Chlorination Disinfection By-products and Risk of Congenital Anomalies in England and Wales

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**Abbreviations:**

- **BDCM** bromodichloromethane
- **BINOCAR** British Isles Network of Congenital Anomaly Registers
- **CI** confidence interval
- **DBP** disinfection by-product
- **GIS** geographical information system
- **HAA** haloacetic acid
- **ICD** International Classification of Diseases
- **LCAR** local congenital anomaly register
- **NCAS** national congenital anomaly system
- **NTD** neural tube defect
- **ONS** Office for National Statistics
- **OR** odds ratio
- **SAHSU** Small Area Health Statistics Unit
- **THM** trihalomethane
- **TTHM** total trihalomethane
Outline

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ABSTRACT

BACKGROUND: Increased risk of various congenital anomalies has been reported associated with trihalomethane (THM) exposure in the water supply.

OBJECTIVES: Registry-based study of relationship between THM concentrations and risk of congenital anomalies in England and Wales.

METHODS: We obtained congenital anomaly data from the National Congenital Anomalies System, regional registries and national terminations registry, and THM data from water companies. Total THM (<30, 30-<60, 60+ µg/l), total brominated (<10, 10-<20, 20+ µg/l) and bromoform exposure (<2, 2-<4, 4+ µg/l) were modelled at place of residence for the first trimester of pregnancy. We included 2,605,226 live and still births and terminations with 22,828 cases of congenital anomalies. Analyses using fixed and random effects models were done for broadly defined groups of anomalies (cleft palate/lip, abdominal wall, major cardiac, neural tube, urinary and respiratory defects), a more restricted set of anomalies with better ascertainment, and for isolated and multiple anomalies. Adjustment was done for sex, maternal age, socio-economic status.

RESULTS: There were no statistically significant trends across exposure categories for either the broadly defined or more restricted sets of anomalies. For the restricted set of anomalies with isolated defects, there were significant (p<0.05) excess risks in the highest exposure categories of total THMs for ventricular septal defects, OR=1.43 (95% CI 1.00-2.04) and of bromoform for major cardiovascular defects and gastroschisis, OR=1.18 (95% CI 1.00-1.39) and OR=1.38 (95% CI 1.00-1.92) respectively.

CONCLUSION: This large national study found little evidence for a relationship between THM concentrations in drinking water and risk of congenital anomalies.
Introduction

Since chlorination disinfection by-products (DBPs) were first reported in drinking water (Rook 1974), there have been concerns about potential adverse reproductive health effects, including low birth weight, spontaneous abortion, still birth and congenital anomalies (Nieuwenhuijsen et al. 2000a), but findings of the studies to date have been inconsistent. Statistically significant positive associations have been reported between trihalomethane (THM) exposure and neural tube defects (Bove et al. 1995; Dodds and King 2001; Klotz and Pyrch 1999), major cardiac defects (Cedergren et al. 2002; Hwang et al. 2002), urinary tract defects (Aschengrau et al. 1993; Hwang et al. 2002; Magnus et al. 1999) and respiratory defects (Aschengrau et al. 1993; Hwang et al. 2002), while other studies did not find such associations (Dodds et al. 1999; Kallen and Roberts 2000; Shaw et al. 2003). Studies on oral cleft or cleft palate have largely been negative, except for the study by Bove et al. (1995). Only Dodds and King (2001) and Shaw et al. (2003) studied the effect of specific THMs. Dodds and King (2001) found a statistically significant association between bromodichloromethane (BDCM) and neural tube defects (NTDs), while Shaw et al. (2003) found a few statistically significant negative associations with NTDs and cleft lip and palate. One of the main limitations in most of these studies has been small sample size, resulting in low power to explore exposure-response relationships.

Here, in the largest study of its kind so far, we report the relationships between THM levels in the public water supply and risk of congenital anomalies across England and Wales. Primary analyses focused on total THM and broad categories of congenital anomalies; secondary
analyses focused on restricted subsets of anomalies, and specific THM groups including bromoform and brominated THMs.

**Methods**

*Study region and years*

The study area was covered by twelve water companies (estimated population) in the UK: United Utilities (formerly North West) (6.8 million), Severn Trent (7.6 million), Northumbrian (2.6 million), Anglian Water (4.0 million), Bristol (1 million), Dwr Cymru Cyfyngedig (3 million), Essex and Suffolk (1.7 million), Southern (2.2 million), South West (1.3 million), Thames Water (7.4 million), Three Valleys (2.4 million), Yorkshire (4.2 million) (Figure 1). Under regulations in force at the time the THM samples were taken, water companies divided their water supply into water supply zones, each zone covering a population of < 50,000 people. Less than 1% of households in the United Kingdom have private water supplies. The study area was chosen because it had considerable variation in THM concentrations between water zones and digital water zone boundaries were available within Geographical Information Systems (GIS). GIS data were available for the following years: Northumbrian, 1997, United Utilities, 1993-1997, and Severn Trent, 1993-1998 from a previous study in these areas (Toledano et al. 2005), and for all the companies for 1998-2001 directly provided by the water companies and checked by the study team. The main method of disinfection during the study period was chlorination with a few
regions having additional chloramination. Ozone was often used primarily for organics removal, but would have acted also as a disinfectant.

**Exposure data**

THM concentrations were used as the marker for chlorine disinfection byproducts in this study. Water samples are routinely collected and analysed from each water zone using random samples at the consumers’ tap. Under regulations in force at the time, the standard sampling frequency for THMs was a minimum of four samples per annum. However, if there was a breach of the standard of 100μg/l for total THMs, the sampling frequency increased to a minimum of 12 or 24 per annum depending on the zone size. Conversely, if the total THM concentration was consistently below 50% of the standard a reduced frequency of a minimum of one per annum could have been used.

Because of the small number of THM measurements in some water zones, the need for quarterly (3 monthly) estimates (to allow for trimester weighted exposure estimates), and the problem of measurements below the limit of detection, it was necessary to model the raw THM data to obtain more robust estimates of the mean THM concentration in each zone. This was done using a hierarchical mixture model in the software WinBUGS (Bayesian inference using Gibbs sampling) (Spiegelhalter et al. 1996), as described elsewhere (Whitaker et al. 2005). Briefly, modelling was carried out separately for each water company and year. The model calculated the mean annual individual THM concentrations for each water zone and subsequently assigned an estimated water source type to each water zone depending on the four THM levels.
within each zone. We fitted a three-component mixture model in which zones were assumed to belong to one or some mixture of three components that we labelled “ground,” “lowland surface,” and “upland surface” waters (the components may not strictly correspond to these three water source types; we simply aimed to group waters with similar THM profiles, which are more likely to be shared among water of the same source type). The hierarchical model enabled zones to “borrow” information from other zones with the same water source type. This resulted in more stable estimates for zones where few samples were taken. For measurements under the detection limit, we used our model to obtain an estimate between zero and the detection limit (rather than arbitrarily assigning half or two-thirds the detection limit, which is common practice). Seasonal variation was taken into account by estimating a quarterly effect common to all zones supplied by the same source type.

Congenital anomaly data

Individual postcoded records were extracted from the national births, stillbirths, terminations and congenital anomalies (National Congenital Anomalies System (NCAS)) registers held at the UK Small Area Health Statistics Unit (SAHSU). In addition, individual postcoded records were obtained from the regional registries via British Isles Network of Congenital Anomaly Registers (BINOCAR), which cover about fifty percent of the population of England and Wales (Figure 2). The data from the national and regional registries were merged to obtain one numerator database. Duplicate records across datasets were removed with regional registry records prioritised. National and regional registry region boundaries as defined by the Office for National Statistics (ONS) were used to delineate NCAS and BINOCAR regions. The main analyses focused on broad categories of congenital anomalies: cleft lip/palate (ICD-10
codes Q35-Q37); diaphragmatic hernia and abdominal wall defects (ICD-10 code Q79); major cardiac defects (ICD10 codes Q20-Q28); neural tube defects (ICD-10 codes Q00, Q01, Q05); urinary tract defects (ICD-10 codes Q60-Q64); and respiratory defects (ICD-10 codes Q30-Q34).

Further analyses were conducted using restricted groups of congenital anomalies that were considered to be etiologically coherent, with better ascertainment, defined as follows: abdominal wall defects (Q79.0, Q79.1, Q79.2, Q79.3), major cardiac defects (Q20, Q21.2, Q21.3, Q22, Q23, Q25.1-Q25.9, Q26), urinary tract defects (Q60, Q61, Q62, Q64 excluding Q62.0, Q64.8, Q64.9) and respiratory defects (Q33). In addition we conducted separate analyses for cleft palate (Q35), cleft lip with and without cleft palate (Q36 – Q37.99), exomphalos (Q79.2), gastroschisis (Q79.3), hypoplastic left heart syndrome (Q23.4), ventricular septal defects (Q21.0), and two subsets of urinary tract defects including renal disease (Q60 and Q61), and obstructive disease (Q62 and Q64). We also included congenital anomalies of the oesophagus (Q39) in these analyses. For earlier years (before 1995), we bridged ICD9 and ICD10 codes manually. Further analyses were conducted excluding cases with anomalies that were found to be part of a chromosomal syndrome (i.e. chromosomal anomalies, any mention of Q9), as well as examining those cases with isolated anomalies only.

The number of anomalies recorded per baby was known to vary across BINOCAR regions, with some regional registries more likely to register a more detailed number of minor anomalies for each baby than others. It was not considered appropriate, therefore, to classify all babies registered with one anomaly as ‘isolated’ and all those registered with more than one anomaly as having ‘multiple anomalies’. Instead, we devised an isolated/multiple classification that we judged to be largely unaffected by differential reporting of minor anomalies. First, we
compiled a list of all other major anomalies not already included in the study (i.e. Q11*, Q12*, Q13.0, Q41*, Q42*, Q54*, Q55.5, Q55.6, Q66.0, Q68*, Q71*, Q72*, Q89.3 (* = any number)). Classification was then undertaken for all broad and restricted category analyses as follows (with the exception of abdominal wall defects): babies were classified as ‘multiple’ if they had more than one anomaly that fell into more than one of the six broad categories (i.e. cleft lip/palate, abdominal wall, major cardiac, neural tube, urinary, respiratory) or if they had one (or more) anomalies from one of the six broad categories together with one (or more) from the list of additional major anomalies above. For abdominal wall anomalies and gastroschisis (Q79.3) and exomphalos only (Q79.2), classification of ‘multiple’ was as set out above, with the addition that, if more than one anomaly was registered from within the same broad abdominal wall category (Q7*), the baby was also classified as having ‘multiple’ anomalies. Thus, for a baby to be classified as having an ‘isolated’ abdominal wall anomaly, there could be only one abdominal wall code.

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

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

GIS methods and data linkage
A postcode to water zone link was created using point-in-polygon methods within the GIS to allocate each postcode to its water supply zone. Postcode locations were derived from the historical postcode file for Great Britain, developed by SAHSU. This file traces postcodes back in time and assigns a grid co-ordinate for each postcode in each year. To take account of changes in the location of both postcodes and water zone boundaries over time, a separate link was created for each year of the study period.

The postcode of the maternal residence at the year of birth was used to identify the water zone of interest and hence the appropriate exposure status for each birth record. The latter was obtained by first calculating a weighted average of the modelled quarterly THM estimates for the appropriate zone for the first 93 days of the pregnancy. For cases, a gestational age was generally available and the first 93 days of pregnancy was calculated. Where gestational age was missing we assigned the anomaly-specific average gestation weeks. The weighting was based on the proportion of the trimester falling into each quarterly period. Where the pregnancy was shorter than 93 days, for example for terminations, we used the whole pregnancy time period. For non-cases, we had to assume that births had gone to term when calculating the first 93 days of the pregnancy, as data on gestation weeks at birth are not recorded on the birth records. Finally, 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+ μg/l), total brominated THMs (<10, 10-<20 and 20+ μg/l) and bromoform (<2, 2-<4 and 4+ μg/l). These were chosen with reference to the published literature on the possible associations of birth
outcomes with THMs and with regard to the joint distribution of numbers of births and THM concentrations across the water regions.

Exclusions and study size

A total of 49,558 pregnancy outcomes, including 377 with congenital anomalies were excluded. The main reasons for exclusion were either that no exposure estimates were available and/or that lagging for the critical exposure period was not possible. This left 2,605,226 births, including live and still births and terminations, for analysis.

Statistical analyses

Using the statistical package R, we carried out descriptive analysis, and univariate and multiple logistic regression modelling with adjustment for potential confounders, as follows: maternal age (for which individual level information was available) categorised as <21, 21-25, 26-30, 31-35 and >35 years; socio-economic status categorised into quintiles of an areal deprivation index (Carstairs and Morris 1991) according to location of the postcode of maternal residence at the time of birth, using a combination of four indicators at the level of 2001 census output area: percentage of people with no car, in overcrowded housing, with head of household in social class IV or V, and percentage of men unemployed; year of birth; and registry (BINOCAR or NCAS region). Interactions between THM exposure and potential confounding variables were tested where appropriate.
We conducted analyses by individual BINOCAR/NCAS region, and tested for heterogeneity of risks associated with THM exposure across the BINOCAR/NCAS regions. We conducted analyses using both fixed effects and random effects models. Where there was significant (p<0.05) heterogeneity, results of the random-effects model was used to obtain an overall summary estimate of the effect of THM, allowing for heterogeneity in the region-specific estimates (Dersimonian and Laird 1986). Where there was no evidence of heterogeneity, we present the fixed effects models.

**Results**

*Descriptive statistics*

Table 1 and 2 describe THM concentrations by exposure categories and the correlation of the various individual THMs. Mean TTHM concentrations ranged from 16.4 µg/l in the lowest category to 72.2 µg/l in the highest. The highest correlations were seen between total brominated THMs and dibromochloromethane (0.93) and between TTHM and chloroform (0.90).

The prevalence of each broad congenital anomaly group by deprivation, sex, maternal age, and BINOCAR/NCAS region is shown in Table 3. The number of anomalies ranged from 1434 for respiratory defects to 8809 for major cardiac defects. There was higher prevalence of each anomaly comparing the most deprived to the most affluent areas. Prevalence in males and females was similar, except for cleft lip/palate and urinary tract 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 maternal age. The reported prevalence of each anomaly was substantially higher in the BINOCAR regions than the NCAS regions, reflecting better ascertainment. Rates also varied among the regional registries (not shown).

Regression models

Unadjusted (data not shown) 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 more restricted sets of anomalies. The only significant associations (p<0.05) with the broadly defined groups of anomalies was a deficit risk of abdominal wall defects in the high TTHM exposure category (OR=0.81, 95%CI 0.68-0.95) and 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) (Table 4). For the restricted set of isolated anomalies, there were 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). 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 (Figure 3).

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 (data not shown). Sensitivity analyses that excluded the NCAS data made little difference to the overall results.
Discussion

This is the largest study to date to study examine the relationship between THM exposure and congenital anomalies, and the first to examine the effects of bromoform on congenital anomalies and the effects of THM exposure on gastroschisis. This study found little evidence for a relationship between concentrations of THMs and a wide spectrum of congenital anomalies. There were no statistically significant exposure-response trends across the exposure categories for any of the anomalies studied. Statistically significant excess risks were seen for isolated anomalies only for ventricular septal defects and oesophageal anomalies in the highest and medium exposure categories, respectively, of TTHMs and for a subset of major cardiac defects and gastroschisis in the highest exposure category of bromoform. In the context of this study, these may have been chance associations; there is still little or no toxicological evidence for reproductive or teratogenic effects of bromoform, or other DBPs (Nieuwenhuijzen et al. 2000a), and the concentrations of bromoform across our study regions were generally very low, with only 19% of the population being exposed to levels above 4 µg/l (high exposure group). In the only other epidemiological study reporting bromoform levels, Savitz et al. (2006) found that mean level at their brominated DBP site (6.4 µg/l) was similar to the mean in our high exposure group; mean levels at their other two sites were also low (0.1 and 0.6 µg/l).

On the other hand, 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). Furthermore, Geter et al. (2005) suggested potential epigenetic effects of bromoform and potential mechanisms such as alteration in DNA methylation resulting in effects on cell proliferation/apoptosis, and increased homocysteine levels that could lead to
oxidative stress which also may feed into cell birth/cell death balance. Further study of these specific anomalies and bromoform exposure may be warranted.

Hwang et al. (2002) also found significant excess risks of ventricular septal defects, using color as a surrogate for DBP exposure. Adjusted odds ratios were 1.63 (95% CI: 1.02, 2.58) and 1.81 (95% CI: 1.05, 3.09) for the medium and high exposure categories respectively; and both Hwang et al. (2002) and Cedergren et al. (2002) found statistically significant associations between major cardiac defects and chlorinated water, and concentrations of TTHM above 10 μg/l. Other studies have reported no associations with cardiac defects (Bove et al. 1995, Magnus et al. 1997, Dodds et al. 1999, Dodds and King 2001, Shaw et al. 2003). Unlike our study, three studies reported significant positive associations between chlorinated water and urinary tract defects (Aschengrau et al. 1993, Hwang et al. 2002, Magnus et al. 1999) and two of three studies to date have found a significant positive association with respiratory defects (Aschengrau et al. 1993; Hwang et al. 2002). Klotz and Pyrch (1999) found a statistically significant association between TTHM and neural tube defects, but not with concentrations of haloacetonitriles and haloacetates. Also, the effects were most pronounced in offspring of women who did not take supplementary vitamins, but these findings were not replicated in the study by Shaw et al. (2003). Moreover, inclusion of information on ingestion, showering, bathing and swimming made little difference to the risk estimates (Klotz and Pyrch 1999). In a meta-analysis, Hwang and Jaakkola (2003) reported a significant association between chlorination by-products exposure and risk of neural tube and urinary system defects, but results for respiratory system, major cardiac and oral cleft defects were heterogeneous and inconclusive.
Various factors may have contributed to the lack of consistency between studies, including differences in exposure and outcome definitions, case ascertainment, exposure misclassification (due in part to the relatively crude methods of exposure assessment), differences in the composition of DBPs in the water supply, and low statistical power due to small sample size. Our study addressed a number of these weaknesses, specifically by paying careful attention to case definition and use of subsets of anomalies, the large sample size and use of modelled trimester-weighted THM exposure estimates to improve exposure classification. The next largest study included approximately 285,000 births and 5,764 cases of congenital anomalies (Hwang et al. 2002).

One of the main limitations of registry-based studies of congenital anomalies is that ascertainment is geographically variable and often incomplete. In the UK, NCAS ascertains only around 40% of the congenital anomalies compared to the BINOCAR registries (Boyd et al. 2005). We similarly found a substantial difference in prevalence rates between the NCAS and BINOCAR registries, and differences in prevalence rates between the various regional registries, which might reflect, in part, differences in methods of ascertainment and completeness of reporting (Rankin et al. 2005). In our study, analysis of just the BINOCAR data (where case ascertainment was higher) made little difference to the overall results. Variation in reporting rates is unavoidable when registration is not a statutory requirement unlike, for example, the registration of births or deaths, though some anomalies such as gastroschisis have good and consistent ascertainment across registries. Such geographical variations should not bias study results provided that completeness of reporting is unrelated to the exposure of interest. We used an isolated/multiple classification among a restricted set of anomalies to overcome differential reporting of minor anomalies, but there was some indication that this may have occurred. We
found opposing trends in NCAS regions -- where ascertainment was highest in the highest exposure categories -- and BINOCAR regions where ascertainment was lowest in the highest exposure categories (though no such trends were apparent for the brominated compounds). Whether such trends reflect differences in case definition or completeness of reporting across registries and exposure categories, and whether these may have led to important biases, is difficult to establish with any certainty.

Further limitations are the lack of information on mobility of women during pregnancy and gestation age which both may have led to exposure misclassification, and hence attenuation in risk estimates.

To take into account heterogeneity between regions served by different registries, we conducted the analyses separately for each registry and used meta-analysis to obtain summary odds ratios. If THMs are an imperfect proxy for other by-products then heterogeneity in risk estimates between regions might be expected, and a random effects model may be most appropriate. If the THMs are the substances of interest instead a fixed effects model may be the most appropriate. In our study, the choice of model made little difference to magnitude of the risk estimates, although the confidence intervals were slightly wider for random effects models.

Whilst one of the main strengths of our study is its size, this and its retrospective nature simultaneously limit the options available for exposure assessment. While the approach used here appears to provide valid estimates of THM exposure for epidemiological study (Keegan et al. 2001; Nieuwenhuijsen et al. 2000b; Toledano et al. 2005; Whitaker et al. 2003), the lack of association between THMs and congenital anomalies does not preclude the possibility of an
association at the individual level, or between other DBPs and congenital anomalies. THM concentrations may not be a good marker of other by-products (e.g. haloacetates) that have recently been implicated with respect to adverse birth outcomes (Hinckley et al. 2006, Porter et al. 2005; Wright et al. 2004). For example, we reported only a moderate correlation between THMs and haloacetic acids (HAAs) in parts of the study area (Malliarou et al. 2005). However, among more than 500 different DBPs that have been identified (Richardson 1998), THMs and HAAs are present in by far the greatest concentrations; others are present at much smaller concentrations, usually less than 1 µg/L.

Currently there is no plausible biological mechanism by which chlorination by-products could cause congenital anomalies, particularly at low concentrations. Nonetheless, the policy of minimising the concentrations of chlorination by-products in the public water supply by removing the natural organic precursors, while simultaneously maintaining the level of protection from disinfection, seems appropriate in view of concerns about possible adverse reproductive health effects (Nieuwenhuijsen et al. 2000a; 2000b). The World Health Organisation has continued to emphasise that high levels of protection from disinfection should never be compromised in trying to reduce disinfection by-product concentrations, and our data do not detract from that view.
References


Hinckley AF, Bachand AM, Reif JS. 2006. Late pregnancy exposures to disinfection by-products and growth-related birth outcomes. Environ Health Perspect 113:1808-1813.


Table 1. Characteristics of the trihalomethane exposure categories (µg/L)

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>sd</th>
<th>min</th>
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<td><strong>Total THMs</strong></td>
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<tr>
<td>Low</td>
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<td>Medium</td>
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<td>High</td>
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<td>10.1</td>
<td>60.0</td>
<td>130.9</td>
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<td>698</td>
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<tr>
<td><strong>Total Brominated THMs</strong></td>
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<td></td>
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<td>Low</td>
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<td>&lt;10.0</td>
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<td>Medium</td>
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<td>10.0</td>
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<td>High</td>
<td>28.3</td>
<td>8.4</td>
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<td>74.9</td>
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<tr>
<td><strong>Bromoform</strong></td>
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<tr>
<td>Low</td>
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<td>0.5</td>
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<td>&lt;2.0</td>
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<td>Medium</td>
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<td>6.7</td>
<td>3.2</td>
<td>4.0</td>
<td>51.8</td>
<td>491333</td>
<td>775</td>
</tr>
</tbody>
</table>

sd, standard deviation
min, minimum
max, maximum
n, number of live and stillbirths and terminations
nzones, number of water zones
Table 2. Pearson correlations between various species of trihalomethanes at water zone level

<table>
<thead>
<tr>
<th></th>
<th>Bromoform</th>
<th>Chloroform</th>
<th>DBCM</th>
<th>TBROM</th>
<th>TTHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDCM</td>
<td>-0.11</td>
<td>0.46</td>
<td>0.50</td>
<td>0.73</td>
<td>0.74</td>
</tr>
<tr>
<td>Bromoform</td>
<td></td>
<td>-0.44</td>
<td>0.61</td>
<td>0.54</td>
<td>-0.18</td>
</tr>
<tr>
<td>Chloroform</td>
<td></td>
<td></td>
<td>-0.30</td>
<td>-0.05</td>
<td>0.90</td>
</tr>
<tr>
<td>DBCM</td>
<td></td>
<td></td>
<td></td>
<td>0.93</td>
<td>0.12</td>
</tr>
<tr>
<td>TBROM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.38</td>
</tr>
</tbody>
</table>

BDCM  Bromodichloromethane

DBCM  Dibromochloromethane

TBROM  Total brominated species (BDCM, DBCM and bromoform)

TTHM  Total trihalomethanes
Table 3. Prevalence rates per 1,000 of various congenital anomalies by potential confounding variables

<table>
<thead>
<tr>
<th></th>
<th>Cleft lip/palate</th>
<th>Abdominal Wall</th>
<th>Major Cardiac</th>
<th>Neural Tube</th>
<th>Urinary Tract</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Terminations</td>
<td>(95%CI)</td>
<td>(95%CI)</td>
<td>(95%CI)</td>
<td>(95%CI)</td>
<td>(95%CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>2605226</td>
<td>3736 (1.39-1.48)</td>
<td>2267 (0.84 - 0.91)</td>
<td>8809 (3.31 - 3.45)</td>
<td>3334 (1.24 - 1.32)</td>
<td>5315 (1.99 - 2.10)</td>
</tr>
<tr>
<td>Deprivation quintiles:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (affluent)</td>
<td>425593 (1.31 - 1.53)</td>
<td>602 (0.61 - 0.77)</td>
<td>1302 (1.43 - 1.67)</td>
<td>470 (1.01 - 1.21)</td>
<td>777 (1.70 - 1.96)</td>
<td>202 (0.41 - 0.54)</td>
</tr>
<tr>
<td>2</td>
<td>442019 (1.22 - 1.44)</td>
<td>585 (0.61 - 0.76)</td>
<td>1419 (1.48 - 1.72)</td>
<td>483 (1.00 - 1.19)</td>
<td>830 (1.75 - 2.01)</td>
<td>203 (0.40 - 0.53)</td>
</tr>
<tr>
<td>3</td>
<td>475900 (1.27 - 1.49)</td>
<td>655 (0.70 - 0.86)</td>
<td>1580 (1.63 - 1.86)</td>
<td>603 (1.17 - 1.37)</td>
<td>909 (1.79 - 2.04)</td>
<td>278 (0.52 - 0.66)</td>
</tr>
<tr>
<td>4</td>
<td>514593 (1.32 - 1.52)</td>
<td>729 (1.05 - 1.24)</td>
<td>1880 (1.68 - 1.91)</td>
<td>724 (1.31 - 1.51)</td>
<td>1165 (2.14 - 2.40)</td>
<td>328 (0.57 - 0.71)</td>
</tr>
<tr>
<td>5 (deprived)</td>
<td>747001 (1.47 - 1.65)</td>
<td>1165 (0.89 - 1.03)</td>
<td>2626 (1.67 - 1.86)</td>
<td>1054 (1.33 - 1.50)</td>
<td>1633 (2.08 - 2.29)</td>
<td>422 (0.51 - 0.62)</td>
</tr>
<tr>
<td>Registry region:</td>
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<td></td>
</tr>
<tr>
<td>NCAS</td>
<td>1060401 (0.90 - 1.02)</td>
<td>1020 (0.48 - 0.57)</td>
<td>1322 (1.18 - 1.32)</td>
<td>905 (0.80 - 0.91)</td>
<td>1112 (0.99 - 1.11)</td>
<td>174 (0.14 - 0.19)</td>
</tr>
<tr>
<td>BINOCAR</td>
<td>1544825 (1.71 - 1.84)</td>
<td>2716 (1.07 - 1.18)</td>
<td>7487 (4.79 - 5.01)</td>
<td>2429 (1.53 - 1.65)</td>
<td>4203 (2.67 - 2.83)</td>
<td>1260 (0.78 - 0.87)</td>
</tr>
</tbody>
</table>
Table 3 continued

Maternal age:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Sample Size</th>
<th>Maternal Age</th>
<th>Abortions</th>
<th>Deaths</th>
<th>Survival</th>
<th>Autopsies</th>
<th>Misses</th>
<th>Miscarriages</th>
<th>Crude Rate</th>
<th>Deaths</th>
<th>Survival</th>
<th>Autopsies</th>
<th>Misses</th>
<th>Miscarriages</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;21 years</td>
<td>294135</td>
<td>1.33</td>
<td>925</td>
<td>431</td>
<td>1.47</td>
<td>635</td>
<td>2.16</td>
<td>170</td>
<td>0.58</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.20 - 1.46)</td>
<td>(2.95 - 3.35)</td>
<td>(1.33 - 1.61)</td>
<td>(2.00 - 2.33)</td>
<td>(0.50 - 0.67)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>21-25 years</td>
<td>550562</td>
<td>1.46</td>
<td>538</td>
<td>746</td>
<td>1.35</td>
<td>1122</td>
<td>2.04</td>
<td>289</td>
<td>0.52</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.37 - 1.57)</td>
<td>(2.79 - 3.08)</td>
<td>(1.26 - 1.46)</td>
<td>(1.92 - 2.16)</td>
<td>(0.47 - 0.59)</td>
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</tr>
<tr>
<td>26-30 years</td>
<td>819488</td>
<td>1.26</td>
<td>514</td>
<td>1034</td>
<td>1.24</td>
<td>1555</td>
<td>1.90</td>
<td>398</td>
<td>0.49</td>
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<tr>
<td></td>
<td></td>
<td>(1.19 - 1.34)</td>
<td>(2.66 - 2.89)</td>
<td>(1.16 - 1.32)</td>
<td>(1.81 - 1.99)</td>
<td>(0.44 - 0.54)</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-35 years</td>
<td>660909</td>
<td>1.30</td>
<td>410</td>
<td>1903</td>
<td>1.22</td>
<td>1201</td>
<td>1.82</td>
<td>320</td>
<td>0.48</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.22 - 1.39)</td>
<td>(2.75 - 3.01)</td>
<td>(1.14 - 1.31)</td>
<td>(1.72 - 1.92)</td>
<td>(0.43 - 0.54)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;35 years</td>
<td>274106</td>
<td>1.56</td>
<td>253</td>
<td>1109</td>
<td>1.19</td>
<td>551</td>
<td>2.01</td>
<td>197</td>
<td>0.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.42 - 1.71)</td>
<td>(3.82 - 4.29)</td>
<td>(1.07 - 1.33)</td>
<td>(1.85 - 2.18)</td>
<td>(0.63 - 0.83)</td>
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<td></td>
<td></td>
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</tbody>
</table>

Sex of baby:

<table>
<thead>
<tr>
<th>Sex</th>
<th>Sample Size</th>
<th>Abortions</th>
<th>Deaths</th>
<th>Survival</th>
<th>Autopsies</th>
<th>Misses</th>
<th>Miscarriages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1332251</td>
<td>1034</td>
<td>408</td>
<td>1232</td>
<td>196</td>
<td>1134</td>
<td>159</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.73 - 0.82)</td>
<td>(0.28 - 0.34)</td>
<td>(0.87 - 0.98)</td>
<td>(0.13 - 0.17)</td>
<td>(0.80 - 0.90)</td>
<td>(0.10 - 0.14)</td>
</tr>
<tr>
<td>Female</td>
<td>1265381</td>
<td>722</td>
<td>343</td>
<td>1092</td>
<td>226</td>
<td>539</td>
<td>134</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.53 - 0.61)</td>
<td>(0.24 - 0.30)</td>
<td>(0.81 - 0.92)</td>
<td>(0.16 - 0.20)</td>
<td>(0.39 - 0.46)</td>
<td>(0.09 - 0.13)</td>
</tr>
</tbody>
</table>

Information on sex of baby was unavailable for terminations (2636, 12%) and was not provided for all cases from LCARs (13085, 57%)
Table 4. The number of cases, adjusted overall odds ratio (OR) and 95% confidence intervals (CI) for various congenital anomalies by TTHM category

<table>
<thead>
<tr>
<th>TTHM category:</th>
<th>Cleft lip palate:OR</th>
<th>Abdominal wall defects:OR</th>
<th>Major cardiac defects:OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>OR</td>
<td>(95%CI)</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1482</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>1505</td>
<td>0.97</td>
<td>(0.88 - 1.05)</td>
</tr>
<tr>
<td>High</td>
<td>530</td>
<td>0.94</td>
<td>(0.83 - 1.06)</td>
</tr>
<tr>
<td>TBROM category:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1242</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>1570</td>
<td>0.98</td>
<td>(0.89 - 1.06)</td>
</tr>
<tr>
<td>High</td>
<td>705</td>
<td>0.96</td>
<td>(0.86 - 1.07)</td>
</tr>
<tr>
<td>BF category:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2206</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>697</td>
<td>1.06</td>
<td>(0.96 - 1.18)</td>
</tr>
<tr>
<td>High</td>
<td>614</td>
<td>1.01</td>
<td>(0.88 - 1.16)</td>
</tr>
</tbody>
</table>
Table 4 continued

<table>
<thead>
<tr>
<th></th>
<th>Neural tube defects:OR</th>
<th>Urinary tract defects:OR</th>
<th>Respiratory defects:OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. OR (95%CI)</td>
<td>No. OR (95%CI)</td>
<td>No. OR (95%CI)</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>Cases</td>
<td>Cases</td>
</tr>
<tr>
<td>TTHM category:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1466 1.00 (0.85 - 1.13)</td>
<td>2019 1.00 (0.91 - 1.23)</td>
<td>664 1.00 (0.86 - 1.11)</td>
</tr>
<tr>
<td>Medium</td>
<td>1437 0.98 (0.85 - 1.14)</td>
<td>2320 1.06 (0.98 - 1.20)</td>
<td>588 0.98 (0.87 - 1.46)</td>
</tr>
<tr>
<td>High</td>
<td>421 0.91 (0.73 - 1.13)</td>
<td>724 0.94 (0.78 - 1.14)</td>
<td>121 1.00 (0.80 - 1.26)</td>
</tr>
<tr>
<td>TBROM category:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1226 1.00 (0.85 - 1.14)</td>
<td>1718 1.00 (0.98 - 1.20)</td>
<td>535 1.00 (0.87 - 1.46)</td>
</tr>
<tr>
<td>Medium</td>
<td>1446 0.98 (0.79 - 1.03)</td>
<td>2412 1.05 (0.89 - 1.25)</td>
<td>264 1.09 (0.80 - 1.49)</td>
</tr>
<tr>
<td>High</td>
<td>652 0.90 (0.89 - 1.25)</td>
<td>933 1.05 (0.89 - 1.25)</td>
<td>264 1.09 (0.80 - 1.49)</td>
</tr>
<tr>
<td>BF category:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2074 1.00 (0.84 - 1.22)</td>
<td>3361 1.00 (0.92 - 1.11)</td>
<td>896 1.00 (0.91 - 1.27)</td>
</tr>
<tr>
<td>Medium</td>
<td>663 1.01 (0.83 - 1.11)</td>
<td>921 1.01 (0.78 - 1.18)</td>
<td>291 1.07 (0.81 - 1.23)</td>
</tr>
<tr>
<td>High</td>
<td>587 0.96 (0.83 - 1.11)</td>
<td>781 0.96 (0.83 - 1.11)</td>
<td>186 0.98 (0.78 - 1.23)</td>
</tr>
</tbody>
</table>
TTHM category (low, <30µg/l; medium 30-60 µg/l; high, >60µg/l), TBROM category (low, <10µg/l; medium 10-20 µg/l; high, >20 µg/l) and BF (low, < 2µg/l; medium 2-4 µg/l; high, >4µg/l).

Overall summary estimates obtained from meta-analysis combining the registry-specific exposure odds ratios adjusted for Carstairs deprivation quintile, year, water company and mother’s age.

The meta-analyses incorporated random effects where necessary to allow for heterogeneity between registries.
Figure legends

Figure 1
Regions covered by water companies included in the analyses.

Figure 1, footnote: The white areas are areas not included in the study.

Figure 2
Regions covered by regional congenital anomalies registries

Figure 3
Adjusted overall odds ratios and 95% confidence intervals for various isolated congenital anomalies by total trihalomethane categories (low <30, medium, 30-<60, high 60+ µg/l), total brominated trihalomethane categories (low <10, medium 10-<20, high 20+µg/l) and bromoform categories (low <2, medium 2-<4, high 4+µg/l), England and Wales, 1993-2001.

Footnote Figure 3
Overall summary estimates obtained by combining the registry-specific exposure odds ratios (using a random effects model allowing for heterogeneity between registries indicated by *; or using a fixed effects model where there was no evidence of heterogeneity), adjusted for deprivation quintile, year, water company and maternal age.

The odds ratios are presented for the medium and high exposure category with the low exposure category as the reference group.
n  number of cases in each anomaly group

Isolated  -- see Methods

CLP  Broad category of cleft lip and palate
CPP3  Restricted group of cleft lip and palate with cleft lip
CLP3  Restricted group of cleft palate
AWD  Abdominal wall defects
EXO3  Exomphalos
GAS3  Gastroschisis
MCD  Major cardiac defects
MCD2  Restricted group of major cardiac defects
HYP3  Hypoplastic left heart syndrome
VSD  Ventricular septal defects
NTD  Neural tube defects
UTD  Broad category of urinary tract defects
UTD2  Restricted category of urinary tract defects
ORD3  Obstructive urinary defects
XRD3  All renal defects
RSD  Broad category of respiratory defects
RSD2  Restricted category of respiratory defects
CMO  Congenital anomaly of the oesophagus