Maternal Exposure to Drinking-water Chlorination By-products and Small-for-gestational-age Neonates

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Background: There is concern about possible effects of disinfection by-products on reproductive outcomes. The purpose of this study was to evaluate the association between maternal exposure to chlorination by-products and the risk of delivering a small for-gestational-age (SGA) neonate.

Methods: We conducted a population-based case-control study in the Québec City (Canada) area. Term newborn cases with birth weights <10th percentile (n = 571) were compared with 1925 term controls with birth weights ≥10th percentile. Concentrations of trihalomethanes and haloacetic acids in the water-distribution systems of participants were monitored during the study period, and a phone interview on maternal habits was completed within 3 months after childbirth. We estimated chlorination by-products ingestion during the last trimester of pregnancy and trihalomethanes doses resulting from inhalation and dermal exposure. We evaluated associations between chlorination by-products in utero exposure and SGA by means of unconditional logistic regression with control of potential confounders.

Results: When total trihalomethanes and the 5 regulated haloacetic acids concentrations were divided into quartiles, no clear dose-response relationship was found with SGA. However, increased risk was observed when haloacetic concentrations were above the fourth quartile and when either trihalomethanes or haloacetic acids concentrations were above current water standards (adjusted OR= 1.5 [95% confidence interval = 1.1–1.9] and 1.4 [1.1–1.9], respectively). Inhalation and dermal absorption of trihalomethanes did not contribute to this risk, but a monotonic dose-response was found with haloacetic acids ingestion.

Conclusion: Oral exposure to high levels of chlorination by-products in drinking water could be a risk factor for term SGA.

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Chlorine is widely used as a drinking water disinfectant due to its efficacy and cost-effectiveness. However, it also reacts with natural organic matter present in water and leads to the formation of potentially toxic chemicals known as chlorination by-products.[1] Trihalomethanes and haloacetic acids are the 2 most prevalent chlorination by-products found in chlorinated drinking water.[2] Because of their potential carcinogenic properties,[3,4] these chemicals are now regulated in North America and in several countries elsewhere, based on an annual mean of quarterly samples.[5,6]

Interest in the possible adverse reproductive effects of disinfection by-products is more recent. The first epidemiologic study on the topic was published in 1992.[7] Thereafter, several studies raised the specter of possible effects on fetal development.[8–12] Although the results of epidemiologic studies conducted primarily on reproductive outcomes are rather inconsistent, the available evidence suggests a positive association between exposure to chlorination by-products and intrauterine growth restriction.[11,12] However, because of severe limitations regarding exposure assessment in particular, the epidemiologic data remain inconclusive, and further studies with improved personal exposure assessment have been recommended.[11–13]

Due to important spatial and seasonal variations of chlorination by-products within and between distribution systems, the use of regulatory measurements of these compounds in drinking water is not considered adequate to assess exposure within a short-time window.[14–16] Consideration of personal water consumption is also important, as are the frequency and duration of showers and baths, because volatile trihalomethanes (unlike haloacetic acids) are easily absorbed by inhalation and dermal contact.[17,18]

The possible effect of chlorination by-products on reproductive outcomes is supported by laboratory studies on animals.[8,9,19] Trihalomethanes have not been found to be

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teratogenic, but severe maternal and fetotoxic effects have been observed at high doses with reduction of fetal body weight and survival.[8] Retarded fetal development and reduced fetal weight, length, and size have been found in pregnant rats, mice, and rabbits subjected to high-dose exposure to chloroform,[9] normally the most abundant trihalomethane. Haloacetic acids have been linked to several fetal malformations; in utero exposure to dichloroacetic acid and trichloroacetic acid (the main haloacetic acids) has also been associated with reduced weight of pups.[9]

Fetal growth is an important public health concern because of its strong relationship to infant morbidity and mortality.[20] Moreover, mounting evidence suggests that babies with growth restriction at birth might be more prone to developing important diseases during adulthood, such as type 2 diabetes, hypertension, metabolic syndrome, and coronary heart disease.[21] Although smoking is a well-recognized risk factor, few other environmental risk factors for fetal growth have been studied.[22,23] Considering the prevalent exposure to chlorination by-products and their toxic potential, we focus here on this possible effect.

The purpose of this study conducted in the Québec City area was to evaluate the association between residential exposure to chlorination by-products (eg, trihalomethanes and haloacetic acids) and fetal growth restriction. The design of the study considered temporal and spatial variations of chlorination by-products in water distribution systems and the multiple pathways of maternal exposure to trihalomethanes during pregnancy.

METHODS

Study Design and Population

We conducted a population-based case-control study in the greater Québec City area (covering some 650,000 inhabitants). It includes the 16 water distribution systems serving the populations of Québec City and the city of Lévis. Among these systems, 9 are supplied by surface water sources and 7 by groundwater sources. All use free chlorine for primary or secondary disinfection, but differ in water source, water treatment processes, population served, system size, and hydraulic conditions.

The study population includes all singleton infants born between August 2006 and April 2008 to women residing in the areas served by the selected facilities. The Commission d'accès à l'information du Québec (the Quebec office for access to information) gave permission to access selected nominal information from the birth certificates of children born to mothers living in the study area shortly after their birth. Cases and controls were selected using information recorded on these birth certificates. To be eligible for the study, the women had to be aged 16 years or older and have resided in no more than 2 residences in the study area during their entire pregnancy. Additionally, they should not have resided away from their residence for more than a month during their pregnancy.

Definition of Cases and Controls

Cases were term small-for-gestational-age (SGA) singletons born at 37 completed weeks or more of pregnancy to women living in the targeted study area during the 23-month recruitment period. A case of SGA corresponds to a neonate weighting less than the sex-specific 10th percentile of weight for gestational age, according to the Canadian sex-specific standards of birth weight for gestational age.[24]

Three controls per case were randomly selected from the live birth database with frequency matching on period of birth. We defined a control as a singleton term infant born the same calendar week as the case with a birth weight at or above the 10th percentile sex-specific weight for gestational age.[24] Because participation was slightly higher for controls, the ratio of controls to cases was 3.4.

Interview of Cases and Controls

An interviewer contacted potential participants by telephone to verify their eligibility and seek their participation. A computer-assisted telephone interview of participants lasting approximately 30 minutes gathered detailed information on all independent variables (water-use behavior and risk factors for SGA), as well as information on the birth outcome (infant weight, duration of pregnancy). In the event of any discrepancies in case status between a mother's interview and a birth certificate, medical records were checked, and corrections were made based on medical records (this was necessary for 3 cases). The participation rates were 91% for eligible cases and 93% for eligible controls. The median time lag for completing an interview after birth was 9.1 weeks for cases and 9.3 for controls. Interview data were available for a total of 571 cases and 1925 controls.

Exposure Assessment

The chlorination by-products exposure of participants was based on assessment of the chlorination by-products concentration in the tap water at the participant's residence, ingestion of trihalomethanes and haloacetic acids, and multiroute exposure to trihalomethanes expressed as total absorbed dose (μg/d). Because the last trimester is usually considered to be the critical period of exposure for intrauterine growth retardation,[7,25–28] it was the main focus of our exposure assessment. However, exposure during the other trimesters of pregnancy was also evaluated.

Chlorination By-products Data Collection

Sampling campaigns tailor-made for the study were conducted from April 2006 to April 2008. We carried out monthly sampling campaigns for trihalomethanes and haloacetic acids measurements at 46 sites distributed in the 9 surface water systems and 7 sites for the 7 systems supplied by groundwater (one site per system). The strategy used to

select the sampling sites in the surface-water systems was based on system characteristics influencing the spatial variability of chlorination by-products. Each system was divided into subsystems according to water supply infrastructure (supplied directly by the treatment plant or through a rechlorination station or a tank). Then, at least one sampling site was located in each subsystem. Details on sampling and analytic procedures are provided elsewhere.[29] Briefly, water samples were collected according to standard procedures after 5 minutes of flushing and were stored at 4°C. Analyses of the 4 trihalomethanes (chloroform, bromodichloromethane, chlorodibromomethane, and bromoform) and 9 haloacetic acids (monochloroacetic, dichloroacetic, trichloroacetic, monobromoacetic dibromoacetic, tribromoacetic, bromochloroacetic, dibromochloroacetic, and bromodichloroacetic acids) were carried out in accordance with EPA method 524.2[30] and EPA method 552.2,[31] respectively. Internal and external quality controls were conducted during the study.

Chlorination By-products Concentration in Tap Water of Participants' Residences

The strategy to estimate the concentration of chlorination by-products at each participant's residence for each trimester of pregnancy considered the spatial and temporal variability of these compounds. For the spatial aspects, the closest sampling sites located in the participant's subsystem were selected. For the temporal aspect, samples taken within or close to the trimester under study were selected. We estimated chlorination by-product concentration by calculating the mean of all these samples with specific weighting factors (see eAppendix 1 http://links.lww.com/EDE/A560 for details). A validation study was conducted on a subsample of participants (n = 115) during the summer of 2008 to validate the strategy used to spatially assign trihalomethanes and haloacetic acids data (from the sampling campaign) to a participant's residence. For each system included in the validation study, no statistical difference ($P < 0.05$) was found between total trihalomethanes and total of the 9 haloacetic acids levels measured on samples taken at the tap of the residences compared with those estimated with our strategy (data not shown).

Ingestion of Chlorination By-products

The doses (expressed in μg/day) of chlorination by-products absorbed by each participant via ingestion during a typical day of the last trimester of pregnancy were calculated for each trihalomethane and haloacetic acid by multiplying the daily ingested volume from various water sources (ie, cold and hot beverages) with the estimated chlorination by-products concentrations in the ingested water during this trimester. We used information reported by the participants during the interview regarding sources of water consumed (ie, bottled water from private source, cold or hot water from public distribution system) and particular water handling (ie, filtering, boiling, storage in fridge) to adjust the chlorination by-products concentration in water actually ingested. The chlorination by-products concentration in water serving the participant's residence was corrected by applying factors (see factors in eAppendices 2 and 3, http://links.lww.com/EDE/A560) derived from a literature review and researchers' experience.

Assessment of Multiroute Exposure to Trihalomethanes

Intakes from inhalation and dermal absorption (expressed as μg/d) during one typical 24-hour day of the last trimester were calculated and added to the previous estimated ingested dose using a physiologically based toxicokinetic model. The details of this model are described in a previous paper published by our team.[18] This model was adapted for SAS, for each trihalomethane, and took into account the increase of body weight and body surface during pregnancy. Such modeling considers simultaneous multiroute exposure and also allows estimating the specific contribution of each pathway (dermal, ingestion, and inhalation) to total absorbed dose of trihalomethanes. More specifically, simulations accounted for dermal exposure during showering or bathing, and 24-hour inhalation of ambient air (from the bathroom during showering or bathing and from the rest of the house otherwise). Self-reported information on duration and frequency of showering and bathing was used to estimate the average time spent in the bathroom per day. Showering and bathing were regarded as equivalent activities by the model. We used trihalomethanes concentrations in water serving the participant's residence as input for the models. From these water concentrations, volatilization models (based on the work of McKone and Knezovich[32] and integrated into the toxicokinetic modeling) served to predict trihalomethanes concentrations in the air in the bathroom and in the rest of the house. Given uncertainty about reported information on room sizes, the standard parameters fixed by Haddad et al[18] were used for all simulations. Finally, exposure of each participant was expressed as total (ingestion + inhalation + dermal) absorbed dose (μg/day).

Potential Confounders

The following variables documented during the interview were considered: maternal age, maternal ethnicity, maternal education, annual household income, working status, marital status, prepregnancy body mass index, parity, history of chronic disease, medical problem during pregnancy, active and passive maternal smoking throughout the pregnancy, coffee and alcohol consumption, and risky occupational exposure.

Statistical Analysis

We analyzed the data using the SAS software package, version 9.1 (SAS Institute Inc., Cary, NC).[33] Exposure was categorized primarily by quartiles of exposure of the

control groups. Other categorizations were based on current chlorination by-products drinking water standards.[5,6] Most of the analyses considered the effect of total trihalomethanes and total haloacetic acids (sum of the 5 regulated haloacetic acids or sum of the 9 measured haloacetic acids). The sum of brominated trihalomethanes was considered as an index of exposure, as well as the concentration of important species (chloroform, bromodichloromethane, dichloroacetic, and trichloroacetic acids). Separate models were constructed for each family of chlorination by-products (trihalomethanes and haloacetic acids) and for the different routes of exposure to trihalomethanes (ingestion vs. inhalation plus dermal absorption). Odds ratios (ORs) and their 95% confidence intervals (CIs) for association with the various indexes of exposure to chlorination by-products were determined using unconditional logistic regression models while controlling for possible covariates and for the calendar week of birth. All variables associated in univariate analysis with SGA (with $P < 0.15$) were included in the multivariate analyses. Tests for trend were based on a Wald χ^2 test conducted by assigning the median value to each level of a categorical variable and treating the variable on a continuous scale in a logistic regression model.

RESULTS

Characteristics of Participants

Most mothers were white and 25 to 34 years of age (Table 1). Case mothers tended to be nulliparous, poorer, and less educated and had a lower body mass index. Chronic diseases were also more prevalent among case mothers than control mothers. Moreover, occurrence of preeclampsia or hypertension during the pregnancy was more frequent among case mothers. Active as well as passive smoking at home was reported about twice as often by case mothers as by control mothers. Consumption of coffee and alcohol during pregnancy was also more frequent among case mothers. For those who worked or studied, we asked about various occupational risk factors for SGA; these were reported with the same frequency by case and control mothers. Of the 571 case infants, 111 (19%) were low birth weight (<2500 g).

Water Exposure and Chlorination By-products Concentrations

Types of water consumption were very similar between case and control mothers (Table 1) as was the quantity consumed for each type (eAppendix 4, http://links.lww.com/EDE/A560). Shower and bath frequencies were also similar between the 2 groups. Swimming pool attendance, especially indoors, was reported slightly more often by the control mothers (Table 1). Modeled mean concentrations of chloroform, total trihalomethanes, and various species of haloacetic acids at the tap water

TABLE 1. Maternal Characteristics and Environmental Exposures of 571 Cases and 1925 Controls Participating in the Québec City Area Study on Exposure to Chlorination By-products and Term SGA, 2006–2008

	Cases No. (%)	Controls No. (%)
Maternal age (years)		
<25	77 (14)	212 (11)
25–29	222 (39)	811 (42)
30–34	191 (34)	673 (35)
≥35	80 (14)	225 (12)
Missing	1	4
Maternal ethnicity		
White	547 (96)	1859 (97)
Other	24 (4)	66 (3)
Highest education level (years)		
≤12	159 (28)	399 (21)
>12	412 (72)	1523 (79)
Missing	0	3
Annual household income ($Canadian)		
<35,000	133 (23)	288 (15)
35,000–69,999	226 (40)	811 (42)
≥70,000	212 (37)	826 (43)
Marital status		
Married	123 (22)	458 (24)
Not married	448 (78)	1467 (76)
Parity and history of low birth weight (LBW)		
Nulliparous	372 (65)	953 (50)
Parous without history of LBW	168 (29)	909 (47)
Parous with history of LBW	31 (5)	62 (3)
Missing	0	1
Body mass index (kg/m^2)		
<19.8	161 (29)	296 (16)
19.8–25.9	308 (55)	1152 (61)
26.0–29.9	51 (9)	239 (13)
>29.9	41 (7)	202 (11)
Missing	10	36
History of chronic disease		
Yes	59 (10)	144 (7)
No	512 (90)	1781 (93)
Medical problem during pregnancy		
Gestational diabetes	25 (4)	96 (5)
Preeclampsia or hypertension	45 (8)	82 (4)
Uterine bleeding in first trimester	94 (16)	286 (15)
Uterine bleeding in last trimester	28 (5)	74 (4)
Missing	0	1
Coffee consumption during pregnancy		
Yes	304 (53)	909 (47)
No	267 (47)	1016 (53)
Fish consumption during last trimester		
Yes	481 (84)	1612 (84)
No	90 (16)	313 (16)
Mean consumption of portion by week (SD)	0.94 (0.80)	0.91 (0.81)

(*Continued*)

TABLE 1. (*Continued*)

	Cases No. (%)	Controls No. (%)
Maternal smoking (active smoking) during pregnancy		
Never	430 (75)	1644 (85)
Only before the third trimester	22 (4)	91 (5)
Ever	119 (21)	190 (10)
Passive maternal smoking at home		
Yes	95 (17)	134 (7)
No	476 (83)	1791 (93)
Alcohol consumption during pregnancy		
Yes	240 (42)	716 (37)
No	331 (58)	1209 (63)
Employed or studying during pregnancy		
Yes	487 (85)	1674 (87)
No	84 (15)	251 (13)
Occupational exposure[a]		
Stand up >6 hours/day	115 (24)	400 (24)
Work >40 hours/week	76 (16)	254 (15)
Carry heavy loads	97 (20)	339 (20)
Rotating working hours	58 (12)	209 (13)
Exposed to passive smoking	11 (2)	40 (2)
Exposed to chemicals	104 (21)	332 (20)
Water consumption during last trimester		
Plain tap water	191 (34)	700 (37)
Filtered tap water	94 (16)	279 (15)
Let water stand in the fridge	45 (8)	144 (8)
Bottled water	208 (37)	707 (37)
Boiled tap water	3 (1)	6 (0)
Other	13 (2)	55 (3)
Do not drink water	2 (0)	4 (0)
Missing	15	30
Bath frequency (baths per day)[b]		
<1	466 (82)	1591 (83)
1	86 (15)	287 (15)
>1	19 (3)	46 (2)
Shower frequency (showers per day)[c]		
<1	167 (30)	535 (28)
1	361 (64)	1282 (67)
>1	38 (7)	102 (5)
Swimming during last trimester		
Indoor pool	115 (20)	473 (25)
Outdoor pool	149 (26)	543 (28)

[a]For women who worked during pregnancy. 1 to 2 missing values for cases and 8 to 14 for controls.
[b]1 missing value for controls.
[c]5 missing values for cases and 6 for controls.

at participants' residences during last trimester were slightly higher for cases than controls (Table 2). Correlations between chloroform or total trihalomethanes and total haloacetic acid (5 or 9 species) were high (≥0.8). In particular, the Spearman correlation coefficient between total trihalomethanes and total haloacetic acids (5 species) was 0.86 (eAppendix 5, http://links.lww.com/EDE/A560).

TABLE 2. Estimation of Third Trimester CBP Concentrations (μg/L) in Tap Water at Participating Residences of SGA Cases and Controls, Québec City Area, 2006–2008

	Chlorination By-products Concentrations (μg/L)	
	Cases Mean (SD)	Controls Mean (SD)
Trihalomethanes[a]		
Chloroform	43.3 (40.7)	41.1 (39.2)
Bromodichloromethane	4.7 (3.1)	4.7 (2.9)
Chlorodibromomethane	1.3 (1.4)	1.3 (1.4)
Bromoform	0.1 (0.3)	0.1 (0.3)
Brominated trihalomethanes	6.1 (4.1)	6.1 (3.9)
Total trihalomethanes	49.3 (39.8)	47.2 (38.3)
Haloacetic acids		
Monochloroacetic acid[a]	2.4 (1.8)	2.3 (1.7)
Dichloroacetic acid[a]	15.8 (15.6)	14.8 (14.6)
Trichloroacetic acid[a]	18.2 (22.2)	16.4 (20.5)
Bromochloroacetic acid[b]	0.9 (0.8)	0.9 (0.7)
Total Haloacetic acids (5 species)[a]	37.0 (38.3)	34.2 (35.7)
Total Haloacetic acids (9 species)[b]	45.2 (38.7)	42.5 (36.1)

[a]7 missing values for cases and 11 for controls.
[b]10 missing values for cases and 18 for controls.

Risk of Small Size for Gestational Age

No clear dose-response relationship was found between quartiles of chlorination by-products concentrations in tap water of the residences during the last trimester of pregnancy and term SGA (Table 3). However, we found an increase of risk for the highest quartile concentration for trichloroacetic acids and total haloacetic acids (5 or 9 species), as well as when chlorination by-products concentrations were dichotomized using either the current total trihalomethanes standard of 80 μg/L (adjusted OR = 1.5 [95% CI = 1.1–1.9]) or the current total haloacetic acids standard of 60 μg/L (1.4 [1.1–1.9]) (Table 3). The associations with exposure to total trihalomethanes and total haloacetic acids were slightly lower when the 2 families of compounds were included in the same model and adjusted for each other. For example, for total trihalomethanes and total haloacetic acids concentrations above current standards, the ORs were: 1.3 (0.8–1.9) and 1.2 (0.8–1.8), respectively. When adjustment was provided for exposure during the previous 2 trimesters, the association with exposure to total trihalomethanes or total haloacetic acids during the last trimester was similar but with wider confidence intervals (data not shown).

The evaluation of the association accounting for multiroute exposure showed that most of the excess risks were explained by oral ingestion (Table 4). We found a slight excess risk for participants in the fourth quartiles of exposure for ingestion of chloroform, total trihalomethanes, and dichloroacetic and trichloroacetic acids. The highest ORs for the fourth quartile of exposure (in comparison with the first

TABLE 3. Association Between Estimations of Third Trimester CBP Concentrations (μg/L) in Tap Water at Participating Residences and Term SGA, Québec City Area, 2006–2008[a]

	Cases No. (%)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Trihalomethanes (μg/L)[2]			
Chloroform			
Quartile 1 (<15.96)[c]	138 (24)	1.0	1.0
Quartile 2 (15.96–27.26)	133 (24)	1.0 (0.7–1.3)	0.9 (0.7–1.3)
Quartile 3 (27.27–51.07)	141 (25)	1.0 (0.8–1.3)	1.0 (0.8–1.4)
Quartile 4 (>51.06)	152 (27)	1.1 (0.8–1.4)	1.2 (0.9–1.7)
Test for trend			$P = 0.10$
Bromodichloromethane			
Quartile 1 (<2.67)[c]	148 (26)	1.0	1.0
Quartile 2 (2.67–3.94)	150 (27)	1.0 (0.8–1.3)	0.9 (0.7–1.2)
Quartile 3 (3.95–5.89)	124 (22)	0.8 (0.6–1.1)	0.8 (0.6–1.1)
Quartile 4 (>5.89)	142 (25)	1.0 (0.7–1.2)	0.9 (0.7–1.2)
Test for trend			$P = 0.70$
Brominated trihalomethanes			
Quartile 1 (<3.11)[c]	142 (25)	1.0	1.0
Quartile 2 (3.12–5.00)	153 (27)	1.1 (0.8–1.4)	1.0 (0.7–1.3)
Quartile 3 (5.01–9.02)	137 (24)	1.0 (0.7–1.3)	0.9 (0.6–1.2)
Quartile 4 (>9.02)	132 (23)	0.9 (0.7–1.2)	0.9 (0.7–1.2)
Test for trend			$P = 0.46$
Total trihalomethanes			
Quartile 1 (<21.57)[c]	142 (25)	1.0	1.0
Quartile 2 (21.57–34.61)	134 (24)	0.9 (0.7–1.2)	0.9 (0.7–1.3)
Quartile 3 (34.62–57.50)	129 (23)	0.9 (0.7–1.2)	0.9 (0.7–1.3)
Quartile 4 (>57.50)	159 (28)	1.1 (0.9–1.5)	1.2 (0.9–1.7)
Test for trend			$P = 0.07$
>80 μg/L vs. <80 mg/L	105/459	1.2 (1.0–1.6)	1.5 (1.1–1.9)
Haloacetic acids (μg/L)[2]			
Dichloroacetic acids			
Quartile 1 (<5.41)[c]	143 (25)	1.0	1.0
Quartile 2 (5.41–9.71)	142 (25)	1.0 (0.8–1.3)	1.0 (0.7–1.3)
Quartile 3 (9.72–18.18)	120 (21)	0.8 (0.6–1.1)	0.9 (0.7–1.2)
Quartile 4 (>18.18)	159 (28)	1.1 (0.9–1.4)	1.2 (0.9–1.6)
Test for trend			$P = 0.11$
Trichloroacetic acids			
Quartile 1 (<5.03)[c]	136 (24)	1.0	1.0
Quartile 2 (5.03–8.98)	148 (26)	1.1 (0.8–1.4)	1.1 (0.8–1.5)
Quartile 3 (8.99–17.78)	113 (20)	0.8 (0.6–1.1)	0.8 (0.6–1.1)
Quartile 4 (>17.78)	167 (30)	1.2 (0.9–1.6)	1.4 (1.0–1.8)
Test for trend			$P = 0.01$
Total haloacetic acids (5 species)			
Quartile 1 (<12.72)[c]	133 (24)	1.0	1.0
Quartile 2 (12.72–21.35)	150 (27)	1.1 (0.9–1.5)	1.2 (0.9–1.6)
Quartile 3 (21.36–39.59)	119 (21)	0.9 (0.7–1.2)	1.0 (0.7–1.3)
Quartile 4 (>39.59)	162 (29)	1.2 (0.9–1.6)	1.4 (1.0–1.8)
Test for trend			$P = 0.03$
>60 μg/L vs. <60 mg/L	110/454	1.3 (1.0–1.7)	1.4 (1.1–1.9)
Total haloacetic acids (9 species)			
Quartile 1 (<21.35)[c]	137 (24)	1.0	1.0
Quartile 2 (21.35–30.02)	147 (26)	1.1 (0.8–1.4)	1.1 (0.8–1.5)
Quartile 3 (30.03–48.47)	117 (21)	0.9 (0.6–1.1)	0.9 (0.7–1.2)
Quartile 4 (>48.47)	163 (29)	1.2 (0.9–1.5)	1.4 (1.0–1.8)
Test for trend			$P = 0.02$

[a]7 missing values for cases and 11 for controls.
[b]Adjusted for maternal age, calendar week, highest education level obtained, annual household income, body mass index, parity and history of LBW, maternal smoking during pregnancy and passive smoking at home, coffee consumption during pregnancy, alcohol consumption during pregnancy, history of chronic disease, and preeclampsia.
[c]Reference category.

quartile) were found for total trihalomethanes (OR = 1.4 [95% CI = 1.0–9 1.9]), dichloroacetic acid (1.4 [1.1–1.9]), total haloacetic acids (5 species) (1.4 [1.0–1.9]), and total haloacetic acids (9 species) (1.4 [1.1–1.9]). Also, we observed a monotonic dose-response for ingested total haloacetic acids.

DISCUSSION

This study did not find a clear dose-response relationship between exposure to chlorination by-products during last trimester of pregnancy and the risk of SGA, using quartiles of concentrations as exposure categories. However, a slight excess risk was found for exposure above the fourth quartiles of concentrations and above the current drinking water standards. Moreover, using a multiroute exposure assessment, we found an increased risk of SGA for women at the highest quartile of ingestion of various chlorination by-product species, and a small dose-response associated with total haloacetic acids ingestion.

Our results are in line with those of the recent prospective study by Hoffman et al,[34] which found a risk ratio of 2.0 (95% CI = 1.1–3.6) for total trihalomethanes levels >80 μg/L in the third trimester and no clear risk using the quartiles categorization. Other published studies on intrauterine growth retardation and chlorination by-products exposure were summarized recently by Grellier et al (2010).[12] Some very limited evidence was found for exposure to total trihalomethanes, with a small increase when levels were above 80 μg/L (meta-OR = 1.1 [95% CI = 1.0–1.2]). However, important limitations of the reviewed studies were acknowledged by the authors, who recommended large and well-designed epidemiologic studies with improved exposure assessment and control of relevant confounders.[12]

Our study was initiated to address these limitations. In particular, our study used a population-based design and had a high rate of participation that precludes important selection bias in our case and control identification. Sample size was

TABLE 4. Association Between Third Trimester Average Exposure to Chlorination By-products and Term SGA According to Route of Exposure, Québec City Area, 2006–2008[a]

	Route of Exposure	Dose (μg/Day)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Chloroform[2]	Ingestion	Quartile 1 (<1.72)[c]	1.00	1.00
		Quartile 2 (1.72–11.88)	1.1 (0.9–1.6)	1.2 (0.9–1.6)
		Quartile 3 (11.89–34.30)	1.1 (0.9–1.5)	1.1 (0.8–1.5)
		Quartile 4 (>34.30)	1.4 (1.1–1.9)	1.3 (1.0–1.8)
		Test for trend		$P = 0.10$
	Inhalation/dermal	Quartile 1 (<31.89)[c]	1.00	1.00
		Quartile 2 (31.89–60.82)	0.8 (0.6–1.1)	0.8 (0.6–1.1)
		Quartile 3 (60.83–131.19)	1.0 (0.8–1.3)	1.0 (0.8–1.4)
		Quartile 4 (>131.19)	0.9 (0.7–1.2)	0.9 (0.7–1.2)
		Test for trend		$P = 0.81$
	Total pathway	Quartile 1 (<42.24)[c]	1.00	1.00
		Quartile 2 (42.24–80.21)	1.0 (0.7–1.3)	0.9 (0.7–1.2)
		Quartile 3 (80.22–169.81)	1.0 (0.8–1.4)	1.0 (0.7–1.3)
		Quartile 4 (>169.81)	1.1 (0.8–1.4)	1.0 (0.8–1.4)
		Test for trend		$P = 0.67$
Brominated trihalomethanes	Ingestion	Quartile 1 (<0.36)[c]	1.00	1.00
		Quartile 2 (0.36–2.19)	1.3 (1.0–1.7)	1.3 (0.9–1.7)
		Quartile 3 (2.20–6.14)	1.4 (1.1–1.9)	1.3 (1.0–1.8)
		Quartile 4 (>6.14)	1.2 (0.9–1.6)	1.1 (0.8–1.5)
		Test for trend		$P = 0.96$
	Inhalation/dermal	Quartile 1 (<5.85)[c]	1.00	1.00
		Quartile 2 (5.85–10.72)	0.9 (0.6–1.2)	0.8 (0.6–1.1)
		Quartile 3 (10.73–19.60)	0.9 (0.7–1.2)	0.8 (0.6–1.1)
		Quartile 4 (>19.60)	0.9 (0.6–1.1)	0.8 (0.6–1.0)
		Test for trend		$P = 0.18$
	Total pathway	Quartile 1 (<7.55)[c]	1.00	1.00
		Quartile 2 (7.55–14.62)	1.0 (0.8–1.4)	0.9 (0.7–1.3)
		Quartile 3 (14.63–26.08)	1.0 (0.8–1.3)	0.9 (0.7–1.3)
		Quartile 4 (>26.08)	0.9 (0.7–1.2)	0.8 (0.6–1.1)
		Test for trend		$P = 0.11$
Total trihalomethanes	Ingestion	Quartile 1 (<2.72)[c]	1.00	1.00
		Quartile 2 (2.72–16.46)	1.2 (0.9–1.6)	1.2 (0.9–1.7)
		Quartile 3 (16.47–41.18)	1.0 (0.8–1.4)	1.0 (0.7–1.3)
		Quartile 4 (>41.18)	1.5 (1.1–1.9)	1.4 (1.0–1.9)
		Test for trend		$P = 0.05$
	Inhalation/dermal	Quartile 1 (<42.88)[c]	1.00	1.00
		Quartile 2 (42.88–76.88)	0.9 (0.7–1.2)	0.9 (0.7–1.2)
		Quartile 3 (76.89–152.65)	1.0 (0.8–1.3)	1.0 (0.7–1.3)
		Quartile 4 (>152.65)	1.0 (0.7–1.3)	0.9 (0.7–1.3)
		Test for trend		$P = 0.89$
	Total pathway	Quartile 1 (<58.02)[c]	1.00	1.00
		Quartile 2 (58.02–102.44)	1.0 (0.7–1.3)	0.9 (0.7–1.2)
		Quartile 3 (102.45–195.73)	1.0 (0.8–1.3)	1.0 (0.7–1.3)
		Quartile 4 (>195.73)	1.0 (0.8–1.4)	1.0 (0.7–1.4)
		Test for trend		$P = 0.76$
Dichloroacetic acid	Ingestion	Quartile 1 (<1.09)[c]	1.00	1.00
		Quartile 2 (1.09–5.61)	1.1 (0.9–1.5)	1.1 (0.8–1.5)
		Quartile 3 (5.62–14.80)	1.1 (0.8–1.5)	1.0 (0.8–1.4)
		Quartile 4 (>14.80)	1.5 (1.1–1.9)	1.4 (1.1–1.9)
		Test for trend		$P = 0.01$

(*Continued*)

TABLE 4. (*Continued*)

	Route of Exposure	Dose (μg/Day)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Trichloroacetic acid	Ingestion	Quartile 1 (<0.98)[c]	1.00	1.00
		Quartile 2 (0.98–5.11)	1.2 (0.9–1.5)	1.1 (0.8–1.5)
		Quartile 3 (5.12–14.13)	1.2 (0.9–1.5)	1.1 (0.8–1.5)
		Quartile 4 (>14.13)	1.4 (1.1–1.8)	1.3 (1.0–1.8)
		Test for trend		$P = 0.06$
Total haloacetic acids (5 species)	Ingestion	Quartile 1 (<2.61)[c]	1.00	1.00
		Quartile 2 (2.61–13.02)	1.2 (0.9–1.5)	1.1 (0.8–1.5)
		Quartile 3 (13.03–33.40)	1.3 (1.0–1.7)	1.2 (0.9–1.6)
		Quartile 4 (>33.40)	1.5 (1.1–1.9)	1.4 (1.0–1.9)
		Test for trend		$P = 0.02$
Total haloacetic acids (9 species)	Ingestion	Quartile 1 (<4.29)[c]	1.00	1.00
		Quartile 2 (4.29–19.35)	1.2 (0.9–1.5)	1.1 (0.8–1.5)
		Quartile 3 (19.36–43.74)	1.1 (0.8–1.5)	1.1 (0.8–1.4)
		Quartile 4 (>43.74)	1.5 (1.2–2.0)	1.4 (1.1–1.9)
		Test for trend		$P = 0.01$

[a]7 missing values for cases and 11 for controls.
[b]Adjusted for maternal age, calendar week, highest education level obtained, annual household income, body mass index, parity and history of LBW, maternal smoking during pregnancy and passive smoking at home, coffee consumption during pregnancy, alcohol consumption during pregnancy, history of chronic disease, and preeclampsia.
[c]Reference category.

large, with statistical power to detect moderate effects. The best available science was applied to improve exposure assessment. Specifically, the temporal and spatial variability of chlorination by-products, important in the distribution systems under study, were taken into consideration using prospective water-quality monitoring and a strategy to assign chlorination by-products data to participants implemented especially for this study. Also, unlike previous studies addressing multiple pathways of exposure,[34,35] we did not apply the same absorption coefficients for all subjects and instead used a pharmacokinetic model developed to predict the absorbed dose based on the physiological characteristics of our subjects. Likewise, we modeled the air concentration of trihalomethanes within participants' residences according to realistic hypotheses,[18] and our analyses considered all important risk factors for growth retardation, including active and passive smoking.

Nevertheless, despite these improvements, there are study limitations that could have led us to underestimate the possible risk associated with in utero chlorination by-products exposure. Exposure habits were assessed through a questionnaire administered retrospectively, which may have introduced some exposure misclassification when evaluating multiple routes of exposure. The corrective factors used to account for particular water-handling habits were derived from limited studies. Moreover, despite improvements to the internal exposure assessment, our ability to model exposure to various trihalomethanes species remained limited due to the uncertainties associated with the model, especially for trihalomethanes other than chloroform.[18] All these measurement errors could partially explain why the multiple-routes-exposure assessment did not provide higher ORs than the use of the simple concentration of chlorination by-products as a measure of exposure. Also, while SGA assessment is a method for evaluating growth retardation in epidemiologic studies, it is well known that SGA is a proxy for intrauterine growth retardation[36] and can lead to misclassifications of growth-retardation status.

Despite improvements in the study design and exposure assessment in particular, our study did not find a higher odds ratios for chlorination by-products exposure compared with previous studies.[12] Indeed, no increased risk was observed for chlorination by-products concentrations under the current US Environmental Protection Agency guidelines, with the exception of total haloacetic acids (5 species) above the fourth quartile (OR = 1.4 [95% CI = 1.0–1.8]). Laboratory studies on rodents found reproductive effects at high doses, but no studies had evaluated such low levels of exposure. Nevertheless, because more than 600 disinfection by-products have been identified[37] and very few have been evaluated for their reproductive toxicity, it is difficult to exclude possible biologic plausibility based on laboratory studies. Consistency of results among epidemiologic studies and increased relative risks at the highest exposure levels are the most robust arguments for a possible causal link. However, we found some discrepancies in comparison with previous studies. In particular, in comparison with the Hoffman et al study,[34] we did not find any increased risk related to absorbed doses of trihalomethanes with inhalation or dermal absorption. Also, despite some suspicion of a possible increase in risk for

exposure to brominated trihalomethanes in previous studies,[34,38] we did not find such a relationship. Unlike Hoffman et al,[34] our results for trihalomethanes and haloacetic acids were similar to each other. However, the 2 families of compounds were correlated in our own study, and we were not able to separate their individual effect. Nevertheless, in light of the consistent association with the oral route and a monotonic dose-response with haloacetic acids ingestion, our study provides some support regarding the effects of nonvolatile haloacetic acids. A few studies have evaluated the effects of haloacetic acids on SGA, but their results are not consistent.[39,40]

Our results support the hypothesis of a possible effect of chlorination by-products on fetal growth and their effect via the oral route during the last trimester. Present guidelines for chlorination by-products in drinking water are based primarily on their potential carcinogenic risk, and use an annual mean to monitor water concentrations. The results of the present study suggest the importance of taking into account the short-term exposure to chlorination by-products during pregnancy in evaluating and managing the potential public health impact of these exposures.

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REFERENCES

1. Rook JJ. Formation of haloforms during chlorination of natural waters. *Water Treat Exam*. 1974;23(suppl 2):234–243.
2. Sadiq R, Rodriguez MJ. Disinfection by-products (DBPs) in drinking water and predictive models for their occurrence: a review. *Sci Total Environ*. 2004;321:21–46.
3. Bull RJ, Kopfler FC. Health effects of disinfectants and disinfection by-products. Denver: American Water Works Foundation and American Water Works Association; 1991.
4. King WD. Epidemiological studies of disinfection by-products and cancer risk. In: Craun GF, Hauchman FS, Robinson DE, eds. *Microbial Pathogens and Disinfection By-products in Drinking Water: Health Effects and Management of Risks*. Washington, DC: ILSI Press; 2001: 243–254.
5. United States Environmental Protection Agency. National primary drinking water regulations; disinfections: disinfectants and disinfection by-products; Final rule. *Federal Regist*. 1998:69390–69476. To be codified at 40 CFR Parts 9, 141, and 142.
6. Gouvernement du Québec. Règlement sur la qualité de l'eau potable du Québec, révisé en juin 2005. *Loi sur la qualité de l'environnement L.R.Q. c. Q-2, juin 2001*. 2005.
7. Kramer MD, Lynch CF, Isacson P, Hanson JW. The association of waterborne chloroform with intrauterine growth retardation. *Epidemiology*. 1992; 3:407–413.
8. Nieuwenhuijsen MJ, Toledano MB, Eaton NE, Fawell J, Elliott P. Chlorination disinfection byproducts in water and their association with adverse reproductive outcomes: a review. *Occup Environ Med*. 2000; 57:73–85.
9. Graves CG, Matanoski GM, Tardiff RG. Weight of evidence for an association between adverse reproductive and developmental effects and exposure to disinfection by-products: a critical review. *Regul Toxicol Pharmacol*. 2001;34:103–124.
10. Bove F, Shim Y, Zeitz P. Drinking water contaminants and adverse pregnancy outcomes: a review. *Environ Health Perspect*. 2002; 110(suppl 1):61–74.
11. Tardiff RG, Carson ML, Ginevan ME. Updated weight of evidence for an association between adverse reproductive and developmental effects and exposure to disinfection by-products. *Regul Toxicol Pharmacol*. 2006;45:185–205.
12. Grellier J, Bennett J, Patelarou E, et al. Exposure to disinfection by-products, fetal growth, and prematurity: a systematic review and meta-analysis. *Epidemiology*. 2010;21:300–313.
13. Arbuckle TE, Hrudey SE, Krasner SW, et al. Assessing exposure in epidemiologic studies to disinfection by-products in drinking water: report from an international workshop. *Environ Health Perspect*. 2002; 110(suppl 1):53–60.
14. Symanski E, Savitz DA, Singer PC. Assessing spatial fluctuations, temporal variability, and measurement error in estimated levels of disinfection by-products in tap water: implications for exposure assessment. *Occup Environ Med*. 2004;61:65–72.
15. Rodriguez MJ, Serodes JB, Levallois P. Behavior of trihalomethanes and haloacetic acids in a drinking water distribution system. *Water Res*. 2004;38:4367–4382.
16. Legay C, Rodriguez MJ, Serodes JB, Levallois P. Estimation of chlorination by-products presence in drinking water in epidemiological studies on adverse reproductive outcomes: a review. *Sci Total Environ*. 2010; 408:456–472.
17. Backer LC, Ashley DL, Bonin MA, Cardinali FL, Kieszak SM, Wooten JV. Household exposures to drinking water disinfection by-products: whole blood trihalomethane levels. *J Expo Anal Environ Epidemiol*. 2000;10:321–326.
18. Haddad S, Tardif GC, Tardif R. Development of physiologically based toxicokinetic models for improving the human indoor exposure assessment to water contaminants: trichloroethylene and trihalomethanes. *J Toxicol Environ Health A*. 2006;69:2095–2136.
19. Mills CJ, Bull RJ, Cantor KP, Reif J, Hrudey SE, Huston P. Workshop report. Health risks of drinking water chlorination by-products: report of an expert working group. *Chronic Dis Can*. 1998;19:91–102.
20. Pallotto EK, Kilbride HW. Perinatal outcome and later implications of intrauterine growth restriction. *Clin Obstet Gynecol*. 2006;49:257–269.
21. Brodsky D, Christou H. Current concepts in intrauterine growth restriction. *J Intensive Care Med*. 2004;19:307–319.
22. Kramer MS. Intrauterine growth and gestational duration determinants. *Pediatrics*. 1987;80:502–511.
23. Triche EW, Hossain N. Environmental factors implicated in the causation of adverse pregnancy outcome. *Semin Perinatol*. 2007;31:240–242.
24. Kramer MS, Platt RW, Wen SW, et al. A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics*. 2001;108:E35.
25. Bove FJ, Fulcomer MC, Klotz JB, Esmart J, Dufficy EM, Savrin JE. Public drinking water contamination and birth outcomes. *Am J Epidemiol*. 1995;141:850–862.
26. Savitz DA, Andrews KW, Pastore LM. Drinking water and pregnancy outcome in central North Carolina: source, amount, and trihalomethane levels. *Environ Health Perspect*. 1995;103:592–596.
27. Gallagher MD, Nuckols JR, Stallones L, Savitz DA. Exposure to trihalomethanes and adverse pregnancy outcomes. *Epidemiology*. 1998;9:484–489.
28. Dodds L, King W, Woolcott C, Pole J. Trihalomethanes in public water supplies and adverse birth outcomes. *Epidemiology*. 1999;10:233–237.
29. Legay C, Rodriguez MJ, Serodes JB, Levallois P. The assessment of population exposure to chlorination by-products: a study on the influence of the water distribution system. *Environ Health*. 2010;9:59.
30. United States Environmental Protection Agency (USEPA). Measurement of purgeable organic compounds in water by capillary column gas chromatography/mass spectrometry, revision 4.1. Method 524.2–1, 1–48. Cincinnati, OH: National center of environmental assessment, Office of research and development, US EPA; 1995.
31. United States Environmental Protection Agency (USEPA). Determination of haloacetic acids and dalapon in drinking water by liquid-liquid extraction, derivatization and gas chromatography with electron capture

detection. Method 552.2. Cincinnati, OH: National center of environmental assessment, Office of research and development, US EPA; 1995.
32. McKone TE, Knezovich JP. The transfer of trichloroethylene (TCE) from a shower to indoor air: experimental measurements and their implications. *J Air Waste Manage Assoc*. 1991;41:832–837.
33. SAS. *User's Guide*. Cary, NC: SAS Institute Inc; 2009.
34. Hoffman CS, Mendola P, Savitz DA, et al. Drinking water disinfection by-product exposure and fetal growth. *Epidemiology*. 2008;19:729–737.
35. Villanueva CM, Cantor KP, Grimalt JO, et al. Assessment of lifetime exposure to trihalomethanes through different routes. *Occup Environ Med*. 2006;63:273–277.
36. Bamberg C, Kalache KD. Prenatal diagnosis of fetal growth restriction. *Semin Fetal Neonatal Med*. 2004;9:387–394.
37. Richardson SD, Plewa MJ, Wagner ED, Schoeny R, Demarini DM. Occurrence, genotoxicity, and carcinogenicity of regulated and emerging disinfection by-products in drinking water: a review and roadmap for research. *Mutat Res*. 2007;636:178–242.
38. Dodds L, King W, Allen AC, Armson BA, Fell DB, Nimrod C. Trihalomethanes in public water supplies and risk of stillbirth. *Epidemiology*. 2004;15:179–186.
39. Porter CK, Putnam SD, Hunting KL, Riddle MR. The effect of trihalomethane and haloacetic acid exposure on fetal growth in a Maryland county. *Am J Epidemiol*. 2005;162:334–344.
40. Hinckley AF, Bachand AM, Reif JS. Late pregnancy exposures to disinfection by-products and growth-related birth outcomes. *Environ Health Perspect*. 2005;113:1808–1813.

