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Original Contribution

Exposure to Drinking Water Disinfection By-Products and Pregnancy Loss

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Previous research has suggested that exposure to elevated levels of drinking water disinfection by-products (DBPs) may cause pregnancy loss. In 2000–2004, the authors conducted a study in three US locations of varying DBP levels and evaluated 2,409 women in early pregnancy to assess their tap water DBP concentrations, water use, other risk factors, and pregnancy outcome. Tap water concentrations were measured in the distribution system weekly or biweekly. The authors considered DBP concentration and ingested amount and, for trihalomethanes only, bathing/showering and integrated exposure that included ingestion. On the basis of 258 pregnancy losses, they did not find an increased risk of pregnancy loss in relation to trihalomethane, haloacetic acid, or total organic halide concentrations; ingested amounts; or total exposure. In contrast to a previous study, pregnancy loss was not associated with high personal trihalomethane exposure ($\geq$75 μg/liter and $\geq$5 glasses of water/day) (odds ratio = 1.1, 95% confidence interval: 0.7, 1.7). Sporadic elevations in risk were found across DBPs, most notably for ingested total organic halide (odds ratio = 1.5, 95% confidence interval: 1.0, 2.2 for the highest exposure quintile). These results provide some assurance that drinking water DBPs in the range commonly encountered in the United States do not affect fetal survival.

abortion, spontaneous; pregnancy; water pollutants

Abbreviations: DBP, disinfection by-product; HAA, haloacetic acid; THM, trihalomethane; TOX, total organic halide.

Editor's note: *An invited commentary on this article appears on page 1052.*

While chlorination of public water supplies has provided substantial public health benefit by controlling infectious disease, the interaction of chlorine with organic material in raw water supplies produces chemical disinfection by-products (DBPs) of health concern, including trihalomethanes (THMs) and haloacetic acids (HAAs) (1–3). Regular consumption of small amounts of DBPs may have adverse health effects (4), with much of the emphasis in the past on carcinogenicity (5).

Concern about potential reproductive health effects of DBPs arose because fetuses are often more susceptible than adults to environmental insults, and experimental studies demonstrated that DBPs can produce fetotoxicity (6, 7) and fetal resorption (8).

Several epidemiologic studies have addressed the potential reproductive toxicity of DBPs (9). The strongest support

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was noted for pregnancy loss, including stillbirth (10–16), with more limited evidence linking DBPs to birth defects and fetal growth restriction. The northern California studies of pregnancy loss are the most informative given their size, quality, and consideration of individual as well as aggregated THMs (15, 16). Although no association was found between consumption of large amounts of cold tap water or receiving tap water with high levels of THMs and pregnancy loss (16), women who consumed five or more glasses of cold tap water per day containing ≥75 μg/liter of THM4 were at increased risk of pregnancy loss (odds ratio = 1.8, 95 percent confidence interval: 1.1, 3.0). Women who consumed five or more glasses per day of cold tap water containing at least 18 μg/liter of one of the THM species, bromodichloromethane, showed a more pronounced increased risk (odds ratio = 3.0, 95 percent confidence interval: 1.4, 6.6). Limitations of these studies include uncertainty regarding dates of pregnancy onset and loss and limited exposure information, but the results strongly encouraged continued evaluation of the potential link between DBPs and pregnancy loss. To our knowledge, we conducted the most extensive study to date to evaluate whether exposure to DBPs in drinking water is associated with an increased risk of pregnancy loss.

MATERIALS AND METHODS

Study site selection and measurement of DBP concentrations in tap water

We selected three US locations, one with moderate levels of chlorinated DBPs (referred to hereafter as ''chlorinated DBP site''), one with moderate levels of brominated DBPs (''brominated DBP site''), and one with low levels of all DBPs (''low DBP site''), maximizing between-site variation. The chlorinated and brominated DBP sites were chosen because they used chloramination rather than free chlorine for terminal disinfection, which results in minimal additional DBP formation within the distribution system (3, 17), minimizing spatial variability and facilitating exposure assessment.

After confirming that THM and HAA levels were spatially uniform throughout the distribution system at the chlorinated and brominated DBP sites by collecting samples from throughout the distribution system and finding minimal differences, a single location was chosen for sample collection and measurement to reflect concentrations throughout the system. Weekly tap water samples were collected and were sent to the University of North Carolina for analysis of total THMs (THM4), all nine HAAs (HAA9), and total organic halide (TOX), reduced to every other week at the low DBP site. At the chlorinated and brominated DBP sites, free chlorine was used to flush the system during certain periods each year. Because free chlorine generates additional DBPs in the distribution system, resulting in spatial variability in DBP concentrations throughout the system, during those periods we sampled at multiple locations and combined results to estimate a system-wide weekly average.

Sample collection vials were washed and labeled, and preservatives appropriate for the target analyte groups were added prior to shipment to each of the three study sites. The vials were filled completely to eliminate headspace and were returned by overnight delivery to the University of North Carolina, where they were inspected and stored in a refrigerator at 4°C. THMs were analyzed by using a modified version of US Environmental Protection Agency Method 551.1 (18) to extract each of the THM4 species from the aqueous samples. The process used a liquid-liquid extraction of salted-out and pH-adjusted 20-ml aqueous samples. The quantitation limits were 0.1 μg/liter, the acceptable relative percent difference for THM analysis of duplicates was <10 percent, and the matrix spike recovery had to be in the range of 80–120 percent. HAAs were analyzed by using standard methods (19–21), with a practical quantitation limit of 2.0 μg/liter for all nine HAAs. Analysis and quantification of the calibration standards and aqueous samples were based on replicate precision of duplicate samples having a relative percent difference of less than 25 percent. TOX analysis was performed by using a model AD-2000 Adsorption Module and TOX Analyzer (Tekmar Dohrmann, Cincinnati, Ohio). We acidified 250-ml samples quenched of residual disinfectant in the field to pH <2 with 50 drops of concentrated sulfuric acid, and the samples were analyzed within 14 days of collection following Standard Method 5320 (21).

Characterization of DBP exposure

The first exposure index considered was tap water DBP concentration, derived as the average of weekly sample values over the time that the pregnancy occurred. We selected DBPs for analysis based on previous epidemiology and toxicology findings, focusing on THM4, bromodichloromethane, HAA9, and TOX.

The second exposure index was ingestion of DBPs, combining water-use behaviors and DBP concentration. Women were asked to indicate the cup or glass size and number of cups or glasses of tap water consumed per day, including hot and cold beverages made from tap water. Doing so generated estimates of ounces per day of cold and hot tap water consumed (1 ounce = 28.3 g). We calculated weighted averages over pregnancy intervals if changes in water use were reported. We addressed home and work consumption separately for those women who worked outside the water service area in which they lived ($n = 197$), but this procedure resulted in higher estimates, so we reduced their cold tap water consumption by 15.3 percent and hot tap water consumption by 18.2 percent to equal that of the other participants. Women reported use of faucet and pitcher water filters at home and work and the proportion of the tap water consumed at home and work that was filtered. Bottled water use was also queried.

With this information, we calculated daily amounts of hot and cold tap water ingested, filtered and unfiltered. Cold, unfiltered tap water was presumed to have the DBP concentration measured in the distribution system. Calculation for hot, unfiltered tap water required adjustment for changes

in DBP levels during the heating process, so experimental studies were conducted to generate estimates specific to each of the DBPs of interest. Essentially 100 percent of THMs were removed after heating, whereas HAAs were reduced by an average of 75 percent. TOX removal because of heating was in the range of 20–30 percent, differing across the study sites, consistent with results reported by others (22–24). Values for individual chemicals were used and then aggregated as needed for the grouped chemicals. DBP levels in a number of bottled waters were measured and were found to be below detection limits; they were treated as zero for exposure assignment.

The impact of filtering water at the point of use was also evaluated empirically for commonly used faucet and pitcher filters to derive removal efficiencies for individual DBPs. For faucet filters, THMs were completely removed, whereas pitcher filters removed 40 percent of THMs on average. Removal of individual HAA species varied, ranging from 8 percent to 91 percent for faucet filters and from 13 percent to 65 percent for pitcher filters. TOX was reduced by 74 percent by faucet filters and by 41 percent by pitcher filters. Integration of the information on DBP concentrations, ingested amounts, and modifications by heating and filtering yielded an estimate of ingested amount of DBPs, expressed in units of micrograms per day (μg/day).

Third, we addressed dermal absorption and inhalation, applicable only to THMs, by considering showering and bathing alone and combined with ingestion. Inhaled and dermally absorbed THMs reach the bloodstream without being metabolized, warranting separate consideration. We derived indices of daily uptake (μg/day) by integrating tap water concentrations, duration of bathing and showering reported in a questionnaire administered to study participants, and estimated uptake factors of 0.001538 μg and 0.001321 μg of THMs in blood per minute per microgram from showering and bathing, respectively (25, 26). Finally, we combined this information with THM intake by ingestion, using an estimated uptake factor of 0.00490, to derive an integrated index of blood concentration, expressed in micrograms per day (27).

Participant recruitment and outcome assessment

To identify and recruit women who were in early pregnancy or were planning to become pregnant during the study period, multiple methods were used. Prenatal care practices were asked to inform their newly enrolled patients about the study, and study materials were placed throughout the community. Women who were potentially eligible were screened to ensure that they lived in the water service area, were trying to become pregnant or had completed less than 12 weeks of gestation, and had access to a telephone for interviews. Eligible pregnant women were enrolled, and those trying to become pregnant were ''preenrolled'' and followed for up to 6 months with free pregnancy test kits to determine whether they had conceived and thus were eligible to enroll in the study.

Upon enrollment, participants were contacted by telephone for an interview addressing potential influences on pregnancy, including water use habits, pregnancy symptoms, health behaviors, and physical activity. The interview was completed as early as possible, in no case later than 16 weeks' gestation. The recruiter arranged a study ultrasound at a participating clinic to determine the gestational age of the fetus and confirm its viability. A follow-up telephone interview was sought at 20–25 weeks' gestation to provide additional information on changes in water use, update the status of the pregnancy, and acquire information on selected other risk factors.

Pregnancy losses were generally identified by self-report, often before the ultrasound could be conducted. Self-report of pregnancy onset was found to be highly reliable for this population of planned pregnancies identified and recruited early in gestation based on the comparison of self-reported dates of the last menstrual period and ultrasound findings among those with healthy pregnancies. Thus, we used self-reported last menstrual period to date onset of pregnancy for the primary analysis. Pregnancy losses were assigned based on the date of self-report, with careful review of medical records of 156 losses revealing only two questionable cases and confirming the accuracy of self-report.

Analytic methods

Discrete-time survival models were used to characterize the rate of pregnancy loss in relation to DBP exposure. Women were followed from enrollment in the study until 20 weeks' gestation with a viable pregnancy, the occurrence of a pregnancy loss, or loss to follow-up. Those whose pregnancies were documented through self-report, medical records, or vital records as having progressed to at least 20 weeks' gestation were included for the entire period, and those women whose last contact was an interview or ultrasound indicative of a viable pregnancy were censored after that contact.

We considered three time windows in relation to pregnancy, using the estimated date of conception to anchor the individual pregnancy by calendar time and thus define the week-specific exposures for the intervals. The ''periconceptional interval'' was defined as 4 weeks before the last menstrual period up to 3 weeks after (assuming that the last menstrual period occurred 2 weeks prior to conception); the ''early gestation interval,'' 3–8 weeks after the last menstrual period, addressing the period of organogenesis; and the ''later gestation interval,'' 9–20 weeks after the last menstrual period, reflecting a period in which direct fetal toxicity could result in loss. DBP exposure was determined for each woman and was averaged over the weeks constituting each interval, and it was truncated at the time of loss for those women experiencing a loss, with comparisons to the exposures for all women with a surviving pregnancy at that time. Exposure was evaluated in quintiles, with the lowest exposure quintile serving as the referent. Because exposure did not change markedly over short time intervals and the patterns of association between DBPs and pregnancy loss were similar across pregnancy windows, we have presented results for early gestation (weeks 3–8) only, with detailed results for the other pregnancy windows available elsewhere (28). We examined associations for losses at less

TABLE 1. Demographics of women included in the analysis of exposure to drinking water DBPs* and pregnancy loss at three US locations, 2000–2004

Characteristic	Women included in the analysis ($n = 2,409$)		Women from the chlorinated DBP site ($n = 1,090$)		Women from the brominated DBP site ($n = 422$)		Women from the low DBP site ($n = 897$)	
	No.	%	No.	%	No.	%	No.	%
Race/ethnicity								
White, non-Hispanic	1,347	56.0	717	65.8	153	36.4	477	53.2
Black, non-Hispanic	763	31.7	290	26.6	99	23.5	374	41.8
Hispanic	208	8.6	30	2.8	158	37.5	20	2.2
Asian	46	1.9	29	2.6	5	1.2	12	1.3
Other	43	1.8	24	2.2	6	1.4	13	1.5
Education (years)								
≤12	713	29.6	201	18.4	231	54.7	281	31.4
>12–<16	517	21.5	200	18.4	107	25.4	210	23.4
≥16	1,178	48.9	689	63.2	84	19.9	405	45.2
Parity								
0	1,040	46.0	545	52.0	137	36.4	358	43.0
1	763	33.8	357	34.0	138	36.7	268	32.2
≥2	455	20.2	147	14.0	101	26.9	207	24.8
Mean age at enrollment (years)	28.3		29.2		26.4		28.1	
Mean gestational age at enrollment (days): total	54.8		52.9		57.8		55.7	
Mean gestational age at enrollment (days): already pregnant	56.2		54.9		58.3		56.8	
Mean gestational age at enrollment (days): became pregnant	39.2		38.0		42.5		40.9	

* DBPs, disinfection by-products.

than 12 versus 12 or more weeks' gestation but found no notable differences in risk (28) and thus present the results for total losses only.

Potential confounding factors consisted of known and strongly suspected influences on pregnancy loss, including maternal age, race, ethnicity, education, marital status, income, smoking, alcohol intake, caffeine consumption, body mass index, age at menarche, employment status, diabetes, pregnancy loss history, induced abortion history, and vitamin use. Those that were associated with pregnancy loss with a p value of 0.10 or less were included in the analysis, although none resulted in changes of 10 percent or more in the associations between DBP exposure and outcome. This criterion resulted in adjustment for maternal age, race, ethnicity, education, marital status, age at menarche, alcohol intake, and vitamin use. We also included a random-effects term for study site in the model for site in an attempt to control for confounding. Season is also a determinant of exposure but was not related to pregnancy loss in our study and was thus not adjusted. Potential effect modification by prior pregnancy loss was assessed but not found ($p > 0.70$).

Using a continuation ratio logit discrete hazard model with weeks as the time unit, we generated adjusted odds ratios for higher compared with lower DBP exposure levels, with 95 percent confidence intervals. This modeling approach allows for variable time of study entry and censoring of women at the last point of study contact, provides a simple form for incorporating the time-varying water exposure variables, and avoids dichotomizing pregnancy losses as present or absent. It allows for a simple nonparametric form of the baseline hazard and is a more natural approach than a continuous time-to-event model (such as the Cox model) because the pregnancy outcome data are collected on a discrete (e.g., days or weeks of gestation) time scale.

RESULTS

A total of 2,766 women enrolled in the study and were eligible for the baseline telephone interview: 1,232 from the chlorinated DBP site, 503 from the brominated DBP site, and 1,031 from the low DBP site (table 1). Approximately half of the women were recruited from prenatal care sites, and about 10 percent (252 in total) were recruited before they conceived. Average gestational age at recruitment was much earlier for women who preenrolled prior to conception (39.2 days) than for women who enrolled while pregnant (56.2 days). Of the total of 2,766 women who enrolled in the study, 357 were excluded because they chose to withdraw from the study ($n = 32$) or they were beyond 12 weeks' gestation at the time of enrollment, they were unreachable by telephone for more than 7 weeks, or they had moved out

TABLE 2. Mean DBP* concentration (μg/liter) across study sites for the periconceptional pregnancy window, three US locations, 2000–2004

DBP	All sites	Chlorinated DBP site	Brominated DBP site	Low DBP site
Total THMs*	42.6	67.1	63.0	3.3
Chloroform	23.9	47.9	12.4	0.2
Bromodichloromethane	10.7	15.0	20.3	1.0
Dibromochloromethane	6.6	4.3	23.8	1.4
Bromoform	1.4	0.1	6.4	0.6
Brominated THMs	18.8	19.4	50.5	3.0
HAAs* ($n = 9$)	29.2	45.2	45.9	1.8
Brominated HAAs	11.5	11.5	32.3	1.7
Total organic halide	117.1	173.7	182.3	17.5

* DBP, disinfection by-product; THMs, trihalomethanes; HAAs, haloacetic acids.

of the study area ($n = 227$). Women experiencing second or third study pregnancies ($n = 69$), with multiple-gestation pregnancies ($n = 21$), or having inconsistent or invalid key data for dating the pregnancy or estimating exposure ($n = 8$) were also excluded, leaving data for 2,409 women in the final analysis. Participants were predominantly White (56 percent) or African American (32 percent), with a sizable Hispanic population at the brominated DBP site. The mean age at enrollment was 28.3 years and the women tended to be highly educated, but this factor varied across study sites (table 1).

Chloroform was the dominant THM species at the chlorinated DBP site, where total THM levels ranged from 20 μg/liter to 120 μg/liter over the sampling period (highest in the summer). At the brominated DBP site, bromodichloromethane was the dominant THM species, and THM4 levels ranged from 30 μg/liter to 80 μg/liter except for notably higher levels when free chlorine was used. The low DBP site had very low levels of all DBPs, with THM4 ranging from 2 μg/liter to 16 μg/liter. The dominant HAA species at the chlorinated site were di- and trichloroacetic acids, whereas the dominant HAA species at the brominated site were the bromine-containing species bromodichloroacetic acid, dibromochloroacetic acid, and dibromoacetic acid (table 2). Average daily THM4 ingestion was 73.7 μg/day, 57.0 μg/day, and 4.7 μg/day across the chlorinated DBP, brominated DBP, and low DBP sites, respectively.

The 2,409 women in the study experienced a total of 258 pregnancy losses, of which 81 (31.4 percent) occurred prior to completion of the initial interview. The pattern by week

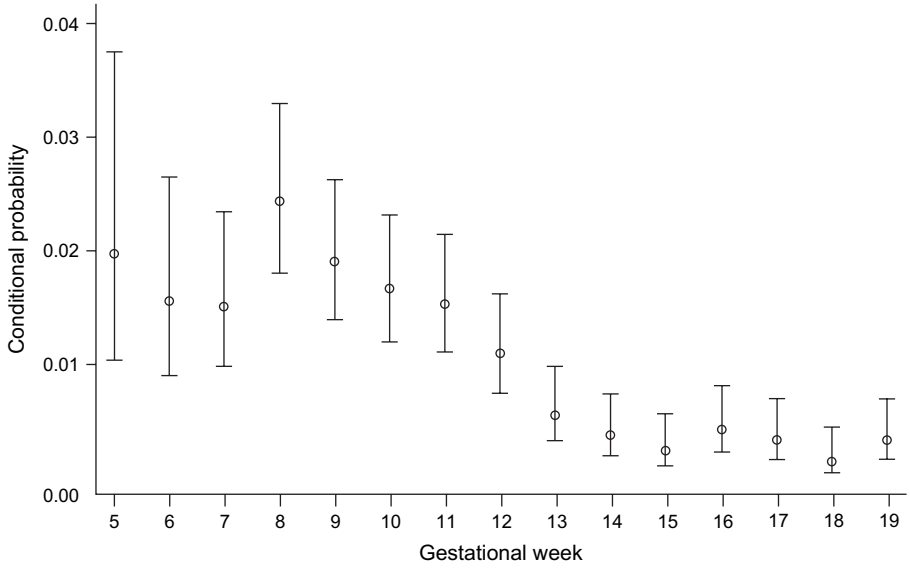

FIGURE 1. Probability of pregnancy loss (and 95% confidence intervals) by completed gestational week, conditional on not experiencing a loss in a previous week, for participants from three US locations, 2000–2004.

TABLE 3. Comparison of results from the present study (three US locations, 2000–2004) with those from the northern California study (16) regarding exposure to DBPs* and pregnancy loss

THM4* exposure	Present study			Northern California study		
	No. of losses	Adjusted OR*,†	95% CI*	No. of losses	Adjusted OR†	95% CI
<75 μg/liter	210	1.0		334	1.0	
≥75 μg/liter	45	1.0	0.7, 1.4	108	1.2	1.0, 1.5
Low personal THM4 exposure (<75 μg/liter or <5 glasses/day)	234	1.0		474	1.0	
High personal THM4 exposure (≥75 μg/liter and ≥5 glasses/day)	21	1.1	0.7, 1.7	19	1.8	1.1, 3.0
Chloroform (μg/liter)‡	28	0.9	0.6, 1.4	86	0.9	0.5, 1.6
Bromoform (μg/liter)‡	25	1.2	0.8, 1.9	97	1.0	0.5, 2.0
Bromodichloromethane (μg/liter)‡	24	1.6	1.0, 2.4	85	2.0	1.2, 3.5
Chlorodibromomethane (μg/liter)‡	29	1.3	0.8, 2.1	84	1.3	0.7, 2.4

* DBPs, disinfection by-products; THM4, trihalomethane; OR, odds ratio; CI, confidence interval.

† Adjusted for maternal age, gestational age at mother's interview, history of spontaneous abortion, race, employment, and cigarette smoking; for individual THMs, the upper quartile was compared with the lower three quartiles.

‡ Number of losses refers to the upper quartile of concentration combined with ≥5 glasses of water/day, and the odds ratio is based on women with lower exposure as the referent.

of gestation (figure 1) showed the greatest risks early in gestation. Because of the importance of the northern California study (16, 26), we directly compared results across the two studies (table 3). Pregnancy loss was not associated with high personal THM exposure (≥75 μg/liter and ≥5 glasses of water/day) (odds ratio = 1.1, 95 percent confidence interval: 0.7, 1.7). Both studies found the strongest association for bromodichloromethane, but the odds ratio of 1.6 was somewhat lower than the comparable finding from the California study (odds ratio = 2.0). Overall, there was notably less support for an association between THM exposure and pregnancy loss compared with the earlier study.

The analysis of the concentration of individual and groups of DBPs in relation to pregnancy loss is summarized in table 4, with the complete set of results available elsewhere (28). There was no indication of an association between THM4 or bromodichloromethane exposure and pregnancy loss. Sporadic, modest elevations in risk were found for HAA9, but in no instance was there a dose-response gradient. Modest associations were found for TOX, but all odds ratios were less than or equal to 1.5, and there was no indication of increasing risk of pregnancy loss with increasing exposure. We also examined the association between exposure above and below the applicable regulatory cutpoint for THM (80 μg/liter) and found an odds ratio of 0.9 (95 percent confidence interval: 0.6, 1.4). Concentrations above the regulatory limit for the five required HAAs (HAA5) of 60 μg/liter were too rare for meaningful analysis.

We analyzed estimated ingested amounts of DBPs in relation to pregnancy loss (table 5). Once again, there was no indication of an association for THM4 and only a slight elevation in risk of losses at 12 or more weeks' gestation for bromodichloromethane (data not shown). Sporadic elevations in risk for HAA9 did not follow any clear pattern by exposure level. The strongest support, although still limited, was found for TOX, with some elevation in risk for all exposure levels above the lowest quintile and the highest risk in the highest quintile, with odds ratios of 1.5 (95 percent confidence interval: 1.0, 2.2) for all losses and 1.7 (95 percent confidence interval: 0.8, 3.7) for losses at 12 or more weeks' gestation (data not shown).

Finally, the results for showering/bathing exposure and integrated exposure to THM4 and bromodichloromethane (table 5) generated limited evidence of an increased risk in the highest quintile for THM4 (odds ratios = 1.2–1.3). Associations were slightly greater for losses at 12 or more weeks' gestation (odds ratios = 1.0–1.1 in the uppermost quintile) than for losses at less than 12 weeks (odds ratios = 1.3–1.7) in the uppermost quintile (data not shown).

DISCUSSION

This study provides little support for the hypothesis that elevated levels of drinking water DBPs are associated with increased risk of pregnancy loss. In fact, given the methodological strengths of the study, including its size, refinement in exposure characterization, and ascertainment of pregnancies and pregnancy losses, the findings of associations close to the null provide credible evidence against a positive association. Relative to previous epidemiologic studies of this issue, the methods of this study are stronger and the evidence for an association weaker. In principle, if the earlier studies had identified a weak signal that was blurred by their methodological limitations, the present study should have observed that signal more markedly and clearly did not.

In a side-by-side comparison with the northern California study (16), we found no support for an overall effect of THM4 but did find an association for bromodichloromethane

TABLE 4. DBPs* and pregnancy loss among women in three US locations, 2000–2004

DBP	No. of pregnancy losses	Adjusted OR*,†	95% CI*	DBP	No. of pregnancy losses	Adjusted OR†	95% CI
THM4*				BDCM*			
Concentration (μg/liter)				Concentration (μg/liter)			
0.0–≤3.2	59	1.0		0.0–≤1.1	60	1.0	
3.3–≤41.0	42	0.7	0.5, 1.0	1.2–≤10.4	44	0.7	0.5, 1.0
42.0–≤57.9	61	1.1	0.8, 1.6	10.5–≤13.6	46	0.8	0.5, 1.1
58.0–≤73.4	50	0.9	0.6, 1.3	13.7–≤18.2	52	1.0	0.7, 1.4
>73.4	46	0.8	0.5, 1.2	>18.2	56	1.0	0.7, 1.5
Ingested amount (μg/day)				Ingested amount (μg/day)			
0.0	51	1.0		0.0	51	1.0	
0.1–≤5.6	44	0.8	0.6, 1.3	0.1–≤1.7	47	0.9	0.6, 1.3
5.7–≤28.0	59	1.0	0.7, 1.5	1.8–≤6.8	50	0.9	0.6, 1.3
28.1–≤93.3	50	0.9	0.6, 1.4	6.9–≤22.9	51	1.0	0.6, 1.4
>93.3	53	1.0	0.7, 1.5	>22.9	58	1.1	0.7, 1.6
HAA9*				TOX*			
Concentration (μg/liter)				Concentration (μg/liter)			
0.0–≤1.9	49	1.0		0.0–≤17.4	44	1.0	
2.0–≤26.9	53	1.1	0.7, 1.6	17.5–≤140.4	60	1.3	0.9, 2.0
27.0–≤42.7	61	1.3	0.9, 2.0	140.5–≤171.8	54	1.2	0.8, 1.8
42.8–≤51.7	56	1.4	0.9, 2.0	171.9–≤186.5	49	1.2	0.8, 1.8
>51.7	39	0.8	0.5, 1.3	>186.5	51	1.4	0.9, 2.1
Ingested amount (μg/day)				Ingested amount (μg/day)			
0.0	53	1.0		0.0–≤14.5	38	1.0	
0.1–≤5.5	39	0.9	0.6, 1.4	14.6–≤40.4	54	1.3	0.8, 1.9
5.6–≤35.6	65	1.2	0.9, 1.8	40.5–≤117.4	57	1.3	0.9, 2.0
35.7–≤84.6	43	1.0	0.6, 1.4	117.5–≤298.6	49	1.2	0.8, 1.9
>84.6	57	1.1	0.8, 1.6	>298.6	59	1.5	1.0, 2.2

* DBPs, disinfection by-products; OR, odds ratio; CI, confidence interval; THM4, trihalomethane; BDCM, bromodichloromethane; HAA9, haloacetic acids ($n = 9$); TOX, total organic halide.

† Adjusted for study site, maternal age, race, ethnicity, education, marital status, age at menarche, alcohol intake, and vitamin use.

comparing women in the uppermost quartile of concentration combined with ingesting five or more glasses of water per day with women whose exposure was lower. In contrast to the more detailed analysis of bromodichloromethane, this result dichotomized women rather than examining multiple ordered groups and combined consumption with concentration. Although the finding should not be dismissed, its significance is tempered by the failure to observe other associations found in the previous study and the absence of association between bromodichloromethane concentrations, ingested amounts, or integrated exposure and pregnancy loss in more detailed analyses. It seems unlikely that this simple dichotomy more accurately reflects exposure than the other indices.

The absence of association for THMs in the aggregate, perhaps with the limited exception of bathing/showering exposure and total integrated exposure, is counter to the suggestions that women who used water with higher levels of THMs were at increased risk of pregnancy loss (11, 14, 15). These earlier studies and their approaches to analysis were far more limited than those of Waller et al. (16, 29) or those of the present study. Although women who consume bottled water may differ in ways that convey a different risk of pregnancy loss compared with women who drink tap water, it is difficult to suggest possible sources of confounding related to variation in tap water DBP concentrations that would have yielded spurious positive associations in the earlier studies.

The only other suggestion of a possible association we found was for TOX, not addressed in any of the previous studies. Given that there are hundreds of chemicals beyond the THMs and HAAs in chlorinated and chloraminated drinking water, possibly differing across the study sites, some harmful constituent may be better reflected in the aggregate measure, TOX, than in any of the other DBP indices examined.

Although there are methodological advantages in the present study compared with previous studies, a number

TABLE 5. Showering/bathing exposure and total integrated exposure to THM4* and BDCM* among women in three US locations, 2000–2004

THM4 concentration (μg/day)	No. of pregnancy losses	Adjusted OR*,†	95% CI*	BDCM concentration (μg/day)	No. of pregnancy losses	Adjusted OR	95% CI
Bathing/showering							
0.0–≤0.1	51	1.0		0.0	53	1.0	
0.2–≤0.5	47	0.8	0.5, 1.2	>0.0–≤0.1	42	0.7	0.5, 1.0
0.6–≤1.1	50	1.0	0.6, 1.4	>0.1–≤0.2	41	0.7	0.5, 1.1
1.2–≤1.9	45	0.9	0.6, 1.4	>0.2–≤0.5	67	1.3	0.9, 1.9
>1.9	63	1.3	0.9, 1.9	>0.5	53	1.1	0.7, 1.7
Total integrated exposure							
0.0–≤ 0.1	52	1.0		0.0	52	1.0	
0.2–≤0.7	46	0.8	0.5, 1.1	>0.0–≤0.1	45	0.7	0.5, 1.1
0.8–≤1.4	45	0.9	0.6, 1.3	>0.1–≤0.3	40	0.7	0.5, 1.1
1.5–≤2.2	53	1.1	0.7, 1.6	0.4–≤0.5	65	1.3	0.9, 1.8
>2.2	60	1.2	0.8, 1.7	>0.5	54	1.1	0.8, 1.7

* THM4, trihalomethane; BDCM, bromodichloromethane; OR, odds ratio; CI, confidence interval.

† Adjusted for study site, maternal age, race, ethnicity, education, marital status, age at menarche, alcohol intake, and vitamin use.

of important limitations remain that could affect the study results. Selecting geographic sites with notably different DBP concentrations ensured sharp contrasts among study participants but raises the question of whether other characteristics of the sites or the ways in which women were recruited across the different sites may have led to biases in the estimated impact of DBP exposure. That is, unmeasured or incompletely controlled demographic, social, or environmental characteristics of the areas may have influenced pregnancy loss and thus distorted the estimated effect of DBP exposure level.

Despite unprecedented efforts to accurately characterize exposure, we have done so incompletely. Tap water concentrations are likely to be accurate given the water systems that were chosen, but they may not reflect individual exposure. We attempted to refine those measures by addressing ingested amounts, but self-reported information on amount ingested and use of filters, including variable effectiveness of filters based on brand and frequency of replacement, is subject to error. Similar challenges apply to the assessment and interpretation of bathing and showering based on self-reported information. We could not address incidental respiratory and dermal exposure from other water use (e.g., washing dishes, clothes) or ambient background levels found in the home. Neither exposures outside the home in other indoor locations nor swimming could be incorporated despite their potential importance (30). Although the extreme contrasts in DBP concentrations across study sites provide assurance that women in each of the sites, on average, would have differing exposures, the ability to capture individual variation in exposure within each geographic site is less certain.

Other concerns arise with the ascertainment of pregnancy occurrence and loss in the early periods of gestation. Even though our analytic methods took staggered entry into account, there is the possibility for biases to arise from self-selection for enrolling prior to conception or being aware of pregnancy very early in gestation being related to water-use behaviors and even to study site (based on differing socioeconomic characteristics across sites). We were not able to complete ultrasound examinations on a high proportion of the women before their loss occurred. While the present study could be improved, the available refinements in capturing individual exposure are limited at this time because we do not have a suitable biomarker, and the financial costs and participant burden of measuring DBPs repeatedly in each participant's tap water place a limit on improving exposure assessment in this manner. The combination of challenges in assessing both the exposure and the outcome, with the many subtleties in studying early pregnancy and absence of registries, logistically limits the design and quality of future studies. Perhaps with further methodological work in exposure assessment and toxicology, there will be opportunities for greater progress in addressing possible health effects of this ubiquitous exposure.

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