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Disinfection by-product exposures and the risk of musculoskeletal birth defects

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Background: Epidemiologic studies suggest that exposure to water disinfection by-products (DBPs) may increase the risk of certain birth defects. However, evidence for musculoskeletal defects (MSDs) is limited. Previous MSD studies have not examined DBPs beyond trihalomethanes (THMs) and have not separately examined limb or diaphragm defects which may have distinct developmental etiologies.

Methods: We calculated adjusted odds ratios (aORs) in a registry-based case-control study of birth defects in Massachusetts with complete quarterly 1999–2004 data on four THMs and five haloacetic acids (HAAs). We matched 10 controls each to 187 MSD cases based on week of conception. Weight-averaged town-level first-trimester DBP exposures were individually assigned based on residence at birth. We adjusted THM models for exposure to the sum of five HAAs (HAA5), and HAA models for the sum of four THMs (THM4).

Results: We detected positive exposure-response associations for all grouped MSDs with THM4 quintiles (aOR range: 1.90–3.18) and chloroform quartiles (aOR range: 1.30–2.21), and for reduction of upper or lower limbs with chloroform quartiles (aOR range: 2.39–3.52). We detected elevated aORs for diaphragmatic hernia with DBP9 (sum of THM4 and HAA5), and chloroform and bromodichloromethane tertiles and an exposure-response relationship for THM4 tertiles (aOR range: 1.67–1.80).

Conclusion: This is the first epidemiologic study to examine HAAs in relation to MSDs. Given the indirect nature of our exposure assessment data and small case numbers, the exposure-response relationships that we detected for THM4 and chloroform warrant further investigation.

Introduction

Annually in the United States ~6000 babies are born with musculoskeletal defects (MSDs)[1]; these include gastroschisis (birth prevalence: 1 in 2,229), upper limb reduction (1 in 2,869), lower limb reduction (1 in 5,949), diaphragmatic hernia (1 in 3,836), and omphalocele (1 in 5,386). The developmental events that lead to most MSDs are unknown[2,3] though some exogenous musculoskeletal teratogens have been established, such as thalidomide[4] and misoprostol.[5] Developmental toxicology studies testing exposures to water disinfection by-products (DBPs) in animals generally have not shown teratogenicity of trihalomethanes (THMs);[6–13] however, two older inhalation studies reported cleft palate in mice[14] and tail defects in rats.[15] Several animal studies with haloacetic acids (HAAs) have indicated cardiac or ocular teratogenicity,[13,16,17] with micro/anophthalmia associated with small orbit. Two animal studies with haloacetonitriles have reported reduced ossification and muscle growth in mice[18] and fused ribs and cervical ribs in rats.[19]

What this study adds

Most birth defects have unknown etiologies; thus, identifying environmental risk factors may offer potential intervention opportunities. Although prior research has found associations between birth defects and water disinfection by-products (DBPs), only five epidemiologic studies examined DBPs and musculoskeletal defects (MSDs), with all reporting some adverse associations for various exposure-outcome combinations. Our study is the first of MSDs to expand the range of exposures to nine specific DBPs, including four trihalomethanes and five haloacetic acids, generally the two most common DBP classes found in drinking water. This is also the first DBP study designed to examine limb defects and diaphragmatic hernia as distinct outcomes.

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Birth defects data were obtained from the Massachusetts Department of Public Health via. their vital records application process; our analyses are not immediately replicable by others due to the use of personally identifiable information.

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Epidemiologic evidence suggests that women exposed to elevated DBP levels have an increased risk of delivering babies with several types of birth defects,[20,21] though evidence for MSDs is limited. Only five previous epidemiologic studies of DBPs examined MSDs;[22–26] each focused on a different combination of MSDs and DBP metrics. These studies found some elevated associations for grouped or individual MSDs with different THM metrics, often the most common halogenated DBP class in treated water systems. Previous epidemiologic studies have not examined MSDs in relation to HAAs, generally the second most prevalent halogenated DBP class.

Although epidemiologic studies commonly use aggregate DBP metrics such as THM4 (sum of bromodichloromethane, dibromochloromethane, bromoform, and chloroform) as proxies for complex DBP mixtures, these limited exposure metrics are unlikely to capture all of the most toxicologically relevant DBPs. The use of such proxies may result in exposure misclassification, which can decrease the sensitivity of a study to detect associations. Due to high correlations between some DBPs in treated water systems, mutually adjusting for THMs and HAAs together might improve the ability to detect associations with specific DBPs.[27] Thus, there is a need to expand the scope of DBP metrics examined in epidemiologic studies beyond THM4 and to consider more complex DBP mixtures. Additionally, it remains unclear whether etiologies and environmental risk factors are shared among different MSDs, reinforcing the need to examine specific birth defect types rather than broad groups.[2,28] The objective of this registry-based case-control study was to examine the risk of five MSD outcomes in relation to first trimester exposures to nine individual and four summary DBP measures.

Methods

Study population and outcome data

We conducted a registry-based case-control study in 78 Massachusetts towns with populations >500 that had complete quarterly THM4 and HAA5 monitoring data from 1999–2004 and data on water source and disinfection type. We restricted the analysis to non-chromosomal birth defects. Cases and controls were singleton live births occurring from 22 to 44 gestational weeks and weighing ≥350 grams. Cases were identified from the Massachusetts Birth Defects Monitoring Program, and controls were sampled from birth records provided by the Massachusetts Department of Public Health.

MSD cases were identified based on the International Classification of Diseases 9th (ICD-9) revision. The outcomes we examined include all grouped MSDs (ICD-9 codes 754-756), reduction of upper or lower limbs (RULL; 755.20 and/or 755.30), reduction of upper limbs (RUL; 755.20), diaphragmatic hernia (DH; 756.6), and the grouped abdominal wall defects gastroschisis or omphalocele (GSOM; 756.79). We randomly selected and individually matched 10 controls without replacement from all live births in Massachusetts based on week of conception to maintain statistical efficiency while addressing potential time-varying confounding.[29,30]

Birth records from 2000 to 2004 were provided by the Massachusetts Department of Public Health and the Massachusetts Birth Defects Monitoring Program. This program collects data from 54 birthing hospitals, two tertiary care hospitals, and one specialty hospital. The registry system identifies and verifies birth defect cases up to 1 year after birth using birth certificates, fetal and infant death certificates, hospital discharge reports, hospital nurseries and neonatal units, and hospital surgical and pathology departments.

Exposure data

All DBP data were obtained from routinely collected monitoring data. Certified laboratories quantified THM concentrations using capillary column gas chromatography with EPA Method 502.2,[31] capillary column gas chromatography/mass spectrometry with EPA Method 524.2[32] and gas chromatography with electron capture detection with EPA Method 551.1.[33] HAA concentrations were quantified with EPA Methods 552.1[34] and 552.2[35] using gas chromatography and electron capture detection plus Standard Method 6251B[36] using micro liquid-liquid extraction gas chromatography. Detection limits ranged from 0.1 to 2.5 µg/L for the THMs and 0.4 to 5.0 µg/L for the HAAs, varying across laboratories and time. We assigned exposure scores of zero to participants with DBP levels below the detection limit and to those using untreated ground water (e.g., private wells).

Exposure assessment

We estimated exposures for nine individual DBPs and four DBP summary measures (bromodichloromethane [BDCM]; chloroform; dibromochloromethane [DBCM]; bromoform; dichloroacetic acid [DCAA]; trichloroacetic acid [TCAA]; monochloroacetic acid [MCAA]; dibromoacetic acid [DBAA]; and monobromoacetic acid [MBAA]) and four summary DBP metrics (THMBr [sum of BDCM, DBCM, and bromoform]; THM4; HAA5 [sum of DCAA, TCAA, MCAA, DBAA, and MBAA]; and DBP9 [sum of THM4 and HAA5]). We estimated week of conception for use in exposure assessment by subtracting clinical estimates of gestational age on birth records from date of birth. We averaged first-trimester DBP exposures across all sample locations within a public drinking water system based on quarterly (or more frequent data, when available) monitoring data assigned to maternal residential ZIP codes at birth. We derived first trimester exposure scores from month of birth and timing of the DBP samples, with temporally weighted averages calculated proportionally when multiple quarters overlapped the first trimester. For instance, an infant born at 38 gestational weeks in January of 2001 would have two first-trimester weeks that occurred in the first quarter of 2000 and the remaining 11 weeks occurring in the second quarter of 2000. Thus, their corresponding exposure score would be calculated as (2/13) times the average DBP concentration for the first quarter plus (11/13) times the average DBP concentration for the second quarter using data from the whole public water system.

Statistical analysis

We used SAS (version 9.4; SAS Institute, Inc., Cary, NC) for statistical analyses. We categorized maternal DBP exposures into tertiles, quartiles, or quintiles based on the exposure distribution among the controls. Because a large proportion of cases had concentrations assigned values of zero, bromoform, MCAA, MBAA, and DBAA were dichotomized at >0 µg/L, and DBCM was dichotomized at the 75th percentile. Births in the lowest DBP exposure category served as the referent. This categorical approach allowed us to evaluate non-linear relationships and heterogeneity across sub-groups based on stratified analyses. To limit the impact of sparse data bias[37] we do not present results for categories with fewer than five exposed cases for less prevalent DBPs.

We calculated Spearman correlation coefficients to compare DBP exposures. We used conditional logistic regression to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for each DBP metric. To assess confounding, we examined individual- and area-level covariates based on a priori knowledge from the source population and the available literature. Given the extensive individual-level covariates available from birth certificates, we also used an empirical >10% change-in-estimate approach to screen potential confounding variables, including type of water source and treatment, infant's sex, maternal weight gain during pregnancy, maternal race,

maternal age, maternal education, marital status (not married vs. married ≤300 days to birth), maternal smoking (cigarettes/day during pregnancy), parity, number of previous pregnancy terminations (elective and unintended), prenatal care payment source, trimester prenatal care began (first or after first), number of prenatal care visits, various clinical factors (abruptio placenta, anemia, cardiac disease, chronic or gestational diabetes, chronic or gestational hypertension, eclampsia, hemoglobinopathy, hepatitis, hydramnios/oligohydramnios, incompetent cervix, complications during labor or delivery, labor induction, lung disease, lupus, pharmaceutical inhibition of labor, previous infant >4,000 g, previous infant with a birth defect, previous premature or small-for-gestational-age infant, premature or prolonged rupture of membrane, renal disease, Rh sensitization, rubella infection, seizure disorder, sickle cell anemia, and uterine bleeding), and area-level median household income obtained from the 2000 U.S. Census (Geolytics, Inc., East Brunswick, NJ). The model adjustment sets are listed in Tables 3–5 and eTables 2 and 3; http://links.lww.com/EE/A70. We included THM4 in HAA models and HAA5 in THM models to isolate independent associations for DBP groups. We did not examine gestational age and birth weight as confounders as they might be influenced both by DBP exposures and by the presence of a birth defect, thus controlling for these factors could introduce collider stratification bias.

Results

Study characteristics

Among all reported births from 2000 to 2004 in the study population, there were 182 MSD cases with a total of 187 MSDs (53 RUL, 22 lower limb reduction, 66 GSOM, and 41 DH). Seventy-five percent (n = 140) of the MSDs occurred in isolation, and 25% (n = 47) occurred with other birth defects. Cases with multiple defects comprised 25% (n = 13) of RUL cases, 32% (n = 7) of lower limb reduction cases, 21% (n = 14) of GSOM cases, and 32% (n = 13) of DH cases. There were five cases with RUL and lower limb reduction, and one RUL case with DH. There was no overlap between cases of lower limb reduction, GSOM, and DH. As shown in Table 1, cases and controls were similar across many study characteristics. We did detect some difference by case status for maternal age, maternal education, marital status, parity, and prenatal care payment source.

DBP ranges

Median and interquartile ranges in micrograms per liter for the nine predominant metrics were as follows: DBP9 (69.5; 44.0–93.2), THM4 (44.1; 29.1–61.3), chloroform (35.8; 18.5–51.5), THMBr (6.4; 4.6–9.7), BDCM (6.0; 4.3–8.2), DBCM (0.5; 0.0–1.3), HAA5 (22.6; 12.0–31.3), TCAA (11.1; 5.6–16.1), and DCAA (10.6; 5.1–14.1) (Table 2). The strongest Spearman correlation coefficients (≥0.9) were detected for DBP9 with THM4 and chloroform, HAA5 with TCAA and DCAA, THM4 with chloroform, and THMBr with BDCM (eTable 1; http://links.lww.com/EE/A70). The strongest brominated correlations were found between BDCM and DBCM (r = 0.7), and between bromoform and DBCM (r = 0.6) and DBAA (r = 0.5).

Regression results

We detected consistently elevated aORs for all grouped MSDs for DBP9 quintiles (aOR range: 1.90–2.70; highest quintile aOR=2.11, 95% CI: 0.79, 5.65), THM4 quintiles (aOR range: 1.90–3.18; highest quintile aOR=3.18, 95% CI: 1.17, 8.63), and chloroform quartiles (aOR range: 1.30–2.21; highest quintile aOR=2.21, 95% CI: 0.99, 4.91), with positive exposure-response relationships for THM4 and chloroform (Table 3). Results for HAAs were largely near the null after adjusting for THM4.

We detected consistently elevated aORs for RULL for DBP9 quartiles (aOR range: 2.50–2.93; highest quartile aOR=2.50, 95% CI: 0.69, 9.14), THM4 quartiles (aOR range: 2.47–4.86; highest quartile aOR=4.86, 95% CI: 1.23, 19.30), and chloroform quartiles (aOR range: 2.39–3.52; highest quartile aOR=3.52, 95% CI: 0.86, 14.41), with a positive exposure-response relationship for chloroform (Table 4). Results for RUL alone were similar, with positive exposure-response relationships for THM4 and chloroform tertiles.

We observed elevated aORs for DH with DBP9 tertiles (aOR range: 3.15–5.43; highest quintile aOR=3.15, 95% CI: 0.81, 12.26), THM4 tertiles (aOR range: 1.67–1.80; highest quartile aOR=1.80, 95% CI: 0.51, 6.39), chloroform tertiles (aOR range: 6.51–6.90; highest tertile aOR=6.51, 95% CI: 1.42, 29.73), with a positive exposure-response relationship for THM4 (Table 5). Results for GSOM were generally near the null.

We present results for models without multi-DBP adjustment in Tables 2 and 3; http://links.lww.com/EE/A70 for limb defects and abdominal wall/diaphragm defects, respectively. Compared with models with multi-DBP adjustment, aORs for models without multi-DBP adjustment for limb defects were slightly less elevated for THM4 and chloroform, whereas aORs were larger for HAA5 and TCAA. In the DH models, aORs for THM4 and chloroform were smaller when not adjusting for HAA5 and were slightly larger for TCAA.

Discussion

We observed the strongest positive exposure-response associations between THM4 and all grouped MSDs, with an aOR of 3.18 (95% CI: 1.17, 8.63) comparing highest (65–141 µg/L) to lowest (0–24 µg/L) exposure quintiles. This monotonicity seemed largely driven by the associations of chloroform with limb reductions and DH. Our results for THM4 and all grouped MSDs were stronger than those of a study in Australia[22] that found an exposure-response association for THM4 with grouped MSDs (aOR=1.48; 95% CI: 0.99, 2.21 for ≥130 vs. <60 µg/L). The Australian water sources were much more heavily brominated, with THM4 comprised of 90% THMBr, compared with 19% in our study. Although their study had high exposure levels similar to our study, our data exhibited wider exposure contrasts enabling use of a much lower-exposed referent population. The advantage of improved contrasts and low-exposed referent in our study should reduce attenuation of effect estimates for upper exposure levels if associations are also present at lower levels. Nieuwenhuijsen et al.[24] reported an inverse association (aOR = 0.81; 95% CI: 0.68, 0.95) for grouped abdominal wall and diaphragm defects for THM4 ranges (60–131 vs. 0.5–<30 µg/L) similar to our study; however, their analyses did not include limb defects, which represented our strongest results. No adverse effects were detected in studies with much smaller contrasts that examined grouped MSDs[23] and grouped cases of GSOM and DH.[25] Källén and Robert[26] examined sodium hypochlorite treatment as a proxy for DBP exposures and reported ORs for limb reductions (OR = 1.6; 95% CI: 0.9, 3.0), DH (OR = 2.0; 95% CI: 0.8, 5.1), and abdominal wall defects (OR = 1.3; 95% CI: 0.4, 4.4). Their results roughly align with the stronger results we observed for RULL and DH compared with null associations for GSOM. In summary, studies with increased sensitivity due to larger THM4 exposure ranges[22] and which included limb defects[22,26] detected patterns comparable with ours for RULL and DH. Studies without limb defects data[24,25] or with smaller exposure contrasts[23,25] observed null or reduced results similar to ours for GSOM and THM4. Some variation in results across studies may be due to differences in temporal exposure assessment. Two studies used first-trimester estimates similar to ours,[24,25] one also examined

Table 1.

Maternal and infant characteristics of MSD cases and controls

	Study population, n (%)	MSD cases, n (%)	Controls, n (%)
Total births	2,057 (100.0)	187 (100.0)	1,870 (100.0)
Infant sex			
Males	1,016 (49.4)	99 (52.9)	917 (49.0)
Females	1,041 (50.6)	88 (47.1)	953 (51.0)
Maternal age (year)			
≤20	233 (11.3)	49 (26.2)	184 (9.8)
>20–25	365 (17.7)	36 (19.3)	329 (17.6)
>25–30	530 (25.8)	37 (19.8)	493 (26.4)
>30–35	607 (29.5)	40 (21.4)	567 (30.3)
>35–40	268 (13.0)	23 (12.3)	245 (13.1)
>40	54 (2.6)	2 (1.1)	52 (2.8)
Maternal race			
White	1,413 (68.7)	132 (70.6)	1,281 (68.5)
African American	197 (9.6)	11 (5.8)	186 (9.9)
Asian	140 (6.8)	9 (4.8)	131 (7.0)
Others	306 (14.9)	34 (18.2)	272 (14.5)
Missing	1 (0.1)	1 (0.5)	0 (0.0)
Maternal education			
Below high school graduate/GED	245 (11.9)	36 (19.3)	209 (11.2)
High school graduate/GED	573 (27.9)	63 (33.7)	510 (24.8)
Some college or associates/technical degree	440 (21.4)	30 (16.0)	410 (19.9)
College or higher	799 (38.8)	58 (31.0)	741 (36.0)
Marital status			
Married	1,402 (68.2)	97 (51.9)	1,305 (69.8)
Unmarried	655 (31.8)	90 (48.1)	565 (30.2)
Number of previous births			
0	944 (45.9)	114 (61.0)	830 (44.4)
1	716 (34.8)	47 (25.1)	669 (35.8)
≥2	396 (19.3)	26 (13.9)	370 (19.8)
Missing	1 (0.1)	1 (0.5)	0 (0.0)
Maternal weight gain during pregnancy (lbs)			
<0	23 (1.1)	3 (1.6)	20 (1.1)
0–25	800 (38.9)	92 (49.2)	708 (37.9)
25–50	1,139 (55.4)	82 (43.9)	1,057 (56.5)
>50	80 (3.9)	9 (4.8)	71 (3.8)
Missing	15 (0.7)	1 (0.5)	14 (0.7)
Maternal smoking during pregnancy			
None	1,894 (92.1)	164 (87.7)	1,730 (92.5)
Any	163 (7.9)	23 (12.3)	140 (7.5)
Number of prenatal care visits			
<9	217 (10.5)	25 (13.4)	192 (10.3)
9–11	491 (23.9)	41 (21.9)	450 (24.1)
12	586 (28.5)	57 (30.5)	529 (28.3)
13–15	558 (27.1)	42 (22.5)	516 (27.6)
>15	194 (9.4)	22 (11.8)	172 (9.2)
Missing	11 (0.5)	0 (0.0)	11 (0.6)
Prenatal care source of payment			
Public	568 (27.6)	77 (41.2)	491 (26.3)
Private	1,327 (64.5)	87 (46.5)	1,240 (66.3)
Other	162 (7.9)	23 (12.3)	139 (7.4)
Trimester prenatal care began			
First trimester	1,700 (82.6)	153 (81.8)	1,547 (82.7)
After first trimester	348 (16.9)	34 (18.2)	314 (16.8)
Missing	9 (0.4)	0 (0.0)	9 (0.5)
Median household income (based on year 2000 ZIP codes)			
$12,307–36,836	482 (23.4)	43 (23.0)	439 (23.5)
>$36,836–45,654	499 (24.3)	59 (31.6)	440 (23.5)
>$45,654–57,815	548 (26.6)	49 (26.2)	499 (26.7)
>$57,815–153,918	528 (25.7)	36 (19.3)	492 (26.3)
Water source and treatment type			
Chlorinated surface water	366 (17.8)	30 (16.0)	336 (18.0)
Chloraminated surface water	959 (46.6)	84 (44.9)	875 (46.8)
Untreated ground water	278 (13.5)	29 (15.5)	249 (13.3)
Other	454 (22.1)	44 (23.5)	410 (21.9)

GED, general educational development.

Table 2.

First trimester averaged DBP (µg/L) exposure levels[a] for the study population

DBP Metric	25th%	50th%	75th%	90th%	Maximum
DBP9	43.95	69.46	93.23	107.19	180.18
THM4	29.06	44.12	61.32	73.18	140.91
Chloroform	18.45	35.81	51.53	63.12	105.59
THMBr	4.62	6.44	9.66	17.36	39.05
BDCM	4.32	5.99	8.20	12.84	34.90
DBCM	0.00	0.51	1.34	3.93	13.97
Bromoform	0.00	0.00	0.00	0.26	6.83
HAA5	12.00	22.61	31.25	42.75	102.03
TCAA	5.55	11.10	16.11	21.66	61.71
DCAA	5.07	10.62	14.06	18.69	34.78
MCAA	0.00	0.06	0.89	1.64	69.54
DBAA	0.00	0.00	0.00	0.46	21.78
MBAA	0.00	0.00	0.00	0.00	6.75

[a]All DBP ranges had minimum values of 0 µg/L.

THMBr, sum of bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform; THM4, sum of chloroform and THMBr; HAA5, sum of MCAA, TCAA, MBAA, and DBAA; DBP9, sum of THM4 and HAA5.

the individual months of the first trimester,[23] and two did not assess exposures temporally.[22,26]

This is the first epidemiologic study to assess MSDs in relation to HAAs and to adjust regression models for multiple DBP exposures. Adjustment for THM4 in HAA models generally resulted in aORs closer to the null, further supporting associations we observed for THM4 and chloroform and suggesting that THM4, if not adjusted for, would be a positive confounder in HAA models. Associations for first trimester HAA exposures were inconsistent, ranging from a high aOR of 2.03 (95% CI: 0.52, 7.90) for the second TCAA quartile with RULL, to a low of 0.33 (95% CI: 0.10, 1.17) for the highest HAA5 tertile with RUL. Adjustment for HAA5 in THM4 and chloroform models increased aORs for all grouped MSDs, RULL, RUL, and DH, but not GSOM. Adjustment for HAA5 in brominated THM models did not materially change the aORs, which would be expected in our data, since brominated THMs are not highly correlated with chlorinated HAA metrics (i.e., TCAA, DCAA, and MCAA) constituting most of HAA5 in these water supplies.

Our results for brominated THMs (THMBr, BDCM, DBCM, and bromoform) were inconsistent and did not exhibit monotonicity. The small number of exposed cases for these rare outcomes precluded our ability to fully assess exposure-response relationships, especially for less prevalent brominated DBPs for which we used dichotomous or tertile-based exposure categories. A large study of 2,267 abdominal wall defect cases[24] did not find elevated associations for bromoform, THMBr, or THM4 in relation to a GSOM and DH grouping, but did report a positive association between gastroschisis and bromoform (aOR=1.38, 95% CI: 1.00, 1.92). Compared with their large sample size and wider exposure ranges, our study was less sensitive to detect associations for the brominated THM measures. Another study[23] detected an exposure-response relationship for all MSDs and DBCM in the first and second months of pregnancy but no associations over the entire first trimester, nor for BDCM. Given the mixed results for the few brominated THM studies and limited examination of brominated HAAs, more research is needed on these relationships. Additional studies integrating individual-level exposures, similar to Grazuleviciene et al.,[23] are also needed.

A limitation of our outcome data is that we were unable to distinguish between gastroschisis and omphalocele, as these conditions were reported under the same ICD-9 code before 2009. The two prior epidemiologic studies[24,25] that examined gastroschisis and omphalocele grouped with DH reported largely null associations similar to our GSOM results. Our observed exposure-response associations for DH with THM4 and the elevated gastroschisis-specific results of Nieuwenhuijsen et al.[24] reinforce the importance of analyzing these outcomes separately, as they likely have distinct etiologies.

Some MSDs co-occur in syndromic patterns that may have distinct etiologies, including genetic risk factors.[38,39] Whereas 75% of the 182 MSD cases in our study had a single diagnosed MSD, we did not conduct sensitivity analyses for cases with multiple birth defects, which could introduce misclassification by grouping outcomes with distinct etiologies. Studies with increased statistical power should examine this.

Toxicology studies testing DBP exposures in animals have generally failed to show teratogenic effects of the THMs, including chloroform,[6–10] BDCM,[9,11,40] DBCM,[8,9] bromoform,[9] or THM4.[13] However, two older studies testing chloroform inhalation did report an increased occurrence of cleft palate in mice[14] and short or absent tails in rats.[15] In contrast, several animal studies have demonstrated teratogenicity of HAAs including TCAA, DCAA, and HAA5,[13,16,17] with most effects noted on the heart or eye. Regarding MSDs, TCAA caused small orbit, associated with micro/anophthalmia.[16] Two animal studies have been conducted with haloacetonitriles, DBPs for which we did not have data. Chloroacetonitrile caused reduced vertebral ossification and muscle growth in mice[18] and dichloroacetonitrile caused fused ribs and cervical ribs in rats.[19] Given the limited number of toxicological and epidemiologic studies of DBPs and MSDs, more research is needed, especially for haloacetonitriles, brominated THMs and HAAs, and other mixtures.

As previously noted, THM4 and HAA5 may not be good proxies for the most toxicologically relevant DBPs for adverse reproductive outcomes. For example, a study[41] of 11 municipal water systems in Spain reported Spearman correlations of 0.25 and −0.27, respectively, for total haloacetonitriles with THM4 and HAA9 (sum of HAA5 and four other HAAs), indicating that THM4 and HAA9 would be poor proxies for total haloacetonitriles. We examined five HAAs and four THMs, providing greater specificity than previous research on MSDs and DBPs. However, >600 DBPs have been identified from various disinfection processes;[42] therefore, some of the elevated aORs we observed may be due to unmeasured DBPs. Righi et al.,[25] for example, reported elevated odds for abdominal wall and diaphragm defects with elevated chlorite (>700 µg/L) and chlorate (>200 µg/L) exposures. Our inclusion of water source (including untreated ground water), treatment type, and THM4 or HAA5 as covariates may control for some potential confounding by unmeasured drinking water contaminants and other differences related to different water sources. Although THMs and HAAs are often correlated in chlorinated water systems, correlations between individual DBPs vary across systems; thus, this potential source of residual confounding remains and is difficult to elucidate. In general, mutual adjustment for correlated exposures can help control confounding in the absence of unmeasured confounders related to both exposures, but can otherwise amplify confounding due to unmeasured components of the exposure mixture.[27]

Although we examined numerous potential confounders, reliance on self-reported lifestyle factors during pregnancy from vital records data is a potential limitation. We did not examine alcohol use during pregnancy due to data validity concerns from the Massachusetts Department of Public Health, which provided the data. We previously reported strong associations between maternal cigarette smoking during pregnancy and fetal growth measures in a similar population based on these birth records data;[43,44] these and other validated data from cotinine studies[45] suggest that birth records data of self-reported maternal cigarette use may accurately reflect smoking habits during pregnancy. There is some epidemiologic evidence for positive associations between maternal smoking and RULL and gastroschisis,[46] but no evidence that smoking is associated with DBP

Table 3.

Adjusted odds ratios between DBP exposures and all MSDs, with and without co-pollutant adjustments

DBP Metrics (µg/L)	n[a]	aOR (95% CI)	aOR (95% CI)[f]
THM4[b]			
0–24.1	36/374	Ref	Ref
>24.1–38.0	34/375	1.90 (0.78, 4.64)	1.79 (0.74, 4.32)
>38.0–50.2	35/373	2.30 (0.91, 5.83)	2.09 (0.85, 5.16)
>50.2–65.2	41/374	3.03 (1.16, 7.92)	2.65 (1.07, 6.54)
>65.2–140.9	41/374	3.18 (1.17, 8.63)	2.77 (1.08, 7.06)
THMBr[c]			
0–4.6	50/467	Ref	Ref
>4.6–6.4	44/467	1.03 (0.55, 1.93)	0.98 (0.53, 1.81)
>6.4–9.7	48/467	1.12 (0.61, 2.06)	1.05 (0.58, 1.91)
>9.7–39.1	44/467	0.99 (0.55, 1.79)	0.95 (0.53, 1.71)
Chloroform[b]			
0–18.2	45/467	Ref	Ref
>18.2–35.5	39/470	1.30 (0.65, 2.60)	1.22 (0.62, 2.37)
>35.5–51.4	52/464	2.09 (1.02, 4.31)	1.87 (0.97, 3.62)
>51.4–105.6	50/467	2.21 (0.99, 4.91)	1.94 (0.95, 3.98)
Bromodichloromethane (BDCM)[c]			
0–4.3	47/469	Ref	Ref
>4.3–6.0	48/465	1.40 (0.75, 2.62)	1.37 (0.73, 2.55)
>6.0–8.2	45/467	1.26 (0.68, 2.34)	1.22 (0.66, 2.26)
>8.2–34.9	46/467	1.23 (0.69, 2.20)	1.22 (0.68, 2.18)
Dibromochloromethane (DBCM)[c]			
0–1.4	145/1,402	Ref	Ref
>1.4–14.0	41/466	0.80 (0.51, 1.26)	0.78 (0.50, 1.22)
Bromoform[c]			
0	166/1,588	Ref	Ref
>0–6.8	20/280	0.62 (0.36, 1.09)	0.61 (0.36, 1.04)
HAA5[d]			
0–11.9	46/468	Ref	Ref
>11.9–22.5	41/467	1.08 (0.55, 2.10)	1.26 (0.66, 2.41)
>22.5–31.3	56/467	1.49 (0.71, 3.09)	1.94 (0.99, 3.80)
>31.3–102.0	44/468	1.00 (0.47, 2.17)	1.38 (0.70, 2.74)
TCAA[d]			
0–5.5	45/463	Ref	Ref
>5.5–11.1	44/463	0.97 (0.49, 1.90)	1.21 (0.64, 2.29)
>11.1–16.1	54/463	1.22 (0.58, 2.58)	1.74 (0.89, 3.41)
>16.1–61.7	42/462	0.79 (0.36, 1.75)	1.21 (0.61, 2.38)
DCAA[d]			
0–5.1	47/462	Ref	Ref
>5.1–10.6	38/464	0.84 (0.44, 1.59)	0.93 (0.49, 1.76)
>10.6–14.1	57/464	1.23 (0.62, 2.42)	1.53 (0.81, 2.91)
>14.1–34.8	43/461	0.86 (0.41, 1.79)	1.13 (0.57, 2.22)
MCAA[d]			
0	95/874	Ref	Ref
>0–69.5	90/977	0.81 (0.57, 1.18)	0.89 (0.62, 1.27)
DBAA[d]			
0	145/1,405	Ref	Ref
>0–21.8	40/446	1.06 (0.70, 1.62)	0.94 (0.62, 1.41)
DBP9[e]			
0–34.0	35/374	Ref	NA
>34.0–60.1	34/374	1.90 (0.75, 4.83)	NA
>60.1–79.8	44/374	2.70 (1.06, 6.88)	NA
>79.8–97.7	40/374	2.40 (0.93, 6.19)	NA
>97.7–180.2	34/374	2.11 (0.79, 5.65)	NA

[a]The numbers represent the case and control distributions across exposure groups prior to modeling.

[b]All MSDs and THM4/chloroform: models adjusted for water source and treatment type, prenatal care source of payment, maternal marital status, maternal age, and HAA5.

[c]All MSDs and THMBr/BDCM/DBCM/bromoform: models adjusted for water source and treatment type, and HAA5.

[d]All MSDs and HAA5/TCAA/DCAA/MCAA/DBAA/MBAA: models adjusted for maternal age, maternal education, maternal marital status, prenatal care source of payment, census tract income, water source and treatment type, and THM4.

[e]All MSDs and DBP9: Models adjusted for maternal age, maternal marital status, prenatal care source of payment, water source, and treatment type.

[f]Models in these columns are identical to models immediately to the left, except for the exclusion of THM4 or HAA5.

exposures in the literature or in our data, and therefore is likely not a confounder.

Exposure misclassification due to the lack of individual-level exposure data (e.g., water use activity patterns) is a limitation of many epidemiologic studies of DBPs. We used routinely collected monitoring data for all water systems with complete quarterly data serving our study area. Given diurnal variability and seasonality of some DBPs,[30,47,48] monitoring samples likely do not represent the full extent of temporal variability needed to evaluate potential impacts of peak exposures or specific developmental windows for MSDs (i.e., weeks 4–7 for the limbs, week 4 for gastroschisis, week 8 for DH, and week 9 for omphalocele). This may explain exposure-response relationships detected in the only study examining monthly estimates early

Table 4.

Adjusted odds ratios between DBP exposures and limb reduction defects

Reduction of upper or lower limbs (RULL)			Reduction of upper limbs (RUL)		
DBP metrics (μg/L)	**n[a]**	**aOR (95% CI)**	**DBP metrics (μg/L)**	**n[a]**	**aOR (95% CI)**
THM4					
0–26.4	17/173	Ref[b]	0–32.4	19/176	Ref[f]
>26.4–41.6	17/173	3.23 (0.93, 11.22)[b]	>32.4–52.2	15/176	1.90 (0.67, 5.34)[f]
>41.6–59.8	13/175	2.47 (0.67, 9.09)[b]	>52.2–92.5	19/176	3.47 (1.03, 11.71)[f]
>59.8–93.2	22/174	4.86 (1.23, 19.30)[b]	—	—	—
THMBr					
0–5.2	25/231	Ref[c]	0–5.2	19/176	Ref[g]
>5.2–8.0	24/233	1.39 (0.59, 3.25)[c]	>5.2–8.3	20/173	1.77 (0.65, 4.81)[g]
>8.0–39.1	19/233	1.00 (0.44, 2.29)[c]	>8.3–35.2	14/177	1.29 (0.48, 3.52)[g]
Chloroform					
0–16.0	17/173	Ref[b]	0–24.0	19/176	Ref[f]
>16.0–33.9	16/175	2.39 (0.70, 8.13)[b]	>24.0–42.9	15/175	1.88 (0.61, 5.84)[f]
>33.9–50.1	15/176	2.58 (0.71, 9.40)[b]	>42.9–79.2	19/177	3.64 (0.98, 13.57)[f]
>50.1–79.2	20/173	3.52 (0.86, 14.41)[b]	—	—	—
Bromodichloromethane (BDCM)					
0–4.8	23/229	Ref[c]	0–4.7	18/177	Ref[g]
>4.8–6.8	23/231	1.84 (0.75, 4.50)[c]	>4.7–7.2	21/174	2.87 (1.03, 8.02)[g]
>6.8–34.6	22/237	1.46 (0.64, 3.29)[c]	>7.2–34.6	14/175	1.58 (0.58, 4.32)[g]
Dibromochloromethane (DBCM)					
0–1.5	54/522	Ref[c]	0–1.7	42/393	Ref[g]
>1.5–14.0	14/175	0.81 (0.36, 1.79)[c]	>1.7–13.3	11/133	0.95 (0.37, 2.46)[g]
Bromoform					
0	59/518	Ref[c]	0	45/431	Ref[g]
>0–6.8	14/179	1.00 (0.41, 2.45)[c]	>0–6.8	8/95	1.01 (0.37, 2.78)[g]
HAA5					
0–10.5	17/172	Ref[d]	0–15.3	22/173	Ref[h]
>10.5–21.6	16/177	1.79 (0.52, 6.10)[d]	>15.3–27.7	17/181	0.62 (0.23, 1.72)[h]
>21.6–30.6	20/174	1.83 (0.48, 7.01)[d]	>27.7–102.0	14/176	0.33 (0.10, 1.17)[h]
>30.6–102.0	16/174	1.28 (0.30, 5.47)[d]	—	—	—
TCAA					
0–4.2	16/172	Ref[d]	0.0–6.8	17/174	Ref[h]
>4–10.3	17/173	2.03 (0.52, 7.90)[d]	>6.8–14.3	19/173	1.76 (0.57, 5.44)[h]
>10.3–16.1	19/172	1.94 (0.44, 8.60)[d]	>14.3–61.7	15/179	0.82 (0.21, 3.23)[h]
>16.1–61.7	15/174	1.11 (0.22, 5.54)[d]	—	—	—
DCAA					
0–5.0	17/172	Ref[d]	0–7.1	20/174	Ref[h]
>5.0–10.2	18/173	1.71 (0.51, 5.69)[d]	>7.1–12.0	17/174	0.79 (0.27, 2.34)[h]
>10.2–13.6	15/188	1.14 (0.30, 4.40)[d]	>12.0–33.3	14/178	0.45 (0.13, 1.59)[h]
>13.6–33.3	17/190	1.23 (0.31, 4.83)[d]	—	—	—
MCAA					
0	40/344	Ref[d]	0	32/268	Ref[h]
>0–69.5	27/347	0.56 (0.30, 1.04)[d]	>0–69.5	19/258	0.61 (0.30, 1.23)[h]
DBAA					
0	50/516	Ref[d]	0	39/396	Ref[h]
>0–19.7	17/175	1.40 (0.72, 2.70)[d]	>0–19.7	12/130	1.36 (0.62, 2.99)[h]
DBP9					
0–39.4	17/173	Ref[e]	0–39.1	14/132	Ref[i]
>39.4–65.0	17/175	2.63 (0.80, 8.68)[e]	>39.1–63.1	13/130	2.62 (0.65, 10.61)[i]
>65.0–90.5	19/175	2.93 (0.88, 9.70)[e]	>63.1–89.6	17/131	3.48 (0.84, 14.35)[i]
>90.5–162.5	16/175	2.50 (0.69, 9.14)[e]	>89.6–162.5	9/130	1.99 (0.43, 9.16)[i]

[a]The numbers represent the case and control distributions across exposure groups prior to modeling.

[b]RULL and THM4/chloroform: models adjusted for maternal race, number of prenatal care visits, ZIP code income, water source and treatment type, and HAA5.

[c]RULL and THMBr/BDCM/DBCM/bromoform: models adjusted for maternal race, number of prenatal care visits ZIP coe income, water source and treatment type, and HAA5.

[d]RULL and HAA5/TCAA/DCAA/MCAA/DBAA/MBAA: models adjusted for maternal race, prenatal care source of payment, number of prenatal care visits, ZIP code income, water source and treatment type, and THM4.

[e]RULL and DBP9: models adjusted for maternal education, maternal race, ZIP code income, and water source and treatment type.

[f]RUL and THM4/chloroform: models adjusted for maternal race, trimester prenatal care began, number of prenatal care visits, prenatal care payment source, maternal health index (includes chronic or gestational diabetes, chronic or pregnancy-related hypertension, hydramnios/oligohydramnios, eclampsia, and cardiac disease), ZIP code income, water source and treatment type, and HAA5.

[g]RUL and THMBr/BDCM/DBCM/bromoform: models adjusted for trimester prenatal care began, number of prenatal care visits, maternal parity, maternal health index (includes chronic or gestational diabetes, chronic or pregnancy-related hypertension, hydramnios/oligohydramnios, eclampsia, and cardiac disease), ZIP code income, water source and treatment type, and HAA5.

[h]RUL and HAA5/TCAA/DCAA/MCAA/DBAA/MBAA: models adjusted for number of maternal marital status, prenatal care visits, prenatal care payment source, maternal health index (includes chronic or gestational diabetes, chronic or pregnancy-related hypertension, hydramnios/oligohydramnios, eclampsia, and cardiac disease), ZIP code income, water source and treatment type, and THM4.

[i]RUL and DBP9: models adjusted for maternal marital status, maternal race, trimester prenatal care began, number of prenatal care visits, prenatal care payment source, maternal weight gain during pregnancy, maternal health index (includes chronic or gestational diabetes, chronic or pregnancy-related hypertension, hydramnios/oligohydramnios, eclampsia, and cardiac disease), ZIP code income, and water source and treatment type.

DBP9, sum of chloroform, BDCM, DBCM, bromoform, MCAA, DCAA, TCAA, MBAA, and DBAA; HAA5, sum of MCAA, DCAA, TCAA, MBAA, and DBAA; THM4, sum of chloroform, BDCM, DBCM, and bromoform; THMBr, sum of BDCM, DBCM, and bromoform. NA=not applicable.

Table 5.

Adjusted odds ratios between DBP exposures and abdominal wall and diaphragm defects

Gastroschisis or omphalocele (GSOM)			Diaphragmatic hernia (DH)		
DBP quantile (μg/L)	**Cases (n)[a]**	**aOR (95% CI)**	**DBP quantile (μg/L)**	**Cases (n)[a]**	**aOR (95% CI)**
THM4					
0–35.3	26/216	Ref[b]	0–32.8	10/134	Ref[f]
>35.3–59.4	24/221	1.19 (0.47, 3.03)[b]	>32.8–51.4	15/133	1.67 (0.54, 5.15)[f]
>59.4–140.9	15/218	0.40 (0.13, 1.24)[b]	>51.4–92.2	15/138	1.80 (0.51, 6.39)[f]
THMBr					
0–5.3	26/217	Ref[c]	0–4.9	9/134	Ref[g]
>5.3–8.5	21/218	0.75 (0.34, 1.67)[c]	>4.9–8.8	21/136	2.78 (0.74, 10.50)[g]
>8.5–35.3	18/228	0.72 (0.31, 1.68)[c]	>8.8–33.1	10/135	1.13 (0.28, 4.61)[g]
Chloroform					
0–26.9	22/219	Ref[b]	0–24.0	7/134	Ref[f]
>26.9–48.9	24/215	1.39 (0.52, 3.71)[b]	>24.0–41.8	17/133	6.90 (1.54, 30.86)[f]
>48.9–105.6	19/219	0.94 (0.28, 3.16)[b]	>41.8–81.4	16/138	6.51 (1.42, 29.73)[f]
Bromodichloromethane (BDCM)					
0–5.0	23/217	Ref[c]	0–4.7	9/135	Ref[g]
>5.0–7.6	24/218	1.12 (0.48, 2.61)[c]	>4.7–7.8	17/133	2.51 (0.78, 8.14)[g]
>7.6–28.9	18/218	0.87 (0.37, 2.06)[c]	>7.8–32.5	14/137	1.64 (0.49, 5.55)[g]
Dibromochloromethane (DBCM)					
0–1.4	49/489	Ref[c]	0–1.6	33/304	Ref[g]
>1.4–13.2	16/164	1.54 (0.69, 3.44)[c]	>1.6–14.0	7/101	0.39 (0.13, 1.15)
Bromoform					
0	59/562	Ref[c]	N/I[i]	—	—
>0–5.2	6/91	0.97 (0.33, 2.84)[c]	N/I[i]	—	—
HAA5					
0–17.9	24/220	Ref[d]	0–16.6	10/134	Ref[h]
>17.9–28.3	17/218	0.75 (0.28, 2.02)[d]	>16.6–29.4	16/135	1.06 (0.33, 3.42)[h]
>28.3–89.7	24/217	1.09 (0.40, 2.96)[d]	>29.4–75.4	14/137	0.84 (0.23, 3.07)[h]
TCAA					
0–8.7	23/217	Ref[d]	0–7.9	9/133	Ref[h]
>8.7–14.7	19/214	0.89 (0.33, 2.41)[d]	>7.9–15.1	20/137	1.44 (0.46, 4.52)[h]
>14.7–42.2	23/215	1.30 (0.44, 3.82)[d]	>15.1–46.7	11/132	0.61 (0.15, 2.50)[h]
DCAA					
0–8.0	22/215	Ref[d]	0–7.6	10/134	Ref[h]
>8.0–12.4	17/215	0.70 (0.26, 1.90)[d]	>7.6–12.8	16/134	1.01 (0.30, 3.44)[h]
>12.4–34.8	26/216	1.23 (0.43, 3.48)[d]	>12.8–33.3	14/134	0.68 (0.17, 2.62)[h]
MCAA					
0	33/306	Ref[d]	0	17/186	Ref[h]
>0–56.5	32/340	0.81 (0.42, 1.55)[d]	>0–31.7	23/216	0.94 (0.41, 2.15)[h]
Dibromoacetic acid (DBAA)					
0	51/495	Ref[d]	0	33/314	Ref[h]
>0–7.9	14/151	0.88 (0.38, 2.00)[d]	>0–14.7	7/88	0.64 (0.23, 1.74)[h]
DBP9					
0–56.1	22/217	Ref[e]	0–52.5	7/139	Ref[i]
>56.1–89.1	28/221	1.77 (0.65, 4.87)[e]	>52.5–83.9	19/130	5.43 (1.43, 20.69)[i]
>89.1–180.2	15/218	0.87 (0.28, 2.74)[e]	>83.9–165.8	14/136	3.15 (0.81, 12.26)[i]

[a]The numbers represent the control distributions across exposure groups prior to modeling.

[b]GSOM and THM4/chloroform: models adjusted for maternal age, maternal education, maternal marital status, maternal race, trimester prenatal care began, number of prenatal care visits, prenatal care payment source, maternal parity, any maternal tobacco smoking, complications during delivery, maternal health index (includes chronic or gestational diabetes, chronic or pregnancy-related hypertension, hydramnios/oligohydramnios, eclampsia, and cardiac disease), ZIP code income, water source and treatment type, and HAA5.

[c]GSOM and THMBr/BDCM/DBCM/bromoform: models adjusted for maternal education, trimester prenatal care began, number of prenatal care visits, prenatal care payment source, child's sex, maternal anemia, induced labor, any maternal tobacco smoking, maternal health index (includes chronic or gestational diabetes, chronic or pregnancy-related hypertension, hydramnios/oligohydramnios, eclampsia, and cardiac disease), water source and treatment type, and HAA5.

[d]GSOM and HAA5/TCAA/DCAA/MCAA/DBAA/MBAA: models adjusted for maternal age, maternal education, maternal marital status, maternal race, trimester prenatal care began, number of prenatal care visits, prenatal care payment source, any maternal tobacco smoking, maternal parity, maternal health index (includes chronic or gestational diabetes, chronic or pregnancy-related hypertension, hydramnios/oligohydramnios, eclampsia, and cardiac disease), ZIP code income, water source and treatment type, and THM4.

[e]GSOM and DBP9: models adjusted for maternal age, maternal education, maternal marital status, trimester prenatal care began, prenatal care payment source, maternal parity, any maternal tobacco smoking, maternal health index (includes chronic or gestational diabetes, chronic or pregnancy-related hypertension, hydramnios/oligohydramnios, eclampsia, and cardiac disease), census tract income, and water source and treatment type.

[f]DH and THM4/chloroform: models adjusted for maternal race, trimester prenatal care began, number of prenatal care visits, induced labor, maternal health index (includes chronic or gestational diabetes, chronic or pregnancy-related hypertension, hydramnios/oligohydramnios, eclampsia, and cardiac disease), town-level income, water source and treatment type, and HAA5.

[g]DH and THMBr/BDCM/DBCM/bromoform: models adjusted for maternal race, trimester prenatal care began, number of prenatal care visits, maternal parity, induced labor, maternal health index (includes chronic or gestational diabetes, chronic or pregnancy-related hypertension, hydramnios/oligohydramnios, eclampsia, and cardiac disease), town-level income, water source and treatment type, and HAA5.

[h]DH and HAA5/TCAA/DCAA/MCAA/DBAA/MBAA: models adjusted for maternal age, maternal race, number of prenatal care visits, induced labor, maternal health index (includes chronic or gestational diabetes, chronic or pregnancy-related hypertension, hydramnios/oligohydramnios, eclampsia, and cardiac disease), town-level income, water source and treatment type, and THM4.

[i]DH and DBP9: models adjusted for maternal age, maternal race, trimester prenatal care began, number of prenatal care visits, induced labor, maternal health index (includes chronic or gestational diabetes, chronic or pregnancy-related hypertension, hydramnios/oligohydramnios, eclampsia, and cardiac disease), town-level income, and water source and treatment type.

[i]Not included due to sparse data (i.e., cell counts <5).

DBP9, sum of chloroform, BDCM, DBCM, bromoform, MCAA, DCAA, TCAA, MBAA, and DBAA; HAA5, sum of MCAA, DCAA, TCAA, MBAA, and DBAA; THM4, sum of chloroform, BDCM, DBCM, and bromoform; THMBr, sum of BDCM, DBCM, and bromoform; NA, not applicable.

in pregnancy.[23] Although we would expect our use of weighted first-trimester average DBP exposures to result in some non-differential exposure misclassification and decreased study sensitivity, we still detected strong exposure-response relationships for some THMs and MSDs using our area-level data. This is inconsistent with two other DBP studies examining other birth defects, which detected higher ORs for individual-level water use metrics than with area-level DBP metrics.[49,50]

Another potential source of exposure misclassification is residential mobility, if the birth address used to assign exposures differed from the residence during the first trimester, when birth defects develop. A study of DBPs and neural tube defects reported stronger associations among mothers with confirmed residences at conception compared with the overall population of confirmed and unconfirmed residences.[51] A review of 14 epidemiology studies with mobility data found that 9%–32% of women moved during pregnancy, with the median distance moved <10 km.[52,53] Previous studies have shown that most moves occur during the second trimester or pregnancy planning/conception period,[53,54] suggesting that although some misclassification of our first trimester exposure estimates likely occurred, the impact of mobility may be limited. Spatial variability and inter-individual water-use patterns may also not be fully captured by town-average DBP concentrations assessed from different sampling locations. Nevertheless, our exposure assessment should largely capture relative rankings of DBP exposures.

A study limitation which could decrease the precision of our estimates and study sensitivity is under-ascertainment of cases from elective termination upon prenatal diagnosis.[55] An analysis of 1987–1996 data from the Hawaii Birth Defects Program showed prenatal diagnosis rates of 76% for gastroschisis and 60% for omphalocele and estimated elective termination rates following prenatal diagnosis of 13% for gastroschisis and 42% for omphalocele.[56] A study in Boston with data from 1972 to 1974 and 1979 to 1994 reported that 20% of fetuses with detected limb reduction defects were terminated.[57] The Massachusetts Birth Defects Monitoring Program did not collect elective termination data during the study years, so our case numbers are likely underestimates, reducing statistical power, but decisions to abort a fetus are unlikely related to DBP levels.

Given that THMs are generally the most prevalent DBP class in treated drinking water systems, and that MSDs can lead to significant disability and costs, our findings of elevated associations for limb defects with increasing THM4 exposure may have public health significance if supported by future research. Additionally, we observed elevated risks at estimated exposures below some current regulatory levels; e.g., >95% of our study population had estimated first trimester average DBP concentrations below USEPA maximum contaminant levels of 80 µg/L for THM4 and 60 µg/L for HAA5. Since our ability to examine brominated HAAs (e.g., DBAA, MBAA) using routinely collected data was limited by having few observations with detectable concentrations, epidemiologic research should expand to include bromochloroacetic acid, bromodichloroacetic acid, chlorodibromoacetic acid, and tribromoacetic acid, and other DBPs such as haloacetonitriles. Challenges in exposure assessment remain due to the wide variety of DBPs, lack of residential-based exposure concentrations, and lack of individual-level data on water use activities that could help better quantify specific exposures to different DBPs of varying volatility. Small case numbers and the practice of combining outcomes also limit the ability to observe potential associations that are small in magnitude, and to assess potential effect measure modification.[2] Although drinking water disinfection is one of the most important public health interventions globally, further research on health impacts of undesirable exposures to chemical contaminants such as DBPs can inform comparative risk efforts for public drinking water systems. Our research helps address knowledge gaps by examining a broader range of more specific DBPs as potential environmental determinants of birth defects.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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