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Trihalomethanes in public drinking water and stillbirth and low birth weight rates: an intervention study

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ABSTRACT

During 2003–2004, United Utilities water company in North West England introduced enhanced coagulation (EC) to four treatment works to mitigate disinfection by-product (DBP) formation. This enabled examination of the relation between DBPs and birth outcomes whilst reducing socioeconomic confounding. We compared stillbirth, and low and very low birth weight rates three years before (2000–2002) with three years after (2005–2007) the intervention, and in relation to categories of THM change.

We created exposure metrics for EC and trihalomethane (THM) concentration change (n = 258 water zones). We linked 429,599 live births and 2279 stillbirths from national birth registers to the water zone at birth. We used Poisson regression to model the differences in birth outcome rates with an interaction between before/after the intervention and EC or THM change.

EC treatment reduced chloroform concentrations more than non-treatment (mean -29.7 μg/l vs. -14.5 μg/l), but not brominated THM concentrations. Only 6% of EC water zones received 100% EC water, creating exposure misclassification concerns. EC intervention was not associated with a statistically significant reduction in birth outcome rates. Areas with the highest chloroform decrease (30 – 65 μg/l) had the greatest percentage decrease in low -9 % (-12, -5) and very low birth weight -16% (-24, -8) rates. The interaction between before/after intervention and chloroform change was statistically significant only for very low birth weight, p = 0.02. There were no significant decreases in stillbirth rates.

In a novel approach for studying DBPs and adverse reproductive outcomes, the EC intervention to reduce DBPs did not affect birth outcome rates. However, a measured large decrease in chloroform concentrations was associated with statistically significant reductions in very low birth weight rates.

1. Introduction

Disinfection by-products in drinking water result from a chemical reaction between treatments such as chlorination and organic and inorganic matter in the water (Rook, 1974). DBPs include over 600 different species such as trihalomethanes (THMs), haloacetic acids (HAAs) and nitrosamines (Richardson et al., 2007). Toxicological studies suggest that some DBPs may cause adverse reproductive effects in animals, albeit at concentrations several orders of magnitude greater than those to which humans are exposed to in tap water (Colman et al., 2011; IPCS, 2000; Tardiff et al., 2006). Meta-analyses report that exposure to some of the individual THMs is associated with increased stillbirth risk (Nieuwenhuijsen et al., 2010, whilst exposure to total THMs (TTHM) is associated with an increased risk of small-for-gestational age (SGA), but not low birth weight, term low birth weight or preterm delivery (Grellier et al., 2010). However, evidence remains inconclusive as both meta-analyses included few studies (n = 5 and n = 6 respectively), and recent studies report mixed results for associations between THMs and preterm delivery (Kumar et al., 2014; Patelarou et al., 2011; Rivera-Núñez and Wright, 2013b; Villanueva et al., 2011) and foetal growth outcomes (Danileviciute et al., 2012; Grazuleviciene et al., 2011; Horton et al., 2011; Kumar et al., 2014; Levallois et al., 2012; Patelarou et al., 2011; Rivera-Núñez and Wright, 2013a, 2013b; Summerhayes et al., 2012; Villanueva et al., 2011).

Abbreviations: BDCM, bromodichloromethane; CI, confidence interval; DBCM, dibromochloromethane; DBP, disinfection by-product; EC, enhanced coagulation; GIS, Geographical Information System; HAA, haloacetic acid; ID, Indices of Deprivation; SGA, small-for-gestational age; Tbrom THM, total brominated THM; THM, trihalomethane; TTHM, total trihalomethanes.

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In North West England, United Utilities supplies drinking water to almost 7 million customers. A previous study found a 20% statistically significant excess risk of stillbirth, low birth weight and very low birth weight associated with high THM concentrations in the United Utilities water region in 1993–1997, the highest risk and THM concentrations of the three regions investigated (Toledano et al., 2005). During 2003 and 2004, United Utilities changed their treatment methods, introducing enhanced coagulation (EC) to four treatment works. EC is a physical–chemical treatment process that improves the removal of DBP precursors in comparison to conventional coagulation, reducing DBP formation potential. United Utilities defines EC as the destabilisation of colloidal and organic matter in water under optimum conditions (United Utilities, 2004). This intervention provided a unique opportunity to study the possible impact of DBPs on adverse birth outcomes in the water region, since other risk factors such as potential socio-economic confounders were unlikely to change over a short period.

1.1. Objective

We compared stillbirth, low and very low birth weight rates three years before (2000–2002) with three years after (2005–2007) the EC intervention took place. We investigated change in rates in treatment areas with non-treatment areas acting as a control. Since THM concentrations may have changed for reasons other than the intervention, we also studied rate change between the time periods in areas of low, medium and high THM change.

2. Methods

2.1. Study population

We extracted all live and stillbirths within the United Utilities water region from 2000 to 2002 and 2005–2007 from the National Birth and Stillbirth Registers. Birth weight, maternal age, sex of baby, information on multiple births and maternal residence at birth postcode were available. Routine birth data in the UK does not contain information on gestation weeks, socioeconomic deprivation, or ethnicity, however, for descriptive purposes area-level 2001 Census data on deprivation and ethnicity were available. Stillbirth refers to foetal deaths after 24 completed weeks of gestation. Live births were categorised: normal (≥2500 g), low birth weight (<2500 g, i.e. including very low birth weight births) and very low birth weight (<1500 g).

2.2. Exposure assessment

United Utilities provided information on chloroform, bromodichloromethane (BDCM), dibromochloromethane (DBCM), bromoform and water zone boundaries for each water zone, 2002–2007. For regulatory purposes, a water zone is a designated supply area within which water quality should be approximately uniform and whose population does not exceed 100,000. In each water zone, geographically random samples must be collected on regular occasions (i.e. scheduled at similar dates and times each year), a minimum four times per annum. Between zone variation is greater than within zone variation for chloroform and BDCM but not DBCM (Keegan et al., 2001). Digital information on water zone boundaries plus THM data for 2000–2001 was available from a previous study (Nieuwenhuijsen et al., 2008). We linked water zone boundary information to THM concentrations using ARCMap, version 9.1 Geographical Information System (GIS). We excluded water zones with boundaries that had been incorporated into other water zones during 2000–2007 (n = 52), leaving 258 water zones for study.

We constructed two exposure metrics for each water zone. EC identified treatment status (No/Yes). We also calculated concentration change for TTHM (the sum of chloroform, BDCM, DBCM and bromoform), total brominated THMs (the sum of BDCM, DBCM and bromoform) and the individual THMs, based on the difference in average concentration in each water zone during the three years (2000–2002) before and the three years (2005–2007) after EC was introduced. We categorised TTHM concentration change to give distribution-based cutpoints as follows: areas with high TTHM decreases (30–65 μg/l), medium TTHM decreases (10–<30 μg/l), areas with low TTHM decreases/increases (decrease <10 μg/l to increase ≤10 μg/l) and, (Supplementary data 1 only), areas with moderate TTHM increases (11–26 μg/l). As the TTHM composition in England is dominated by chloroform, we used the TTHM category cutpoints for chloroform as well.

In order to assign the birth to the correct water zone where the majority of exposure would have occurred, we linked the postcode of maternal residence at birth to the water zone boundary in use during the year of birth using point-in-polygon methods in GIS. Births occurring during the first six weeks of the year were linked to the water zone boundary of the preceding year when the majority of the pregnancy (i.e. up to and including the majority of the third trimester), would have occurred, ensuring that the exposure metrics based on annual average THM data covered the entire pregnancy that may be relevant for stillbirth and the birth weight outcomes (Pedersen et al., 2013). We extracted 472,526 live births and 2631 stillbirths for the United Utilities region. Before linking to water zones, we excluded births during the first six weeks of 2000 (before) or 2005 (after) (n = 18,896 live, n = 102 stillbirths) and multiple births (n = 12,414 live, n = 190 stillbirths). A total of 441,216 live and 2339 stillbirths were available for exposure assessment. Of these, we georeferenced and linked 432,019 (98%) live births and 2293 (98%) stillbirths to 258 water zones. Finally, we excluded births in four water zones with a large chloroform increase 11–26 μg/l due to small numbers of stillbirths (n = 2420 live, n = 14 stillbirths), and births from the birth weight analyses with unreliable birth weights recorded i.e. <200 g (n = 895). This left 429,599 live births and 2279 stillbirths for the stillbirth analysis and 27,664 low, 4209 very low and 401,040 normal weight births in the birth weight analyses.

2.3. Analysis of socioeconomic confounders in water zones

We analysed income deprivation sub-scores from the English Indices of Deprivation (ID) at the water zone level to test the assumption that there was little change in socioeconomic factors between 2000–2002 and 2005–2007. At lower level super output area (a super output area is typically an aggregation of 4 to 6 census output areas and the lower level contains about 1500 people), ID were available for 2004 and 2007, based on data collected in 2001 and 2005 respectively (Noble et al., 2004, 2007) and covering 7 domains of deprivation. The income domain of the ID, reflecting means tested state-provided benefits, is expressed as a proportion, which we converted from super output area to water zone level using postcode-weighting methods (Briggs et al., 2008). For ID 2004, income was highly correlated with employment ($r = 0.90$) and the composite index of multiple deprivation that combines the 7 domains ($r = 0.96$) (Briggs et al., 2008). We calculated income deprivation scores for 'before' and 'after' intervention periods, as well as calculating income deprivation change from 2000–2002 to 2005–2007.

We also had deprivation information at a more refined resolution that has been calculated at the postcode sector level (Carstairs Index), but was only available for 2001 (Census is every 10 years) and would not capture change over time. We assigned each woman the Carstairs score for her postcode sector and used this in the descriptive statistics.

2.4. Statistics

We tested correlations between EC, THM, and income deprivation variables before and after the intervention, using Spearman's rho or Pearson's R as appropriate. We examined rates of stillbirth, low and

very low birth weight before and after the introduction of EC and used Poisson regression to model rate change as a rate ratio. We then modelled the differences in small-area rates before and after the intervention against THM concentration change categories. We assessed rate change modelled against tertiles of income deprivation change to check possible influence of income on birth outcome rates. Including the exposure variable in the model (i.e. EC, THM change, income deprivation change), could only estimate rates within the exposure categories regardless of time period; adding a before/after variable could allow for the estimation of average rate change between time periods but irrespective of exposure category. However, we needed to determine whether the rate changes were different for different exposure categories. Therefore, to estimate the difference in rates before and after the intervention and across the exposure categories, we used a term for interaction between before/after and each exposure. We tested the overall significance of the interaction term using the likelihood ratio test. Rate change is expressed as percentage change and was calculated as the exponential of the regression coefficient (i.e. rate ratio of after/before) minus 1 and multiplied by 100. We did not adjust for multiple testing. All analyses were conducted using R version 2.9.0 (R Development Core Team, 2008).

3. Results

3.1. Study population

Maternal age was a risk factor for all three outcomes. Women living in poorer areas (based on Carstairs Deprivation Index 2001 Carstairs and Morris, 1991) or areas with a higher non-white percentage were at greater risk of having a stillbirth, low or very low birth weight baby. Compared with male babies, females had a statistically significant lower risk of stillbirth before but not after and an increased risk of low birth weight in both periods (Supplementary data 2).

3.2. Socioeconomic confounders

There was a strong correlation between English ID income deprivation scores in water zones before and after the intervention ($r = 0.96$), with a mean change of 1.2% (±2.9%) between the periods. No correlation was observed between TTHM concentration change and income deprivation change ($r = 0.05$).

3.3. THM concentrations

Table 1 shows annual average THM concentrations for each year of the study, 'before' and 'after' average concentrations, and the distribution of THM change. There was an overall statistically significant reduction in TTHM, chloroform, total brominated THMs and BDCM concentrations. Categories of chloroform concentration change corresponded closely to average chloroform concentration before the intervention, but this was less so for BDCM and there was no such relationship for DBCM and bromoform (Supplementary data 3).

3.4. Effect of enhanced coagulation on THMs

3.4.1. TTHM

Of 258 water zones, 88 received EC treatment while 166 did not. Over the study period there was a background mean TTHM concentration decrease of 15.1 μg/l in non-EC water zones and a statistically significant greater mean decrease of 30.5 μg/l ($p = <0.01$) in EC water zones (Table 2). There was a statistically significant difference between the TTHM concentration change categories in the EC and non-EC water zones. 5.6% of water zones that changed to EC were in the high increase, or increase/decrease categories, compared with 48% of those that did not change ($p = <0.01$) (Supplementary data 1).

3.4.2. Individual THMs

TTHM change was strongly correlated with chloroform change ($r = 0.99$), but not total brominated THM change ($r = 0.07$). Water zones that changed to EC had statistically significantly greater chloroform reductions than water zones that did not (−29.2 vs. −14.0 μg/l, $p = <0.01$). BDCM, the brominated THM with the greatest chlorine incorporation, had borderline significantly greater reductions in EC compared with non-EC water zones (−1.4 vs. −1.0 μg/l, $p = 0.05$), but this was not the case for the other brominated THMs (Table 2).

Since the proportion of TTHM constituents changed over time (due to a greater decrease in chloroform than the brominated compounds) the final analyses focused on chloroform, the THM most affected by EC.

3.5. Enhanced coagulation intervention and birth outcome rates

Over the study period, stillbirth rates remained constant whilst those for low and very low birth weight decreased (Table 3). As expected, individual-level potential confounders infant sex, parity and maternal age did not affect the rates and unadjusted rates are presented. There were statistically significant overall reductions in low and very low birth weight, but not stillbirth rates in the after compared with the before period. However, there were no statistically significant interactions between before/after and change to EC (Table 3).

3.6. THM concentration change and birth outcome rates

For chloroform, the greatest percentage decrease in rate was in areas (intervention and non-intervention) with the highest chloroform decrease (30–65 μg/l): stillbirth −4% (−16, 8), low −9% (−12, −5) and very low birth weight −16% (−24, −8). However, the interaction between before/after and chloroform change was statistically significant only for very low birth weight, $p = 0.02$ (stillbirth $p = 0.62$; low birth weight $p = 0.29$) (Table 4). There were statistically significant differences in rate changes associated with some BDCM and DBCM concentrations, although there were no statistically significant interactions between before/after and changes in concentrations (Supplementary data 4 and 5).

Table 1
Annual average THM concentrations in United Utilities water zones per year, before (2000-2002) and after (2005-2007), and distribution of change (μg/l).

	THM concentrations: Mean (±SD)								THM change		
	2000	2001	2002	2005	2006	2007	Before (2000–2002)	After (2005–2007)	Mean (±SD)	Min	Max
TTHM	55.2 (22.8)	45.3 (19.4)	47.4 (20.3)	27.6 (8.1)	28.8 (8.5)	30.3 (9.7)	49.3 (5.2)	28.9 (1.4)	−20.4 (17.6)[a]	−64.7	25.4
Chloroform	43.3 (22.9)	35.3 (20.0)	37.2 (21.0)	18.3 (7.0)	19.8 (7.5)	20.1 (8.6)	38.6 (4.2)	19.4 (1.0)	−19.2 (17.6)[a]	−64.0	20.5
TbromTHM	11.8 (4.2)	9.9 (4.7)	10.3 (4.3)	9.3 (3.2)	9.0 (3.1)	10.2 (3.7)	10.7 (1.0)	9.5 (0.6)	−1.2 (2.5)[a]	−13.6	8.1
BDCM	8.4 (2.8)	6.9 (2.7)	7.2 (2.5)	6.2 (2.0)	6.1 (2.0)	6.8 (2.3)	7.5 (0.8)	6.3 (0.4)	−1.2 (1.7)[a]	−8.2	5.0
DBCM	2.5 (1.9)	2.5 (2.1)	2.4 (2.0)	2.4 (1.5)	2.1 (1.4)	2.6 (1.8)	2.5 (0.1)	2.4 (0.2)	−0.1 (1.0)	−5.4	3.2
Bromoform	1.0 (0.8)	0.5 (1.0)	0.6 (1.1)	0.7 (0.6)	0.8 (0.7)	0.8 (0.6)	0.7 (0.2)	0.8 (0.6)	0.1 (0.5)	−3.8	1.8

TTHM, total trihalomethane; Tbrom, THM total brominated trihalomethane; BDCM, bromodichloromethane; DBCM, dibromochloromethane.
In 258 water zones used for exposure assessment.
[a] $p < 0.01$.

Table 2
Distribution of THM concentration change (μg/l) by enhanced coagulation, United Utilities water region, 2000-2002 and 2005-2007.

THM	EC	Mean change (±SD)	Min	Percentile			Max	p-Value[a]
				25	50	75		
TTHM	No	−15.1 (17.3)	−64.7	−23.9	−9.8	−2.8	25.4	<0.01
	Yes	−30.5 (13.2)	−54.3	−38.5	−31.5	−23.3	17.1	
Chloroform	No	−14.0 (17.4)	−64.0	−24.3	−7.8	−1.4	20.5	
	Yes	−29.2 (13.2)	−53.4	−35.2	−31.3	−22.5	15.7	<0.01
Tbrom THM	No	−1.1 (2.5)	−9.6	−2.1	−0.8	0.2	8.1	
	Yes	−1.3 (2.6)	−13.6	−1.6	−1.0	0.0	1.5	0.42
BDCM	No	−1.0 (1.6)	−4.8	−2.0	−0.9	−0.2	5.0	
	Yes	−1.4 (1.7)	−8.2	−1.9	−1.3	−0.7	4.7	0.05
DBCM	No	−0.1 (1.0)	−3.2	−0.6	−0.1	0.5	3.2	
	Yes	0.1 (1.1)	−5.4	0.0	0.4	0.6	1.4	0.24
Bromoform	No	0.05 (0.5)	−3.8	0.1	0.2	0.2	1.8	
	Yes	0.04 (0.5)	−3.1	0.1	0.2	0.2	0.5	0.89

Mean changes based on difference of annual averages summed for 2000–2002 and 2005–2007in 258 water zones used for exposure assessment.
EC, enhanced coagulation; TTHM, total trihalomethane; Tbrom, THM total brominated trihalomethane; BDCM, bromodichloromethane; DBCM, dibromochloromethane.
[a] Welch two sample T-test for mean changes in EC and non-EC water zones.

4. Discussion

We found that the EC intervention to reduce DBPs did not lead to a corresponding reduction in rates of these outcomes. However, in areas (intervention and non-intervention) with a measured high decrease in chloroform concentrations, compared with low change in concentrations, we found reductions in low (4%) and very low birth weight (9%), statistically significant for the latter. Chloroform may be a proxy for other chlorinated DBPs, which may also have decreased proportionally, compared with the brominated compounds. Previous epidemiologic studies have reported statistically significant positive associations between TTHM, chloroform and BDCM and stillbirth (Dodds et al., 1999, 2004; King et al., 2000; Toledano et al., 2005), as has a meta-analysis (Nieuwenhuijsen et al., 2010). Spontaneous abortion has also been associated with TTHM (Waller et al., 1998, 2001) and BDCM (Savitz et al., 2006; Waller et al., 1998, 2001). Toxicological evidence suggests that exposure to chloroform and the brominated THM with greatest chlorine incorporation, BDCM, may result in pregnancy loss in rats (Bielmeier et al., 2007; Narotsky et al., 2011). We found a non-significant difference in stillbirth rates of 9% comparing areas with the greatest decrease with decrease/increase in chloroform concentrations, corresponding with the statistically significant positive association between TTHM and stillbirth reported in the meta-analysis (Grellier et al., 2010).

This is the first study to investigate the relation between chlorination DBPs and birth outcomes, using an intervention design to address potential residual confounding. The intervention design assumed that few social class factors changed over time. Based on aggregated census-level data, we also found temporal consistency in income deprivation, supporting the intervention as a method for controlling confounding by income. The income domain measures financial poverty and there may have been changes in other forms of deprivation (i.e. poor housing conditions), which could have influenced the rates. However, people experiencing multiple forms of deprivation almost always have very little income or other resources (Townsend, 1987), and income is a good proxy as it was highly correlated with the composite index of multiple deprivation (Briggs et al., 2008). There was no correlation between change in income deprivation and change in THM concentration, suggesting that these results are unlikely to be confounded by changes in deprivation, and this was supported by the sensitivity analysis. We had no information about any changes in ethnic composition due to migration over the 8 years of this study, and related biological and/or lifestyle factors may explain the differential rate changes.

Low birth weight rates were 4% lower in water zones with 30–65 μg/l chloroform decrease compared with lower decrease/increase, however, this was not statistically significant. This is similar to the excess risk for SGA of 1% (95% CI, 0 to 2%) per 10 μg/l reported in the meta-analysis, although there was no statistically significant excess risk for low birth weight or term low birth weight (Grellier et al., 2010). Very low birth weight rates were 9% lower in all water zones with 30–65 μg/l chloroform decrease compared with lower decrease/increase, however, only one study has reported an association between very low birth weight and TTHM, also in the United Utilities water region (Toledano et al., 2005). Although the epidemiological evidence is mixed, toxicological evidence suggests that chloroform exposure is a plausible cause of adverse foetal development, although only at high doses associated with foetal and maternal toxicity (Murray et al., 1979; Ruddick et al., 1983; Schwetz et al., 1974; Thompson et al., 1974).

Due to the legal requirement to register stillbirths and births, it is unlikely that local differences in registration could have led to the

Table 3
Effect of change to enhanced coagulation on stillbirth, low birth weight and very low birth weight rates, United Utilities water region, 2000–2002 and 2005–2007.

Outcome	EC	WZ	Before (2000–2002)			After (2005–2007)				p-Value[b]
			Live birth/ normal (%)	outcome (%)	Rates[a]	Live birth/ normal (%)	outcome (%)	Rates[a]	% change (95% CI)	
Stillbirth	All	254	198,990	1052	5.26 (4.95–5.59)	230,609	1227	5.29 (5.00–5.60)	0 (−2 to 9)	
	No	166	131,877 (66.3)	694 (66.0)	5.23 (4.85–5.64)	153,770 (66.7)	831 (67.7)	5.38 (5.02–5.75)	2 (−7 to 13)	
	Yes	88	67,113 (33.7)	358 (34.0)	5.31 (4.77–5.89)	76,839 (33.3)	396 (32.3)	5.13 (4.63–5.66)	−4 (−17 to 11)	0.50
LBW	All	254	185,500	13,314	6.70 (6.58–6.81)	215,540	14,350	6.24 (6.14–6.35)	−7 (−9 to −5)	
	No	166	123,052 (66.3)	8741 (65.7)	6.63 (6.49–6.77)	143,796 (66.7)	9441 (65.8)	6.16 (6.04–6.29)	−7 (−10 to −4)	
	Yes	88	62,448 (33.7)	4573 (34.3)	6.82 (6.63–7.02)	71,744 (33.3)	4909 (34.2)	6.40 (6.23–6.59)	−6 (−10 to −2)	0.75
VLBW	All	254	185,500	2032	1.08 (1.04–1.13)	215,540	2177	1.00 (0.96–1.04)	−8 (−13 to −2)	
	No	166	123,052 (66.3)	1332 (65.6)	1.07 (1.06–1.08)	143,796 (66.7)	1426 (65.5)	0.98 (0.98–0.99)	−8 (−15 to −1)	
	Yes	88	62,448 (33.7)	700 (34.4)	1.11 (1.10–1.12)	71,744 (33.3)	751 (34.5)	1.04 (1.03–1.04)	−7 (−16 to 3)	0.85

LBW: low birth weight; VLBW: very low birth weight; WZ: water zone; EC: enhanced coagulation; CI: confidence interval.
[a] Rates per 1000 for stillbirth and per 100 for LBW and VLBW, unadjusted.
[b] Likelihood ratio test for models with and without the interaction term between before/after and change to EC.

Table 4
Effect of change in chloroform concentrations on stillbirth, low birth weight and very low birth weight rates, United Utilities water region, 2000–2002 and 2005–2007.

Outcome	Chloroform change	WZ	Before (2000–2002)			After (2005–2007)				
			Live birth/ normal (%)	outcome (%)	Rates[a]	Live birth/ normal (%)	outcome (%)	Rates[a]	% change (95% CI)	*p*-Value[b]
Stillbirth	All	254	198,990	1052		230,609	1227			
	Low	96	65,618 (33.0)	333 (31.7)	5.05 (4.52–5.62)	75,218 (32.6)	401 (32.7)	5.30 (4.80–5.85)	5 (−9 to 20)	
	Medium	70	55,382 (27.8)	278 (26.4)	4.99 (4.42–5.62)	62,062 (26.9)	320 (26.1)	5.13 (4.58–5.72)	2 (−13 to 20)	
	High	88	77,990 (39.2)	441 (41.9)	5.62 (5.11–6.17)	93,329 (40.5)	506 (41.2)	5.39 (4.93–5.88)	−4 (−16 to 8)	0.62
LBW	All	254	185,500	13,314		215,540	14,350			
	Low	96	61,529 (33.2)	4050 (30.4)	6.18 (5.99–6.37)	70,628 (32.8)	4386 (30.6)	5.85 (5.68–6.02)	−5 (−9 to −1)	
	Medium	70	51,500 (27.8)	3812 (28.6)	6.89 (6.67–7.11)	57,889 (26.9)	4039 (28.1)	6.52 (6.32–6.73)	−5 (−9 to −1)	
	High	88	72,471 (39. 1)	5452 (40.9)	7.00 (6.81–7.18)	87,023 (40.4)	5925 (41.3)	6.37 (6.21–6.54)	−9 (−12 to −5)	0.29
VLBW	All	254	185,500	2032		215,540	2177			
	Low	96	61,529 (33.2)	626 (30.8)	1.01 (1.00–1.02)	70,628 (32.8)	666 (30.6)	0.93 (0.93–0.94)	−7 (−17 to 3)	
	Medium	70	51,500 (27.8)	564 (27.8)	1.08 (1.07–1.09)	57,889 (26.9)	661 (30.4)	1.13 (1.12–1.14)	4 (−7 to 16)	
	High	88	72,471 (39. 1)	842 (41.4)	1.15 (1.14–1.16)	87,023 (40.4)	850 (39.0)	0.97 (0.96–0.97)	−16 (−24 to −8)	0.02

LBW: low birth weight; VLBW: very low birth weight; WZ: water zone; EC: enhanced coagulation; CI: confidence interval; low increase ≤10/decrease <10 μg/l; medium decrease 10–<30 μg/l; high decrease 30–65 μg/l.
[a] Rates per 1000 for stillbirth and per 100 for LBW and VLBW, unadjusted.
[b] Likelihood ratio test for models with and without the interaction term between before/after and THM change categories.

differential changes in rates associated with decreases in chloroform concentration. In the low birth weight analysis we could not distinguish between babies who did not reach term (and were more likely to be of low birth weight) and those who did, or between babies of low birth weight due to constitution rather than growth restriction since we had no information on gestational age. Very low birth weight produced a clearer relationship with chloroform; this measure may be a preferred measure since the majority of such births are preterm, whilst the low birth weight classification mixes growth restricted and preterm births (Savitz et al., 2000).

Overall, routine maternity statistics suggest that there was a reduction in preterm delivery rates between the two periods at the geographical level of the North West region, in which United Utilities water region is located (Hospital Episodes Statistics, 2001–2010). This is in line with the overall reduction in low and very low birth weight rates that we observed regardless of water zone THM concentrations, and suggests an overall increase in gestational age. If the increase is uniform or randomly spread across the water zones, the relative difference in the percentage change of the low and very low birth weight rates between 'low chloroform change' and 'high chloroform change' water zones should not be affected. However, if the increase in gestational age was systematically only occurring in areas with low chloroform change or high chloroform change, this might lead to an underestimation or overestimation of the impact of chloroform change on these birth outcomes.

Our results for very low birth weight may be indicative of a relation between chloroform and preterm births. Although a previous meta-analysis found no association between TTHM and preterm birth (Grellier et al., 2010), 2 recent registry-based studies each with a sample size of more than 600,000, have found an association between preterm birth and water zone concentrations of chloroform (Rivera-Núñez and Wright, 2013b) and TTHM (Grazuleviciene et al., 2011). Although these studies, like ours, may be subject to misclassification due to their ecological design, chloroform may be a better proxy than TTHM for the exposure of concern, and due to considerable exposure variability in most studies it remains a good metric to achieve sufficient statistical power to detect small associations with a rare outcome. In a previous study chloroform (and, to a greater extent, BDCM) exposure was associated with asphyxia-related stillbirths (King et al., 2000), however, we did not have enough power for a cause-specific stillbirth analysis.

DBP uptake may occur through multiple pathways (Nieuwenhuijsen et al., 2000). There was no information available on the mothers' individual water use, and it is possible that water consumption patterns may have changed between the two periods, following publication of the 2005 study (Toledano et al., 2005). This would not result in exposure misclassification if all women reduced their water consumption as their relative exposure assessment would be correct. Furthermore, there was no correlation between SES and THM concentrations. However, had just those living in high THM concentration areas reduced their consumption then exposure misclassification would have occurred. The main route of exposure for the volatile THMs is through showering and bathing rather than through drinking (Villanueva et al., 2007; Whitaker et al., 2003), so we do not think this would have had any major impact on exposure to THMs that would be sufficient to affect rates of these birth outcomes. Future studies designed to assess individual exposure to THMs using DBP biomarker concentrations are warranted, although this is an area that requires further development (Savitz, 2012).

This is the first study to investigate the effect of changes to EC and reproductive outcomes. The introduction of EC resulted in a statistically significantly greater reduction in chloroform concentrations in comparison with areas where it was not introduced. There was a background reduction in chloroform concentration over the intervention period, which followed the introduction of the EC Drinking Water Directive, and may be due to greater awareness of THM control on the part of the water company. The intervention was not clear cut because few water zones (n = 15, 6%) were supplied by 100% EC water, and this may have limited our ability to detect differences in rate changes due to the intervention. This was one reason why we also studied actual THM concentration changes as well. Most water zones were mixed with traditionally treated water and the mixing of water was assumed to have occurred prior to entry into the zone. The percentages provided by the water company were approximations and not necessarily constant due to seasonal and operational variations. Greater reductions in rates of stillbirth (−9%, 95% CI −32 to 23), low (−10%, 95% CI −18 to −3) and very low birth weight (−13%, 95% CI −29 to 7) were found in areas with 100% EC water but were not statistically significant. United Utilities' EC process focuses on optimizing the chemical added (rather than just increasing the dose of coagulant), by ensuring that other factors such as timing of dose and pH are also optimal. Addition of the correct amount of chemical reduces the amount of sludge formed, and may therefore be a cost effective procedure (Campbell, 2011).

5. Conclusion

Our findings suggest a high decrease in chloroform concentrations is associated with a statistically significant reduction in very low birth weight rates. DBPs are a public health concern and future studies should focus on narrow outcome definitions such as cause-specific stillbirth or very low birth weight in order to increase specificity. DBP biomarkers need to be developed to improve exposure assessment to help elucidate the relation between THMs and these birth outcomes.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2014.08.006.

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