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# The Effect of Water Disinfection By-products on Pregnancy Outcomes in Two Southeastern U.S. Communities

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## Abstract

**Objective—**To determine if exposure to DBPs during gestation increases the risk of adverse birth outcomes, specifically term small for gestational age (SGA) birth, preterm birth (PTB), and very PTB (<32 weeks gestation).

**Methods—**We used weekly measurements total trihalomethanes (TTHMs), 5 haloacetic acids (HAA5), and total organic halides (TOX) collected from two distribution systems to evaluate the associations between DBP concentrations and term SGA, PTB and very PTB using logistic regression.

**Results—**We found no associations between DBPs and term-SGA. In the site with higher concentrations of bromine-containing DBPs, we found an association between TOX and PTB; this association was larger, though less precise, for very PTB.

**Conclusions—**Our results do not support an association between TTHMs or HAA5 and the birth outcomes investigated, but an association was found between increased TOX and PTB.

## Introduction

Chlorine, used to disinfect drinking water, reacts with natural organic matter in water, resulting in the formation of a complex mixture of disinfection by-products (DBPs), including trihalomethanes (THMs), haloacetic acids (HAAs), and other halogenated

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organics. Total THM (TTHM) is an aggregate measure of the 4 most commonly found trihalomethane species: chloroform ($CHCl_3$), bromodichloromethane ($BrCl_2CH$), dibromochloromethane ($Br_2ClCH$) and bromoform ($CHBr_3$). Total organic halide (TOX) is sometimes used as a surrogate measure of all halogen-containing DBPs, some of which were first discovered in drinking water over 36 years ago.[1,2] DBPs form during water disinfection and the proportional distributions of individual chemicals within a class and across classes can vary by source water quality and by distribution systems, resulting in a gradient of concentrations.[3] A variety of factors influence DBP formation, including organic precursor type, precursor concentration, chlorine dosage, temperature, pH, bromide concentrations and reaction time.[4,5]

A sizable body of research has accumulated addressing the potential reproductive toxicity of DBPs. A recent comprehensive review of this topic has reported inconsistent associations with a wide range of outcomes, including spontaneous abortion, stillbirth, birth defects, preterm birth, and reduced birth weight.[6] This review identifies exposure assessment as the principal limitation to epidemiologic studies of DBPs and adverse pregnancy outcomes. A recent meta-analysis suggests possible evidence of association between DBPs and SGA, but little to no evidence of association between DBPs and the birth outcomes of low birth weight and preterm delivery.[7] Additional studies have provided support for an association between exposure to TTHMs and stillbirths,[8,9] fetal growth restriction,[10–13] and preterm delivery.[10,12,14] Other studies have generated evidence against such associations for some adverse pregnancy outcomes, including preterm delivery[15] and pregnancy loss[16].

In most epidemiologic studies, the exposure assessment is based on concentrations from one or two samples available from the public water utility monitoring data during the period of etiologic interest. Such an approach can lead to significant misclassification of exposure depending on the degree of temporal and spatial variation in DBP concentrations across the water distribution system.[17–20] Through a previously conducted study, we have information on DBP concentrations available from weekly or biweekly measurements of water samples at three geographic sites in the Southern US. The three study sites were selected to reflect a range of DBP exposure profiles across sites and speciation typical of those found across the US. One site had moderate levels of chlorinated DBPs (referred to here as the “chlorinated DBP site”), one had moderate levels of brominated DBPs (“brominated DBP site”), and one had low levels of all DBPs (“low DBP site”).

A series of recent publications utilized these DBP data to characterize the risk of small-for-gestational-age (SGA), preterm-birth (PTB), and low birth weight (LBW) among term births in a cohort of women from these three communities while they were planning to become pregnant or early in pregnancy (≤12 weeks).[15,21] The results of these studies did not suggest an adverse effect of DBPs on PTB or LBW, and an association of TTHMs with SGA was observed only for the small number of participants with average residential TTHM concentrations above the current regulatory standard of 80 μg/L. Women who volunteered to participate in the study were not a random or necessarily representative sample of the general female population and thus these results may not be generalizable to all of the women in these communities. In the chlorinated DBP site, study participants were more highly educated, more likely to be non-Hispanic white, less likely to be Hispanic, and more likely to be nulliparous than the general population. Age was similar in study participants and the overall population at this site. In the brominated DBP site, participants were more likely to be Hispanic and more likely to be nulliparous than the general population. The study participants and overall female population were similar in age and education level in this site.[22] Our objective was to use weekly exposure data from the previous study and publicly available vital records data, which eliminate the concern with selective participation and markedly expands the study size, to evaluate whether women exposed to higher

concentrations of DBPs during specific periods of gestation have increased risk of adverse birth outcomes, specifically term-SGA, PTB, and very PTB.

## Methods

### Subjects

This study was approved by the University of North Carolina School of Public Health's Institutional Review Board. We obtained birth records with addresses at date of birth that had ZIP codes that were included within the boundary of the water distribution area to maximize likelihood of water measures representing home concentrations of the women. The sampling strategy included one group of births from a site with moderate levels of chlorine-containing DBPs and lower levels of bromine-containing DBPs (the "chlorinated" DBP site) and one group from a site with moderate levels of bromine-containing DBPs and lower levels of chlorine-containing DBPs (the "brominated" DBP site). (There were three sites considered in Hoffman et al.,[15,21] but the third site (low DBP site) was not considered in this analysis due to extremely low exposure levels such that within-site comparisons are uninformative but regional demographic differences render the site susceptible to bias as a low-exposure referent.) The term "moderate" is used here to describe exposures that approach but are still below the limits established by the U.S. EPA for regulated DBPs (i.e., 80 μg/L TTHM and 60 μg/L HAA5).[23] There were 27,062 births in the chlorinated DBP site during the study period and in the target ZIP codes. There were 3,946 births in the brominated DBP site during the study period and in the target ZIP codes. Table 1 gives descriptive statistics of the variables for both sites.

### Exposure Data and Assignment

Our investigation made use of exposure data collected for a previous study. The water sampling and analytic methodologies from this study have been described previously.[16,22] Water was sampled at weekly intervals at a representative location in each of the study sites and analyzed for TTHM, the sum of 9 HAA species (HAA9) and TOX (Table 2). Samples were periodically collected at several points in the distribution system to verify that the sampling locations chosen had TTHM, HAA and TOX concentrations that were indeed representative of the entire system on that day. Because the sites used combined chlorine as a terminal disinfectant, very little spatial variability in DBP concentration was observed on any given day. The addition of ammonia to chlorinated water to form monochloramine is a widely accepted water treatment practice to control the regulated DBPs because monochloramine does not form THMs and HAAs to any appreciable degree. Additionally, monochloramine forms much lower levels of TOX than free chlorine. Sample collection was performed by field personnel in accordance with a specified protocol. Residual chlorine concentrations and temperature were also measured at the time of DBP sample collection. Samples were collected near midday from a cold water tap that had been run for at least 5 minutes before sample collection. Weekly tap water samples were collected from the chlorinated DBP site between October 10, 2000 and February 29, 2004, and from the brominated DBP site between June 3, 2002 and September 5, 2004.

Continuous and categorized forms of the water quality variables were used in the analysis. Categorization was created using the minimum, 50$^{th}$ percentile, 75$^{th}$ percentile, 90$^{th}$ percentile, and the maximum of the exposures over the time of water collection for each site separately (Table 3). Third trimester exposures were used in the term-SGA analysis whereas second trimester exposures were used in the PTB and very PTB analyses. Third trimester exposure averages include data up to time of birth. Since the two sites used in these analyses were chosen for the relative contribution of chlorine- and bromine-containing DBPs, all these DBPs in the two sites were categorized as indicated above for categorical analysis

(Table 3). For this study, the sum of five haloacetic acids (HAA5) includes ClAA, $Cl_2AA$, $Cl_3AA$, BrAA and $Br_2AA$. HAA5 was used in this analysis for comparability with results from Hoffman et al.[15,21] and EPA standards.[23] HAA9 was considered in the analysis of term-SGA, PTB, and very PTB and results were similar to those for HAA5 (see Table, Supplemental Digital Content 1, http://links.lww.com/JOM/A67, which gives odds ratios and confidence intervals for HAA9 by site). We also evaluated the "unaccounted" portion of TOX; that is we subtracted the sum of THM4 and HAA9 (when converted to TOX as Cl) from the TOX variable in order to evaluate whether the non-THM and non-HAA species of TOX were more or less strongly associated with the adverse birth outcomes being investigated. In all categorical analyses, the lowest level of exposure was used as the referent group.

### Statistical Analysis

The analysis used covariates available in birth records data that may be related to the birth outcomes of interest, including maternal age, maternal race, marital status, maternal education level, tobacco use, alcohol use, and parity. Three response variables were considered: term-SGA, PTB, and very PTB. Birth weight as a continuous measure was also evaluated and yielded results similar to those for term-SGA (see see Table, Supplemental Digital Content 2, http://links.lww.com/JOM/A68, which illustrates the change in birth weight associated with DBP exposure). PTB was defined as birth at less than 37 weeks of gestation; very PTB was defined as birth at less than 32 weeks of gestation, and term-SGA was created for infants who were non-Hispanic white, non-Hispanic black, and Hispanic based on the availability of published data for these three groups. The cut-points used to define term-SGA were the 10th percentiles from Overpeck et al.[24] for non-Hispanic White and Hispanic mothers, and the cut-points for non-Hispanic Black mothers come from Zhang and Bowes.[25] The race variable created for the SGA analysis was used in the PTB and very PTB analyses. Only births of 37 to 42 weeks of gestation were used in the term-SGA analysis.

The association between DBP concentrations and the three responses of interest (term-SGA, PTB, and very PTB) were assessed using logistic regression in SAS.V9.1 (SAS Institute, Cary, NC). Results with a p-value less than 0.05 were considered statistically significant. In the brominated DBP site, 20.7% of birth records used in the analysis did not include a value for parity. Multiple imputations were implemented using PROC MI in SAS (SAS Institute, Cary, NC) for parity.[26] Five imputations were created for evaluation. Imputations were carried out as if variables were continuous to reduce bias.[27] When modeling term-SGA, PTB, and very PTB, the imputed continuous parity variable was used, but to compute term-SGA values the parity values were rounded. Logistic regression was used to assess the association between term-SGA, PTB, and very PTB, while accounting for the five sets of multiple imputations, using PROC MIANALYZE (SAS Institute, Cary, NC).

## Results

Table 4 presents the odds ratios and 95% confidence intervals for the categorical and continuous exposure variables for SGA, PTB and very PTB among the births occurring in the chlorinated DBP site. The three primary measures of DBPs were unrelated to term-SGA, PTB or very PTB for the chlorinated DBP site.

Table 5 presents the odds ratios and 95% confidence intervals for the categorical and continuous exposure variables for term-SGA, PTB and very PTB among the births occurring in the brominated DBP site. In the brominated DBP site, there was little indication of an exposure-response relationship of TTHM or HAA5 with any of the pregnancy outcomes. However, both categorical and continuous TOX indicated an increased risk of PTB with

increased exposure. Categorical and continuous TOX both suggest a markedly increased risk of very PTB with increased exposure, but the four-fold increase in risk for very PTB when those with the highest group of TOX exposure were compared to those with the lowest was based on just 3 cases.

Table 6 presents the odds ratios and 95% confidence intervals for the aggregated chlorinated and brominated DBP exposure variables for term-SGA, PTB and very PTB among the births occurring in the chlorinated and brominated DBP sites. While there was some evidence for an increased association for very PTB for both the categorized chlorine- and bromine-containing DBP exposure variables in the brominated DBP site, there was no evident exposure-response pattern for either of the exposure variables.

Table 7 gives odds ratios and 95% confidence intervals for the “unaccounted” TOX DBP exposures. In the chlorinated site, there was an increased odds of PTB with increased levels of continuous “unaccounted” TOX. Also, there is an increased odds of very PTB for the higher level of categorical “unaccounted” TOX for the chlorinated site. In the brominated site, for both continuous and categorized forms of “unaccounted” TOX, there is an increased odds of PTB and very PTB. Generally, the results for the “unaccounted” TOX were similar to those for TOX.

## Discussion

The water distribution systems in the two sites are characterized by a larger relative contribution of either chlorine- or bromine-containing DBPs. We conducted within-site analyses that separated the chlorine-containing THMs and HAAs from the bromine-containing THMs and HAAs into separate groups. Overall, we report no associations in the chlorinated and brominated DBP sites between DBPs and term-SGA. In the brominated DBP site we found positive associations between higher concentrations of TOX and PTB and very PTB, with the latter showing large but very imprecise measures of association.

Previous studies have reported a moderately increased risk of delivering an SGA infant among women exposed to high levels of TTHM,[12–14,21,28,29] while others have found no association.[11,30] Porter et al.[30] found an increased risk of intrauterine growth retardation for subjects exposed to higher levels of HAA5 in the third trimester. Hoffman et al.[21] reported some evidence of an association between increasing TTHM exposure and increasing risk of SGA birth in the chlorinated DBP site but not in the brominated DBP site and evidence of increased HAA5 exposure and increased risk of SGA birth in the brominated DBP site but not in the chlorinated DBP site. They found no association between TOX exposure and SGA. We found no associations in either site between any exposures and term-SGA. These differences likely reflect differences in the recruited subjects used by Hoffman et al. and those in the general population, as well as differences in the type and quality of the data used in the our analyses and the analyses by Hoffman et al. Whereas Hoffman et al. had much more detailed information on the study participants, our study population is much larger and less susceptible to bias related to self-selection for participation (i.e., planned pregnancies, motivation to participate in research).

There is little evidence from previous studies to suggest an association between DBPs and PTB.[12,15,18,28,29,31,32] Studies examining the association between TTHM and preterm birth generally have indicated no association, with estimated relative risks for preterm birth ranging between 0.7 and 1.2 and no notable exposure-response trends.[12,15,18,28,29,31,32] However a modest inverse relationship between TTHM and preterm birth (i.e., lower risk with higher exposure) was reported in recent studies by Wright et al.[12], Hoffman et al.[15], and Lewis et al.[33] Similarly, our results show a lack of association with TTHM and the

outcomes of interest. Hoffman et al.[15] reported an absence of an association between both HAA5 and TOX exposure and PTB. We also examined the association of HAA5 and TOX concentrations with both PTB and very PTB, and found the strongest association for TOX and very PTB in the brominated DBP site. Our results indicating an association between TOX and very PTB in the brominated DBP site are novel, as few studies have examined the association between DBPs and very PTB as an outcome. It is possible that there is less misclassification in very PTB than PTB, and that this could account for the observed effect for very PTB and the weaker association observed in our study and the lack of an association observed in previous investigations for PTB. Alternately, these results could be due to chance or confounding.

We used term-SGA as a surrogate for fetal growth restriction because it is conventionally used to identify more severe growth restriction in epidemiologic research and has been examined in previous DBP studies. However, not all infants who are small at birth are growth-restricted and vice-versa. The use of term-SGA as a surrogate for fetal growth restriction may be a limitation in our study and in many other epidemiologic evaluations concerned with fetal growth. Analyses of birth weight as a continuous measure yielded similar patterns as were found for term-SGA (see see Table, Supplemental Digital Content 2, http://links.lww.com/JOM/A68, which illustrates the change in birth weight associated with DBP exposure).

The strong relationship between residential location (i.e. study site) and tap water DBP concentration in our study is a strength for the internal comparisons (within-site) that we have made, but a limitation in that analyses that integrate across sites are susceptible to confounding by population characteristics. By design, and because the sites used combined chlorine as a terminal disinfectant to reduce spatial variability, exposure differences within sites occur solely due to temporal differences in tap water concentrations. Thus, by limiting the study to within-site analyses, only attributes that might covary with time of pregnancy (e.g., seasonal illnesses or variation in physical activity) could be potential confounders.

A limitation to our study is the lack of a completely unexposed reference group, so that we are only able to examine variation within the range that was present. This was a limitation of a previous study which did not find an association between PTB and TTHMs and for several previous studies that examined HAAs.[29] Adverse pregnancy outcomes associated with low DBP concentrations (down to 5 μg/L BDCM and 20 μg/L TTHM) have been suggested in other studies. Therefore if effects do occur at those levels, including low or unexposed individuals in the referent group (up to ~60 μg/L TTHM in our study) would limit our ability to discern differences in risk related to the truncated range of exposure we were able to examine.

Our study is strengthened by the concurrent measurement of DBP concentrations over the course of pregnancy, which included weekly DBP measurements collected to capture temporal variability in DBP concentrations and allowed estimation of trimester-specific average exposures based on more measurements (generally 12–13) made at regular intervals rather than the typical case of 1 day of monitoring during a 3-month period. Validation of this water sampling strategy ensured that the concentrations throughout the water distribution systems serving the study participants' homes are accurately represented, thereby reducing spatial variability in exposure during any given week.[22] The resulting assignment of residential DBP concentrations averaged over a trimester should be more accurate than in previous studies.

In conclusion, our results provide evidence against an association of DBP measures with adverse birth outcomes, with the possible exception of TOX and PTB and very PTB in the

brominated site. Additional research to disentangle the effects of specific individual DBPs or groups of DBPs, specifically TOX, is warranted.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1**

Water exposure data (Analysis dataset)

| | Chlorinated DBP site | | Brominated DBP site | |
|---|---|---|---|---|
| | N | % | N | % |
| Small for gestational age | | | | |
| term, SGA | 1667 | 6.1 | 247 | 6.3 |
| term, not SGA | 21781 | 80.1 | 2662 | 67.5 |
| preterm | 2201 | 8.1 | 438 | 11.1 |
| Missing | 1528 | 5.6 | 599 | 15.2 |
| Preterm birth | | | | |
| Preterm | 2201 | 8.1 | 438 | 11.1 |
| not Preterm | 24976 | 91.9 | 3508 | 88.9 |
| Missing | 0 | 0 | 0 | 0 |
| Very preterm birth | | | | |
| Very preterm | 381 | 1.4 | 83 | 2.1 |
| not Very preterm | 26796 | 98.6 | 3863 | 97.9 |
| Missing | 0 | 0 | 0 | 0 |
| Maternal age | | | | |
| <20 | 1760 | 6.5 | 624 | 15.8 |
| 20–24 | 5100 | 18.8 | 1257 | 31.7 |
| 25–29 | 7333 | 27.0 | 1042 | 26.4 |
| 30–34 | 8392 | 31.0 | 675 | 17.1 |
| 35–39 | 3859 | 14.2 | 281 | 7.1 |
| >=40 | 733 | 2.7 | 67 | 1.7 |
| Missing | 0 | 0 | 0 | 0 |
| Maternal race | | | | |
| White, Non-Hispanic | 14308 | 52.7 | 1528 | 38.7 |
| Black, Non-Hispanic | 6756 | 24.9 | 916 | 23.2 |
| Hispanic | 4477 | 16.5 | 1366 | 34.6 |
| Missing/Other | 1636 | 6.0 | 136 | 3.4 |
| Marital status | | | | |
| Married | 19560 | 72.0 | 1844 | 46.7 |
| Not married | 7617 | 28.0 | 1807 | 45.8 |
| Missing | 0 | 0 | 295 | 7.5 |
| Highest education attained | | | | |
| High school | 9515 | 35.0 | 2550 | 64.6 |
| Some college | 4968 | 18.3 | 788 | 20 |
| College degree or more | 12613 | 46.4 | 589 | 14.9 |
| Missing | 81 | 0.3 | 19 | 0.5 |
| Tobacco use | | | | |
| Yes | 1343 | 4.9 | 328 | 8.3 |
| No | 25819 | 95.0 | 3326 | 84.3 |

| | Chlorinated DBP site | | Brominated DBP site | |
|---|---|---|---|---|
| | N | % | N | % |
| Missing | 15 | 0.1 | 292 | 7.4 |
| Alcohol use | | | | |
| Yes | 128 | 0.5 | 74 | 1.9 |
| No | 27028 | 99.5 | 3580 | 90.7 |
| Missing | 21 | 0.1 | 292 | 7.4 |
| Parity | | | | |
| Nulliparous | 12093 | 44.5 | 1407 | 35.7 |
| Parous | 15075 | 55.5 | 1724 | 43.7 |
| Missing | 9 | 0.0 | 815 | 20.7 |

## Table 2

Average Residential DBP Concentrations (μg/L) in the chlorinated and brominated DBP sites

| DBP | Chlorinated DBP site Mean (SD) | Brominated DBP site Mean (SD) |
|---|---|---|
| Trihalomethanes | | |
| Chloroform ($CHCl_3$) | 45.6 (19.7) | 11.9 (7.5) |
| Bromodichloromethane ($BrCl_2CH$) | 13.8 (4.9) | 19.7 (6.8) |
| Dibromochloromethane ($Br_2ClCH$) | 3.9 (2.1) | 22.4 (8.1) |
| Bromoform ($CHBr_3$) | 0.1 (0.3) | 6.5 (5.1) |
| TTHM[a] | 63.3 (23.1) | 60.4 (20.7) |
| Haloacetic acids | | |
| Chloroacetic acid (ClAA) | 2.4 (1.9) | 2.4 (2.5) |
| Dichloroacetic acid ($Cl_2AA$) | 17.5 (5.7) | 6.6 (3.1) |
| Trichloroacetic acid ($Cl_3AA$) | 12.5 (6.1) | 4.7 (3.2) |
| Bromochloroacetic acid (BrClAA) | 4.1 (1.7) | 8.1 (1.8) |
| Bromodichloroacetic acid ($BrCl_2AA$) | 4.4 (2.0) | 8.3 (2.8) |
| Dibromochloroacetic acid ($Br_2ClAA$) | 1.3 (1.2) | 5.5 (1.8) |
| Bromoacetic acid (BrAA) | 0.1 (0.2) | 0.8 (0.9) |
| Dibromoacetic acid ($Br_2AA$) | 0.7 (0.8) | 6.9 (3.2) |
| Tribromoacetic acid ($Br_3AA$) | 0.2 (0.7) | 2.5 (1.6) |
| HAA5[b] | 33.2 (12.1) | 21.5 (5.9) |
| HAA9[c] | 43.2 (14.4) | 45.7 (9.0) |
| Total organic halides (TOX) | 170.8 (32.3) | 186.1 (35.1) |
| Unaccounted TOX | 95.7 (25.7) | 127.7 (32.7) |
| Chlorinated DBPs[d] | 105.4 (33.9) | 89.6 (24.2) |
| Brominated DBPs[e] | 28.6 (9.9) | 80.5 (21.0) |

[a] TTHM is the sum of the 4 THM species

[b] HAA5 is the sum of ClAA, $Cl_2AA$, $Cl_3AA$, BrAA, and $Br_2AA$

[c] HAA9 is the sum of the 9 haloacetic acid species

[d] Chlorinated DBPs are the sum of $CHCl_3$, $BrCl_2CH$, $Br_2ClCH$, ClAA, $Cl_2AA$, $Cl_3AA$, BrClAA, $BrCl_2AA$, $Br_2ClAA$

[e] Brominated DBPs are the sum of $CHBr_3$, $BrCl_2CH$, $Br_2ClCH$, BrAA, $Br_2AA$, $Br_3AA$, BrClAA, $BrCl_2AA$, $Br_2ClAA$

## Table 3

Distribution of DBP levels by site

| Groups | TTHM (μg/L) | HAA5 (μg/L) | HAA9 (μg/L) | TOX (μg/L) | Unaccounted TOX (μg/L) | Chlorinated (μg/L) | Brominated (μg/L) |
|---|---|---|---|---|---|---|---|
| **Chlorinated DBP site** | | | | | | | |
| **< 50th percentile** | 24.7–60.7 | 12.1–31.9 | 15.4–41.5 | 104–167.5 | 16.5–96.0 | 40.1–106.1 | 13–25.8 |
| **50th to 75th percentile** | 60.7–75.9 | 31.9–41.1 | 41.5–54.3 | 167.5–192.5 | 96.0–109.9 | 106.1–125.8 | 25.8–31.9 |
| **75th to 90th percentile** | 75.9–88.5 | 41.1–50.5 | 54.3–63.5 | 192.5–213 | 109.9–128.2 | 125.8–143.5 | 31.9–43.8 |
| **> 90th percentile** | 88.5–148.6 | 50.5–62.2 | 63.5–78.9 | 213–269 | 128.2–179.3 | 143.5–222.4 | 43.8–59.8 |
| **Brominated DBP site** | | | | | | | |
| **< 50th percentile** | 26.6–58.9 | 13.2–20 | 30.4–44.7 | 111–183 | 34.7–127.7 | 50–87.95 | 41.8–77.6 |
| **50th to 75th percentile** | 58.9–67.4 | 20–23.2 | 44.7–48.9 | 183–205 | 127.7–148.8 | 87.95–98.2 | 77.6–93.7 |
| **75th to 90th percentile** | 67.4–80.6 | 23.2–26.2 | 48.9–54.7 | 205–234 | 148.8–169.5 | 98.2–106.5 | 93.7–106.9 |
| **> 90th percentile** | 80.6–165 | 26.2–53.1 | 54.7–98.9 | 234–290 | 169.5–223.5 | 106.5–238.1 | 103.9–168 |

Note: Taken from water system measures.

## Table 4

Adjusted Odds Ratios and 95% Confidence Intervals for Categorical and Continuous DBP Exposures – Chlorinated DBP site

| Outcome | Exposure Variable | Number of Cases TTHM/HAA5/TOX | Number of Controls TTHM/HAA5/TOX | TTHM | HAA5 | TOX |
|---|---|---|---|---|---|---|
| Term-SGA[a] | < 50th percentile | 684/730/653 | 9179/9378/8481 | 1 | 1 | 1 |
| | 50th to 75th percentile | 481/427/678 | 6290/5304/8685 | 1.02 (0.91,1.15) | 1.02 (0.9,1.16) | 1.01 (0.90,1.13) |
| | 75th to 90th percentile | 250/346/151 | 2949/4567/2144 | 1.12 (0.96,1.30) | 0.97 (0.85,1.11) | 0.91 (0.76,1.09) |
| | > 90th percentile | 128/40/61 | 1587/756/695 | 1.06 (0.87,1.29) | 0.68 (0.49,0.94) | 1.13 (0.86,1.49) |
| | Continuous (per 10 μg/L) | 1543 | 20005 | 1.01 (0.98,1.04) | 0.96 (0.91,1.01) | 1.00 (0.97,1.03) |
| PTB[a] | < 50th percentile | 1046/1050/948 | 11503/11784/10444 | 1 | 1 | 1 |
| | 50th to 75th percentile | 570/538/855 | 6673/5718/9827 | 0.93 (0.84,1.04) | 1.05 (0.94,1.17) | 0.96 (0.87,1.05) |
| | 75th to 90th percentile | 341/430/224 | 3672/5140/2356 | 1.01 (0.89,1.14) | 0.94 (0.84,1.06) | 1.02 (0.88,1.19) |
| | > 90th percentile | 118/57/48 | 1423/629/644 | 0.91 (0.74,1.11) | 1.04 (0.79,1.38) | 0.84 (0.62,1.13) |
| | Continuous (per 10 μg/L) | 2075 | 23271 | 0.98 (0.95,1.00) | 0.98 (0.94,1.03) | 0.99 (0.97,1.01) |
| Very PTB[a] | < 50th percentile | 160/169/154 | 12389/12665/11238 | 1 | 1 | 1 |
| | 50th to 75th percentile | 104/103/158 | 7139/6153/10524 | 1.12 (0.87,1.43) | 1.25 (0.97,1.60) | 1.09 (0.87,1.36) |
| | 75th to 90th percentile | 75/70/37 | 3938/5500/2543 | 1.43 (1.08,1.89) | 0.96 (0.73,1.27) | 1.02 (0.71,1.47) |
| | > 90th percentile | 17/14/7 | 1524/672/685 | 0.86 (0.52,1.43) | 1.63 (0.94,2.85) | 0.78 (0.36,1.67) |
| | Continuous (per 10 μg/L) | 356 | 24990 | 1.0 (0.95,1.07) | 1.04 (0.93,1.16) | 1.01 (0.96,1.07) |

Note: Following Hoffman et al., third trimester exposures used for SGA analysis while second trimester exposures used for Preterm and very Preterm analyses.

[a]Adjusted for maternal age, maternal race, marital status, maternal education, tobacco use, alcohol use, and parity

## Table 5

Adjusted Odds Ratios and 95% Confidence Intervals for Categorical and Continuous DBP Exposures – Brominated DBP site

| Outcome | Exposure Variable | Number of Cases TTHM/HAA5/TOX | Number of Controls TTHM/HAA5/TOX | TTHM | HAA5 | TOX |
|---|---|---|---|---|---|---|
| Term-SGA[a] | < 50th percentile | 103/124/97[b] | 1161/1278/1015[b] | 1 | 1 | 1 |
| | 50th to 75th percentile | 32/82/110[b] | 409/872/1185[b] | 0.81 (0.53,1.24) | 1.00 (0.74,1.34) | 0.98 (0.73,1.31) |
| | 75th to 90th percentile | 107/39/45[b] | 1027/458/434[b] | 1.21 (0.91,1.63) | 0.86 (0.59,1.26) | 1.07 (0.73,1.57) |
| | > 90th percentile | 21/18/11[b] | 177/166/140[b] | 1.26 (0.76,2.08) | 1.07 (0.62,1.83) | 0.86 (0.44,1.68) |
| | Continuous (per 10 μg/L) | 263[b] | 2774[b] | 1.06 (0.96,1.16) | 0.97 (0.59,1.59) | 1.00 (0.99,1.01) |
| PTB[a] | < 50th percentile | 207/157/162 | 1667/1191/1462 | 1 | 1 | 1 |
| | 50th to 75th percentile | 41/144/170 | 312/1008/1276 | 1.16 (0.77,1.74) | 1.17 (0.89,1.53) | 1.16 (0.90,1.49) |
| | 75th to 90th percentile | 137/78/60 | 934/771/332 | 1.19 (0.92,1.55) | 0.74 (0.53,1.02) | 1.69 (1.17,2.44) |
| | > 90th percentile | 16/22/9 | 196/139/39 | 0.77 (0.44,1.37) | 1.29 (0.73,2.28) | 1.99 (0.85,4.67) |
| | Continuous (per 10 μg/L) | 401 | 3109 | 1.00 (0.92,1.09) | 0.68 (0.42,1.12) | 1.09 (1.03,1.16) |
| Very PTB[a] | < 50th percentile | 34/32/26 | 1840/1316/1598 | 1 | 1 | 1 |
| | 50th to 75th percentile | 14/29/31 | 339/1123/1415 | 2.36 (1.21,4.62) | 1.16 (0.68,1.98) | 1.29 (0.75,2.22) |
| | 75th to 90th percentile | 23/11/16 | 1048/838/376 | 1.08 (0.62,1.90) | 0.56 (0.27,1.14) | 2.43 (1.22,4.84) |
| | > 90th percentile | 5/4/2003 | 207/157/45 | 1.63 (0.62,4.33) | 1.23 (0.41,3.67) | 4.17 (1.14,15.32) |
| | Continuous (per 10μg/L) | 76 | 3434 | 1.03 (0.86,1.23) | 0.47 (0.17,1.30) | 1.23 (1.09,1.39) |

Note: Following Hoffman et al., third trimester exposures used for SGA analysis while second trimester exposures used for Preterm and very Preterm analyses.

[a] Adjusted for maternal age, maternal race, marital status, maternal education, tobacco use, alcohol use, and parity

[b] The rounded average over imputations is used because SGA is defined by an imputed value.

## Table 6

Adjusted Odds Ratios and 95% Confidence Intervals for Categorical and Continuous DBP Exposures stratified by chlorinated and brominated species of THMs and HAAs

| Outcome | Exposure Variable | Chlorinated DBP site | | Brominated DBP site | |
|---|---|---|---|---|---|
| | | Chlorinated[a] DBPs | Brominated[b] DBPs | Chlorinated[a] DBPs | Brominated[b] DBPs |
| Term-SGA[c] | < 50th percentile | 1 | 1 | 1 | 1 |
| | 50th to 75th percentile | 0.95 (0.84,1.07) | 1.03 (0.91,1.16) | 0.93 (0.68,1.26) | 1.02 (0.72,1.43) |
| | 75th to 90th percentile | 1.10 (0.95,1.28) | 1.10 (0.94,1.27) | 1.03 (0.69,1.54) | 1.27 (0.93,1.75) |
| | > 90th percentile | 0.99 (0.79,1.24) | 1.16 (0.96,1.41) | 1.17 (0.77,1.78) | 1.19 (0.71,2.00) |
| | Continuous (per 10 μg/L) | 1.00 (0.98,1.02) | 1.05 (0.99,1.12) | 1.02 (0.91,1.14) | 1.05 (0.97,1.13) |
| PTB[c] | < 50th percentile | 1 | 1 | 1 | 1 |
| | 50th to 75th percentile | 0.94 (0.85,1.04) | 1.04 (0.94,1.16) | 1.18 (0.90,1.54) | 0.78 (0.58,1.05) |
| | 75th to 90th percentile | 1.06 (0.92,1.21) | 0.97 (0.84,1.13) | 1.49 (1.00,2.20) | 1.05 (0.77,1.45) |
| | > 90th percentile | 0.85 (0.68,1.06) | 1.15 (0.97,1.37) | 0.89 (0.58,1.35) | 0.83 (0.47,1.48) |
| | Continuous (per 10 μg/L) | 0.99 (0.97,1.01) | 1.03 (0.97,1.09) | 1.01 (0.90,1.12) | 0.98 (0.91,1.05) |
| Very PTB[c] | < 50th percentile | 1 | 1 | 1 | 1 |
| | 50th to 75th percentile | 1.15 (0.91,1.45) | 1.09 (0.86,1.39) | 0.98 (0.56,1.73) | 0.88 (0.48,1.61) |
| | 75th to 90th percentile | 1.15 (0.84,1.57) | 1.16 (0.84,1.62) | 2.13 (1.08,4.21) | 0.66 (0.32,1.37) |
| | > 90th percentile | 0.75 (0.43,1.33) | 1.15 (0.77,1.72) | 0.65 (0.24,1.75) | 2.29 (1.01,5.21) |
| | Continuous (per 10 μg/L) | 1.01 (0.97,1.05) | 1.08 (0.95,1.22) | 1.04 (0.83,1.31) | 0.98 (0.85,1.14) |

Note: Following Hoffman et al., third trimester exposures used for SGA analysis while second trimester exposures used for Preterm and very Preterm analyses.

[a] Chlorinated DBPs are the sum of $CHCl_3$, $BrCl_2CH$, $Br_2ClCH$, ClAA, $Cl_2AA$, $Cl_3AA$, BrClAA, $BrCl_2AA$, $Br_2ClAA$

[b] Brominated DBPs are the sum of $CHBr_3$, $BrCl_2CH$, $Br_2ClCH$, BrAA, $Br_2AA$, $Br_3AA$, BrClAA, $BrCl_2AA$, $Br_2ClAA$

[c] Adjusted for maternal age, maternal race, marital status, maternal education, tobacco use, alcohol use, and parity

## Table 7

Adjusted Odds Ratios and 95% Confidence Intervals for Categorical and Continuous Unaccounted TOX exposure

| | | Chlorinated Site | | Brominated Site | |
|---|---|---|---|---|---|
| | **Exposure Variable** | **Number of Cases/Controls** | **Unaccounted TOX** | **Number of Cases/Controls** | **Unaccounted TOX** |
| **Term-SGA**[a] | **< 50th percentile** | 728/9305 | 1 | 88/946 | 1 |
| | **50th to 75th percentile** | 743/9665 | 0.99 (0.89,1.11) | 149/1616 | 0.98 (0.73,1.32) |
| | **> 75th percentile** | 75/1100 | 0.877 (0.69,1.12) | 49/510 | 1.06 (0.71,1.57) |
| | **> 90th percentile** | 0/0 | - | 3/51 | 0.90 (0.27,3.00) |
| | **Continuous (per 10 μg/L)** | 1543/20005 | 0.99 (0.93,1.05) | 289/3123 | 0.98 (0.91,1.06) |
| **PTB**[a] | **< 50th percentile** | 1063/12300 | 1 | 219/1948 | 1 |
| | **50th to 75th percentile** | 1012/11426 | 1.03 (0.94,1.13) | 316/2489 | 1.19 (0.92,1.55) |
| | **> 75th percentile** | 126/1135 | 1.24 (1.02,1.52) | 121/827 | 1.66 (1.12,2.45) |
| | **Continuous (per 10 μg/L)** | 2075/23271 | 1.06 (1.00,1.12) | 656/5264 | 1.11 (1.04,1.19) |
| **Very PTB**[a] | **< 50th percentile** | 184/13179 | 1 | 31/2136 | 1 |
| | **50th to 75th percentile** | 166/12272 | 0.96 (0.77,1.20) | 56/2749 | 1.80 (1.00,3.24) |
| | **> 75th percentile** | 31/1230 | 1.681 (1.13,2.51) | 32/916 | 3.62 (1.75,7.52) |
| | **Continuous (per 10 μg/L)** | 356/24990 | 1.02 (0.90,1.16) | 119/5801 | 1.30 (1.13,1.50) |

Note: Following Hoffman et al., third trimester exposures used for SGA analysis while second trimester exposures used for Preterm and very Preterm analyses.

[a]Adjusted for maternal age, maternal race, marital status, maternal education, tobacco use, alcohol use, and parity