Drinking water disinfection byproducts and risk of orofacial clefts in the National Birth Defects Prevention Study

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Abstract

Background: Maternal exposure to drinking water disinfection byproducts (DBP)s may contribute to orofacial cleft (OFC) development, but studies are sparse and beset with limitations.

Methods: Population-based, maternal interview reports of drinking water filtration and consumption for 680 OFC cases (535 isolated) and 1826 controls were linked with DBP concentration data using maternal residential addresses and public water system monitoring data. Maternal individual-level exposures to trihalomethanes (THM)s and haloacetic acids (HAA)s (μg/L of water consumed) were estimated from reported consumption at home, work, and school. Compared to no exposure, associations with multisource maternal exposure <1/2 or ≥1/2 the Maximum Contaminant Levels (MCL)s for total THMs (TTHM)s and HAAs (HAA5) or Maximum Contaminant Level Goals (MCLG)s for individual THMs and HAAs (if non-zero) were

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estimated for all OFCs and isolated OFCs, cleft palate (CP), and cleft lip ± cleft palate (CL/P) using logistic regression analyses.

Results: Compared to controls, associations were near or below unity for maternal TTHM, HAA5, and individual THM exposures with all OFCs and isolated OFCs, CP, and CL/P. Associations also were near or below unity for individual HAAs with statistically significant, inverse associations observed with each OFC outcome group except CL/P.

Conclusions: This study examined associations for maternal reports of drinking water filtration and consumption and maternal DBP exposure from drinking water with OFCs in offspring. Associations observed were near or below unity and mostly nonsignificant. Continued, improved research using maternal individual-level exposure data will be useful in better characterizing these associations.

Keywords

1 | INTRODUCTION

Orofacial clefts (OFC)s are among the most common human birth defects and are estimated to affect 1 per 700 live births worldwide (Mossey & Castillia, 2003). Disruption of the development of the lip or palate may result in distinct OFC subtypes, including cleft lip only (CL), cleft lip with cleft palate (CLP), or cleft palate only (CP) (Burdi, 2006). Numerous candidate gene studies and more recent genome-wide association studies have identified several susceptibility loci for OFCs. Similarly, numerous epidemiologic studies have examined maternal and paternal exposures for OFCs (reviewed in Leslie & Marazita, 2013; reviewed in Mehrotra, 2015). With the exception of maternal cigarette smoking (Little, Cardy, & Munger, 2004; Sabbagh et al., 2015), findings for most exposures investigated are mixed (Mossey, Little, Munger, Dixon, & Shaw, 2009), and studies of some exposures, such as drinking water contaminants, are sparse (Brender et al., 2013; reviewed in Nieuwenhuijsen et al., 2009).

Water disinfection byproducts (DBP)s are common drinking water contaminants and are formed when disinfectants (e.g., chlorine) react with bromide and natural organic matter in raw (untreated) water during the drinking water treatment process (Singer, 1994). Under the Safe Drinking Water Act, the United States (U.S.) Environmental Protection Agency (EPA) has set National Primary Drinking Water Regulations for several DBPs, including the more commonly measured trihalomethanes (THM)s and haloacetic acids (HAA)s. The U.S. EPA currently regulates THMs as total THMs (TTHM)s—the sum of bromoform, chloroform, bromodichloromethane, and dibromochloromethane; the Maximum Contaminant Level (MCL) for TTHM is currently set at 80 μg/L (U.S. EPA, 2010). HAAs are regulated as HAA5—the sum of monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, bromoacetic acid, and dibromoacetic acid; the MCL for HAA5 is currently set at 60 μg/L (U.S. EPA, 2010). With more than 300 million people in the U.S. receiving their drinking water from public water systems (U.S. EPA, 2015), exposure to TTHMs and HAA5 is quite common among U.S. residents.

The role of THMs and HAAs in abnormal fetal development is unclear. In some animal studies, THMs and HAAs have been reported to decrease birth weight, increase pregnancy loss, and increase the risk of various birth defects (reviewed in Graves, Matanoski, & Tardiff, 2001; reviewed in Tardiff, Carson, & Ginevan, 2006). One study reported a significant increase in CP in the offspring of mice exposed to inhaled chloroform during days 8 through 15 of gestation (Murray, Schwetz, McBride, & Staples, 1979). Few epidemiologic studies, however, have explored associations between drinking water DBPs and OFCs. A record linkage study conducted in New Jersey (Bove et al., 1995) reported a statistically significant, positive association between mothers with public water system concentrations of TTHMs during pregnancy   100 μg/L compared to concentrations of TTHMs   20 μg/L and OFCs in their offspring. A recent study conducted in Massachusetts also reported a statistically significant, positive association for maternal exposure to a combination of nine DBPs (TTHM + HAA5) with CP, as well as positive associations for HAA5 and several individual THMs and HAAs with CP; associations for CL/P were largely near or below unity (Kaufman et al., 2018). Additional studies of TTHM exposures have reported either nonsignificant, positive associations (Hwang, Jaakkola, & Guo, 2008; Righi et al., 2012; Shaw et al., 2003) or null associations (Dodds, King, Woolcott, & Pole, 1999; Nieuwenhuijsen et al., 2008) between varying levels of maternal TTHM exposures measured in public water systems and OFCs in offspring. A study that examined maternal exposure to individual THMs reported positive associations between OFCs and mothers exposed to concentrations of chloroform between 50 and 74 μg/L and   100 μg/L (Dodds & King, 2001). A recent meta-analysis reported no associations between OFCs and any water chlorination or TTHM exposure (Nieuwenhuijsen et al., 2009).

To date, epidemiologic studies of DBPs and OFCs have relied on ecological measures of DBP exposures only, rather than measures generated from individual-level reports of estimated water consumption, which may have introduced exposure misclassification. Also, no study considered individual-level estimates of water consumption outside of the home (e.g., at work or school) or of alternative routes of DBP exposure (e.g., through bathing or showering), also potentially introducing exposure misclassification. To improve upon these limitations, we linked interview reports of water filtration and consumption from a large, U.S. population-based case-control study with public water system monitoring data, accounting for temporal and spatial fluctuations in DBP concentrations, to examine associations of maternal individual-level estimates of exposure to THMs and to HAAs with OFCs in their offspring.

2 | METHODS

2.1 | Study sample

The National Birth Defects Prevention Study (NBDPS) was a multisite, population-based case-control study funded by the Centers for Disease Control and Prevention. As detailed elsewhere (Reefhuis et al., 2015), interview reports were collected from mothers of cases and controls with estimated dates of delivery (EDD)s from October 1, 1997–December 31, 2011. Case deliveries were live births, stillbirths, or elective terminations diagnosed with one or more of over 30 major structural birth defects identified from the population-based birth

defect surveillance program at each NBDPS site; cases with monogenic or chromosomal etiologies or whose OFCs were secondary to another defect were excluded. Eligible cases for the current project were those diagnosed with CL (modified British Paediatric Association [BPA] codes 749.101–749.103, 749.110, 749.120, 749.195); CP (BPA codes 749.001–749.003, 749.010, 749.020, 749.030, 749.041–749.043, 749.050, 749.060, 749.070, 749.090); or CLP (BPA codes 749.201–749.203, 749.210, 749.220, 749.290). OFC cases were further classified as isolated (no other major defects) or multiple (at least one additional major, unrelated defect) (Rasmussen et al., 2003). Eligible controls were live births without major birth defect diagnoses randomly selected from birth certificates or birth hospitals in the corresponding surveillance catchment areas for each NBDPS site. The NBDPS sites were Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. North Carolina and Utah joined the NBDPS in 2003. For this analysis, cases and controls from California and New Jersey were excluded because access to water quality data from individual public water systems at these sites was not available, and controls from Utah delivered in 2003 were excluded because Utah did not contribute OFC cases during that year.

2.2 | Data collection

Mothers of eligible OFC cases and controls were asked to complete the NBDPS interview by telephone in either English- or Spanish-language (a copy of the interview is available from the corresponding author upon request). Briefly, the interview included items regarding parental sociodemo-graphics, family history of birth defects, and occupation as well as maternal medical history, prenatal care, diet, lifestyle, and residence history beginning three months prior to conception (B3) through the EDD or end of pregnancy. Interviews conducted with mothers of cases and controls delivered between January 1, 2000 and December 31, 2005 included a detailed drinking water module that asked about maternal water sources, residential water treatment, drinking water consumption, and additional water use activities. Participation rates for the interview for all study years (1997–2011) were 71% for mothers of OFC cases and 64% for mothers of all controls. Our analyses included 1582 mothers of OFC cases and 3962 mothers of controls who completed an interview with the detailed drinking water module.

2.3 | DBP concentration estimates

The critical period for lip and palate development is the first three months of gestation (Burdi, 2006). The estimated date of conception (EDC) for each mother was calculated by subtracting 280 days (40 weeks) from the EDD to obtain the last menstrual period date, then adding 14 days. Using the EDC and assigning 30 days per month, we estimated maternal exposure to DBPs from tap water for the preconception month (B1) immediately before the EDC through the first three months of pregnancy (P1, P2, P3) by applying a structured algorithm that combined interview data and DBP water sample results. The preconception month was included as part of the critical exposure period due to the potential for maternal prepregnancy behaviors to extend into early pregnancy.

In the interview, mothers were asked to report the full address, along with the residency start date (month, year) and end date (month, year), for each residence reported. Addresses were

geocoded using Centrus (Group 1 Software; Lanham, MD); 97% of addresses were matched at any level, and 89% were matched at the address level. Public water systems were identified by linking the geocoded maternal residence to digitized public water system service area maps; 2010 census place shapes were used to approximate service boundaries if the public water system service area map was not available. For a city served by multiple public water systems that lacked information on the public water system boundaries within the district, the public water system that served the largest number of residences in the city was linked to the maternal geocoded residence.

An attempt was made to obtain DBP sampling results (contaminant levels, sampling date, location) from linked public water systems. DBP data are available on monitoring schedules for all public water systems in accordance with Safe Drinking Water Act regulations and guidelines (U.S. EPA, 2010). Nationally, public water systems are required to monitor THM and HAA levels; however, the frequency of mandatory reporting varies depending on the size of the public water system and the population served. Larger systems are required to monitor quarterly—compliance is based on a running annual average of quarterly samples. Small surface water and small groundwater systems are required to monitor annually. As such, for some cases and controls, TTHM or HAA5 levels were not available from the linked public water systems that served the respective maternal geocoded residences from B1 through P3.

Exposure measurement error can occur when sampling results from a public water system are assigned to a single residence due to temporal (e.g., monthly or seasonal) and spatial fluctuations in DBP concentrations throughout the system. To account for these fluctuations, we estimated an inverse-time weighted mean using all sample measurement days (up to a maximum of 10) for each available THM and HAA during the critical exposure period for each case and control mother, giving a higher weight to those measurements that occurred closest to the EDC. For mothers served by systems with multiple DBP sample measurements taken in a single day at different locations throughout the system during the critical exposure period, we used the mean concentration for each THM and HAA to estimate exposure for that day. Additionally, we explored a weighting factor to reduce the statistical contribution of mothers whose public water systems had high spatial variability in DBP concentrations throughout the system within individual measurement days (Waller, Swan, Windham, & Fenster, 2001); this factor was omitted from our final analyses due to a large proportion of mothers in our analytic sample whose public water systems provided only a single measurement for each DBP per measurement day.

2.4 | Maternal water consumption estimates

During the interview, mothers were asked whether: the drinking water at the residence closest to the EDC was from a private well or public water system; the water was chemically disinfected (private well only); and the water used for drinking or cooking was filtered (none, whole house filter, faucet filter, etc.), and if filtered, the type of filter (membrane, charcoal, etc.) and frequency of filter changes per year. For each reported residence, mothers were also asked about the water source(s) (unfiltered tap, filtered tap, bottled, other) used for drinking, number of 8 oz. glasses of water consumed per day from each source, sources used

to make hot drinks and for cooking, and details about changes in drinking water consumption from B3 through the end of the pregnancy (the month of a change in amount, number of 8 oz. glasses of water consumed per day after a change in amount, water sources used after a change in source). Additionally, mothers were asked about the water source(s) (unfiltered tap, filtered tap, drinking fountain [coded as unfiltered tap], bottled/cooler, brought from home, other) used for drinking at school (if enrolled) or at each job (if employed), and the average number of 8 oz. glasses of water consumed per day from each source at school and work. We reviewed the "other" responses for water source at home, work, and school and recoded them into one of the predefined sources, where possible. Additional interview items asked about water use activities, including washing dishes and clothes, showering and bathing, and swimming.

Total water consumption during the critical exposure period from each water source was estimated using the number of 8 oz. glasses of water consumed per day at home and while at each job and school, and the estimated number of days spent at each job and school during the critical exposure period (for an example, see Box 1). We did not use the responses about water sources used to make hot drinks and for cooking, as associated consumption amounts were not reported. A mother's estimated average daily consumption from a water source was calculated by dividing her total estimated consumption by 120 days.

For mothers who reported changing their daily amount of water consumption or starting or stopping living at a residence, working at a job, or attending school, the date of each event was collected in the interview at the level of calendar month and year. If the year was reported but not the month, the change was assumed to occur in July. To determine if and when any of these events occurred during the critical exposure period, we converted the calendar month and year to the 30-day period (B1, P1, P2, P3) that contained the largest number of days within the identified calendar month. For example, January would be assigned P1 for a mother with an EDC of January 10th but assigned B1 for a mother with an EDC of January 20th. If two 30-day periods contained the same number of days for a given calendar month, the earlier 30-day period was assigned. Changes to consumption amount were assumed to apply to one-half of the 30-day period during which they were reported. Mothers were assumed to be at a residence, job, or school during one-half of the 30-day period during which they started or stopped being at that location.

Although the interview asked about the timing of any change in the amount of drinking water consumed at home, it did not ask about the distribution of the change by water source. If more than one water source was reported, we estimated the source distribution of total home drinking water consumption after the change using unweighted and weighted approaches (Figure 1). Our unweighted approach distributed total consumption across reported water sources according to the proportions before the change in consumption amount. Our weighted approach used a ranking (lowest to highest) of water sources by DBP concentration (bottled water, filtered tap water, unfiltered tap water). Arbitrary weights of 3, 2, and 1 were used if all three water sources were reported, and arbitrary weights of 3 and 1 were used if only two water sources were reported. Our low-DBP-weighted approach assigned the highest weight value to the water source with the assumed lowest DBP concentration. Conversely, our high-DBP-weighted approach assigned the highest weight

value to the water source with the assumed highest DBP concentration (for an example, see Box 2).

Although a mother could report a change in water source, the interview did not ask about the date corresponding to the change. As such, we estimated consumption from each water source using two different assumptions for mothers who reported changing sources. The first assumption was that the change in water source occurred before the critical exposure period; the second assumption was that the change in water source occurred after the critical exposure period. For the first assumption, because the interview did not ask about the distribution of total water consumption by water source after a reported change in source, we estimated the distribution to be proportional to the weights of the respective consumption estimation approach (for an example, see Box 3). For the second assumption, the water source change did not affect consumption estimates because it did not apply to the critical exposure period. In calculating total consumption that included amounts from work or school, we assumed the distribution of water sources that a mother reported bringing from home to work or school was proportional to the estimated distribution of home water consumption.

2.5 | Maternal DBP ingestion estimates from public water systems

In our analyses, a mother's exposure to DBPs in tap water depends on the levels of DBPs in the public water system(s) serving her residence, work, and school; her average daily water consumption from each water source; and the use of any water filters at her residence, work, and school that affected DBP levels. We assumed that private well water (due to minimal reported disinfection treatments) and bottled water had 0 μg/L of DBP exposure. We also assumed a mother's work and school were in the same water district as her residence. If a mother reported use of a filtration system at home, the reported brand names for filtration systems and filters provided were queried in the list of NSF International certified drinking water treatment units (http://info.nsf.org/Certified/DWTU/) to determine whether the system or filter could remove DBPs. If no brand name was reported, the effectiveness in DBP removal of the filter or system was determined by the description of the filtration method. Types of filters that are known to remove DBPs were estimated to reduce the DBP concentration to 10% of that measured in the public water system. Reported types of filters unable to remove DBPs or those with undetermined capacity to remove DBPs were assumed to reduce the DBP concentration to 90% of that measured in the public water system. The interview did not ask about information regarding the types of filters used at work or school, so these filters also were assumed to reduce the DBP concentration to 90% of that measured in the public water system.

2.6 | Maternal dermal and inhalation DBP exposures

A positive association between longer showers taken by mothers (duration 15 min) and cleft lip ± cleft palate (CL/P) has been previously reported using NBDPS data (Agopian, Waller, Lupo, Canfield, & Mitchell, 2013); therefore, we included average shower duration in our analysis as a covariate. Because our focus was on DBP exposures from drinking water consumption, we did not consider additional reported dermal or inhalation exposures from washing dishes, washing clothes, bathing, and swimming in our analyses.

2.7 | Statistical analysis

Case and control mothers were excluded from analysis if they reported a diagnosis of pregestational diabetes due to the strong association between pregestational diabetes and birth defects, particularly OFCs (Aberg, Westbom, & Kallen, 2001; Becerra, Khoury, Cordero, & Erickson, 1990; Correa et al., 2008; Spilson, Kim, & Chung, 2001). Mothers were eligible to be included in the analyses if they resided at the same residence throughout the critical exposure period, and they either did not drink tap water provided by a public water system during the critical exposure period, or they drank tap water provided by a public water system during the critical exposure period and their DBP ingestion could be estimated. Mothers' DBP ingestion could be estimated if: (a) they reported the year(s) and number of days per week they attended every reported job and school outside the home; (b) they reported water sources and consumption amounts at their residence and at all jobs and schools outside the home during the critical exposure period; (c) all reported water sources could be categorized as "unfiltered tap," "filtered tap," or "bottled;" (d) their residence was successfully geocoded; (e) the public water system that served their residence was identified; and (f) the DBP measurements of that water system were known while they resided at that address during the critical exposure period.

Selected child and maternal characteristics and maternal exposures during the critical exposure period were assessed as covariates. To evaluate the representativeness of OFC cases and controls available for analysis, we compared their covariates to those of all OFC cases and all controls delivered during 2000–2005, respectively, using chi-square goodness-of-fit tests (calculating exact p-values if expected cell counts <5). We also compared covariates of all OFC cases and controls eligible for analysis using chi-square tests of independence or Fisher's exact tests (if expected cell counts <5) to determine statistically significant differences ($p < .05$).

Child characteristics examined were sex (male, female), gestational age (<37, 37–45 weeks), family history of OFC (first-degree relative, other relative, none), and plurality (single birth, twin, other multiple birth). Maternal characteristics examined were age at delivery (<20, 20–24, 25–29, 30–34, 35 years), education at delivery (<12, 12, 13–15, 16 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), gravidity (first pregnancy, second pregnancy, third or higher pregnancy), prepregnancy body mass index (BMI) (<18.5, 18.5–25.0, 25.0–30.0, 30.0 kg/m^2), and study site (Arkansas, Georgia, Iowa, Massachusetts, New York, North Carolina, Texas, Utah). Maternal exposures during the critical exposure period examined were cigarette smoking (no active or passive smoking, active smoking only, passive smoking only [exposed to cigarette smoking at home or workplace], active and passive smoking), alcohol consumption (no drinking, binge drinking [4 drinks on one occasion], drinking but no binge drinking), use of a folic acid-containing supplement (yes, no), and average shower duration (<15, 15 min).

Crude odds ratios (cORs), adjusted odds ratios (aORs), and 95% confidence intervals (CI)s were estimated using logistic regression analysis. Associations between OFCs and DBPs were analyzed for all OFCs, isolated OFCs, and two subtypes of isolated OFCs: CP and CL/P. We examined potential associations between each outcome group and maternal exposure to TTHMs and HAA5 in μg per liter of water consumed. Categories of exposure

were based on one-half the MCLs (40 μg/L for TTHMs and 30 μg/L for HAA5), and mothers unexposed to TTHMs or HAA5 were used as the referent groups for the respective analyses. Crude analyses were conducted only for categories of TTHM and HAA5 exposures that included at least three exposed and three referent case mothers.

Adjusted analyses were conducted only for categories of TTHM and HAA5 exposures that included at least five exposed and five referent case mothers. Covariates that were found to be statistically associated ($p < .05$) with the outcome group and exposure using chi-square tests of independence or Fisher's exact tests (if expected cell counts <5) were added separately to the exposure-only model; covariates that changed the cOR estimate by more than 10% were included in the adjusted model. Because a previous NBDPS study reported that increases in maternal water consumption were inversely associated with CL (Alman, Coffman, Siega-Riz, Luben, & National Birth Defects Prevention Study, 2017), we considered total maternal water consumption during the critical exposure period as a potential covariate in adjusted analyses. We observed that total maternal water consumption was not associated with any OFC outcome group using logistic regression analysis, and thus, it was not included in any adjusted models.

We also examined potential associations between the outcome groups and individual THM and HAA contaminants in μg per liter of water consumed. Categories of exposure were based on one-half the Maximum Contaminant Level Goals (MCLG)s, if available and non-zero (35 μg/L for chloroform, 30 μg/L for dibromochloromethane, 35 μg/L for monochloroacetic acid, and 10 μg/L for trichloroacetic acid) (U.S. EPA, 2010). Contaminants with MCLGs of 0 μg/L (bromoform, bromodichloromethane, and dichloroacetic acid) or no MCLGs (bromoacetic acid and dibromoacetic acid) (U.S. EPA, 2010) were analyzed as dichotomous indicators of any maternal exposure from drinking water. Mothers unexposed to a specific contaminant were used as the referent group for the analyses of that contaminant. Mothers from Massachusetts and Utah were excluded from our analysis of individual contaminants because these sites did not report individual THM and HAA contaminant concentrations.

As a subanalysis, we examined potential associations between the same outcome groups and concentrations of TTHMs, HAA5, and individual THM and HAA contaminants in the public water systems linked to maternal residences without accounting for filtration and consumption. These results are more directly comparable to previous studies that lacked this information (Dodds et al., 1999; Hwang et al., 2008; Kaufman et al., 2018; Nieuwenhuijsen et al., 2008; Righi et al., 2012; Shaw et al., 2003). Concentrations less than one-half the MCLs or MCLGs were used as the referent groups, except for contaminants with MCLGs of 0 μg/L or no MCLGs for which concentrations of 0 μg/L were used.

To assess the magnitude of improvement of exposure classification in our study compared to ecological studies, we compared mothers' classifications of TTHM and HAA5 exposures per liter of water consumed with their classifications of TTHM and HAA5 concentrations in public water systems. All analyses were conducted using the Statistical Analysis System (SAS) version 9.4 statistical software (SAS institute, Cary, NC).

3 | RESULTS

Overall, 5544 (cases = 1582, controls = 3962) mothers completed an interview. Of these, 66 (cases = 29, controls = 37) mothers were excluded due to a reported diagnosis of pregestational diabetes or an incomplete response for diagnosis or type of diabetes. Using the assumption that any reported source changes occurred after the critical exposure period, among the remaining 5478 (cases = 1553, controls = 3925) mothers, 1346 (cases = 409, controls = 937) had insufficient interview data or relocated during the critical exposure period, 1367 (cases = 377, controls = 990) reported that they did not drink tap water provided by a public water system during the critical exposure period, and 2765 (cases = 767, controls = 1998) reported that they drank tap water provided by a public water system during the critical exposure period. Of the last group, 1139 (cases = 303, controls = 836) mothers had their addresses successfully geocoded and were linked to a public water system for which DBP measurements were available; these 1139 mothers along with the 1367 mothers who reported no tap water consumption were eligible for analysis (cases = 680, controls = 1826). The 680 eligible OFC cases included 535 isolated cases, 146 with CP and 389 with CL/P; the remaining 145 OFC cases had multiple defects.

No statistical differences ($p < .05$) were observed for child characteristics between controls eligible for analysis and all controls whose mothers completed the interview and reported no pregestational diabetes; likewise, no statistical differences were observed between eligible OFC cases and all OFC cases. For maternal characteristics and exposures, statistical differences were observed between mothers of eligible controls and all controls for age at delivery, gravidity, prepregnancy BMI, study site, and smoking. Furthermore, statistical differences were observed between mothers of eligible OFC cases and all OFC cases for age at delivery, education at delivery, and study site (Table 1).

Comparing child characteristics between eligible OFC cases and controls, cases were statistically more likely to be male, preterm, and have a first-degree relative or other relative with an OFC. We also observed statistical differences between mothers of eligible cases and controls for education, race/ethnicity, BMI, and study site. Comparing exposures between mothers of eligible cases and controls, we also observed an excess of case mothers who were active or passive smokers and case mothers who took 15 min showers (Table 1).

Table 2 presents results for associations for all OFCs and isolated OFCs, CP, and CL/P with maternal THM and HAA exposure per liter of water consumed, estimated using the unweighted algorithm and assuming any reported source changes occurred after the critical exposure period. If no covariates met the criteria for inclusion in an adjusted model, the cOR and 95% CI was reported for the given association. No statistically significant, positive associations were observed for any OFC outcome group with maternal exposure to TTHMs, HAA5, or individual contaminants. We observed significant, inverse associations for all OFCs with any maternal exposure to bromoacetic acid, for isolated OFCs with any maternal exposure to dibromoacetic acid, and for CP with maternal exposure to monochloroacetic acid less than one-half the MCLG of 35 μg/L (no mothers had an average ingestion concentration of 35 μg/L or greater) and any maternal exposure to bromoacetic acid and dibromoacetic acid. No substantive differences in the pattern of results were found using the

weighted exposure estimation approaches or the assumption that any reported source changes occurred before the critical exposure period (data not shown).

Results of the subanalysis of associations of the OFC outcome groups with THM and HAA concentrations in public water systems are presented in Table 3. Similar to the analysis of THM and HAA exposures per liter of water consumed, there were no statistically significant, positive associations for any OFC outcome group with concentration of TTHMs, HAA5, or individual contaminants. We observed significant, inverse associations for all OFCs, isolated OFCs, and isolated CL/P with non-zero concentration of dibromoacetic acid and for CP with concentration of TTHMs at above one-half the MCL of 40 μg/L, concentration of chloroform at or above one-half the MCLG of 35 μg/L, concentration of trichloroacetic acid at or above one-half the MCLG of 10 μg/L, and non-zero concentration of bromoacetic acid.

To examine the potential for misclassification of maternal DBP exposure, Table 4 shows our results classifying maternal DBP exposure applying the conventional ecologic exposure assessment versus our more detailed, individual level exposure assessment. Overall, 1629 of 5478 (29.7%) mothers were eligible for both analyses of TTHM exposure, and 1216 (22.2%) mothers were eligible for both analyses of HAA5 exposure. Classification of TTHM exposure was the same in both analyses for 832 (51.1%) mothers, and classification of HAA5 exposure was the same in both analyses for 609 (50.1%) mothers.

4 | DISCUSSION

To examine the relation between individual-level DBP exposure and OFCs, we linked maternal interview reports of water filtration and consumption during pregnancy from the NBDPS with public water system monitoring data. Compared to controls, no statistically significant associations were observed for all OFCs or isolated OFCs, CP, or CL/P with maternal exposure to TTHMs, HAA5, or individual THMs from drinking water during the critical exposure period, with most estimates near unity. No significant, positive associations were observed for any OFC outcome group with exposure to individual HAAs; significant, inverse associations were observed for all OFCs with bromoacetic acid, for isolated OFCs with dibromoacetic acid, and for CP with monochloroacetic acid, bromoacetic acid, and dibromoacetic acid.

Our study incorporated maternal individual-level water filtration and consumption information to estimate the relation between DBP exposure and OFCs; as such, the results of our analysis of DBP exposure per liter of water consumed could not be compared directly to previous studies. Conversely, the results of our subanalysis of DBP concentrations in public water systems did not rely upon maternal individual-level water filtration and consumption information, and therefore are more comparable to previous studies. Our findings of no statistically significant, positive associations between DBPs and OFCs were similar to those of most studies using ecological measures of DBP exposure (Dodds et al., 1999; Hwang et al., 2008; Nieuwenhuijsen et al., 2008; Righi et al., 2012; Shaw et al., 2003), as well as a meta-analysis examining chlorination and TTHM exposure (Nieuwenhuijsen et al., 2009). Similarly, our findings of no significant, positive associations between OFCs and chloroform

were similar to previous studies that examined individual THMs (Dodds & King, 2001; Kaufman et al., 2018). Our findings of no significant, positive associations between HAAs and CL/P and a significant, inverse association between dibromoacetic acid and CP parallel associations reported from a previous Massachusetts study, although the inverse associations we observed between HAAs and CP generally contrast the Massachusetts study's positive or near-unity associations for monochloroacetic acid, dichloroacetic acid, and trichloroacetic acid with CP (Kaufman et al., 2018). Some previous animal studies have reported no teratogenic effects following maternal administration of several DBPs (reviewed in Graves et al., 2001); one animal study reported a significant increase in CP in offspring of mice exposed to 100 ppm inhaled chloroform, although the effect was observed at doses that likely exceed those seen in humans (Murray et al., 1979).

A strength of our study was the use of data from the NBDPS, a large, population-based case control study. Review of medical record data by clinical geneticists reduced the potential for case misclassification and allowed for the examination of individual OFC subtypes. The NBDPS interview collected information on use of water from a private well or public water system, which allowed improved specificity in assigning DBP concentrations to public water users only. Furthermore, the NBDPS interview also collected detailed information on individual water consumption at home, work, and school, as well as water filtration at home for the critical exposure period. This information helped to reduce potential exposure misclassification (Whitaker, Nieuwenhuijsen, & Best, 2003) that may occur from use of residence location as a proxy for DBP exposure, as used in previous studies (Bove et al., 1995; Dodds et al., 1999; Dodds & King, 2001; Hwang et al., 2008; Nieuwenhuijsen et al., 2008; Righi et al., 2012; Shaw et al., 2003). Mothers also reported information on shower and bathing habits, which may influence OFC risk (Agopian et al., 2013); heating of water may volatilize DBPs, leading to inhalation and dermal exposures. Our study was also able to examine individual THMs and HAAs; the metabolism and toxicity of individual DBPs may vary and use of TTHMs or HAA5 as a proxy measure for individual DBPs may mask the effects of individual DBPs. Furthermore, potential temporal and spatial fluctuations of DBPs were addressed in the estimation of DBP exposure for each mother.

Although our study had numerous strengths and improved upon the methods used in previous studies, several limitations remained. The primary limitation of our study was the proportion of mothers ineligible for any exposure analyses due to our inability to link these mothers to their corresponding DBP values from their water systems. Even with successful linkage, the use of maternal retrospective self-reports created the potential for imprecision in recall of water consumption during pregnancy. Related to this, some estimates observed were based on small numbers of exposed mothers and were imprecise. Also, although mothers could report changes in water consumption amount at home during pregnancy, the distribution of the change by water source could not be reported. To attempt to address this limitation, we estimated changes to the source distribution of home drinking water consumption when multiple sources were reported using unweighted and weighted approaches; the results of analyses using these approaches were not substantively different. Another limitation was that mothers could report changes in water sources at home during pregnancy, but the timing of a change in source was not requested. We attempted to address this limitation by estimating DBP exposure using two assumptions. One assumption was that

changes in source occurred before the critical exposure period, and the other was that such changes occurred after the critical exposure period; results did not differ substantively between these assumptions. Also, mothers reported the source of water for hot drinks, but corresponding consumption estimates were not requested, potentially leading to exposure misclassification. Additionally, we only were able to estimate associations for the individual THMs and HAAs regulated by the U.S. EPA; unmeasured DBPs may present different risks than those measured. Although participant mothers of controls in the NBDPS were previously found to be statistically similar for several characteristics to mothers of all live births in the same geographic areas (Cogswell et al., 2009), we observed that the eligible mothers in our analyses were not representative of NBDPS mothers of OFC cases and controls for some characteristics and exposures; however, only one characteristic (study site) was retained in any of our adjusted models. Lastly, we did not control for multiple comparisons; thus, findings observed may have been due to chance.

Using maternal reports of water filtration and consumption data from the NBDPS, we observed associations near or below unity for all OFCs, isolated OFCs, CL/P, and CP with TTHMs, HAA5, and individual THMs and HAAs. No statistically significant, positive associations were observed for any outcome groups with any exposure groups; however, statistically significant, inverse associations were observed for all OFCs with bromoacetic acid, isolated OFCs with dibromoacetic acid, and CP with monochloroacetic acid, bromoacetic acid, and dibromoacetic acid. Compared to our subanalysis that did not account for filtration and consumption, the exposure classifications using information on filtration and consumption for TTHMs and HAA5 were discrepant for nearly one-half of mothers, reducing potential overestimation of these exposures. Continued, improved research using maternal individual-level exposure data could be impactful in better characterizing the relation between DBPs and OFCs.

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BOX 1

Water consumption example without amount or source changes

Assume a mother reported drinking 6 glasses of filtered tap water per day at home during the 120-day critical exposure period. Her estimated consumption of filtered tap water at home would be 120 days × 6 glasses per day = 720 glasses. If the mother also worked at a job 5 days per week during the entire 120-day critical exposure period and reported drinking 4 glasses of filtered tap water per day at this job, her estimated consumption of filtered tap water at work would be $120 \times \frac{5}{7}$ days × 4 glasses per day = 342.86 glasses. As such, the mother's total estimated consumption of filtered tap water would be 720+342.86=1062.86 glasses. If the mother from this example stopped working during the third month of her pregnancy, 105 days would be used instead of 120 days when estimating her total consumption at work.

BOX 2

Water consumption example with amount change

Assume a mother reported drinking 2 glasses of unfiltered tap water per day ($g_h = 2$), 2 glasses of filtered tap water per day ($g_l = 2$), and an increase to 8 glasses of water per day ($t_a = 8$) in the second month of pregnancy ($m_b = 2.5, m_a = 1.5$). Because she reported no glasses of bottled water, she has two water sources ($n_b = 2$, $I_b = 0$, $g_m = 0$). Her total estimated consumption before the change month would be $30 m_b g_l = 150$ glasses of filtered tap water and $30 m_b g_h = 150$ glasses of unfiltered tap water. Using the high-DBP-weighted approach, her estimated total consumption during and after the change month would be $30 m_a \dfrac{1 g_l t_a}{1 g_l + 2 I_b g_m + 3 g_h} = 90$ glasses of filtered tap water and

$30 m_a \dfrac{3 g_h t_a}{1 g_l + 2 I_b g_m + 3 g_h} = 270$ glasses of unfiltered tap water; thus, her total estimated consumption during the critical exposure period would be $150 + 90 = 240$ glasses of filtered tap water and $150 + 270 = 420$ glasses of unfiltered tap water.

BOX 3

Water consumption example with source change

Assume a mother reported drinking 4 glasses of filtered tap water per day ($t_b = 4$) during the entire critical exposure period ($m_b = 4$) and a change in source to filtered tap and bottled water ($n_a = 2$, $I_a = 0$). Using the low-DBP-weighted approach and the assumption that the water source change occurred before the critical exposure period, her estimated total consumption during the critical exposure period would be $30 m_b \dfrac{1 t_b}{3 + 2 I_a + 1} = 120$

glasses of filtered tap water and $30 m_b \dfrac{1 t_b}{3 + 2 I_a + 1} = 360$ glasses of bottled water.

Assume the mother from this example also reported a change in her daily consumption to 8 glasses ($t_a = 8$) during the first month of her pregnancy. We would apply the weights to that amount for one-half of that month and for the following months, ($m_b = 1.5$, $m_a = 2.5$). Hence, her total estimated consumption during the critical exposure period would be

$30 m_b \dfrac{1 t_b}{3 + 2 I_a + 1} + 30 m_a \dfrac{1 t_a}{3 + 2 I_a + 1} = 195$ glasses of filtered tap water and

$30 m_b \dfrac{3 t_b}{3 + 2 I_a + 1} + 30 m_a \dfrac{3 t_a}{3 + 2 I_a + 1} = 585$ glasses of bottled water.

Reported		Approach			Estimated	
Amount Change	Source Change	Assumed Timing of Source Change	Weights	Water Source by Rank of Assumed DBP Concentration	Total Glasses of Water Consumed from Water Source (B1-P3)	
					Before Amount Change	After Amount Change
Yes	Yes	Before B1	Unweighted	Any source	$30m_b \dfrac{t_b}{n_a}$	$30m_a \dfrac{t_a}{n_a}$
			Low-DBP	Lowest	$30m_b \dfrac{3t_b}{3+2I_a+1}$	$30m_a \dfrac{3t_a}{3+2I_a+1}$
				Middle	$I_a\left(30m_b \dfrac{2t_b}{3+2+1}\right)$	$I_a\left(30m_a \dfrac{2t_a}{3+2+1}\right)$
				Highest	$30m_b \dfrac{1t_b}{3+2I_a+1}$	$30m_a \dfrac{1t_a}{3+2I_a+1}$
			High-DBP	Lowest	$30m_b \dfrac{1t_b}{3+2I_a+1}$	$30m_a \dfrac{1t_a}{3+2I_a+1}$
				Middle	$I_a\left(30m_b \dfrac{2t_b}{3+2+1}\right)$	$I_a\left(30m_a \dfrac{2t_a}{3+2+1}\right)$
				Highest	$30m_b \dfrac{3t_b}{3+2I_a+1}$	$30m_a \dfrac{3t_a}{3+2I_a+1}$
		After P3	Unweighted	Any source i	$30m_b g_i$	$30m_a \dfrac{g_i}{t_b} t_a$
			Low-DBP	Lowest	$30m_b g_l$	$30m_a \dfrac{3g_l t_a}{3g_l+2I_b g_m+1g_h}$
				Middle	$I_b(30m_b g_m)$	$I_b\left(30m_a \dfrac{2g_m t_a}{3g_l+2g_m+1g_h}\right)$
				Highest	$30m_b g_h$	$30m_a \dfrac{1g_h t_a}{3g_l+2I_b g_m+1g_h}$
	No	NA	High-DBP	Lowest	$30m_b g_l$	$30m_a \dfrac{1g_l t_a}{1g_l+2I_b g_m+3g_h}$
				Middle	$I_b(30m_b g_m)$	$I_b\left(30m_a \dfrac{2g_m t_a}{1g_l+2g_m+3g_h}\right)$
				Highest	$30m_b g_h$	$30m_a \dfrac{3g_h t_a}{1g_l+2I_b g_m+3g_h}$
No	Yes	Before B1	Unweighted	Any source	$30m_b \dfrac{t_b}{n_a}$	NA
			Low-DBP	Lowest	$30m_b \dfrac{3t_b}{3+2I_a+1}$	
				Middle	$I_a\left(30m_b \dfrac{2t_b}{3+2+1}\right)$	
				Highest	$30m_b \dfrac{1t_b}{3+2I_a+1}$	
			High-DBP	Lowest	$30m_b \dfrac{1t_b}{3+2I_a+1}$	
				Middle	$I_a\left(30m_b \dfrac{2t_b}{3+2+1}\right)$	
				Highest	$30m_b \dfrac{3t_b}{3+2I_a+1}$	
		After P3	NA	Any source i	$30m_b g_i$	
	No	NA				

FIGURE 1.

Algorithm developed to estimate distribution of total water consumption when multiple sources were reported, National Birth Defects Prevention Study (2000–2005 deliveries). B1 = preconception month; EDC = estimated date of conception; NA = not applicable; P3 = third month of pregnancy.

g_l = glasses of water consumed per day from source with lowest DBP concentration before any reported source or amount change.

g_m = glasses of water consumed per day from source with middle DBP concentration before any reported source or amount change.

g_h = glasses of water consumed per day from source with highest DBP concentration before any reported source or amount change.

$I_b = 1(n_b = 3)$ = indicator that three water sources are reported before any reported water source change.

$I_a = 1(n_a = 3)$ = indicator that three water sources are reported after any reported water source change.

m_b = number of pregnancy months in critical exposure period living at residence closest to EDC before any reported amount change.

m_a = number of pregnancy months in critical exposure period living at residence closest to EDC after any reported amount change.

n_b = number of water sources reported before any reported water source change.

n_a = number of water sources reported after any reported water source change.

$t_b = g_l + I_b g_m + g_h$ = total number of glasses of water consumed per day before any reported amount change.

t_a = total number of glasses of water consumed per day after any reported amount change.

TABLE 1

Comparison of child and maternal characteristics and maternal exposures during the critical period, National Birth Defects Prevention Study (2000–2005 deliveries)

Covariate[b]	All Controls N[c]	All Controls %	Eligible[a] Controls N[c]	Eligible[a] Controls %	All OFCs N[c]	All OFCs %	Eligible[a] OFCs N[c]	Eligible[a] OFCs %	Eligible vs All Controls p	Eligible vs All OFCs p	Eligible Controls vs Eligible OFCs p
Total	3925		1826		1553		680				
Child characteristics											
Sex									.971	.865	**.001**
Male	2017	51.4	937	51.4	919	59.3	401	9.0			
Female	1904	48.6	886	48.6	631	40.7	279	41.0			
Gestational age (weeks)									.711	.511	**<.001**
Preterm (<37)	395	10.1	179	9.8	255	16.4	118	17.4			
Term (≥ 37)	3530	89.9	1647	90.2	1298	83.6	562	82.7			
Family history of OFC									.346	.918	**<.001**
First-degree relative	10	.3	3	.2	92	5.9	39	5.7			
Other relative	42	1.1	25	1.4	217	14.0	92	13.5			
None	3873	98.7	1798	98.5	1244	80.1	549	80.7			
Plurality									.822[d]	.892[d]	.317
Single birth	3794	97.5	1763	97.2	1481	96.3	648	96.1			
Twin	91	2.3	46	2.5	52	3.4	23	3.4			
Other multiple birth	7	.2	4	.2	5	.3	3	.5			
Maternal characteristics											
Age at delivery (years)									**.001**	**.004**	.491
<20	388	9.9	147	8.1	150	9.7	53	7.8			
20–24	893	22.8	367	20.1	398	25.6	154	22.7			
25–29	1065	27.1	502	27.5	431	27.8	174	25.6			
30–34	1024	26.1	516	28.3	353	22.7	180	26.5			
≥ 35	555	14.1	294	16.1	221	14.2	119	17.5			
Education at delivery (years)									.494	.159	**.032**

Covariate[b]	All Controls N[c]	All Controls %	Eligible[a] Controls N[c]	Eligible[a] Controls %	All OFCs N[c]	All OFCs %	Eligible[a] OFCs N[c]	Eligible[a] OFCs %	Eligible vs All Controls p	Eligible vs All OFCs p	Eligible Controls vs Eligible OFCs p
<12	610	15.8	282	15.4	252	16.4	91	13.4			
12	926	24.0	442	24.2	432	28.1	188	27.7			
13–15	1008	26.1	454	24.9	407	26.5	191	28.1			
16	1314	34.1	648	35.5	448	29.1	210	30.9			
Race/Ethnicity									.142	.824	.001
Non-Hispanic white	2414	61.9	1095	60.3	1044	67.5	454	67.0			
Non-Hispanic black	487	12.5	237	13.1	111	7.2	51	7.5			
Hispanic	711	18.2	362	19.9	273	17.7	126	18.6			
Other	291	7.5	122	6.7	118	7.6	47	6.9			
Gravidity									.033	.052	.436
First pregnancy	1148	29.3	484	26.5	481	31.0	182	26.8			
Second pregnancy	1169	29.8	567	31.1	479	30.9	227	33.4			
Third or higher pregnancy	1602	40.9	775	42.4	590	38.1	271	39.9			
Pre-pregnancy BMI (kg/m^2)									.008	.622	.006
Underweight (<18.5)	206	5.5	68	3.9	107	7.2	42	6.4			
Normal (18.5–25.0)	2055	54.5	953	54.6	792	52.9	342	52.4			
Overweight (25.0–30.0)	877	23.3	444	25.4	335	22.4	143	21.9			
Obese (≥30.0)	632	16.8	281	16.1	262	17.5	126	19.3			
Study Site									<.001	.018	.002
Arkansas	651	16.6	273	15.0	216	13.9	80	11.8			
Georgia	536	13.7	235	12.9	246	15.8	108	15.9			
Iowa	540	13.8	257	14.1	229	14.8	94	13.8			
Massachusetts	573	14.6	327	17.9	252	16.2	141	20.7			
New York	410	10.5	156	8.5	174	11.2	64	9.4			
North Carolina[e]	406	10.3	223	12.2	101	6.5	53	7.8			
Texas	582	14.8	295	16.2	236	15.2	106	15.6			
Utah[f]	227	5.8	60	3.3	99	6.4	34	5.0			
Maternal exposures											

Covariate[b]	All Controls N[c]	All Controls %	Eligible Controls[a] N[c]	Eligible Controls[a] %	All OFCs N[c]	All OFCs %	Eligible OFCs[a] N[c]	Eligible OFCs[a] %	Eligible vs All Controls p	Eligible vs All OFCs p	Eligible Controls vs Eligible OFCs p
Cigarette smoking									**<.001**	.081	**<.001**
No active or passive smoking	2603	67.5	1295	71.2	917	59.6	427	62.9			
Active smoking only	293	7.6	135	7.4	149	9.7	69	10.2			
Passive smoking only	507	13.1	232	12.8	212	13.8	93	13.7			
Active and passive smoking	454	11.8	158	8.7	260	16.9	90	13.3			
Alcohol consumption									.174	.129	.169
No drinking	2466	64.3	1200	66.2	930	60.8	418	62.3			
Binge drinking (4 drinks/occasion)	430	11.2	183	10.1	202	13.2	71	10.6			
Drinking but no binge drinking	940	24.5	430	23.7	397	26.0	182	27.1			
Folic-acid containing supplement									.084	.850	.073
Yes	3406	88.1	1623	89.4	1332	87.1	586	86.8			
No	462	11.9	193	10.6	198	12.9	89	13.2			
Average shower duration									.191	.901	**.003**
<15 min	1935	51.9	947	53.4	694	46.8	307	46.6			
15 min	1794	48.1	825	46.6	788	53.2	352	53.4			

BMI = body mass index; OFC = orofacial cleft.

Because of rounding, percentages might not total 100. Bold p-value indicates p-value < .05.

[a]Unweighted exposure estimation assuming any source change occurred after the critical exposure period.

[b]Daily maternal water consumption was analyzed as a continuous variable (data not shown).

[c]Missing values not included in chi-square tests.

[d]Exact p-value.

[e]Includes deliveries during 2003–2005.

[f]Includes deliveries during 2004–2005.

TABLE 2

Odds ratios for OFCs and exposure to THMs and HAAs per liter of water consumed, National Birth Defects Prevention Study (2000–2005 deliveries)

Exposure[a]	Controls N	Controls %	All OFCs N	All OFCs %	All OFCs OR (95% CI)	Isolated OFCs N	Isolated OFCs %	Isolated OFCs OR (95% CI)	Isolated CP N	Isolated CP %	Isolated CP OR (95% CI)	Isolated CL/P N	Isolated CL/P %	Isolated CL/P OR (95% CI)
TTHMs[b]														
No exposure	1005	55.3	388	57.1	Reference	303	56.7	Reference	81	57.0	Reference	222	56.6	Reference
<½ MCL	640	35.2	236	34.8	1.0 (.8–1.2)[i]	191	35.8	1.0 (.8–1.2)[i]	52	36.6	1.0 (.7–1.4)	139	35.5	1.0 (.8–1.2)
½ MCL	174	9.6	55	8.1	.9 (.7–1.3)[i]	40	7.5	.9 (.6–1.3)[i]	9	6.3	.6 (.3–1.3)	31	7.9	.8 (.5–1.2)
Individual THMs														
Bromoform[c]														
No exposure	1018	74.5	373	76.9	Reference	304	77.8	Reference	87	81.3	Reference	217	76.4	Reference
Exposed	348	25.5	112	23.1	.9 (.7–1.1)	87	22.3	.8 (.6–1.1)	20	18.7	.7 (.4–1.1)	67	23.6	.9 (.7–1.2)
Chloroform[d]														
No exposure	760	55.6	280	57.7	Reference	223	57.0	Reference	62	57.9	Reference	161	56.7	Reference
<½ MCLG	523	38.3	181	37.3	.9 (.8–1.2)	150	38.4	1.0 (.8–1.2)	41	38.3	1.0 (.6–1.4)	109	38.4	1.0 (.8–1.3)
½ MCLG	83	6.1	24	5.0	.8 (.5–1.3)	18	4.6	.7 (.4–1.3)	4	3.7	.6 (.2–1.7)	14	4.9	.8 (.4–1.4)
Bromodichloromethane[c]														
No exposure	760	55.7	276	56.9	Reference	220	56.3	Reference	61	57.0	Reference	159	56.0	Reference
Exposed	605	44.3	209	43.1	1.0 (.8–1.2)	171	43.7	1.0 (.8–1.2)	46	43.0	.9 (.6–1.4)	125	44.0	1.0 (.8–1.3)
Dibromochloromethane[e]														
No exposure	792	58.0	284	58.6	Reference	228	58.3	Reference	62	57.9	Reference	166	58.5	Reference
<½ MCLG	570	41.8	200	41.2	1.0 (.8–1.2)	162	41.4	1.0 (.8–1.2)	45	42.1	1.0 (.7–1.5)	117	41.2	1.0 (.8–1.3)
½ MCLG	3	.2	1	.2	NC	1	.3	NC	0	0.0	NC	1	.4	NC
HAA5[f]														
No exposure	1018	63.7	396	65.8	Reference	308	65.5	Reference	81	66.4	Reference	227	65.2	Reference
<½ MCL	475	29.7	173	28.7	1.0 (.8–1.2)[i]	139	29.6	1.0 (.8–1.2)[i]	37	30.3	1.0 (.7–1.5)	102	29.3	1.0 (.8–1.3)[i]
½ MCL	105	6.6	33	5.5	.9 (.6–1.4)[i]	23	4.9	.8 (.5–1.3)[i]	4	3.3	.5 (.2–1.3)	19	5.5	.9 (.5–1.5)[i]
Individual HAAs														

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Exposure[a]	Controls N	Controls %	All OFCs N	All OFCs %	All OFCs OR (95% CI)	Isolated OFCs N	Isolated OFCs %	Isolated OFCs OR (95% CI)	Isolated CP N	Isolated CP %	Isolated CP OR (95% CI)	Isolated CL/P N	Isolated CL/P %	Isolated CL/P OR (95% CI)
Monochloroacetic acid[d]														
No exposure	944	75.3	347	79.8	Reference	277	79.6	Reference	77	85.6	Reference	200	77.5	Reference
<½ MCLG	309	24.7	88	20.2	.9 (.6–1.2)[i]	71	20.4	.9 (.6–1.2)[i]	13	14.4	**.5 (.3–.9)**	58	22.5	.9 (.6–1.2)
½ MCLG	0	0.0	0	0.0	NC	0	0.0	NC	0	0.0	NC	0	0.0	NC
Dichloroacetic acid[c]														
No exposure	763	60.9	275	63.2	Reference	218	62.6	Reference	59	65.6	Reference	159	61.6	Reference
Exposed	490	39.1	160	36.8	.9 (.7–1.1)	130	37.4	.9 (.7–1.2)	31	34.4	.8 (.5–1.3)	99	38.4	1.0 (.7–1.3)
Trichloroacetic acid[g]														
No exposure	772	61.6	281	64.6	Reference	228	63.8	Reference	59	65.6	Reference	163	63.2	Reference
<½ MCLG	349	27.9	113	26.0	.9 (.7–1.1)	98	28.2	1.0 (.7–1.3)	25	27.8	.9 (.6–1.5)	73	28.3	1.0 (.7–1.3)
½ MCLG	132	10.5	41	9.4	.9 (.6–1.2)	28	8.1	.7 (.5–1.1)	6	6.7	.6 (.3–1.4)	22	8.5	.8 (.5–1.3)
Bromoacetic acid[h]														
No exposure	1019	81.3	378	86.9	Reference	302	86.8	Reference	85	94.4	Reference	217	84.1	Reference
Exposed	234	18.7	57	13.1	**.7 (.5–.9)**	46	13.2	**.7 (.5–1.0)**[k]	5	5.6	**.3 (.1–.6)**	41	15.9	1.0 (.7–1.4)[k]
Dibromoacetic acid[h]														
No exposure	969	77.3	358	82.3	Reference	291	83.6	Reference	79	87.8	Reference	212	82.2	Reference
Exposed	284	22.7	77	17.7	.7 (.6–1.0)	57	16.4	**.7 (.5–.9)**	11	12.2	**.5 (.2–.9)**	46	17.8	.7 (.5–1.0)

CI = confidence interval; HAAs = haloacetic acids; HAA5 = group of five most common haloacetic acids; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NC = not calculated; OFC = orofacial cleft; OR = odds ratio; THMs = trihalomethanes; TTHMs = total trihalomethanes.

Because of rounding, percentages might not total 100.

[a] Unweighted exposure estimation assuming any source change occurred after the critical exposure period.

[b] ½ MCL for TTHMs is 40 μg/L.

[c] MCLG for bromoform, bromodichloromethane, and dichloroacetic acid is 0 μg/L.

[d] ½ MCLG for chloroform and monochloroacetic acid is 35 μg/L.

[e] ½ MCLG for dibromochloromethane is 30 μg/L.

[f] ½ MCL for HAA5 is 30 μg/L.

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[g]½ MCLG for trichloroacetic acid is 10 μg/L.

[h]No MCLG for bromoacetic acid or dibromoacetic acid.

[i]Adjusted for study site.

[j]Adjusted for maternal race/ethnicity.

[k]Adjusted for family history of OFC.

TABLE 3

Odds ratios for OFCs and concentration of THMs and HAAs in public water systems, National Birth Defects Prevention Study (2000–2005 deliveries)

Exposure	Controls		All OFCs			Isolated OFCs			Isolated CP			Isolated CL/P		
	N	%	N	%	OR (95% CI)	N	%	OR (95% CI)	N	%	OR (95% CI)	N	%	OR (95% CI)
TTHMs[a]														
<½ MCL	705	55.2	278	57.1	Reference	224	58.0	Reference	68	68.0	Reference	156	54.6	Reference
½ MCL	573	44.8	209	42.9	1.0 (.8–1.3)[h]	162	42.0	1.0 (.8–1.3)[h]	32	32.0	**.6 (.4–.9)**	130	45.5	1.2 (.9–1.5)[h]
Individual THMs														
Bromofom[b]														
No exposure	401	42.3	164	47.3	Reference	134	48.2	Reference	42	53.2	Reference	92	46.2	Reference
Exposed	548	57.7	183	52.7	.6 (.4–1.0)[h]	144	51.8	.6 (.4–1.0)[h,i]	37	46.8	.6 (.4–1.0)	107	53.8	0.7 (0.5–1.0)[i]
Chloroform[c]														
<½ MCLG	697	73.5	256	73.8	Reference	211	75.9	Reference	67	84.8	Reference	144	72.4	Reference
½ MCLG	252	26.6	91	26.2	1.0 (0.7–1.3)	67	24.1	0.9 (0.6–1.2)	12	15.2	**0.5 (0.3–0.9)**	55	27.6	1.1 (0.8–1.5)
Bromodichloromethane[b]														
No exposure	25	2.6	14	4.0	Reference	10	3.6	Reference	4	5.1	Reference	6	3.0	Reference
Exposed	923	97.4	333	96.0	0.6 (0.3–1.3)	268	96.4	0.8 (0.4–1.8)[h]	75	94.9	0.5 (0.2–1.5)	193	97.0	1.0 (0.4–2.4)[i]
Dibromochloromethane[d]														
<½ MCLG	938	99.0	343	98.9	Reference	276	99.3	Reference	79	100.0	Reference	197	99.0	Reference
½ MCLG	10	1.1	4	1.2	1.1 (0.3–3.5)	2	0.7	NC	0	0.0	NC	2	1.0	NC
HAA5[e]														
<½ MCL	587	61.7	239	65.1	Reference	186	65.3	Reference	48	69.6	Reference	138	63.9	Reference
½ MCL	365	38.3	128	34.9	1.0 (.8–1.3)[h]	99	34.7	1.0 (.7–1.3)[h]	21	30.4	.7 (.4–1.2)	78	36.1	1.1 (.8–1.5)[h]
Individual HAAs														
Monochloroacetic acid[c]														
<½ MCLG	773	99.6	273	99.6	Reference	215	99.5	Reference	55	100.0	Reference	160	99.4	Reference
½ MCLG	3	.4	1	.4	NC	1	.5	NC	0	0.0	NC	1	.6	NC
Dichloroacetic acid[b]														

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Exposure	Controls		All OFCs			Isolated OFCs			Isolated CP			Isolated CL/P		
	N	%	N	%	OR (95% CI)	N	%	OR (95% CI)	N	%	OR (95% CI)	N	%	OR (95% CI)
No exposure	34	4.4	13	4.7	Reference	7	3.2	Reference	2	3.6	Reference	5	3.1	Reference
Exposed	742	95.6	261	95.3	.9 (.5–1.8)	209	96.8	1.4 (.6–3.1)	53	96.4	NC	156	96.9	1.7 (.6–4.4)[i]
Trichloroacetic acid[f]														
<½ MCLG	374	48.2	146	53.3	Reference	120	55.6	Reference	35	63.6	Reference	85	52.8	Reference
½ MCLG	402	51.8	128	46.7	.8 (.6–1.1)	96	44.4	.7 (.6–1.0)	20	36.4	**.5 (.3–0.9)**	76	47.2	1.0 (.7–1.3)[i]
Bromoacetic acid[g]														
No exposure	436	56.2	170	62.0	Reference	131	60.7	Reference	41	74.6	Reference	90	55.9	Reference
Exposed	340	43.8	104	38.0	.8 (.6–1.0)	85	39.4	.8 (.6–1.1)	14	25.5	**.4 (.2–.8)**	71	44.1	1.3 (.8–2.0)[h]
Dibromoacetic acid[g]														
No exposure	329	42.4	136	49.6	Reference	110	50.9	Reference	31	56.4	Reference	79	49.1	Reference
Exposed	447	57.6	138	50.4	**.7 (.5–.9)**[i]	106	49.1	**.6 (.4–.8)**[i]	24	43.6	.6 (.3–1.0)	82	50.9	**.6 (.4–0.9)**[i]

CI = confidence interval; HAAs = haloacetic acids; HAA5 = group of five most common haloacetic acids; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NC = not calculated; OFC = orofacial cleft; OR = odds ratio; THMs = trihalomethanes; TTHMs = total trihalomethanes.

Because of rounding, percentages might not total 100.

[a] ½ MCL for TTHMs is 40 μg/L.

[b] MCLG for bromoform, bromodichloromethane, and dichloroacetic acid is 0 μg/L.

[c] ½ MCLG for chloroform and monochloroacetic acid is 35 μg/L.

[d] ½ MCLG for dibromochloromethane is 30 μg/L.

[e] ½ MCL for HAA5 is 30 μg/L.

[f] ½ MCLG for trichloroacetic acid is 10 μg/L.

[g] No MCLG for bromoacetic acid or dibromoacetic acid.

[h] Adjusted for study site.

[i] Adjusted for maternal race/ethnicity.

TABLE 4

Comparison of exposure to TTHMs and HAA5 per liter of water consumed and concentration in public water systems, National Birth Defects Prevention Study (2000–2005 deliveries)

	Concentration in Tap Water			
	<½ MCL		½ MCL	
Exposure[a] per liter of water consumed	N	%	N	%
TTHMs[b]				
No exposure	299	18.4	225	13.8
<½ MCL	603	37.0	273	16.8
½ MCL	0	0.0	229	14.1
HAA5[c]				
No exposure	288	23.7	142	11.7
<½ MCL	471	38.7	177	14.6
½ MCL	0	0.0	138	11.3

HAA5 = group of five most common haloacetic acids; MCL = maximum contaminant level; TTHMs = total trihalomethanes.

Because of rounding, percentages might not total 100.

[a]Unweighted exposure estimation assuming any source change occurred after the critical exposure period.

[b]½ MCL for TTHMs is 40 μg/L.

[c]½ MCL for HAA5 is 30 μg/L.