routinely collected individual and total THM data from drinking water companies (averaged measurements over first trimester). Tap water consumption at home and subject information (outcome and personal characteristics) were also obtained by telephone interview. A companion paper by Swan *et al*<sup>54</sup> had analysed water consumption

relative to spontaneous abortion and found an excess risk in spontaneous abortion with an increase in water consumption in one out of the three regions studied. In the study of Waller *et al*<sup>53</sup> women with a high intake of TTHMs ( $\geq 5$  glasses a day and  $\geq 75 \mu\text{g/l}$  TTHM) showed a higher risk (OR 1.8, 95%CI 1.1 to 3.0) of spontaneous abortion compared with women with a low intake of TTHMs ( $<5$  glasses a day and  $<75 \mu\text{g/l}$  TTHM), in particular when they were not employed outside the home (OR 3.0 95%CI 1.2 to 7.9), but there were differences between regions in risks. Analyses of the person's THMs showed an association with high bromodichloromethane intake only ( $\geq 5$  glasses a day and  $\geq 18 \mu\text{g/l}$ ) and not with any of the other THMs (OR 3.0, 95%CI 1.4 to 6.6). There was no association between swimming or showering and spontaneous abortion, and information on bathing was not available. The strengths of this study include its prospective nature, which avoided recall and selection bias, the high ascertainment of pregnancy outcomes (99%), the use of total and individual THM data and the wide range of exposures. Activities such as washing dishes and clothes, and bathing were not included, however, and analyses were limited by the use of a dichotomous exposure index, and the lack of a total THM index combining information on ingestion, showering, and swimming. This issue was set out in a letter to the editor by Waller and Swan.<sup>55</sup> They calculated a total TTHM index by combining information on ingestion of TTHM and showering (with various assumptions) and used this index in their analysis. This analysis resulted in an unadjusted OR for spontaneous abortion of 1.1 (95%CI 0.7 to 1.7). It is possible that the association is attenuated by exposure misclassification—for example, by making the wrong assumptions or because TTHMs act as a proxy for other substances—such as non-volatile DBPs.

Klotz and Pynch<sup>56</sup> carried out a population based case-control study in New Jersey during 1993 and 1994 to determine the relation between public monitoring data of THM and estimates of THM, HAN, and HAA in tap water and neural tube defects. They ascertained 112 eligible cases and 248 controls. They excluded term births weighing  $<2500 \text{ g}$  as well as infants with other defects. They obtained data on—for example, demographics, pregnancy, and medical history, parental occupation, ingestion of tap water, showering, bathing, and swimming patterns. The strongest relation was found between public data from monitoring TTHM and isolated cases of neural tube defects with known residency at conception (OR 2.1 95%CI 1.1 to 4.0 for  $<5 v >40 \mu\text{g/l}$ ). The results were not disproportionately attributable to chloroform or brominated THMs. Only a slight, but not significant, excess risk was found for HANs and HAAs and neural tube defects, and there was no association between showering, bathing, and swimming and neural tube defects. No changes were found when ingested doses were calculated and used.



## Discussion

Relatively few toxicological and epidemiological studies have been carried out examining the effects of DBPs on reproductive health outcomes. The main outcomes of interest so far have been low birth weight, preterm delivery, spontaneous abortions, stillbirth, and birth defects—mainly central nervous system, respiratory, major cardiac, oral cleft, and neural tube defects. Various toxicological and epidemiological studies point towards an association between THMs and low birth weight,<sup>14 15 17 46 48–50 52</sup> although the evidence is not conclusive. Administered doses in toxicological studies have been high and even though epidemiological studies have mostly shown excess risks, these were often not significant and the assessment of exposure was often limited. A recent large epidemiological study found no association with birth weight, but exposures seemed to be relatively high and there was a limited contrast in exposure.<sup>51</sup> Evidence of associations for other outcomes—such as spontaneous abortions, stillbirth, and birth defects from epidemiological studies is weaker but gaining ground, although there is no evidence for an association between THMs and preterm delivery.<sup>47–53 56</sup> Waller *et al*<sup>53</sup> showed a twofold to threefold excess risk of spontaneous abortion relative to ingestion of THMs, in particular bromodichloromethane, in a well designed and conducted study, but found no associations for other routes of uptake such as swimming and showering. This is surprising given their potential importance for uptake of THMs,<sup>4 58 59</sup> but may also point towards THMs being a proxy for, for example, non-volatile DBPs such as HAAs for which ingestion seems to be the major route of uptake.<sup>8 60</sup> Savitz *et al*<sup>52</sup> found a much weaker non-significant association for THMs and spontaneous abortion with categorical data, although this may reflect a weaker study.

A large epidemiological study by Dodds *et al*<sup>51</sup> found an excess risk of stillbirth with higher THM concentrations, but Bove *et al*<sup>49</sup> found no excess risk of stillbirth. Aschengrau *et al*<sup>45</sup> found no excess risk for stillbirth when comparing ground or mixed water with surface water, but did when comparing chloraminated with chlorinated water. Aschengrau *et al*,<sup>45</sup> Bove *et al*,<sup>49</sup> Dodds *et al*,<sup>51</sup> Magnus *et al*,<sup>47</sup> and Klotz and Pynch<sup>56</sup> showed excess risks for congenital defects, particularly for all defects,<sup>45 47 49</sup> neural tube defects,<sup>47 49 51 56</sup> and urinary defects.<sup>45 47</sup> Only two of the four studies on neural tube defects showed significant excess risk,<sup>49 56</sup> but the other two studies had either fairly low concentrations of DBPs<sup>47</sup> or almost no low concentrations of DBPs,<sup>51</sup> which resulted in more limited contrast in exposures and hence the reduced potential to detect increased risks. Chen and Sever<sup>57</sup> recently suggested a mechanism whereby chloroform could plausibly contribute to the formation of neural tube defects through inhibition of the use of folate in the conversion of homocysteine to methionine, whereas Hunter *et al*<sup>53</sup> found changes in neural tube development when they exposed mouse embryos to HAAs. Two

studies<sup>45 47</sup> included urinary defects and one central nervous system defects,<sup>49</sup> and all three found significantly increased risks. Evidence for an association between DBPs and major cardiac,<sup>47 49 51</sup> respiratory,<sup>45 47</sup> and oral cleft<sup>47 49 51</sup> defects is less clear with only one study for each defect showing a significant excess risk, but again two of the studies that showed no significant excess risk had either fairly low concentrations of DBPs<sup>47</sup> or almost no low concentrations of DBPs,<sup>51</sup> which reduced the contrast in exposures and hence the potential to detect increased risks. Still, for congenital malformations, stillbirth and spontaneous abortions there are potential problems with case ascertainment, completeness of the case register, confounding—for example, by other substances in the water, the lack of toxicological evidence (table 1), few cases for some defects, and the limited assessment of exposure—making the observed excesses in risk more difficult to interpret.

In animal tests THMs have generally shown no direct evidence of teratogenicity, but neural tube and craniofacial defects have been found with administration of dichloroacetic or trichloroacetic acid in rats,<sup>28</sup> and cardiac malformations have been induced at high doses of dichloroacetic acid.<sup>25</sup> Hunter *et al*<sup>53</sup> found changes in neural tube development when they exposed mouse embryos to HAAs. Several chloroacetonitrile compounds have shown an increase in malformations of the cardiovascular, digestive, soft tissue, and urinogenital systems.<sup>35 36</sup> 2-Chlorophenol has also been associated with subfertility and stillbirths.<sup>23</sup> The epidemiological studies have focused on THMs, at least as a marker of DBPs. Animal tests seem to show effects with DBPs other than THMs but this may still seem to provide some mechanistic support for some of the epidemiological findings on congenital malformations and stillbirth. However, the toxicological effects are found at high doses and should be interpreted with caution, in particular when extrapolating these results to humans. Toxicological studies test substances in isolation whereas in practice people are exposed to a mixture. It should also be noted that most substances were given by gavage, whereas humans show a different pattern of exposure and can also be exposed by inhalation and skin contact, particularly for THMs. It should also be noted that some toxicological studies showed effects on male reproduction, particularly sperm count, morphology and motility, but no epidemiological work has been undertaken in this area as far as we are aware.

As noted, one of the main limitations of the epidemiological studies to date has been the assessment of exposure. There are very real difficulties in making any accurate assessment of DBP exposure and uptake because of the potential for variation in concentrations of DBPs in different parts of the distribution system, at different times of the year, and as a consequence of individual differences in behaviour in the home and at work. The problem is further complicated by the lack of analytical data on most DBPs other than THMs, and the

fact that exposure to volatile DBPs will be increased by inhalation during showering, bathing, or swimming.<sup>3-8</sup> Clearly there is a need for better characterisation of exposure and the studies to date have used several approaches to overcome the difficulties with varying success. However, it seems reasonable to regard TTHMs, if used carefully, as a surrogate for the overall load of DBPs in the supply of drinking water, although the use of individual DBPs would be preferred. More work is needed to find if routinely collected data on TTHM are good markers for uptake of various DBPs. Various studies<sup>49-52 56</sup> used TTHM exposures, but several others have used individual THMs and showed independent effects, particularly for bromodichloromethane.<sup>48 53</sup> The largest proportion of TTHM is often chloroform but TTHM shows little correlation with the other THMs.<sup>50 61</sup> This suggests that when studies have used TTHM as an exposure index, they were most likely examining the effects of chloroform or other substances strongly correlated with TTHM or chloroform.<sup>49-52 56</sup>

In epidemiological studies where exposure estimates for total or individual THMs were used, generally only a few measurements (normally four a year) were available for each water zone. This makes it difficult to produce accurate and precise exposure estimates, in particular for pregnancy trimesters, given the temporal variation in concentrations of THM. A combination of measurement and modelling could potentially improve the assessment of exposure.<sup>50 51</sup>

As discussed already, humans are not only exposed to DBPs through drinking tap water. The THMs for example are volatile and can enter the body through inhalation or dermal absorption—for example, during swimming, bathing, or showering resulting in substantial uptake.<sup>3-8</sup> By contrast, for the main non-volatile DBPs, the HAAs, ingestion seems to be the major route of uptake.<sup>8 60</sup> This difference in routes of uptake may explain differences in epidemiological findings and potentially allows inferences about putative agents.<sup>52-56</sup> For the main THM, chloroform, exposure and estimated internal dose due to inhalation and dermal absorption of a 10 minute shower or a half hour bath are equivalent to the dose from ingesting 2 litres of tap water.<sup>6</sup> Uptake is temperature dependent. Dermal absorption during bathing is 30 times higher in water at 40°C than in water at 30°C.<sup>62</sup> Swimming provides a source of uptake—a 1 hour swim can result in a dose of 65 µg/kg/day, 141 times the dose from a 10 minute shower.<sup>5</sup> Food is also a possible source of exposure to chloroform. Exposure route is important for metabolism—ingested chloroform seems to be completely metabolised before entering the bloodstream, whereas doses from other routes seem to be distributed about the body in the bloodstream.<sup>6</sup> Differences in potentially biologically active dose depend on route, target organ, and whether it is the contaminant or a metabolite that is biologically active.<sup>6</sup>

Various studies have estimated patterns of water consumption (including tap water and

bottled water) and time spent showering or bathing, and showed considerable differences between people—for example, between men and women, employed and unemployed.<sup>63-69</sup> Ideally all this information on the determinants of DBP uptake would need to be taken into account when conducting an epidemiological study to reduce the potential for exposure misclassification and attenuation of risk estimates. This will include data on the variation in exposure concentrations and composition of DBPs, various exposure routes (ingestion, inhalation, or skin absorption), activity and consumption patterns including use of bottled water, boiled water, and private wells. However it is important to take repeated measurements. Most studies have used some kind of zonal exposure estimate which does not take into account consumption, showering, bathing, and swimming patterns,<sup>45-51</sup> two studies obtained information on consumption patterns,<sup>52 53</sup> one study obtained information on showering and swimming, but not bathing<sup>53</sup> and only one study<sup>56</sup> obtained information on all, but did not combine the information to calculate total exposure. Savitz *et al*<sup>72</sup> obtained information on use of private wells.

As well as THMs other substances occur in drinking water—for example, DBPs such as HAAs, haloacetonitriles, and hydroxyfuranones, along with inorganic elements and occasionally pesticides and solvents—of which some have been associated with reproductive outcomes<sup>40 45 49 70-79</sup> and could be potential confounders, but have not been taken into account in most epidemiological studies. Bove *et al*<sup>69</sup> and Aschengrau *et al*<sup>45</sup> made allowance for at least some of the other substances in water, although it was a limited number, and only one study, by Klotz and Pynch,<sup>56</sup> had estimates on HAAs and HANs.

A limitation of all the epidemiological studies to date has been that only THM exposures at home were taken into account and not those outside the home—for example, at work, where THM concentrations might be different, and this may lead to exposure misclassification. Water consumption outside the home can be considerable.<sup>66 67</sup> Waller *et al*<sup>63</sup> carried out separate analyses for women employed outside the home, and found that risk estimates for those employed outside the home were considerably lower than those at home, suggesting either attenuation of risk estimates as a result of misclassification of exposure or a confounding factor associated with the home (TTHM OR 3.0 95%CI 1.2 to 7.4 *v* OR 1.5 95%CI 0.8 to 2.7). Also, given that an American study found that >20% of pregnant women moved residence between the time of conception and delivery,<sup>80</sup> the possibility of confounding or risk attenuation from residential mobility during pregnancy cannot be ruled out.

Birth weight (low birth weight, growth retardation, or small for gestational age) is a relatively common and easy to ascertain outcome compared with, for example, birth defects, which makes it easier to study. Various studies have tried to categorise several exposures, which often leads to small numbers of

cases in the high exposure categories that are hard to interpret, in particular for birth defects.<sup>46 48-51 56</sup> Although categorisation of exposure leading to exposure-response relations is informative and important, there should be enough cases in the various categories to allow meaningful interpretation.

Little is known of which exposure period is likely to be the most important for the developing foetus for exposure to DBPs, although most studies have taken exposure measurements during the first trimester as being the most critical for structural abnormalities and spontaneous abortion,<sup>49 51-53 56</sup> and the last trimester as being important for growth retardation in utero.<sup>50 51</sup> Preconceptional or paternal exposure has not as yet been considered. This may be important, as subfertility effects—such as reduced sperm count and altered morphology—have been found in toxicological studies with HAAs, BDCM, and bromate, although only at high doses.<sup>26 27 29-32</sup> Also, epidemiological findings suggest that paternal occupational exposure may be related to spontaneous abortion.<sup>81</sup>

Maternal age was taken into account in all the studies as a potential confounder. Other potential confounders regularly included were ethnicity,<sup>45 49 52 53 56</sup> maternal smoking,<sup>46 48 50-53</sup> and alcohol intake.<sup>45 46 52</sup> Other potential confounders such as maternal occupational exposure or socioeconomic status were only considered occasionally or not at all, or for socioeconomic status, a surrogate such as education level was used. Some of these potential confounders are actually unlikely to be true confounders, because they are unlikely to be associated with the exposure indices, except perhaps for socioeconomic status. Some differences in consumption patterns seem to exist between socioeconomic classes.<sup>67 68</sup>

Although the available evidence suggests that the risks, if any, are small, the large numbers of people exposed to chlorinated water supplies means that the population attributable risk is potentially high. The inability to eliminate the possibility that other risk factors or possible biases might explain these small excess risks, coupled with the insufficient animal data to evaluate the biological mechanisms by which these agents may exert teratogenic and other birth effects, makes interpretation of such small increases in risks difficult. Moreover, many of these apparent associations have been found at TTHM concentrations well below the established maximum standards, currently at 100 µg/l in the United Kingdom and the United States. Reducing concentrations of chlorination DBPs further while still using chlorine becomes increasingly difficult. It must be remembered that the public health benefits of chlorination in terms of microbiological safety far exceed the potential health risks, but alternatives to chlorination should and are being explored—for example, the use of ozone.

### Recommendations

Toxicological assessments are invaluable as an initial step to help identify the specific compo-

nents which are of most aetiological concern to the developing foetus, and which may help to focus on the type of exposure measure needed. Although there are data on the reproductive toxicology of several of the byproducts, the data are by no means comprehensive. There is a need to prioritise DBPs for thorough reproductive and developmental toxicity testing, taking into account relevant exposure routes and data on pharmacokinetics and metabolism. Further research into the possibility of interactive effects of such compounds which commonly exist in chlorinated drinking water also needs to be carefully assessed.

Further epidemiological studies are recommended for reproductive outcomes such as low birth weight, stillbirth, spontaneous abortion, and birth defects—for example, heart defects, cleft lip, respiratory defects, urinary tract defects, neural tube defect, and central nervous system defects—and for studies of adult male fertility based on the current available toxicological and epidemiological evidence. Such studies should use appropriate designs such as a cohort study design for more common outcomes, or case-control study design for the rarer outcomes, with sufficient sample sizes, good case ascertainment, inclusion of relevant confounders, and in depth assessment of exposure. In practice this may not always be possible, partly due to the cost involved, but some of these issues could be investigated in subsets of the populations. Also differences in culture and water treatment should be considered. Most studies so far have been carried out in the United States, Canada, and Norway, and a United Kingdom study is needed to take into account specific factors in the United Kingdom.

Future epidemiological studies will remain relatively crude until assessment of exposure improves. Some of the factors that need to be considered are spatial and temporal variability in individual and total THMs and other byproducts, correlation between different substances, large samples where feasible, the relative contribution of different exposure routes (inhalation, ingestion, dermal absorption), consumption patterns (including tap water and bottled water, hot and cold drinks, and food) and daily activities including showering, bathing, and swimming. Although it is unlikely that a single study could be carried out taking into account all these factors, future studies need to try and minimise the potential for bias from these sources, possibly by carrying out more detailed exposure characterisation among a subset of the population. This should lead to a better understanding of the distribution and determinants of uptake of chlorination DBPs, and the design of statistical models to predict dose estimates for epidemiological and risk assessment studies.

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