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Author manuscript

Occup Environ Med. Author manuscript; available in PMC 2019 October 01.

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Published in final edited form as:

Occup Environ Med. 2018 October ; 75(10): 742–751. doi:10.1136/oemed-2017-104861.

Exposure to disinfectant byproducts and the risk of stillbirth in Massachusetts

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Abstract

Objectives—We examined stillbirths in relation to disinfection byproduct (DBP) exposures including chloroform, bromodichloromethane (BDCM), dibromochloromethane (DBCM), bromoform, trichloroacetic acid (TCAA), dichloroacetic acid (DCAA), monobromoacetic acid (MBAA), and summary DBP measures (THM4 (trihalomethanes), HAA5 (haloacetic acids), brominated trihalomethanes (THMBr), and DBP9 (sum of THM4 and HAA5)).

Methods—We randomly selected 10 controls for each of the 2460 stillbirth cases with complete quarterly 1997–2004 THM4 and HAA5 town-level drinking water data. Adjusted odds ratios (aORs) were calculated based on weight-averaged second-trimester DBP exposures.

Results—We detected statistically significant associations for stillbirths and the upper DCAA quartiles (aOR range: 1.50–1.71). We found positive associations between stillbirths and chloroform exposure (aOR range: 1.29–1.36) and unexplained stillbirths and BDCM exposure (aOR range: 1.51–1.78). We also found positive associations for the upper four HAA5 quintiles and different stillbirth cause of death categories that were examined including unexplained stillbirth (aOR range: 1.24–1.72), compression of umbilical cord (aOR range: 1.08–1.94), prematurity (aOR range: 1.37–2.88), placental separation and hemorrhage (aOR range: 1.44–2.01), and asphyxia/hypoxia (aOR range: 1.52–1.97). We saw no evidence of exposure-response relationships for any categorical DBP metrics.

Conclusions—Consistent with some previous studies, we found associations between stillbirths and chloroform and unexplained stillbirth and BDCM exposures. These findings strengthen existing evidence of prenatal THM exposures increasing the risk of stillbirth. Additionally, we saw statistically significant associations between DCAA and stillbirth. Future research should examine cause-specific stillbirths in relation to narrower critical windows and additional DBP exposure metrics beyond trihalomethanes and haloacetic acids.

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The views expressed in this manuscript are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

Keywords

disinfection byproducts; stillbirth; trihalomethanes; haloacetic acids; chloroform; fetal loss

INTRODUCTION

In the United States, 24,000 stillbirths occur every year.¹ The Centers for Disease Control and Prevention defines stillbirth as fetal death at 20 weeks of gestation or greater during pregnancy.¹ The etiology of the majority of stillbirths is unknown, with the remaining causes largely due to placental or umbilical cord complications, birth defects, genetic abnormalities and certain maternal health conditions such as hypertension.¹ Associations between stillbirths and environmental exposures including air pollution, household fumes (eg, from cooking fuels), and tobacco smoke have been previously reported in epidemiological studies.² Epidemiological evidence for associations between stillbirths and drinking water contaminants, including disinfection byproducts (DBPs), is less clear in the literature. DBP formation occurs when chlorine and other disinfectants react with naturally occurring organic matter. From the nine published studies examining stillbirths and DBPs,^{3–11} four have reported positive associations^{3, 4, 7, 10} with three of these four based on Canadian studies with overlapping study populations.^{3, 4, 10}

Most epidemiological studies evaluating DBPs have focused on trihalomethanes (THMs), especially THM4, a summary measure of the four predominant THM species: chloroform, bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform. Although the authors of a meta-analysis of five THM4 studies reported considerable heterogeneity due to differences in exposure assessment methods, they showed an increased risk (odds ratio (OR)= 1.21; 95% confidence interval (CI): 1.02–1.43) of stillbirth in relation to THM4 exposures.¹¹ One of the two studies in the meta-analysis examining individual THMs^{7, 10} detected an increased risk of stillbirth with exposure to chloroform and BDCM.¹⁰ Data from animal studies provide further evidence for the effect of BDCM on pregnancy loss^{12, 13} but other individual THMs have not been examined. A study on F344 rats examining in utero exposure to DBP mixtures (ie, THM4, HAA5 (haloacetic acid, HAA5: the sum of monochloroacetic acid [MCAA], dichloroacetic acid [DCAA], trichloroacetic acid (TCAA), monobromoacetic acid (MBAA), dibromoacetic acid [DBAA]), DBP9 [ie, the sum of THM4 and HAA5]) administered by gavage at 1 mL kg⁻¹ body weight once daily, reported pregnancy loss caused by all three mixtures¹⁴. Another study in Sprague-Dawley rats reported no associations for a DBP mixture including 75 priority and regulated DBPs.¹⁵

At the time of this publication, only one previous epidemiological study has examined HAA exposures in relation to stillbirth⁸ and found an increased risk of stillbirth for the upper two HAA5 tertiles (OR range: 1.35–2.35) compared to unexposed study participants. This Canadian study also reported effect estimates similar in magnitude for both DCAA and TCAA concentrations >0 µg L⁻¹ (OR ranges: 1.17–1.99 and 1.13–1.54, respectively); however, these associations were not statistically significant after adjusting for total daily THM4 exposure (ingestion, showering, and bathing). Specific causes of fetal death in relation to DBP exposure were also examined in retrospective cohort and case-control

studies in Nova Scotia, which reported consistently increased risk ratios for asphyxia-related stillbirths (defined as placental, umbilical cord, and labor and delivery complications) and different exposure metrics including THM4, chloroform, and BDCM.^{3,10}

Exposure assessment of DBPs remains one of the main challenges in epidemiological studies of stillbirth and other developmental outcomes including the use of indirect exposure measures from monitoring data with limited spatial and temporal resolution. For example, there is often a temporal disconnect between the available DBP sampling data and the most critical exposure window(s) which may not be fully known. Some studies of stillbirths have examined pregnancy average exposure measures^{3–6, 11} while others used gestational age- or trimester-specific exposure measures.^{7–10} Additionally, the majority of epidemiological studies focused on the most prevalent DBPs (ie, THMs) or summary measures (ie, THM4), but these may not be the best surrogates for the complex DBP mixtures found in disinfected drinking water. Furthermore, HAAs (haloacetic acids; the second most prevalent DBP group) are rarely evaluated despite evidence from animal studies showing adverse effects including post-implantation and pregnancy loss.¹⁶ If DBP surrogates based on temporally averaged data do not capture the most relevant toxic DBP mixture combinations or the most critical etiological window, information bias from exposure misclassification can occur. To address methodological challenges from previous studies including limited individual and group DBP measures, different exposure windows, and several individual causes of death, we examined the risk of stillbirth in relation to second- and third-trimester DBP exposures.

METHODS

Outcome data

The Massachusetts Department of Public Health (Boston, MA) issues individual birth certificates for live infants and fetal death certificates for stillbirths. In Massachusetts, a fetal death is reported if a fetus is of 20 weeks of gestation or greater or weighs 350 grams or more. We conducted a case-control study of stillbirths in 138 Massachusetts towns with complete THM4 and HAA5, water source, and disinfection type data for the period from 1997–2004. We restricted the analysis to singleton pregnancies and randomly selected (without replacement) 10 controls per case from all live births in the 138 Massachusetts towns for a total study population of 27 060. The selection of 10 controls from a sufficient number of controls (>600,000 live births) is statistically more efficient than other study design such as thousand controls per each case. Gestational age was derived from clinical estimates according to birth records and was subtracted from the date of birth to determine the week of conception for exposure assessment purposes. Only study participants with a recorded gestational age in the birth records were included in the analysis; the control group was also restricted to those with plausible gestational age values (ie, between 20 and 42 weeks).

Cases occurring during 1998–1999 were reported based on the 9th International Classification of Diseases (ICD-9), while cases occurring during 2000–2004 were reported based on ICD-10. We used the General Equivalence Mappings (developed by the Department of Health and Human Services, Centers for Medicare and Medicaid Services) to address differences between ICD-9 and –10 and to group cases according to cause of death

category.¹⁷ We focused on five particular causes of death because a) they were sufficiently prevalent to yield statistically robust results, and b) they have been associated with DBP exposures which allowed for comparison purposes to previous studies. These causes of death were: (i) unexplained stillbirth (unknown cause of death), (ii) compression of umbilical cord, (iii) prematurity, (iv) placental separation and hemorrhage, and (v) birth asphyxia and intrauterine hypoxia (asphyxia/hypoxia). Seven cases were excluded from the analysis when the descriptions of cause of death category could not be matched between the two different ICD codes. A detailed description of ICD codes included in the analysis can be found in supplemental Table 1.

Exposure data

The exposure data was provided by the Massachusetts Department of Environmental Protection and individual public water utilities. THM concentrations were quantified by certified laboratories using capillary column gas chromatography based on EPA Method 502.2,¹⁸ capillary column gas chromatography/mass spectrometry based on EPA Method 524.2¹⁹ and gas chromatography with electron capture detection based on EPA Method 551.1.²⁰ HAA concentrations were quantified based on EPA Methods 552.1 and 552.2 using gas chromatography and electron capture detection²¹ and Standard Method 6251B using micro liquid-liquid extraction gas chromatography.²² Detection limits, while variable across laboratories and time, ranged from 0.1 to 2.5 µg/L for the THMs and 0.4 to 5.0 µg/L for the HAAs. Study participant exposure scores were assigned values of zero for any samples with levels below the detection limit.

We linked public drinking water source, disinfection type, and DBP data based on quarterly sampling (1997–2004) to birth and death records by town of residence and date of birth. The trimester-specific DBP exposure scores were based on weighted averages for multiple quarters overlapping the second or third trimesters derived from the date of birth and the timing of quarterly DBP samples previously reported.²³ For example, a stillbirth of 37 gestational weeks delivered in January 2000 would have nine second-trimester weeks that occurred in quarter 4 of 1999 and four second-trimester weeks that occurred in quarter 3 of 1999. Therefore, the exposure score would be [(4/13) times the average DBP concentration for quarter 4 of 1999]*[(9/13) times the average DBP concentration for quarter 3 of 1999] using data from the entire public water system. DBP formation would not be expected to occur in water supplies that are not disinfected. Therefore, residents using untreated ground water (eg, private wells) were assigned DBP concentrations of zero.

Exposures were estimated for nine individual DBPs as well as summary measures of DBP mixtures including THM4, HAA5, DBP9, and THMBr (ie, the sum of BDCM, DBCM, and bromoform). We categorized maternal DBP exposure levels for the individual and summary DBP measures into tertiles, quartiles, or quintiles based on the distribution of the data among the control population. Because of a paucity of occurrence data, DBCM and MCAA were dichotomized at the 90th percentile (4.6 µg L⁻¹ and 3.8 µg L⁻¹ respectively), while bromoform, DBAA, and MBAA were dichotomized at 0 or >0 µg L⁻¹ concentrations. Study participants in the lowest DBP exposure category served as the referent for comparison with the other categories. Due to a smaller number of cases, we conducted a separate analysis to

evaluate asphyxia/hypoxia deaths. The exposure metrics cut-points for this analysis were as follow: tertiles for THM4, chloroform, THMBr, and HAA5 and median (dichotomized) for BDCM, TCAA, and DCAA.

Statistical analysis

The Statistical Analysis System software version 9.4 (SAS Institute, Cary, NC, USA) was used for the statistical analyses. Frequency distributions and chi-square statistics were calculated for all categorical socio-demographic variables. Spearman correlation coefficients were used to compare individual and summary DBP measures. Unconditional logistic regression was used to estimate *p*-values for trends, ORs, adjusted ORs (aOR), and 95% CIs for stillbirths. Statistical significance was based on alpha <0.05. The following potential confounders from individual birth records were examined: maternal age, race, education, smoking (ie, the number of cigarettes per day during pregnancy), parity, the number of prenatal visits, prenatal care source of payment (ie, private, government, other), income (median household income), marital status, maternal medical conditions (eg, diabetes, chronic hypertension, lung disease, renal disease) and reproductive health factors (eg, hydramnios/oligohydramnios, incompetent cervix, preeclampsia, previous preterm birth, weight gain during pregnancy), seasonality (ie, quarter of the year at birth), drinking water source (ie, surface, ground, and mixed), type of water disinfectants used (ie, untreated, chlorination, chloramination, other), and THM4/HAA5 concentrations in drinking water. Income data was obtained from the 2000 Census (Geolytics, Inc., East Brunswick, NJ) and was assigned using the census tract corresponding to maternal residential ZIP code at time of birth. Confounding factors were separately evaluated based on percentage change in regression (Beta) coefficient estimates in each multivariate model (THMs and HAAs) compared to bivariate models, and included only those variables changing the coefficient estimate >10%. The following covariates were identified as confounders and adjusted for in the multivariate stillbirth regression models: race/ethnicity, education, marital status, smoking, drinking water source, and THM4 or HAA5 concentrations. THM4 and HAA5 concentration and smoking (ie, number of cigarettes during pregnancy) were adjusted as continuous variables while the remaining variables were categorized.

If five or fewer cases were available for analysis in any DBP categories, associations were not examined to minimize the potential for sparse data bias.²⁴ In a sensitivity analysis, we examined asphyxia-related stillbirth (ie, compression of umbilical cord, placental separation and hemorrhage, and labor and delivery complications) as one category of death for comparison purposes with previous studies.^{3, 10} Labor and delivery complications were not examined individually, but were considered as part of this grouped category (ie., asphyxia-related stillbirth). We also conducted sensitivity analyses to examine the relationship between third-trimester DBP exposures and all stillbirths.

RESULTS

Complete DBP exposure data was available for 2460 stillbirths that occurred in Massachusetts from 1998 to 2004. The majority of stillbirths were due to unexplained

causes (40%) followed by compression of the umbilical cord (12%) and prematurity (9%) (table 1).

Cases and controls were similar with respect to most sociodemographic covariates, although significant differences were found in maternal race, education, and marital status. For example, cases were more likely born to unmarried (39% of cases compared to 28% of controls), African-American (18% of cases compared to 8% of controls) and less educated women (39% of cases had less than a high school diploma compared to 14% of controls) (table 2).

Table 3 shows the second-trimester distribution for the 13 DBP metrics that we examined. The chlorinated THMs and HAAs were the predominant species, and some brominated DBPs, such as MBAA, were rarely detected. We observed second-trimester Spearman correlation coefficients greater than or equal to 0.9 for the following: DBP9 with THM4, chloroform, and HAA5; THM4 and chloroform; HAA5 with TCAA and DCAA; and BDCM and THMBr (supplemental table 2). We found correlations between 0.70 and 0.90 for the following: HAA5 with THM4 and chloroform; TCAA with DBP9, THM4, and chloroform; DCAA with DBP9, THM4, and chloroform; and between THMBr and BDCM.

We did not detect an increased risk for stillbirth and second-trimester THM4 exposures, but there were statistically significant associations for each of the DCAA quartiles (aOR range: 1.50–1.71), MBAA dichotomized exposures (aOR= 1.89; 95% CI: 1.15–3.10) (see the multi-DBP adjusted models in table 4). Non-statistically significant increased odds were detected for each of the chloroform (aOR range: 1.29–1.51) and HAA5 quintiles (aOR range: 1.41–1.74). We also detected a statistically significant decreased risk of stillbirth and the two lowest THMBr quintiles compared to the first quintile (aOR range: 0.68–0.70; adjusted THMBr model, table 4). Table 5 shows statistically significant associations for unexplained stillbirth and the two highest BDCM tertiles (aOR range: 1.51–1.78), as well as increased adjusted odds for compression of umbilical cord among all of the chloroform quintiles (aOR range: 1.40–2.21) and the DCAA quartiles (aOR range: 2.11–3.29) (table 5).

Although not statistically significant, increased adjusted ORs were detected between the upper four HAA5 quintiles and all individual causes of death examined including unexplained stillbirth (aOR range: 1.24–1.72), compression of umbilical cord (aOR range: 1.08–1.94), prematurity (aOR range: 1.37–2.88), and placental separation and hemorrhage (aOR range: 1.44–2.01) (table 5). Statistically significant associations larger in magnitude were detected between dichotomized MBAA exposures and compression of umbilical cord (aOR= 3.55; 95%CI: 1.25–10.12) as well as between prematurity-related stillbirths and each TCAA quartile (aOR range: 4.00–5.30). Although the analysis was limited to fewer exposure categories due to small cell sizes, elevated but imprecise aORs were detected for asphyxia/hypoxia and second trimester DBP9 and some haloacetic acid exposure (supplemental table 3).

DISCUSSION

The epidemiological weight of evidence for DBPs and stillbirths is mixed, with four of the nine published studies reporting associations between THM4 and stillbirth.^{3, 4, 7, 10} We did not detect any associations with THM4 and all stillbirths, but we observed increased odds (aOR range: 1.29–1.51) for stillbirths associated with chloroform exposures. Although no exposure-response relationships were detected for any of the DBP metrics, we did find associations consistent in magnitude between stillbirth and exposures to DCAA (aOR range: 1.50–1.71). Associations similar in magnitude were found for compression of the umbilical cord (aOR range: 1.42–2.21) and chloroform, and unexplained stillbirth and BDCM (OR range: 1.51–1.78). Other epidemiological studies examining etiologically similar outcomes have reported associations between spontaneous abortion and BDCM.^{25, 26} Data from animal studies also lend some support for our results, as associations have been reported between BDCM and pregnancy loss^{12, 13} and fetotoxicity following chloroform exposures.^{27, 28}

Comparison between different epidemiological studies is difficult mainly because of the variation in outcomes examined and differences in exposure assessment and modeling approaches. One of the strengths of our study was the ability to examine individual and summary DBP exposures in relation to individual causes of death as well as grouped measures that may have similar etiologies such as asphyxia-related stillbirth. Although some of these results may be due to chance, the most consistent associations across DBP metrics that we found were for compression of the umbilical cord, followed by unexplained stillbirths, and placental separation and hemorrhage. As shown in supplemental table 4, our THM4 sensitivity analysis results (aOR range: 2.05–2.50) for combined asphyxia-related stillbirth were very similar to those reported by Dodds *et al*¹⁰ (OR range: 2.0–2.4). Additionally, we found moderately stronger associations (aOR range: 2.19–3.90) than Dodds *et al*¹⁰ (OR range: 1.3–2.3) for chloroform and this combined group. The asphyxia-related analysis may be the most relevant study finding since complications of umbilical cord and placenta are etiologically similar causes of death. An interesting finding was the decreased risk of stillbirth and THMBr exposure (aOR range: 0.68–0.70; adjusted THMBr model table 4). No other study has examined these three brominated THMs as an exposure metric hence, we were not able to compare our results. There is some evidence that chloroform and BDCM may accumulate in the amniotic fluid of pregnant mice.^{29,30} BDCM, for example, can disrupt placental trophoblast differentiation and inhibit chronic gonadotropin secretion in vitro.³⁰ Other DBPs, such as chloroacetonitrile, have also been identified as transplacental toxicants in animal experiments.³¹ These animal studies lend some biological plausibility to the epidemiological findings related to fetal viability, since they indicate that placental transfer and uptake of DBPs can occur at toxic levels.

Despite considerable research to identify specific causes of stillbirths, almost half of all stillbirths remain unexplained in the general population. In Massachusetts, unexplained stillbirths are slightly lower (40%) than the national average, which may reflect on the state's efforts to conduct comprehensive assessments when a stillbirth occurs. Although our analyses were limited to the principal cause of death, stillbirths can also result from multiple conditions. Among the unexplained stillbirths, for example, undiagnosed fetal malnutrition,

chromosomal aberrations, or infections may all play a role.³² Limited fetal autopsies for these unexplained deaths, mostly due to cost and lack of trained pathologists³³ may lead to misclassification of stillbirths. This could impact the ability to examine the relationship between DBP exposures and individual cause of death.

Another potential source of error arises from the use of two different ICD revisions, since Massachusetts switched from ICD-9 and ICD-10 in 2000. There are structural and conceptual changes between ICD-9 and ICD-10 coding systems including character length, specificity, and medical advances and technology. To minimize the potential for outcome misclassification, we only included codes that had a clear one-to-one match. This resulted in the exclusion of seven out of 2460 cases that had multiple translations between ICD codes. Since we saw no pattern of possible causes of death among these excluded cases, we do not expect this to have a significant impact on our study results.

A key limitation in most DBP studies is the lack of individual-level exposure data which may lead to exposure misclassification. For example, we did not have individual-level water intake or water use practice data to assess inter- and intra-individual variability that may modify DBP exposure. We relied on quarterly collected monitoring data that may not reflect actual internal or biologically effective doses. Although we only included water systems with complete data, quarterly data may not fully capture the temporal variability that some of the water systems undergo over the course of a year. Additionally, exposure categories may not accurately define dose-response doses. Unlike other adverse birth outcomes such as congenital anomalies, stillbirth can occur over a wider time window making it difficult to determine the critical exposure periods. For example, stillbirths typically peak during 20–26 and 36–42 gestational weeks.³⁴ Weeks 14–15 of gestation have been suggested as the critical exposure period for stillbirth;¹⁰ hence, we recognize that examining second trimester exposures may have limited our ability to detect associations if this did not correspond well to the most critical exposure window. Based on our sensitivity analyses of third-trimester THM4 exposures, we found slightly higher odds ratios (aOR range: 1.23–1.37) compared to second-trimester exposures (aOR range 1.08–1.17) (supplemental table 5). We saw slightly lower ORs for third-trimester HAA5 and chloroform exposures (aOR range: 1.26–1.62 and OR range: 1.16–1.35, respectively) compared to second-trimester exposures (aOR range: 1.41–1.74 and aOR range: 1.29–1.51, respectively). Overall, associations between stillbirth and other third-trimester DBP exposure metrics were similar to those we found for the second-trimester window.

Residential mobility during pregnancy is a potential source of error that may lead to exposure misclassification in our study and other vital records based studies (ie, if the address reported in the birth certificate is different from the mother's second-trimester residential address). According to a review of 14 environmental epidemiological studies of pregnancy outcomes, among those women who relocated to another address during pregnancy, a relatively small proportion moved during second (9–32%) and third (4–8%) trimesters.³⁵ However, previous research shows that only 8% of such moves resulted in relocating to a different county, suggesting that in the majority of the cases women likely continued to rely on the same source of drinking water during these different exposure periods.³⁶

A strength of our study was its ability to examine multiple stillbirth predictors, including various maternal risk factors that could act as confounders. Similar to other adverse birth outcomes, such as preterm birth and infant mortality, persistent social disparities exist for stillbirth incidence.³⁷ We found differences between cases and controls in maternal race, education, and marital status. Our study population was similar to that shown across the entire U.S. population where fetal mortality rates for non-Hispanic black women are twice as high as those for white women, and one-half of all fetal deaths were to unmarried women.¹ Macdorman and Gregory¹ also showed that having more than 12 years of education conferred a 30% reduction in stillbirth risk for white women but only a 9% reduction among black women. We were able to adjust for education and other individual-level sociodemographic confounders in our regression models but do acknowledge the potential for residual confounding in our results due to mis-measured or missing covariate data. The use of census data to examine household income could result in residual confounding if the neighborhood-level categorizations do not adequately estimate individual levels or if there are differences occurring at different socioeconomic status contextual levels.

Another strength of our study was the extensive exposure data from Massachusetts which allowed us to examine various DBP exposure variables, including water source, type of disinfection and individual DBPs, with more specificity. Similar to previous studies by us and others, we used multi-pollutant models to evaluate confounding by other DBP measures (THM4 and HAA5).^{8, 10, 23, 38} The only other study to examine HAAs reported no association between stillbirth and the aggregated HAA measure or any of the individual HAAs after adjustment for THM4 exposure.⁸ Our HAA results were comparable irrespective of whether we adjusted for THM4 in the multivariate models. Water source was a strong confounder in our data and may had a larger impact on our multivariate results than adjustment for DBP concentrations; this may limit the ability to directly compare our results to earlier Canadian studies which did not adjust for water source. Additionally, since more than 600 DBPs have been identified in drinking water³⁸, our results and those of the Canadian studies may be markers of unknown or unmeasured DBPs. THM4 and HAA5 may be poor surrogates of other DBPs that are most toxicologically significant for adverse birth outcomes. For example, weak correlations have been reported between THM4 and HAA9 (sum of HAA5 and four other HAAs) and total acetonitriles (0.25 and -0.27, respectively)⁴⁰. The issue of surrogacy may also be a potential explanation for our THMBr results and stillbirth. The use of multi pollutant models may assist in assessing potential risk from complex DBP mixtures found in chlorinated drinking water but more research is needed to further elucidate the contribution of individual DBPs and complex DBP mixtures.

CONCLUSIONS

Although we did not see strong relationships with THM4, we detected associations between stillbirths and exposure to individual THMs, such as chloroform and BDCM, strengthening the weight of evidence of prenatal THM exposures increasing the risk of stillbirth.¹¹ In contrast to the only other study examining HAA exposures, we saw consistent associations between HAA5 and DCAA with stillbirth and individual cause of deaths. Hwang and Jaakkola¹¹ identified exposure assessment methods (eg, individual vs. aggregate exposure data) as the main source for heterogeneity in a meta-analysis of stillbirth and DBP exposure

studies. This could also result from differences in levels of vulnerability across heterogeneous study populations and from different DBP exposure comparisons including distinct exposure mixtures across disparate water sources and treatment. These challenges and others related to the inability to accurately define the etiology sub-types may be why stillbirths have been relatively understudied as an adverse birth outcome potentially related to DBP exposures. Thus, future studies are needed to examine cause-specific stillbirths in relation to more refined critical windows and more regulated and non-regulated DBP exposure metrics to draw more definitive conclusions regarding the weight of evidence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY MESSAGES

What is already known about this subject?

Previous epidemiological studies have shown some associations between disinfectant byproducts (DBPs) and the risk of stillbirth.

Most studies have focused on trihalomethanes (THMs) while other DBP groups such as haloacetic acids (HAAs) have been rarely examined.

What are the new findings?

Positive associations were observed between HAAs exposures and all examined individual causes of stillbirth. Results for chloroform and bromodichloromethane exposures and stillbirth support associations from previous studies.

These results strengthen the evidence of prenatal DBPs exposures increasing the risk of stillbirth.

How might this impact on policy or clinical practice in the foreseeable future?

Additional research including regulated and non-regulated DBP exposure metrics would be needed to draw more definitive conclusions regarding the weight of evidence for DBPs exposure and the risk of stillbirth.

Table 1

Description of stillbirth cases in Massachusetts from 1998–2004 by primary cause of death category

Immediate cause of death	n	%
Unexplained	988	40.2
Compression of umbilical cord	283	11.5
Prematurity	228	9.3
Placental separation & hemorrhage	197	8.0
Premature rupture of membranes	122	5.0
Congenital anomalies	99	4.0
Asphyxia/Hypoxia	80	3.3
Cardiac arrest of fetus	66	2.7
Chorioamnionitis & other abnormalities of the chorion and amnion membranes	47	1.9
Maternal hypertensive disorders	40	1.6
Other causes of death	310	12.5
Total	2460	100

Table 2

Study characteristics of stillbirths cases and controls born during 1998–2004 in 138 Massachusetts towns with complete exposure data

	Study population [*] n (%)	Cases n (%)	Controls n (%)	p-value [‡]
Sex				
Male	13 916 (51)	1321 (54)	12 595 (51)	0.0526
Female	13 112 (48)	1107 (45)	12 005 (49)	
Missing	32 (0)	32 (1)	0 (0)	
Marital status				
Married	19 206 (71)	1480 (60)	17 726 (72)	<0.0001
Non married	7832 (29)	959 (39)	6873 (28)	
Missing	22 (0)	21 (1)	1 (0)	
Maternal weight gain during pregnancy (Kg)				
<11	3622 (28)	141 (6)	3481 (14)	0.1891
11–22	15 625(55)	1160 (47)	14 465 (59)	
>22	6821 (13)	526 (21)	6295 (26)	
Missing	992 (4)	633 (26)	359 (1)	
Maternal age (years)				
12–20	629 (2)	112 (5)	517 (2)	0.0911
21–25	3898 (14)	464 (19)	3434 (14)	
26–30	8228 (30)	655 (27)	7573 (31)	
31–35	7336 (27)	557 (23)	6779 (28)	
36–40	4366 (16)	393 (16)	3973 (16)	
41–64	2600 (10)	276 (11)	2324 (9)	
Missing	3 (0)	3 (0)	0 (0)	
Maternal race				
Caucasian	19 491 (72)	1481 (60)	18 060 (73)	<0.0001
African American	2292 (9)	473 (19)	1859 (8)	
Asian	1606 (6)	126 (5)	1480 (6)	
American Indian	41 (0)	2 (0)	39 (0)	
Other	3519 (13)	365 (15)	3154 (13)	
Missing	111 (0)	93 (4)	18 (0)	
Maternal education				
<High school graduate	4379 (16)	966 (39)	3413 (14)	<0.0001
High school graduate	9502 (35)	277 (11)	9225 (38)	
Associate/certification	2709 (10)	255 (10)	2454 (10)	
Bachelor	6793 (25)	499 (20)	6294 (26)	
Graduate	3429 (13)	215 (9)	3214 (13)	
Missing	248 (1)	248 (10)	0 (0)	
Household income (\$)				
44 531	4464 (16)	321 (13)	4143 (17)	0.0501

	Study population [*] n (%)	Cases n (%)	Controls n (%)	p-value [‡]
>44 531–49 583	5882 (22)	670 (27)	5212 (21)	
>49 583–54 419	5951 (22)	513 (21)	5438 (22)	
>54 419–68 800	5358 (20)	455 (18)	4903 (20)	
>68 800	5405 (20)	501 (20)	4904 (20)	
Prenatal care source of payment				
Public	7160 (26)	122 (17)	7038 (29)	
Private	19 541 (72)	2145 (74)	17 396 (71)	0.0631
Other	351 (1)	187 (8)	164 (1)	
Missing	8 (0)	6 (0)	2 (0)	
Maternal smoking [†]				
0	24 161 (89)	1940 (79)	22 221 (90)	0.0901
1–5	1021 (4)	112 (5)	909 (4)	
6–10	1003 (4)	118 (5)	885 (4)	
>10	634 (2)	89 (4)	545 (2)	
Missing	241 (1)	201 (8)	40 (0)	
Water source				
Mixed	2688 (10)	199 (8)	2489 (10)	0.0899
Surface	17 787 (66)	1751 (71)	16 036 (65)	
Ground	6585 (24)	510 (21)	6075 (25)	
Disinfection treatment				
Chlorination	13 022 (48)	1118 (45)	11 904 (48)	0.0987
Chloramination	8757 (32)	855 (35)	7902 (32)	
Other	2576 (10)	274 (11)	2302 (9)	
Untreated	270 5(10)	213 (9)	2492 (10)	
Year of birth or death				
1998	3939(15)	383(16)	3556(14)	0.1128
1999	3911(14)	359(15)	3552(14)	
2000	3937(15)	353(14)	3584(15)	
2001	3836(14)	336(14)	3500(14)	
2002	3811(14)	306(12)	3505(14)	
2003	3844(14)	378(15)	3466(14)	
2004	3782(14)	345(14)	3437(14)	

* Singleton live births and stillbirths, 20–42 gestational weeks or 350 grams.

[†] Number of cigarettes per day.

[‡] p-values from Chi-square analysis.

Table 3Second-trimester disinfectant by product (DBP) ($\mu\text{g/L}$) exposure levels for cases and controls, 1998–2004

DBP Metric	Mean	Std dev	25th%	50th%	75th%	90th%	Max
THM4	39.8	26.7	20.6	38.5	58.6	73.2	196.0
Chloroform	31.9	23.9	12.0	29.3	48.0	64.5	192.1
BDCM	6.4	5.3	3.2	5.5	8.5	13.1	49.5
DBCM	1.6	2.2	0	0.8	2.5	4.6	32.9
Bromoform	0.2	0.6	0	0	0	0.7	11.8
THMBR	8.8	6.7	4.4	6.9	11.7	18.2	72.4
HAA5	21.6	16.6	7.8	20.6	32.4	43.7	126.1
TCAA	11.0	9.4	2.8	9.9	16.4	22.8	95.9
DCAA	9.4	7.4	2.5	9.3	14.1	19.6	40.9
MCAA	1.1	3.5	0	0	1.3	2.3	73.4
MBAA	0.0	0.3	0	0	0	0	12.5
DBAA	0.2	1.0	0	0	0	0.8	25.6
DBP9	61.4	40.2	31.7	63.1	92.4	110.2	224.4

Note: THM: trihalomethane, BDCM: bromodichloromethane; DBCM: dibromochloromethane; THMBR: brominated trihalomethanes; HAA: haloacetic acids, TCAA: trichloroacetic acid; DCAA: dichloroacetic acid; MCAA: monochloroacetic acid; MBAA: monobromoacetic acid; DBAA: dibromoacetic acid; THM4: sum of chloroform, BDCM, DBCM, and bromoform; THMBR: sum of BDCM, DBCM, and bromoform; HAA5: sum of MCAA, DCAA, TCAA, MBAA, and DBAA; DBP9: sum of THM4 and HAA5.

Std Dev: standard deviation; Max: maximum.

Table 4

Unadjusted and adjusted odds ratios between second-trimester DBP exposures and all causes of stillbirths in Massachusetts during 1998–2004

DBP	Cases [*]	Controls	Model 1 OR ^{**}	95%CI	Model 2 aOR [†]	95%CI	Model 3 aOR [‡]	95%CI
THM4								
14.1	449	3943	1.00	REF	1.00	REF	1.00	REF
>14.1–32.9	483	3900	1.11	0.95–1.29	0.96	0.72–1.30	1.10	0.69–1.76
>32.9–46.6	508	3876	1.24	1.07–1.44	1.01	0.74–1.37	1.17	0.72–1.90
>46.6–63.7	508	3860	1.25	1.08–1.45	1.10	0.81–1.49	1.08	0.65–1.79
>63.7–196.0	512	3876	1.20	1.03–1.39	0.84	0.62–1.15	1.10	0.66–1.85
p-value for trend			0.0238		0.4064		0.6109	
Chloroform								
6.2	435	4089	1.00	REF	1.00	REF	1.00	REF
>6.2–23.5	485	3866	1.21	1.04–1.41	1.07	0.80–1.44	1.36	0.85–2.17
>23.5–37.4	495	3838	1.31	1.13–1.52	1.26	0.93–1.70	1.51	0.94–2.42
>37.4–54.0	520	3932	1.33	1.14–1.54	1.27	0.94–1.72	1.37	0.83–2.26
>54.0–192.1	500	3727	1.30	1.12–1.52	1.01	0.74–1.38	1.29	0.78–2.16
p-value for trend			0.0088		0.9192		0.5662	
BDCM								
4.1	767	6544	1.00	REF	1.00	REF	1.00	REF
>4.1–7.2	825	6301	1.14	1.02–1.28	1.00	0.83–1.21	1.11	0.84–1.46
>7.2–49.5	828	6547	1.01	0.90–1.13	0.85	0.70–1.03	0.93	0.69–1.23
p-value for trend			0.7119		0.1170		0.0510	
DBCM								
4.6	2048	15 521	1.00	REF	1.00	REF	1.00	REF
>4.6–32.9	372	1743	0.81	0.69–0.97	0.88	0.68–1.12	0.74	0.53–1.04
Bromoform								
0	1965	14 178	1.00	REF	1.00	REF	1.00	REF
>0–11.8	441	3086	0.78	0.68–0.89	0.86	0.70–1.06	0.84	0.62–1.13
THMBr								
3.9	573	3362	1.00	REF	1.00	REF	1.00	REF
>3.9–5.8	503	3463	0.78	0.68–0.90	0.96	0.78–1.19	0.92	0.68–1.24
>5.8–8.1	481	3491	0.73	0.63–0.84	0.76	0.61–0.95	0.76	0.56–1.03
>8.1–13.5	433	3512	0.64	0.55–0.74	0.69	0.55–0.85	0.70	0.51–0.95
>13.5–72.4	430	3568	0.62	0.54–0.72	0.70	0.56–0.87	0.68	0.49–0.93
p-value for trend			<0.0001		0.0631		0.0521	
HAA5 [§]								
3.0	324	2603	1.00	REF	1.00	REF	1.00	REF
>3.0–16.4	354	2633	1.12	0.93–1.35	1.43	0.88–2.33	1.46	0.89–2.39
>16.4–25.2	390	2521	1.34	1.11–1.61	1.71	1.03–2.83	1.74	1.03–2.95

DBP	Cases [*]	Controls	Model 1 OR ^{**}	95%CI	Model 2 aOR [†]	95%CI	Model 3 aOR [‡]	95%CI
>25.2–35.4	363	2474	1.24	1.03–1.49	1.37	0.82–2.29	1.41	0.81–2.43
>35.4–126.1	373	2533	1.25	1.04–1.51	1.61	0.97–2.68	1.67	0.97–2.89
p-value for trend			0.0056		0.1676		0.1480	
DCAA [§]								
2.5	400	3375	1.00	REF	1.00	REF	1.00	REF
>2.5–9.3	457	3164	1.28	1.08–1.51	1.49	1.03–2.15	1.50	1.03–2.18
>9.3–14.1	487	3104	1.47	1.25–1.73	1.67	1.14–2.44	1.71	1.16–2.53
>14.1–40.9	460	3136	1.31	1.11–1.55	1.62	1.11–2.37	1.67	1.11–2.51
p-value for trend			0.0057		0.1088		0.0167	
TCAA [§]								
2.8	404	3369	1.00	REF	1.00	REF	1.00	REF
>2.8–9.9	471	3138	1.32	1.12–1.56	1.25	0.88–1.79	1.27	0.88–1.82
>9.9–16.4	459	3140	1.27	1.08–1.51	1.15	0.80–1.66	1.20	0.81–1.77
>16.4–95.9	470	3132	1.32	1.12–1.56	1.37	0.96–1.96	1.46	0.98–2.18
p-value for trend			0.0030		0.0460		0.0350	
MCAA [§]								
3.8	1050	10 167	1.00	REF	1.00	REF	1.00	REF
>3.8–73.4	46	422	1.06	0.77–1.44	0.91	0.59–1.40	0.83	0.53–1.31
DBAA [§]								
0	902	8248	1.00	REF	1.00	REF	1.00	REF
>0–25.6	194	2170	0.82	0.70–0.96	1.01	0.85–1.32	1.05	0.84–1.32
MBAA [§]								
0	1066	10 197	1.00	REF	1.00	REF	1.00	REF
>0–12.5	30	221	1.30	0.88–1.91	1.89	1.15–3.09	1.89	1.15–3.10
DBP9								
16.4	221	2528	1.00	REF	1.00	REF	NA	
>16.4–50.8	271	2552	1.22	1.01–1.46	1.20	0.71–2.03	NA	
>50.8–74.8	223	2310	1.10	0.91–1.34	1.25	0.72–2.16	NA	
>74.8–96.9	295	2538	1.33	1.11–1.60	1.25	0.72–2.16	NA	
>96.9–224.4	286	2764	1.18	0.99–1.42	1.20	0.69–2.07	NA	
p-value for trend			0.0162		0.3683			

Note: OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval; REF: referent; DBP: disinfection byproduct; THM: trihalomethane, BDCM: bromodichloromethane; DBCM: dibromochloromethane; THMBr: brominated trihalomethanes; HAA: haloacetic acids; TCAA: trichloroacetic acid; DCAA: dichloroacetic acid; MCAA: monochloroacetic acid; MBAA: monobromoacetic acid; DBAA: dibromoacetic acid; THM4: sum of chloroform, BDCM, DBCM, and bromoform; THMBr: sum of BDCM, DBCM, and bromoform. HAA5: sum of MCAA, DCAA, TCAA, MBAA, and DBAA; DBP9: sum of THM4 and HAA5; NA, not applicable.

^{*} The numbers represent the univariate case distribution across exposure category.

^{**} Model 1: Unadjusted model.

[†] Model 2: Adjusted for maternal race, education, marital status, source of water.

[‡]Model 3: Adjusted for maternal race, education, marital status, source of water, THM4 or HAA5.

[§]Multivariate haloacetic models also adjusted for smoking.

Exposure cut points: THM4, chloroform, THMBr and HAA5: quintiles; BDCM: tertiles; DBCM: 90th percentile; BF >0; DCAA and TCAA: quartiles; MCAA: 95th percentiles; bromoform, DBAA and MBAA >0.

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Table 5

Adjusted odds ratios between second-trimester disinfection byproduct (DBP) exposures and individual immediate causes of death in Massachusetts 1998–2004

	Unexplained still births			Compression of umbilical cord			Prematurity			Placental separation & hemorrhage		
	n [†]	aOR	95%CI	n [†]	aOR	95%CI	n [†]	aOR	95%CI	n [†]	aOR	95%CI
THM4												
14.1	141	REF	REF	49	REF	REF	21	REF	REF	28	REF	REF
>14.1–32.9	160	0.88	0.55–1.40	41	1.15	0.54–2.42	39	0.66	0.25–1.75	26	0.78	0.16–3.84
>32.9–46.6	171	1.01	0.62–1.62	39	1.36	0.62–2.96	37	0.34	0.12–0.99	26	1.57	0.32–7.65
>46.6–63.7	168	1.12	0.69–1.79	47	1.55	0.71–3.37	51	0.62	0.23–1.69	42	1.56	0.31–7.90
>63.7–196.0	162	0.88	0.54–1.42	44	1.17	0.52–2.60	37	0.37	0.13–1.05	29	1.17	0.22–6.26
Chloroform												
6.2	138	REF	REF	48	REF	REF	19	REF	REF	27	REF	REF
>6.2–23.5	167	0.98	0.62–1.54	38	1.42	0.68–2.98	41	1.16	0.44–3.07	28	0.74	0.17–3.23
>23.5–37.4	163	1.14	0.72–1.80	43	2.18	1.04–4.56	33	0.77	0.27–2.17	41	1.94	0.49–7.69
>37.4–54.0	172	1.15	0.73–1.83	52	2.21	1.04–4.70	53	1.20	0.44–3.26	42	1.56	0.37–6.70
>54.0–192.1	157	0.98	0.61–1.57	39	1.40	0.63–3.15	38	0.69	0.24–1.99	30	1.38	0.31–6.10
BDCM												
4.1	252	REF	REF	78	REF	REF	52	REF	REF	54	REF	REF
>4.1–7.2	291	1.78	1.20–2.63	56	0.95	0.57–1.59	71	1.12	0.68–1.85	64	1.35	0.67–2.72
>7.2–49.5	251	1.51	1.01–2.27	86	1.40	0.87–2.22	61	0.77	0.44–1.34	50	0.66	0.30–1.49
DBCM												
4.6	661	REF	REF	172	REF	REF	159	REF	REF	144	REF	REF
>4.6–32.9	61	0.97	0.68–1.41	22	1.40	0.80–2.45	13	0.87	0.35–2.19	9	0.35	0.11–1.11
Bromoform												
0	616	REF	REF	158	REF	REF	154	REF	REF	138	REF	REF
>0–11.8	108	1.20	0.89–1.61	36	1.06	0.63–1.79	18	0.72	0.32–1.62	15	0.48	0.22–1.04
THMBr												
3.9	197	REF	REF	64	REF	REF	42	REF	REF	45	REF	REF
>3.9–5.8	160	1.14	0.84–1.55	31	0.87	0.49–1.53	47	1.31	0.77–2.23	42	1.62	0.76–3.47
>5.8–8.1	165	1.10	0.78–1.44	38	0.92	0.53–1.60	37	0.69	0.37–1.28	29	0.79	0.35–1.50

	Unexplained still births			Compression of umbilical cord			Prematurity			Placental separation & hemorrhage		
	n [†]	aOR	95%CI	n [†]	aOR	95%CI	n [†]	aOR	95%CI	n [†]	aOR	95%CI
>8.1–13.5	141	1.00	0.73–1.36	42	0.74	0.42–1.32	35	0.76	0.41–1.43	23	0.46	0.17–1.26
>13.5–72.4	132	0.92	0.67–1.27	45	1.11	0.66–1.88	23	0.40	0.18–0.90	30	0.70	0.28–1.74
HAA5 [‡]												
3.0	86	REF	REF	31	REF	REF	16	REF	REF	16	REF	REF
>3.0–16.4	103	1.24	0.58–2.67	21	1.10	0.32–3.84	26	1.37	0.28–6.76	26	2.01	0.38–10.70
>16.4–25.2	117	1.72	0.78–3.82	28	1.94	0.52–7.30	37	2.42	0.47–12.52	24	1.44	0.24–8.73
>25.2–35.4	106	1.37	0.60–3.12	27	1.81	0.45–7.25	36	2.88	0.54–15.42	22	1.86	0.30–11.51
>35.4–126.1	111	1.40	0.61–3.21	23	1.08	0.25–4.60	21	1.82	0.33–9.96	23	1.66	0.26–10.45
DCAA [‡]												
2.5	108	REF	REF	33	REF	REF	20	REF	REF	22	REF	REF
>2.5–9.3	139	1.25	0.71–2.20	29	2.11	0.73–6.08	30	1.26	0.36–4.45	32	0.90	0.34–2.41
>9.3–14.1	128	1.52	0.85–2.71	38	3.29	1.11–9.74	53	2.57	0.74–8.93	30	0.92	0.33–2.59
>14.1–40.9	139	1.39	0.76–2.53	28	2.15	0.69–6.71	31	2.30	0.63–8.43	26	0.64	0.21–1.96
TCAA [‡]												
2.8	108	REF	REF	39	REF	REF	19	REF	REF	21	REF	REF
>2.8–9.9	125	1.31	0.75–2.27	22	0.75	0.29–1.94	43	5.30	1.44–19.39	36	1.53	0.49–4.92
>9.9–16.4	145	1.23	0.68–2.22	39	1.10	0.43–2.77	39	4.00	1.01–16.43	18	0.77	0.21–2.86
>16.4–95.9	136	1.29	0.70–2.37	28	0.93	0.36–2.41	33	4.80	1.12–20.58	35	1.91	0.54–6.79
MCAA [‡]												
3.8	425	REF	REF	96	REF	REF	117	REF	REF	88	REF	REF
>3.8–73.4	17	0.73	0.36–1.53	14	0.86	0.20–3.58	5	0.70	0.17–2.96	16	1.41	0.43–4.68
DBAA [‡]												
0	367	REF	REF	79	REF	REF	105	REF	REF	81	REF	REF
>0–25.6	75	0.97	0.69–1.37	21	1.18	0.64–2.21	17	0.53	0.33–1.27	13	0.45	0.17–1.16
MBAA [‡]												
0	431	REF	REF	96	REF	REF	120			93		
>0–12.5	11	1.10	0.44–2.74	11	3.55	1.25–10.12	2	NE		1	NE	
DBP9												

	Unexplained still births			Compression of umbilical cord			Prematurity			Placental separation & hemorrhage		
	$\dot{n}^{\dagger}$	aOR	95%CI	$\dot{n}^{\dagger}$	aOR	95%CI	$\dot{n}^{\dagger}$	aOR	95%CI	$\dot{n}^{\dagger}$	aOR	95%CI
16.4	86	REF	REF	31	REF	REF	14	REF	REF	17	REF	REF
>16.4-50.8	118	0.91	0.41-2.05	24	1.40	0.39-4.97	32	1.10	0.20-6.09	29	1.09	0.18-6.72
>50.8-74.8	86	0.90	0.39-2.09	20	1.65	0.43-6.34	27	1.08	0.19-6.29	26	2.15	0.34-13.52
>74.8-96.9	109	0.96	0.42-2.21	28	1.31	0.34-5.12	39	0.64	0.11-3.80	24	1.34	0.21-8.71
>96.9-224.4	122	0.88	0.38-2.04	26	1.22	0.31-4.84	31	1.12	0.19-6.48	20	1.18	0.18-7.80

Note: OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval; REF: referent; THM: trihalomethane, BDCM: bromodichloromethane; DBCM: dibromochloromethane; THMBr: brominated trihalomethanes; HAA: haloacetic acids; TCAA: trichloroacetic acid; DCAA: dichloroacetic acid; MCAA: monochloroacetic acid; MBAA: monobromoacetic acid; THM4: sum of chloroform, BDCM, DBCM, and bromoform; THMBr: sum of BDCM, DBCM, and bromoform. HAA5: sum of MCAA, BCAA, TCAA, DCAA, and DBAA; DBP9: sum of THM4 and HAA5; NE: not estimable due to insufficient number of cases.

* Model adjusted for maternal race, education, marital status, source of water, and THM4 or HAA5.

† The numbers represent the univariate case distribution across exposure category.

‡ Haloacetic models also adjusted for smoking.

Exposure cut points: THM4, chloroform, THMBr and HAA5: quintiles; BDCM: tertiles; DBCM: 90th percentile; BF >0; DCAA and TCAA: quartiles; MCAA: 95th percentile; bromoform, DBAA and MBAA >0.