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Associations Between Disinfection By-Product Exposures and Craniofacial Birth Defects

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Abstract

Objective—Examine associations between craniofacial birth defects (CFDs) and disinfection by-product (DBP) exposures, including the sum of four trihalomethanes (THM4) and five haloacetic acids (HAA5) (i.e., DBP9).

Methods—We calculated first trimester adjusted odds ratios (aORs) for different DBPs in a matched case-control study of 366 CFD cases in Massachusetts towns with complete 1999-2004 THM and HAA data.

Results—We detected elevated aORs for cleft palate with DBP9 (highest quintile aOR=3.52; 95% CI: 1.07, 11.60), HAA5, trichloroacetic acid (TCAA), and dichloroacetic acid. We detected elevated aORs for eye defects with TCAA and chloroform.

Conclusion—This is the first epidemiological study of DBPs to examine eye and ear defects, as well as HAAs and CFDs. The associations for cleft palate and eye defects highlight the importance of examining specific defects, and of examining DBPs beyond THM4.

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INTRODUCTION

Oral clefts are among the most common congenital anomalies¹ and can cause substantial impacts on the health, quality of life, and financial wellbeing of affected individuals and their families². The causes of most oral cleft cases are unknown. Due to etiological differences in genetic risk factors, oral clefts are often described as either cleft lip with or without cleft palate (CL±P) or cleft palate without cleft lip (CP)^{3,4}. In the U.S. each year there are approximately 4,440 new cases of CL±P (birth prevalence: 1 in 940 births) and 2,650 new cases of CP (birth prevalence: 1 in 1,574 births; 2004-2006 data¹). Microphthalmia/anophthalmia (small/absent eye) and microtia/anotia (small/absent external ear) are much less common, with approximately 780 new cases of eye defects (birth prevalence: 1 in 5,349 births; 2004-2006 data¹) and 420 to 830 new cases of ear defects (birth prevalence: 1 in 10,000 to 1 in 5,000 births depending on diagnosis criteria; 2004-2008 data⁵) each year in the U.S.

Water disinfection byproducts (DBPs) form when chemical disinfectants (e.g. chlorine, chloramine) combine with organic matter present in water. While hundreds of different types of DBPs can form depending on characteristics of the source water and treatment type^{6,7}, the most commonly occurring are the trihalomethanes (THMs) and haloacetic acids (HAAs), which are nearly ubiquitous in treated water systems. Toxicological studies have reported eye defects following exposure to HAAs in rats⁸⁻¹⁰, in mouse whole embryo culture¹¹, and in rat whole embryo culture¹². Eye defects have also been detected in zebrafish following exposure to THMs including chloroform, bromoform, and bromodichloromethane¹³. Toxicological evidence for cleft palate following DBP exposures is more limited, with one study reporting positive associations in mice exposed to chloroform on gestation days 8-15, but not days 6-15¹⁴. A study in zebrafish reported mouth or jaw malformations following exposure to the HAA dichloroacetic acid (DCAA)¹⁵. Ear defects in rat whole embryo culture were reported in one study following exposure to DCAA¹².

Epidemiological evidence suggests that women exposed to elevated levels of DBPs in treated water have an increased risk of delivering babies with certain congenital anomalies, such as ventricular septal defects^{16,17}. Though evidence for oral clefts is limited, most previous studies have grouped CL±P and CP together as one outcome to increase statistical power, at the cost of being able to observe potentially different associations for etiologically distinct defects. A 2009 meta-analysis by Nieuwenhuijsen et al.¹⁷ reported a combined odds ratio (OR) of 0.98 [95% confidence interval (CI): 0.88, 1.08] for cleft lip and/or cleft palate with DBP exposure, based on seven studies up to 2008. Two of the seven studies reported elevated but non-statistically significant adjusted odds ratios (aOR) of 3.17 (95%CI: 0.97, 10.32)¹⁸ and 1.90 (95%CI: 0.81, 4.50)¹⁹ for high versus low exposures to THM4, the sum of four THMs. Of a total of ten previous epidemiological studies on oral clefts and DBPs, three used chlorination and/or water color as proxies for DBP exposure²⁰⁻²², six used THM4 concentrations as proxies for all DBPs^{18,19,23-26}, and one examined chloroform and bromodichloromethane²⁷. Studies with DBP concentration data have varying exposure ranges due to differences in source water and treatment processes across public water systems. Additionally, limited temporal and spatial resolution of DBP monitoring data and lack of direct measures of exposure remain a challenge in evaluating causality. We are

unaware of any previous epidemiological studies examining oral clefts in relation to HAAs, generally the second most prevalent group of DBPs in chlorinated water systems after THMs. No epidemiological studies of DBPs and eye or ear defects have been conducted to date. Although aggregate DBP exposure metrics such as THM4 are commonly used as surrogates for complex DBP exposures in epidemiological studies, they may not fully capture the most toxicologically relevant DBPs of concern, and may lead to measurement error and exposure misclassification bias¹⁷. Thus, there is a need to expand the scope of DBP metrics examined in epidemiological studies.

Our objective was to examine associations between five craniofacial defect (CFD) outcomes [cleft lip with or without cleft palate (CL±P), cleft palate without cleft lip (CP), cleft lip and/or cleft palate (CL/CP), eye defects, and ear defects] and estimates of first trimester exposures for nine individual DBPs [chloroform; bromodichloromethane (BDCM); dibromochloromethane (DBCM); bromoform; trichloroacetic acid (TCAA); dichloroacetic acid (DCAA); monochloroacetic acid (MCAA); dibromoacetic acid (DBAA); and monobromoacetic acid (MBAA)] and four summary DBP metrics [THMBr (sum of BDCM, DBCM, and bromoform); THM4 (sum of THMBr and chloroform); HAA5 (sum of DCAA, TCAA, MCAA, DBAA, and MBAA); and DBP9 (sum of THM4 and HAA5)].

METHODS

Outcome Data

We conducted a case-control study of CFD cases in 113 Massachusetts towns with populations greater than 500 with complete THM4, HAA5, water source, and disinfection type data from 1999-2004. We restricted the analysis to non-chromosomal craniofacial congenital anomalies (n=366 cases, five with multiple CFDs, for a total of 371 CFDs). We individually matched 10 controls to each case, randomly selected without replacement from all live births in Massachusetts based on week of conception, for a total study population of 4,026.

Craniofacial defect cases were diagnosed based on the International Classification of Diseases 9th revision (ICD-9). This included CL±P (ICD-9 codes 749.1, 749.2), CP (749.0), CL/CP (749), anophthalmia (743.0), microphthalmia (743.1), anotia (744.01), and microtia (744.23) up to age one. Cases and controls were singleton live births who weighed at least 350 grams and were between 22 and 44 gestational weeks. For matching and exposure assessment purposes, we calculated week of conception by subtracting gestational age derived from clinical estimates on the birth certificate from the date of birth.

The Massachusetts Department of Public Health provided birth records from 2000 to 2004. The Massachusetts Birth Defects Monitoring Program maintains an active surveillance system which collects data from multiple institutions, including 53 birthing hospitals, one tertiary care hospital, and one specialty hospital in Massachusetts, and from one Rhode Island birth hospital and one Rhode Island tertiary care hospital near the border of the two states. In order to ascertain and confirm cases, their registry system uses multiple data sources including birth certificates, fetal and infant death certificates, hospital discharge

reports, hospital nurseries and neonatal units, and hospital surgical and pathology departments.

Exposure Assessment

We linked public water system data on water source, disinfection treatment type, and DBP concentrations based on quarterly sampling (1999-2004) to birth records by town of residence and month of birth. The Massachusetts Department of Environmental Protection and individual public water utilities supplied these exposure data. THM concentrations were quantified by certified laboratories using capillary column gas chromatography based on EPA Method 502.2²⁸, capillary column gas chromatography/mass spectrometry based on EPA Method 524.2²⁹ and gas chromatography with electron capture detection based on EPA Method 551.1³⁰. The HAA concentrations were quantified based on EPA Methods 552.1 and 552.2³¹ using gas chromatography and electron capture detection and Standard Method 6251B³² using micro liquid-liquid extraction gas chromatography. Detection limits, while variable across laboratories and time, ranged from 0.1 to 2.5 µg/L for the THMs and 0.4 to 5.0 µg/L for the HAAs. Study participant exposure scores were assigned values of zero for any quarterly samples with levels below the detection limit.

We created first trimester DBP exposure scores for nine individual DBPs and four summary DBP mixture measures by averaging quarterly DBP monitoring data across sampling locations within the public drinking water system serving the mother's residential address at birth. Exposure scores were weight-averaged to proportionally reflect the temporal overlap when multiple monitoring quarters coincided with the first trimester. For example, an infant born at gestational age of 38 weeks in January of 2000 would have two first trimester weeks that occurred in the first quarter of 1999 and 11 first trimester weeks that occurred in the second quarter of 1999. Thus, the exposure score would be: ((2/13) times the average DBP concentration for quarter 1 of 1999) + ((11/13) times the average DBP concentration for quarter 2 of 1999) using data from the entire public water system. Residents relying on untreated ground water (e.g., private wells) were assigned DBP concentrations of zero, as untreated groundwater supplies without DBP precursors would not be expected to have any DBP formation. The maternal DBP exposure categories (quintiles, quartiles, or tertiles) for the summary and individual DBP measures were based on the distribution of the available data for oral cleft and eye defect cases and controls. Due to a large proportion of cases with concentrations equal to zero µg/L, DBCM (except for ear defect models), bromoform, MCAA, MBAA, and DBAA were dichotomized at >0 µg/L. To reduce the potential for small cell bias and instability due to small case numbers, ear defect exposure groups were dichotomized at the median across cases and controls for DBP9, THM4, chloroform, THMBr, BDCM, DBCM, HAA5, TCAA, and DCAA. For all analyses, the referent group was based on births in the lowest DBP exposure category.

Statistical Analysis

We used SAS (version 9.4; SAS Institute, Inc., Cary, NC) for statistical analyses. We used Spearman correlation coefficients to compare summary and individual DBP measures. We used conditional logistic regression to estimate aORs and 95% CIs for each of the DBP exposure categories. Given the extensive amount of available birth data, we used a >10%

change-in-estimate approach to identify potential confounding variables. The covariates examined included type of water source (ground or surface) and treatment (chlorination, chloramination, ozone, UV, chlorine dioxide, or untreated), infant's sex, maternal weight gain during pregnancy (modeled as a continuous variable), maternal race (categorized as white, African American, Asian, or others), maternal age (modeled as a continuous variable), maternal education, marital status (not married vs. married, including within 300 days prior to birth), maternal smoking (number of cigarettes per day during pregnancy), parity, number of previous pregnancy terminations, prenatal care payment source, area-level income, trimester prenatal care began (first or after first), number of prenatal care visits, and various clinical factors (abruptio placentae, 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 >4000 grams, previous infant with a congenital anomaly, 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). Birth weight was not included in the models due to the potential for collider bias, as there is evidence that DBPs can affect different fetal growth indices^{33,34}, and low birth weight is more common among babies born with birth defects than those without birth defects³⁵.

All of the covariates we examined were based on individual birth records data except for income, DBP concentrations, type of water source, and type of water treatment. Median household income data for maternal residence at birth were obtained from the 2000 U.S. Census (Geolytics, Inc., East Brunswick, NJ). Aggregate-level income covariates were examined at the town, ZIP code, and census tract levels. We present results based on final models without DBP adjustment as well as multipollutant models adjusting for THM4 in all of the HAA models and adjusting for HAA5 in all of the THM models. Differences in aORs by infant sex were examined via stratification. We performed sensitivity analyses on cases with isolated CFDs by running CP and eye models on cases without multiple anomalies. To evaluate our ability to adequately control for maternal risk factors for oral clefts, we assessed the reliability of self-reported smoking during pregnancy data by comparing associations reported in the literature to univariate models with smoking as the independent variable and CP and CL±P as the dependent variables.

RESULTS

Study Population Characteristics and Congenital Anomalies

Among all reported births from 2000 to 2004 in the study population, there were 371 CFDs occurring in 366 births, comprised of 147 CL±P cases (40% of CFDs; 57 female, 90 male), 131 CP cases (35% of CFDs; 69 female, 62 male), 67 eye defect cases (18% of CFDs; 37 female, 30 male), and 26 ear defect cases (7% of CFDs; 10 female, 16 male).

Eighty-three percent (n=303) of the 366 CFD cases examined had isolated anomalies, whereas 17% (n=63) of the cases had multiple defects, counting CL±P as a single defect distinct from CP. Cases with multiple defects comprised 10% (n=14) of CL±P cases, 23% (n=30) of CP cases, 24% (n=16) of eye cases, and 31% (n=8) of ear cases. By definition, CL

$\pm P$ and CP had no overlapping cases, and no CL $\pm P$ cases had either eye or ear defects. Among the 30 CP cases with multiple anomalies, three had eye defects and two had ear defects. Eye and ear defect cases did not overlap. As shown in Table 1, CFD cases and controls were largely similar across most of the available demographic, socioeconomic, and maternal health history characteristics (descriptive statistics for each specific anomaly are in Supplemental Table 5). However, compared to case mothers, control mothers were more likely to have a college degree (42% vs 32%) and to be married at the time of birth (69% vs 61%).

DBP Ranges and Correlations

Median and interquartile ranges ($\mu\text{g/L}$) for the nine primary DBP metrics were the following: DBP9 [69.1; 41.5-91.1], THM4 [43.7; 28.4-76.2], chloroform [35.4; 15.7-50.2], THMBr [6.4; 4.6-9.4], BDCM [6.0; 4.3-8.0], DBCM [0.5; 0-1.2], HAA5 [22.9; 11.1-31.5], TCAA [11.3; 4.816.4], and DCAA [10.7; 5.0-14.0] (Table 2). We detected Spearman correlation coefficients greater than or equal to 0.9 for the following: DBP9 with THM4, HAA5, chloroform, and TCAA; for HAA5 with TCAA and DCAA; for THM4 with chloroform; and for THMBr with BDCM. Correlations between 0.7 and 0.9 were found for the following combinations: DBP9 with DCAA; HAA5 with THM4 and chloroform; THM4 with DCAA and TCAA; THMBr with DBCM; chloroform with TCAA and DCAA; TCAA with DCAA; and BDCM with DBCM. The strongest correlations among the individual brominated DBPs were between BDCM and DBCM ($r = 0.72$) and between bromoform and DBCM ($r = 0.55$) and DBAA ($r = 0.51$) (Supplemental Table 1).

Confounding Analysis

Covariates identified as potential confounding variables using a $>10\%$ change in estimate standard for inclusion in adjusted regression models are listed in footnotes for Tables 3–5. Additionally, we included THM4 in the fully adjusted models for HAAs and included HAA5 in fully adjusted models for THMs to try to isolate the potential effects of correlated DBPs between these groups.

Main Results

Comparing the highest to lowest exposure groups in the DBP adjusted models, we detected elevated aORs for CP with the predominant HAAs (TCAA and DCAA) and metrics largely comprised of these HAAs (HAA5, DBP9): DBP9 quintiles (aOR range: 1.41-3.52; highest quintile aOR=3.52, 95%CI: 1.07, 11.60), HAA5 quintiles (aOR range: 1.92-2.95; highest quintile aOR=2.91, 95%CI: 0.70, 12.06), TCAA quartiles (aOR range: 1.51-2.66; highest quartile aOR=2.66, 95%CI: 0.90, 7.80), and the upper two DCAA quartiles (aOR range: 2.05-2.34; highest quartile aOR=2.05, 95%CI: 0.78, 5.42) (Table 3). There were no consistent patterns detected between CL $\pm P$ and high exposures across the different DBP measures.

Results for all grouped oral clefts (CL/CP; $n=278$) were largely null, with slightly elevated aORs for several of the same DBP metrics that were elevated for CP, including TCAA quartiles (aOR range: 1.22-1.87; highest quartile aOR=1.87, 95%CI: 0.94, 3.75) and the upper three quintiles of both DBP9 (aOR range: 1.19-1.38; highest quintile aOR=1.31,

95%CI: 0.64, 2.67) and HAA5 (aOR range: 1.28-1.58; highest quintile aOR=1.58, 95%CI: 0.70, 3.58) (Supplemental Table 4).

As shown in the multi-DBP adjusted models from Table 4, elevated aORs for eye defects were detected for all TCAA quartiles (aOR range: 2.12-3.53; highest quartile aOR=3.53, 95%CI: 0.71, 17.49), THM4 quintiles (aOR range: 1.61-3.94; highest quintile aOR=2.31, 95%CI: 0.34, 15.56), and chloroform quartiles (aOR range: 2.83-3.22; highest quartile aOR=2.83, 95%CI: 0.55, 14.56). We detected elevated aORs for eye defects for only the second (2.29; 95%CI: 0.67, 7.82) and fourth (2.42; 95%CI: 0.57, 10.33) highest HAA5 quartiles. Similarly to oral clefts, we did not detect any discernible exposure-response patterns across the various DBP metrics. Although we saw several aORs <1.00 for ear defects, results for ear defects were very unstable due to small cell sizes (Table 5). Given the potential for sparse data bias³⁶, we do not include aORs for categories with fewer than 5 exposed cases including all MBAA models, bromoform and eye defects, and DBAA and ear defects.

Stratification and Sensitivity Analyses

We observed larger aORs for bromoform in females with CL±P and in males with CP, for chloroform in males with CL±P and females with CP, for TCAA in males with CL±P and in females with CP, for MCAA in females with CL±P and females with CP, and for THM4 in males with CL±P and males with CP (Supplemental Tables 2 and 3). Among females, we also detected some anomalously low aORs between CL±P and THM4 and chloroform exposures. Overall, small case numbers resulted in imprecision of these stratified effect estimates, especially for bromoform and MCAA.

We conducted a sensitivity analysis of cases with only isolated CFDs to examine whether the DBP associations differed among cases with isolated versus multiple defects, because cases with multiple anomalies occurring together may reflect a syndrome (i.e. multiple defects related by etiology or pathology) with different etiologies than isolated anomalies^{37,38}. While most aORs only differed slightly in magnitude, aORs were higher for CP and THM4 quintiles (aOR range: 1.40-4.69; highest quintile aOR=4.69; 95%CI: 1.04, 21.21), and were lower for eye defects and TCAA (aOR range: 1.20-2.34; highest quintile aOR=1.82; 95%CI: 0.32, 9.63) and chloroform (aOR range: 1.80-2.58; highest quintile aOR=1.80; 95%CI: 0.29, 11.00) (data not shown).

We ran univariate models that only included maternal tobacco smoking during pregnancy as the independent variable and CL±P and CP as the dependent variables to assess reliability of self-reported maternal smoking data. The ORs were 1.46 (95% CI: 0.92, 2.26) for CL±P and 1.40 (95% CI: 1.02, 1.93) for CP.

DISCUSSION

This is the first epidemiological study of oral clefts to examine HAA exposures, and the first epidemiological study to examine eye and ear defects with DBPs. Whereas most previous studies of oral clefts and DBPs examined both cleft lip and palate defects together (CL/CP), largely with null results, we found several elevated aORs for CP but none for CL±P. Our

results for CL/CP were slightly elevated for the same DBPs as for CP, but were somewhat attenuated due to the inclusion of CL±P. This reinforces the importance of examining these two outcomes separately, as they have distinct etiologies^{3,4}. Although some of our results are due to chance given the large number of odds ratios that were generated in our study, the similarities with some toxicological studies and patterns in associations that we detected across chemically similar DBPs seem noteworthy.

Various differences across epidemiological studies complicate making direct comparisons between studies which examined a grouped CL/CP outcome, including unknown proportions of CP and CL±P. In a meta-analysis including seven studies on oral clefts and DBPs, Nieuwenhuijsen et al.¹⁷ reported a combined aOR for CL/CP of 0.98 (95%CI: 0.88, 1.08), similar to our estimate for CL/CP with the highest THM4 quintile (aOR=1.02; 95%CI 0.46, 2.25). When they restricted the meta-analysis to three studies of isolated CP with quantitative THM4 data, the combined aOR changed slightly to 1.14 (95%CI: 0.80, 1.62). We found a nearly two-fold increased odds of CP with the highest THM4 quintile, the metric examined by most previous studies.

Another challenge to directly comparing our results to those of other studies is the variation in DBP concentrations in different regions, and thus the variation in DBP ranges used to create exposure categories. Of the seven previous studies of DBPs and oral clefts which used quantitative DBP measurements to assign exposures, five had THM4 ranges similar to our study population^{18,19,24,25,27} and two had much lower ranges^{23,26}, leading to the use of different categorical cutpoints and referent groups. In comparing odds of oral clefts with THM4 exposure categories, we used a referent and high exposure group with ranges of 0-20 vs. 64-118 µg/L respectively, while the contrasts in other studies were 0-49 vs. >100 µg/L²⁵, <30 vs. 60-131 µg/L²⁴, 20 vs. >100 µg/L¹⁸, 0 vs. 50-75 µg/L¹⁹, 0-4 vs. 20-33 µg/L²³, and 5 vs. >10 µg/L²⁶.

There is limited evidence from animal studies with which to compare our results for oral clefts. An inhalation study in mice reported CP defects following exposure to chloroform on gestation days 8-15, but not for exposure on days 6-15¹⁴. Other developmental toxicity studies in rodents or rabbits failed to show teratogenicity for chloroform and the brominated THMs^{39,40,41,42,43,44}. Our results for CP with chloroform (highest quintile aOR=1.33; 95%CI: 0.39, 4.56) were weaker than for THM4 (highest quintile aOR=1.91; 95%CI: 0.56, 6.58), the metric used by most previous epidemiological studies on oral clefts and DBPs. We detected elevated aORs for CP with TCAA and DCAA. Although we found a zebrafish study that reported mouth or jaw malformations following DCAA exposure¹⁵, we identified no additional toxicological studies in the literature for comparison.

We did not observe any consistent patterns in elevated aORs for oral clefts with brominated THM exposures, similar to the null results found by the three previous studies to have examined THMBr²⁴, BDCM^{19,27}, DBCM²⁷, and bromoform²⁴. Brominated THM exposure categories varied somewhat between our study and previous studies, though all generally had low concentration ranges. For example, we used referent and high exposure groups for BDCM of 4.8 vs. >7.1 µg/L, whereas Dodds and King²⁷ used <5 vs. 20 µg/L, and Shaw et al.¹⁹ used <9.6 vs. 9.6 µg/L. To our knowledge, there are no toxicological studies

demonstrating cleft defects following prenatal exposure to brominated DBPs^{44,45}. We observed elevated though imprecise associations for eye defects with HAA5, TCAA, and chloroform. Although previous epidemiological studies of DBPs and eye defects were not identified, eye defects have been reported in animal developmental toxicity studies with HAA5¹⁰, TCAA^{9,11}, and chloroform¹³. We did not see any strong evidence for associations between DBP exposures and ear defects, but the ear and eye defect analyses had limited statistical power.

We examined five individual HAAs and four individual THMs, which provided greater specificity than examined in previous research on oral clefts and DBPs. However, over 600 different DBPs have been identified from various disinfection processes^{6,7}, so some of the elevated aORs that we observed may be markers for the effects of unmeasured or unknown DBPs. Thus, commonly measured DBP mixture metrics like THM4 and HAA5 may be poor surrogates for the most toxicologically relevant DBPs for adverse reproductive outcomes. For example, a previous study⁴⁶ of 11 municipal water systems in Spain reported Spearman correlations of $r=0.25$ and $r=-0.27$, respectively, for total acetonitriles with THM4 and HAA9 (sum of HAA5 and four other HAAs), indicating that THM4 and HAA9 would be poor proxies for acetonitrile concentrations. The inclusion of water source, treatment type, and THM4 or HAA5 as covariates in our models may control for some potential confounding by unmeasured drinking water contaminants, including DBPs. For example, we saw smaller aORs in most of our elevated results following DBP adjustment. While THMs and HAAs are often correlated in chlorinated drinking water systems, correlations between individual species vary in different water systems, so the impact of confounding by DBPs in other studies is unknown.

A primary limitation in most epidemiological studies of DBPs is the potential for misclassification of exposure due to the absence of individual-level exposure data, since inter- and intra-individual variability in water use patterns is not considered. Our exposure data were quarterly monitoring data collected routinely for all water systems in our study area. Some DBPs, such as the THMs, are known to vary seasonally⁴⁷. Therefore, quarterly data likely do not fully capture temporal variability that may impact exposure and effect estimates, preventing considerations of peak exposures during specific critical windows of fetal development. For example, the critical *in utero* exposure period for CFDs is during the fourth through ninth weeks of gestation (weeks four to seven for cleft lip, six to nine for cleft palate, four to eight for eye defects, and four to nine for ear defects⁴⁸), but we did not have samples that corresponded exactly with that time period. Thus, our use of weighted first-trimester average DBP exposures may result in exposure misclassification, which we would largely expect to be non-differential with respect to case status.

In addition to uncaptured temporal variability, town-level average DBP concentrations in public water systems with significant spatial variability may not accurately reflect residential values. We are confident, however, that our exposure assessment approach generally captures relative rankings of overall DBP exposure categories. We recognize that such potential measurement error sources can lead to exposure misclassification, which may bias our results and impact our ability to detect exposure-response relationships that may exist. We did not have individual-level addresses for study participants, which precluded more

spatially-resolved exposure estimates. Therefore, future research should further quantify the impact of spatial variability on exposure scores or use more sophisticated approaches to link sampling location-specific data with individual addresses and/or model or collect residential-level data.

Another potential source of exposure misclassification is due to residential mobility, where the reported address at birth differed from residential address during the critical first-trimester exposure window. A review of 14 environmental epidemiological studies of birth outcomes demonstrated that most residential moves occurred during the second trimester among the 9-32% of women who reported moving during pregnancy⁴⁹. Residential moves during pregnancy are frequently short in distance, with just 8% of cases relocating to a different county during pregnancy^{49,50}. This implies that many moves during pregnancy probably occur between residences that are on the same public water system. The impact of mobility on our study results is difficult to determine, however, a previous study of neural tube defects and DBPs found stronger associations among mothers with confirmed residences at conception when compared to the overall study population⁵¹. We would expect residential mobility to be non-differential with respect to case status, thus the impact of residential mobility on our results is likely minimal.

One concern when analyzing congenital anomaly data is that some cases are missed due to elective termination upon prenatal diagnosis of a congenital anomaly. Oral clefts generally have a positive prognosis, so elective termination rates are lower than for congenital anomalies with lower survival rates, such as neural tube defects and chromosomal disorders⁵². An analysis of 1987 to 1996 data from the Hawaii Birth Defects Program calculated prenatal diagnosis rates of 14% for cleft lip and 0% for cleft palate⁵³. Of the 32 cleft lip cases identified prenatally, 11 were electively terminated; however, these cases also had prenatal diagnoses of more serious congenital anomalies. This study estimated an increase of five percent in the prevalence of cleft lip cases in Hawaii when rates among elective terminations were included with rates among livebirths and stillbirths. We do not believe that significant under-ascertainment of oral clefts occurred in our study, given that the Massachusetts Birth Defects Monitoring System is an active surveillance system that follows births up to one year.

Globally, it is estimated that approximately one third of oral cleft cases occur as part of a syndrome of multiple congenital anomalies, with the occurrence of syndromic cases higher among CP (approximately 50%) than CL±P (approximately 14%)^{54,55}. Syndromic cases are thought to have different pathogeneses than oral clefts occurring alone^{37,38}. Thus, some of the 63 CFD cases in our dataset that also had other congenital anomalies could have had syndromic birth defects. As part of our sensitivity analysis of isolated cases only, we did not see substantial changes in aORs, except for an increase for CP with THM4 quintiles from a range of 1.03-1.91 to a range of 1.40-4.69 (highest quintile aOR=4.69; 95%CI: 1.04, 21.21) (data not shown). This restricted subset may more accurately reflect THM4 associations for specific CFDs like CP, although our ability to more fully examine the potential impact of DBPs on syndromic versus isolated cases was limited given small case numbers with multiple anomalies and the variety of syndromes involving oral clefts.

Male infants are more likely to have CL±P, whereas female infants are slightly more likely to have CP⁵⁶. Our study had 90 males and 57 females with CL±P, and 69 females and 62 males with CP. Though we observed some large differences in aOR when stratified by sex for certain DBPs, it is unclear how sex would interact with DBP exposure to influence risk. The largest differences were seen for CL±P with chloroform exposure quintiles, for which aORs ranged from 2.56 to 4.04 for males and from 0.10 to 0.14 for females. We suspect that these anomalously low aORs may be due to chance, since we are not aware of any biologically plausible explanations for these inverse associations based on the existing weight of epidemiologic and toxicological evidence. Statistical power limitations also hindered our ability to examine effect measure modification, as well as some of our main analyses for these rare outcomes.

We addressed the ability of vital records data to accurately reflect the prevalence of important maternal risk factors for congenital anomalies. The Massachusetts Department of Public Health advised that the birth records data on self-reported maternal alcohol consumption are considered of questionable validity, thus we did not examine this potential confounder. Evidence for positive associations between maternal alcohol use during pregnancy and oral clefts is mixed^{57–63}, with the strongest evidence for binge-level drinking^{56,58}. Given that alcohol use during pregnancy is unlikely to vary with DBP concentrations, we would not expect residual confounding from alcohol use to bias our study results. We had more confidence in the self-reported smoking data, since previous research has indicated concordance between cotinine levels and mothers' self-reported cigarette use during pregnancy⁶⁴. We have also previously shown strong relationships between maternal cigarette smoking during pregnancy and fetal growth measures based on these birth records data^{65,66}. In the current study, univariate results that only included maternal tobacco smoking during pregnancy [ORs = 1.46 (95% CI: 0.92, 2.26) for CL±P and 1.40 (95% CI: 1.02, 1.93) for CP] were similar to those of a 2004 meta-analysis based on 24 studies that estimated relative risks from any maternal smoking during pregnancy [RRs=1.34 (95% CI: 1.25, 1.44) for CL±P and 1.22 (95% CI: 1.10, 1.35) for CP]⁶⁷. These data, therefore, would suggest that risk ratios around 1.4 are unlikely explanations for the results that we detected that were considerably larger in magnitude.

CONCLUSION

Given that HAAs are generally the second most prevalent group of DBPs after THMs, and that oral clefts are among the most common congenital anomalies, our findings of elevated odds between CP and HAA5, TCAA, and DCAA may have public health significance if supported by future research. Since our ability to examine brominated HAAs was limited to DBAA, epidemiological research should expand on the HAAs that we examined to include MBAA, bromochloroacetic acid (BCAA), bromodichloroacetic acid (BDCAA), chlorodibromoacetic acid (CDBAA), and tribromoacetic acid (TBAA), as well as to other DBPs such as haloacetonitriles. Additional toxicological research on HAAs and specific oral cleft defects could elucidate some associations observed in our study and help indicate which DBP mixtures are most relevant to examine. Challenges in exposure assessment remain due to the wide variety in formation and presence of DBPs, lack of individual-level exposure concentrations, and lack of data on relative contributions from different water-

related activities (i.e. drinking, bathing, swimming, cooking, washing dishes, etc.). Small case numbers for congenital anomalies limited the ability to observe potential associations small in magnitude and to assess potential effect measure modification, so future studies should be designed to address these issues. Although disinfection of water is one of the most important public health interventions globally, further research on health impacts of unwanted chemical contaminants such as DBPs can inform comparative risk efforts related to public drinking water.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Study Characteristics of Craniofacial Defect (CFD) Cases and Controls

	Study Population, <i>n</i> (%)	CFD Cases, <i>n</i> (%)	Controls, <i>n</i> (%)
Total Births	4,026 (100)	366 (100)	3,660 (100)
Infant Sex			
Male	2,076 (51.6)	196 (53.6)	1,880 (51.4)
Female	1,950 (48.4)	170 (46.4)	1,780 (48.6)
Maternal Age (year)			
20	375 (9.3)	39 (10.7)	336 (9.2)
>20–25	687 (17.1)	74 (20.2)	613 (16.7)
>25–30	1,045 (26.0)	84 (23.0)	961 (26.3)
>30–35	1,224 (30.4)	104 (28.4)	1,120 (30.6)
>35–40	600 (14.9)	56 (15.3)	544 (14.9)
>40	95 (2.4)	9 (2.5)	86 (2.3)
Maternal Race			
White	2,649 (65.9)	248 (67.8)	2,401 (65.6)
African American	388 (9.7)	23 (6.3)	365 (10.0)
Asian	308 (7.7)	29 (7.9)	279 (7.6)
Others	677 (16.8)	66 (18.0)	611 (16.7)
Missing	4 (0.1)	0 (0)	4 (0.1)
Maternal Education			
Below high school graduate/GED	499 (12.4)	55 (15.0)	444 (12.1)
High school graduate/GED	1,072 (26.6)	121 (33.1)	951 (26.0)
Some college or associates/technical degree	819 (20.3)	74 (20.2)	745 (20.4)
College or higher	1,636 (40.6)	116 (31.7)	1,520 (41.5)
Marital Status			
Married	2,763 (68.6)	224 (61.2)	2,539 (69.4)
Unmarried	1,263 (31.4)	142 (38.8)	1,121 (30.6)
Number of Previous Births			
0	1,831 (45.5)	169 (46.2)	1,662 (45.4)
1	1,314 (32.7)	119 (32.5)	1,195 (32.7)
2	876 (21.8)	78 (21.3)	798 (21.8)
Missing	5 (0.1)	0 (0)	5 (0.1)
Maternal Weight Gain during Pregnancy			
<0	54 (1.4)	6 (1.6)	48 (1.3)
0–25	1,544 (38.7)	155 (42.3)	1,389 (38.0)
25–50	2,262 (56.7)	189 (51.6)	2,073 (56.6)
>50	132 (3.3)	14 (3.8)	118 (3.2)
Missing	34 (0.8)	2 (0.5)	32 (0.9)

	Study Population, <i>n</i> (%)	CFD Cases, <i>n</i> (%)	Controls, <i>n</i> (%)
Maternal Smoking during Pregnancy (# cigarettes during pregnancy)			
0	3,703 (92.0)	330 (90.2)	3,373 (92.2)
1–5	122 (3.0)	10 (2.7)	112 (3.1)
6–10	134 (3.3)	19 (5.2)	115 (3.1)
>10	67 (1.7)	7 (1.9)	60 (1.6)
Number of Prenatal Care Visits			
<9	423 (10.5)	47 (12.8)	376 (10.3)
9–11	995 (24.7)	76 (20.8)	919 (25.1)
12	1,180 (29.3)	100 (27.3)	1080 (29.5)
13–15	1,042 (25.9)	103 (28.1)	939 (25.7)
>15	368 (9.1)	38 (10.4)	330 (9.0)
Missing	18 (0.4)	2 (0.5)	16 (0.4)
Prenatal Care Source of Payment			
Public	1,085 (27.0)	117 (32.0)	968 (26.4)
Private	2,627 (65.3)	218 (59.6)	2,409 (65.8)
Other	314 (7.8)	31 (8.5)	283 (7.7)
Trimester Prenatal Care Began			
First trimester	3279 (81.4)	292 (79.8)	2987 (81.6)
After first trimester	731 (18.2)	74 (20.2)	657 (18.0)
Missing	16 (0.4)	0 (0.0)	16 (0.4)
Median Household Income (based on ZIP code from 2000)			
\$12,307–36,836	1,006 (25.0)	105 (28.7)	901 (24.6)
>\$36,836–45,654	951 (23.6)	86 (23.5)	865 (23.6)
>\$45,654–57,815	997 (24.8)	89 (24.3)	908 (24.8)
>\$57,815–153,918	1,072 (26.6)	86 (23.5)	986 (26.9)
Complications during labor and delivery			
Yes	898 (22.3)	98 (26.8)	800 (21.9)
No	3,118 (77.4)	267 (73.0)	2,851 (77.9)
Missing	10 (0.2)	1 (0.3)	9 (0.2)
Induced labor			
Yes	724 (18.0)	72 (19.7)	652 (17.8)
No	3,293 (81.8)	293 (80.1)	3,000 (82.0)
Missing	9 (0.2)	1 (0.3)	8 (0.2)

Note: GED = General Educational Development

Table 2
First Trimester Disinfection Byproduct (µg/L) Exposure Levels for the Study Population

DBP Metric	Mean	Std Dev	25 th %	50 th %	75 th %	90 th %	Maximum
DBP9	64.10	37.08	41.52	69.13	91.09	107.64	166.20
THM4	41.66	24.22	28.38	43.69	59.67	71.88	118.35
Chloroform	33.85	21.65	15.67	35.44	50.17	62.07	99.49
THMBr	7.81	6.26	4.60	6.41	9.40	17.33	35.68
BDCM	6.51	4.82	4.30	6.03	8.03	12.65	34.90
DBCM	1.20	1.95	0.00	0.46	1.24	3.81	14.24
Bromoform	0.10	0.40	0.00	0.00	0.00	0.18	5.91
HAA5	22.44	15.02	11.12	22.90	31.50	42.30	94.62
TCAA	11.52	8.45	4.85	11.27	16.42	22.50	67.69
DCAA	10.00	6.76	4.99	10.72	14.01	18.61	38.89
MCAA	0.76	2.64	0.00	0.07	0.82	1.50	35.89
DBAA	0.15	0.61	0.00	0.00	0.00	0.45	17.68
MBAA	0.02	0.22	0.00	0.00	0.00	0.00	9.63

Abbreviations: DBP, disinfection by-product; DBP9, sum of chloroform, bromodichloromethane (BDCM), dibromochloromethane (DBCM), bromoform, monochloroacetic acid (MCAA), dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), bromoacetic acid, (BMAA), and dibromoacetic acid (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.

Table 3

Adjusted Odds Ratios (aORs) between Disinfection By-product (DBP) Exposures and Cleft Lip with or without Cleft Palate and Cleft Palate without Cleft Lip

DBP Metrics ($\mu\text{g/L}$)	Cleft Lip with or without Cleft Palate (CL $\pm$ P)		Cleft Palate without Cleft Lip (CP)	
	n ^a	aOR (95% CI)	n ^a	aOR (95% CI) ^f
THM4				
0.00-20.27	37	Ref ^b	21	Ref ^f
>20.27-37.69	24	0.75 (0.31, 1.84) ^b	24	1.03 (0.35, 3.03) ^f
>37.69-49.90	31	0.98 (0.39, 2.45) ^b	32	1.67 (0.55, 5.06) ^f
>49.90-63.86	28	0.89 (0.34, 2.33) ^b	22	1.06 (0.33, 3.41) ^f
>63.86-118.35	27	0.66 (0.24, 1.87) ^b	31	1.91 (0.56, 6.58) ^f
THMBr				
0.00-5.16	66	Ref ^c	43	Ref ^g
>5.16-8.11	33	0.51 (0.29, 0.90) ^c	37	0.84 (0.45, 1.56) ^g
>8.11-35.68	48	0.73 (0.44, 1.21) ^c	50	1.18 (0.65, 2.15) ^g
Chloroform				
0.00-10.88	37	Ref ^b	21	Ref ^f
>10.88-29.91	28	0.84 (0.35, 2.03) ^b	21	0.83 (0.28, 2.43) ^f
>29.91-41.89	28	0.76 (0.29, 1.99) ^b	38	1.72 (0.56, 5.27) ^f
>41.89-54.53	27	0.71 (0.26, 1.97) ^b	24	0.93 (0.29, 3.05) ^f
>54.53-99.49	27	0.59 (0.20, 1.58) ^b	26	1.33 (0.39, 4.56) ^f
Bromodichloromethane (BDCM)				
0.00-4.84	63	Ref ^c	45	Ref ^g
>4.84-7.06	39	0.68 (0.39, 1.19) ^c	34	0.64 (0.35, 1.19) ^g
>7.06-34.90	45	0.74 (0.45, 1.23) ^c	51	1.04 (0.60, 1.80) ^g
Dibromochloromethane (DBCM)				

DBP Metrics (µg/L)	Cleft Lip with or without Cleft Palate (CL±P)		Cleft Palate without Cleft Lip (CP)	
	n ^a	aOR (95% CI)	n ^a	aOR (95% CI) ^j
0.00	61	Ref ^c	43	Ref
>0.00-14.24	86	0.69 (0.40, 1.21) ^c	87	1.11 (0.62, 1.99) ^g
Bromoform				
0.00	126	Ref ^c	117	Ref
>0.00-5.91	21	1.17 (0.63, 2.17) ^c	13	0.84 (0.41, 1.69) ^g
HAA5				
0.00 – 7.38	38	Ref ^d	19	Ref
>7.38-19.62	21	0.60 (0.25, 1.46) ^d	25	1.92 (0.54, 6.87) ^h
>19.62-26.34	35	1.18 (0.46, 3.04) ^d	24	1.97 (0.51, 7.64) ^h
>26.34-34.20	20	0.59 (0.20, 1.75) ^d	33	2.95 (0.72, 12.04) ^h
>34.20-94.62	33	0.98 (0.34, 2.77) ^d	30	2.91 (0.70, 12.06) ^h
Trichloroacetic acid (TCAA)				
0.00-4.85	41	Ref ^d	23	Ref
>4.85-11.27	39	1.28 (0.60, 2.72) ^d	36	1.78 (0.71, 4.47) ^h
>11.27-16.42	27	0.91 (0.37, 2.27) ^d	30	1.51 (0.53, 4.32) ^h
>16.42-67.69	39	1.20 (0.48, 3.01) ^d	41	2.66 (0.90, 7.80) ^h
Dichloroacetic acid (DCAA)				
0.00-4.99	44	Ref ^d	25	Ref
>4.99-10.72	33	0.90 (0.44, 1.85) ^d	26	1.11 (0.47, 2.61) ^h
>10.72-14.01	34	0.90 (0.40, 2.02) ^d	44	2.34 (0.93, 5.85) ^h
>14.01-38.89	35	0.80 (0.33, 1.92) ^d	35	2.05 (0.78, 5.42) ^h
Monochloroacetic acid (MCAA)				
0.00	75	Ref ^d	56	Ref
>0.00-35.89	71	1.11 (0.73, 1.68) ^d	74	0.99 (0.65, 1.52) ^h

DBP Metrics (µg/L)	Cleft Lip with or without Cleft Palate (CL±P)		Cleft Palate without Cleft Lip (CP)		
	n ^a	aOR (95% CI)	aOR (95% CI) ^j	n ^a	aOR (95% CI)
Dibromooacetic acid (DBAA)					
0.00	110	Ref ^d	Ref	110	Ref ^h
>0.00-14.72	36	1.23 (0.78, 1.94) ^d	1.24 (0.80, 1.93)	20	0.55 (0.32, 0.95) ^h
DBP9					
0.00-30.66	38	Ref ^e	NA	20	Ref ⁱ
>30.66-59.96	31	0.93 (0.41, 2.08) ^e	NA	22	1.41 (0.45, 4.43) ^j
>59.96-78.69	20	0.62 (0.26, 1.50) ^e	NA	33	2.71 (0.87, 8.46) ^j
>78.69-96.32	33	1.10 (0.47, 2.56) ^e	NA	25	2.06 (0.64, 6.59) ^j
>96.32-166.20	25	0.63 (0.26, 1.54) ^e	NA	30	3.52 (1.07, 11.60) ^j

Note: CI = confidence interval; DBP9 = sum of chloroform, BDCM, DBCM, bromoform, MCAA, DCAA, TCAA, BMAA, and DBAA; HAA5 = sum of MCAA, DCAA, TCAA, BMAA, and DBAA; THM4 = sum of chloroform, BDCM, DBCM, and bromoform; THMBr = sum of BDCM, DBCM, and bromoform. NA=not applicable.

^aThe numbers represent the case distribution across exposure groups prior to modeling.

^bCL±P & THM4/chloroform: Models adjusted for water treatment type, maternal education, census tract income, HAA5

^cCL±P & THMBr/BDCM/DBCM/bromoform: Models adjusted for water source and treatment type, census tract income, HAA5

^dCL±P & HAA5/TCAA/DCAA/MCAA/DBAA: Models adjusted for water source and treatment type, census tract income, THM4

^eCL±P & DBP9: Models adjusted for water source and treatment type, census tract income

^fCP & THM4/chloroform: Models adjusted for water source and treatment type, zip code income, trimester prenatal care began, maternal race, number of prenatal care visits, HAA5

^gCP & THMBr/BDCM/DBCM/bromoform: Models adjusted for water source and treatment type, census tract income, number of prenatal care visits, HAA5

^hCP & HAA5/TCAA/DCAA/MCAA/DBAA: Models adjusted for water source and treatment type, zip code income, maternal race, THM4

ⁱCP & DBP9: Models adjusted for water source and treatment type, zip code income, maternal race, number of prenatal care visits

^jModels in these columns are identical to models immediately to the left, except for the exclusion of THM4 or HAA5.

Table 4

Adjusted Odds Ratios (aORs) between Disinfection By-product (DBP) Exposures and Eye Defects

DBP Metrics (µg/L)	Eye Defects		
	n ^a	aOR (95% CI)	aOR (95% CI) ^f
THM4^b			
0.00-19.54	15	Ref	Ref
>19.54-39.80	11	1.61 (0.30, 8.46)	1.52 (0.30, 7.82)
>39.80-50.54	11	1.91 (0.32, 11.25)	1.75 (0.32, 9.62)
>50.54-62.53	18	3.94 (0.66, 23.67)	3.54 (0.65, 19.12)
>62.53-110.72	12	2.31 (0.34, 15.56)	2.00 (0.36, 11.21)
THMBr^c			
0.00-5.56	25	Ref	Ref
>5.56-7.62	22	1.08 (0.46, 2.54)	1.07 (0.45, 2.52)
>7.62-33.08	20	0.77 (0.33, 1.79)	0.76 (0.33, 1.78)
Chloroform^b			
0.00-15.67	16	Ref	Ref
>15.67-38.02	20	3.22 (0.84, 12.31)	3.12 (0.85, 11.48)
>38.02-49.79	16	2.87 (0.67, 12.31)	2.71 (0.69, 10.60)
>49.79-99.49	15	2.83 (0.55, 14.56)	2.62 (0.60, 11.53)
Bromodichloromethane (BDCM)^c			
0.00-5.11	25	Ref	Ref
>5.11-6.69	21	1.15 (0.48, 2.79)	1.16 (0.48, 2.81)
>6.69-32.53	21	0.88 (0.39, 1.99)	0.90 (0.40, 2.02)
Dibromochloromethane (DBCM)^c			
0.00	27	Ref	Ref
>0.00-9.84	40	0.82 (0.36, 1.88)	0.79 (0.35, 1.77)
HAA5^d			
0.00-9.96	17	Ref	Ref
>9.96-24.54	20	2.29 (0.67, 7.82)	2.38 (0.75, 7.57)
>24.54-31.62	10	1.04 (0.24, 4.50)	1.11 (0.29, 4.19)
>31.62-66.36	20	2.42 (0.57, 10.32)	2.59 (0.74, 9.14)
Trichloroacetic acid (TCAA)^d			
0.00-4.62	16	Ref	Ref
>4.62-11.83	19	3.05 (0.78, 11.95)	2.96 (0.80, 10.88)
>11.83-17.02	12	2.12 (0.45, 10.07)	2.02 (0.49, 8.39)
>17.02-40.77	19	3.53 (0.71, 17.49)	3.34 (0.83, 13.45)
Dichloroacetic acid (DCAA)^d			
0.00-5.03	21	Ref	Ref

DBP Metrics (µg/L)	Eye Defects		
	n ^a	aOR (95% CI)	aOR (95% CI) ^f
>5.03-10.81	15	0.59 (0.20, 1.71)	0.73 (0.27, 1.97)
>10.81-14.37	14	0.46 (0.14, 1.56)	0.63 (0.21, 1.90)
>14.37-33.22	16	0.48 (0.13, 1.72)	0.72 (0.24, 2.13)
Monochloroacetic acid (MCAA)^d			
0.00	29	Ref	Ref
>0.00-15.44	37	1.29 (0.67, 2.48)	1.33 (0.70, 2.54)
Dibromoacetic acid (DBAA)^d			
0.00	59	Ref	Ref
>0.00-2.69	7	0.39 (0.17, 0.93)	0.39 (0.17, 0.90)
DBP9^e			
0.00-29.11	15	Ref	NA
>29.11-62.86	12	1.38 (0.28, 6.89)	NA
>62.86-79.57	14	1.76 (0.33, 9.32)	NA
>79.57-95.45	13	2.03 (0.36, 11.39)	NA
>95.45-156.10	13	1.57 (0.28, 8.73)	NA

Note: CI = confidence interval; DBP9 = sum of chloroform, BDCM, DBCM, bromoform, MCAA, DCAA, TCAA, BMAA, and DBAA; HAA5 = sum of MCAA, DCAA, TCAA, BMAA, and DBAA; THM4 = sum of chloroform, BDCM, DBCM, and bromoform; THMBr = sum of BDCM, DBCM, and bromoform. NA=not applicable.

^aThe numbers represent the case distribution across exposure groups prior to modeling.

^bTHM4/chloroform: Models adjusted for water source and treatment type, zip code income, trimester prenatal care began, number of prenatal care visits, HAA5

^cTHMBr/BDCM/DBCM: Models adjusted for water source and treatment type, number of prenatal care visits, complications during labor and delivery, HAA5

^dHAA5/TCAA/DCAA/MCAA/DBAA: Models adjusted for water source and treatment type, zip code income, trimester prenatal care began (1st, >1st), number of prenatal care visits, THM4

^eDBP9: Models adjusted for water source and treatment type, zip code income, trimester prenatal care began (1st, >1st), number of prenatal care visits

^fModels in this column are identical to models immediately to the left, except for the exclusion of THM4 or HAA5.

Table 5

Adjusted Odds Ratios (aORs) between Disinfection By-Product (DBP) Exposures and Ear Defects

DBP Metrics (µg/L)	Ear Defects		
	n ^a	aOR (95% CI)	aOR (95% CI) ^f
THM4^b			
0.00-43.58	14	Ref	Ref
>43.58-100.61	11	0.50 (0.14, 1.74)	0.54 (0.17, 1.75)
THMBr^c			
0.00-7.49	10	Ref	Ref
>7.49-35.21	15	1.65 (0.43, 6.40)	1.65 (0.43, 6.41)
Chloroform^b			
0.00-34.33	13	Ref	Ref
>34.33-85.50	12	0.87 (0.24, 3.22)	0.88 (0.26, 3.00)
Bromodichloromethane (BDCM)^c			
0.00-6.55	11	Ref	Ref
>6.55-34.61	14	1.21 (0.35, 4.15)	1.21 (0.36, 4.12)
Dibromochloromethane (DBCM)^c			
0.00-0.62	9	Ref	Ref
>0.62-13.92	16	1.59 (0.44, 5.82)	1.53 (0.44, 5.36)
Bromoform^c			
0.00	18	Ref	Ref
>0.00-5.35	7	1.74 (0.39, 7.69)	1.76 (0.41, 7.64)
HAA5^d			
0.00-21.19	14	Ref	Ref
>21.19-70.31	11	0.77 (0.22, 2.68)	0.75 (0.23, 2.50)
Trichloroacetic acid (TCAA)^d			
0.00-10.96	13	Ref	Ref
>10.96-38.92	11	0.94 (0.23, 3.88)	0.87 (0.24, 3.16)
Dichloroacetic acid (DCAA)^d			
0.00-10.11	13	Ref	Ref
>10.11-30.54	11	0.87 (0.25, 3.07)	0.84 (0.24, 2.88)
Monochloroacetic acid (MCAA)^d			
0.00	14	Ref	Ref
>0.00-28.13	10	0.23 (0.07, 0.73)	0.25 (0.08, 0.76)
DBP9^e			
0.00-67.75	13	Ref	NA
>67.75-158.71	12	0.99 (0.29, 3.36)	NA

Note: CI = confidence interval; DBP9 = sum of chloroform, BDCM, DBCM, bromoform, MCAA, DCAA, TCAA, BMAA, and DBAA; HAA5 = sum of MCAA, DCAA, TCAA, BMAA, and DBAA; THM4 = sum of chloroform, BDCM, DBCM, and bromoform; THMBr = sum of BDCM, DBCM, and bromoform. NA=not applicable.

^aThe numbers represent the case distribution across exposure groups prior to modeling.

^bTHM4/chloroform: Models adjusted for water source and treatment type, area level income, maternal education, prenatal care payment source, maternal health index (includes chronic or pregnancy-related hypertension, chronic or gestational diabetes, cardiac disease, eclampsia, hydramnios/oligohydramnios), maternal marital status, induced labor, infant's sex, maternal weight gain during pregnancy, maternal age, parity, number of prenatal care visits, HAA5

^cTHMBr/BDCM/DBCM/bromoform: Models adjusted for water source and treatment type, area level income, maternal education, prenatal care payment source, maternal weight gain during pregnancy, induced labor, complications during labor and delivery, maternal health index (includes chronic or pregnancy-related hypertension, chronic or gestational diabetes, cardiac disease, eclampsia, hydramnios/oligohydramnios), maternal age, parity, number of previous pregnancy terminations, number of prenatal care visits, HAA5

^dHAA5/TCAA/DCAA/MCAA: Models adjusted for water source and treatment type, area level income, maternal education, prenatal care payment source, maternal marital status, induced labor, complications during labor and delivery, maternal health index (includes chronic or pregnancy-related hypertension, chronic or gestational diabetes, cardiac disease, eclampsia, hydramnios/oligohydramnios), number of prenatal care visits, maternal age, parity, THM4

^eDBP9: Models adjusted for water source and treatment type, area level income, prenatal care payment source, maternal health index (includes chronic or pregnancy-related hypertension, chronic or gestational diabetes, cardiac disease, eclampsia, hydramnios/oligohydramnios), maternal marital status, induced labor, infant's sex, maternal weight gain during pregnancy, complications during labor and delivery, maternal age, parity, number of prenatal care visits

^fModels in this column are identical to models immediately to the left, except for the exclusion of THM4 or HAA5.