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Women exposure during pregnancy to haloacetaldehydes and haloacetonitriles in drinking water and risk of small-for-gestational-age neonate

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ABSTRACT

Background: Past studies have examined the effects of maternal exposure to water chlorination disinfection by-products (DBPs), such as trihalomethanes (THMs) and haloacetic acids (HAAs) during pregnancy. However, no human-based study has yet evaluated the effect of emerging DBPs, such as haloacetaldehydes (HAs) and haloacetonitriles (HANs) on small-for-gestational-age (SGA) status in newborns.
Objective: This study aims to assess the association between maternal multiroute exposure to HAs and HANs during the third trimester of pregnancy and SGA status at birth, among neonates delivered by women residing in the Quebec City area (Province of Quebec, Canada). We also evaluated the interaction between exposure to these emerging unregulated by-products and regulated DBPs also found in drinking water (THMs and HAAs), for which a positive association with adverse reproductive outcomes has been suggested in previous studies.
Methods: We conducted a population-based case-control study in the Quebec City area. SGA newborns ($n=330$) were compared to 1100 controls, with matching based on calendar week of birth. HA and HAN concentrations in drinking water at participant's tap were estimated using spatio-temporal strategy based on bimonthly measurements carried out at several locations in the participant's distribution system. A computer-assisted telephone interview was completed to collect information on individual habits of water consumption and water related activities in order to determine individual multiroute exposure. This enabled us to estimate the dose of HAs and HANs absorbed daily by each participant. Associations between total HA, HAN concentrations in drinking water and SGA were analyzed. Associations between the daily-absorbed doses of these emerging DBPs and SGA were also analyzed. Odds ratios (ORs) comparing the 4th quartile of exposure to the reference group (the first three quartiles) were obtained by means of conditional logistic regression, and controlling for potential confounders.
Results: Globally, no evidence of increased risk of SGA was found with total HA and HAN concentrations in tap water when participants in the 4th quartile of exposure were compared to the first three quartiles (OR=1.0; 95% CI [0.7–1.5] and OR=0.8; 95% CI [0.6–1.2], respectively). Similarly, no association was found with the daily-absorbed doses of total HAs or HANs (OR=0.9; 95% CI [0.6–1.3] and OR=1.1; 95% CI [0.7–1.6], respectively). However, a small non statistically significant association was found between the dose of brominated HA and SGA (OR=1.4; 95% CI [0.9–2.1]). Also, in spite of the lack of interaction between other DBP classes, an unexpected negative interaction was observed between concentration of chloral hydrate (CH) (which represents the main HA species), and regulated DBPs ($P=0.006$).
Conclusion: In this population, exposure to low levels of HAs and HANs during the third trimester of pregnancy through drinking water was not associated to SGA status in newborns. Nonetheless, more

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research is needed to clarify possible effect of brominated compounds and interaction between different DBPs.

1. Introduction

Most drinking water treatment plants use chlorine to disinfect water and prevent the spread of waterborne pathogens (World Health Organization (WHO), 2011). Unfortunately, chlorine's interaction with organic matter present in water can trigger the formation of chlorination by-products. Over 600 disinfection by-products (DBPs) have been identified in drinking water (Richardson et al., 2007) and this number continues to grow. These DBPs are commonly found in complex mixtures that can lead to interactions among compounds (Simmons et al., 2002).

Research has shown that many DBPs may have adverse effects on human health (Bove et al., 2002; Graves et al., 2001; Grellier et al., 2010; Hrudey, 2009; Krasner, 2009; Nieuwenhuijsen et al., 2000; Tardiff et al., 2006). Studies suggested a positive association between the most common compounds in chlorinated drinking water [trihalomethanes (THMs) and haloacetic acids (HAAs)], and some measures of growth retardation [such as intra-uterine growth retardation (IUGR) and small-for-gestational-age (SGA)] (Graves et al., 2001; Grellier et al., 2010; Levallois et al., 2012; Tardiff et al., 2006). Such effects are paramount, as growth retardation is an important precursor of childhood morbidity and stillbirth (Gibson et al., 2006; Mandruzzato, 2008; Rosenberg, 2008), and has also been linked to several diseases occurring during adulthood, such as type 2 diabetes and coronary heart diseases (Varvarigou, 2010).

Although THMs and HAAs are currently subjected to regulations in Canada, the reproductive toxicity in humans of emerging DBPs has been the focus of few epidemiological studies. However, toxicological studies with rodents have led to the observation of reproductive and developmental effects after exposure to such emergent DBPs. For instance, chloral hydrate (CH), a HA species commonly used as a neonatal sedative, has been shown to cause a decrease in growth and differentiation, as well as increases in the incidence of morphological abnormalities in rat embryo in vitro cultures (Johnson et al., 1998; Kallman et al., 1984; Saillenfait et al., 1995). HANs are also known to cause in utero toxicity, with severity proportional to the increasing halogen substitution (Smith et al., 1986). In rats, trichloroacetonitrile (TCAN) and dichloroacetonitrile (DCAN) caused a decrease in fertility, increased early implantation failure, and reduced pup birth weight and perinatal survival (Smith et al., 1987). Therefore, there is a biological rationale to study the effects of intrauterine exposure to HAs and HANs (Graves et al., 2001).

Measuring the population exposure to DBPs in drinking water has always been a challenge. In fact, DBPs are generally known for their spatio-temporal variability in drinking water distribution systems (Legay et al., 2010b; Mercier Shanks et al., 2013; Rodriguez et al., 2004a, 2004b). Most studies investigating DBP potential reproductive outcomes have relied on quarterly data measured at a few sampling sites, but those data do not allow taking into account short-term temporal and spatial fluctuations of DBP concentrations at the subject's residence (Legay et al., 2010b; Mercier Shanks et al., 2013). Furthermore, individual exposure to DBPs is influenced by the type of water manipulation used at home (water filter pitchers, boiling, etc.). Water use behavior, such as showering and bathing can also contribute to exposure to some DBPs through inhalation and dermal absorption (Lin and Hoang, 2000; Weisel et al., 1999). Thus, it has been recommended that these exposure routes be taken into account when evaluating total exposure to DBPs (Arbuckle et al., 2002; Graves et al., 2001; Grellier et al., 2010; Legay et al., 2010b; Nieuwenhuijsen et al., 2009; Tardiff et al., 2006).

The objective of this study was to evaluate the association between maternal multiroute exposure to HAs and HANs during pregnancy, and SGA. The third trimester of pregnancy was chosen as the exposure period for this study because most of fetal growth takes place at that time (Kramer et al., 1992b; Olsen et al., 2010). Exposure of the study population to THMs and HAAs had been measured as part of another study (Levallois et al., 2012), and these regulated DBPs have previously been associated with adverse reproductive outcomes (Graves et al., 2001; Grellier et al., 2010; Tardiff et al., 2006). Therefore, interactions between emerging and regulated DBPs were also evaluated.

2. Materials and methods

2.1. Study design and population

Women and newborns participating to this population-based case-control study are a subsample of participants to a previous case-control study conducted in the metropolitan area of Quebec City (Province of Quebec, Canada) in 2006–2008 (Levallois et al., 2012). The study area included nine distribution systems supplied by surface water sources: two lakes and four rivers. The same river supplied four of the systems, but the location of the raw water intake and the water treatment plant were different for each system. The nine systems differed in the water treatment processes and distribution characteristics (system size, hydraulic conditions, pipe characteristics, presence of re-chlorination stations or tanks), but all used sodium hypochlorite or gaseous chlorine for primary or secondary disinfection. Supplemental information on these systems is given in Legay et al. (2010a). Recruitment method and eligibility criteria have been described in details previously (Levallois et al., 2012). For this new study, participating mothers were selected among cases and controls if they had given birth to singletons between October 1st 2006 and December 31st 2007 (inclusively), and had resided in municipalities served by one of the nine distribution systems under study. Furthermore, water samples analyzed for HAs and HANs had to be available for at least 1 month during the third trimester of their pregnancy.

2.2. Definition of cases and controls

The study population includes all singleton infants born to women residing in the areas served by the selected facilities. SGA cases ($n=330$) were neonates born after 31 weeks of pregnancy with a birth weight inferior to the 10th percentile of the Canadian reference curve of birth weight for specific gestational age and sex (Kramer et al., 2001). Controls ($n=1100$) were defined as children born after 31 weeks of pregnancy, with a birth weight equal or greater than the 10th percentile of the reference curve. Birth weight, sex and gestational age were obtained through medical birth certificates, after approval of the *Commission d'accès à l'information du Québec* (the Quebec office for access to information). Controls were randomly selected from the live birth database, with frequency matching based on the week of birth. The ratio of controls to case was 3.3. Participation rate for the total original

sample was very high (over 90% for both cases and controls) (Levallois et al., 2012).

2.3. Water sampling and analyses

Samples of emerging DBPs (HAs and HANs) were collected bi-monthly between August 2006 and December 2007, in 34 sites. For technical reasons, HANs and HAs could not be measured during February 2007. HAs and HANs were analyzed by Health Canada (Environmental Health Science and Research Bureau).[1] A detailed description of the methodology used for the analyses of these DBPs can be found elsewhere (Dion-Fortier et al., 2009; Koudjonou and LeBel, 2006; LeBel and Benoit, 2000; LeBel and Williams, 1996). Seven HA species (dichloroacetaldehyde, CH, bromochloroacetaldehyde, dibromoacetaldehyde, bromodichloroacetaldehyde, chlorodibromoacetaldehyde, tribromoacetaldehyde) and four HAN species (TCAN, DCAN, bromochloroacetonitrile, dibromoacetonitrile) were analyzed.

As previously mentioned, the samples of regulated DBPs (THMs and HAAs) were collected and analyzed as part of a previous study (Levallois et al., 2012). In this study, THMs included four species (chloroform, bromodichloromethane, dibromochloromethane, bromoform) and HAAs included five species (monochloroacetic, dichloroacetic, trichloroacetic, dibromoacetic, and monobromoacetic acids). The detection limit (DL) associated to each analyzed DBP species are listed in Table A.1. of the Supplementary data.

2.4. Estimation of DBP concentrations in tap water

Since HA and HAN concentrations in drinking water were not directly measured at each participant's residence, a strategy using data collected during sampling campaigns and taking into account spatio-temporal variability of DBPs was used to estimate their concentration at each participant's residence. This strategy was already applied to estimate THM and HAA concentrations in tap water and it is described in Levallois et al. (2012). Briefly, each distribution system was divided into subsystems based on the water supply infrastructures. For each participant, the closest sampling sites located in their residence's subsystem were selected. The estimation of DBP concentrations at their residence's tap was based on data from sampling campaigns associated to the selected sampling sites, weighted by specific factors accounting for the geographical location of each selected site, and the temporal exposure window around the sampling date (± 30 days for HAs and HANs, and ± 15 days in the case of THMs and HAAs). HAs and HANs were not measured in sub-systems for 14% of all participants (34 sampling sites were used for the present study versus 46 sampling sites for THMs and HAAs in Levallois et al. (2012)). For these participants, the estimation of HA and HAN concentrations at residence's tap was based on sampling sites located in a subsystem located in the same distribution system for which THM and HAA concentrations were comparable to the concentrations measured at the participant's subsystem (assuming similar water characteristics).

The concentrations of some HA and HAN species were found below the DL, which resulted in missing values. Data modeling using β-substitution was carried out to estimate these concentrations (Hewett and Ganser, 2010). This approach was used for species detected in at least 20% of the distribution system's samples, whereas the null value (0) was assigned when the species were detected in less than 20% of distribution system's samples (see Table A.2. in Supplementary data for details). Since this last scenario was observed in all distribution systems for dibromoacetaldehyde, tribromoacetaldehyde and TCAN, the effect of these three species on SGA could not be evaluated. However, only 3% of CH and 6% and DCAN (our most prevalent emerging DBPs) had to be modeled in one of the water-distribution systems under study, as their concentrations in other distribution systems were all above the LD.

2.5. Multiroute exposure assessment

The rationale and calculations used to estimate each participant's multiroute exposure are presented in Supplementary data A.1. and A.2., respectively. Briefly, a 30-minutes computer-assisted telephone interview was scheduled with the participants 2 months after they had given birth in order to collect information on individual habits of water consumption and manipulation at home, water-use behavior, water-related activities, and risk factors for SGA. The daily doses of HANs and HAs (expressed in μg/day) absorbed by each woman during the last trimester of pregnancy were calculated using the daily consumption of tap-water, the estimated concentrations of DBPs at the tap, and the participant's water use habits (presence of a point-of-use filtration system at the house, shower frequency and duration, etc.). For each emerging DBP species, the doses attributed to each absorption pathway (ingestion, inhalation, dermal absorption) were summed to obtain the total daily-absorbed dose. In other words, the ingestion daily-absorbed dose of each HA and HAN species for each participating mother consisted of the sum of each beverage dose contribution on an average day:

$$\sum_{\text{beverage type}_i} [\text{volume ingested} \times \text{concentration in tap water} \times \text{treatment correction factor}]$$

The water treatment correction factors used for HANs and HAs were, respectively: bottled water, 0 for both DBP classes; boiled water, 0 for both DBP classes; filtered water (point-of-use filtration system), 0 for HANs and 0.70 for HAs (details can be found in Supplementary data A.1.). The daily-ingested doses of individual DBP species were summed for each of both DBP classes, to obtain a daily total ingestion dose of HANs and HAs.

For HAs and HANs, the inhalation and dermal route of exposure were estimated using a liter equivalent (L-eq) multiroute methodology (Krishnan and Carrier, 2008).

Inhalation was not included in the analyses since it was deemed unlikely for HAs and HANs, based on their low volatility properties and the low contribution of inhalation to total absorbed dose, (see Supplemental data A.1. and Table A.3.). Dermal absorption was considered significant for HANs, but not for HAs. Dermal absorption was based on total daily showers and baths durations, DBP concentrations in tap water, skin's permeability coefficient, fraction of the absorbed dose, and the exposed skin surface.

For THMs, the daily-dose absorbed by multiroute exposure was previously estimated by Levallois et al. (2012) by means of physiologically based pharmacokinetic (PBPK) modeling. The daily-absorbed dose of HAAs only includes ingestion due to the low volatility of this class of compounds, and was also estimated in Levallois et al. (2012).

2.6. Statistical Analyses

All statistical analyses were performed using SAS 9.2 software (SAS Institute Inc., 2008). The concentrations in tap water and absorbed doses for HANs and HAs were categorized by quartiles

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based on the control group exposure, and associations with SGA were determined by comparing the fourth quartile (the exposed category) with the first three quartiles of exposure (the reference category). This choice was made because exposure levels were very low, and several contaminants had values below their respective LD. Compounds were grouped according to their class for analyses (total HAs, and total HANs), and additional analyses were performed for brominated compounds (brominated HAs, and brominated HANs), as well as for the most prevalent chemical in each group (CH for HAs, and DCAN for HANs). In Levallois et al. (2012), categorizations for THM and HAA concentrations in tap water were based on current DBP drinking water standards (guidelines of 80 μg/L and 60 μg/L, for THMs and HAAs, respectively) (Gouvernement du Québec, 2012; United States Environmental Protection Agency, 1998), whereas their absorbed doses were treated using the same approach as for HAs and HANs. Univariate logistic regression and multivariate conditional logistic regression with matching between cases and controls based on calendar week of birth were used to calculate odds ratios (ORs) and their 95% confidence interval (CI). Known SGA and IUGR risk factors were added to the regression model: prematurity, maternal age, maternal pre-pregnancy body mass index (BMI), maternal history of chronic disease, preeclampsia during pregnancy, uterine bleeding at the beginning of the pregnancy, uterine bleeding at the end of the pregnancy, gestational diabetes, maternal and paternal height, maternal ethnicity, maternal education level, maternal coffee and alcohol consumption during third trimester, maternal smoking during third trimester, maternal exposure to second hand smoke at home throughout pregnancy, maternal use of recreational drugs use throughout pregnancy, marital status, annual household income, nulliparity, and occupational exposure to lead or solvents during pregnancy. Potential confounders and variables for which the association with SGA yielded a *P*-value inferior to 0.20 in multivariate analyses were kept in the model: prematurity, mother's pre-pregnancy BMI, preeclampsia during pregnancy, gestational diabetes, uterine bleeding at the beginning of the pregnancy, nulliparity, mother's height, age, and level of education, marital status, maternal alcohol consumption during the third trimester of pregnancy, exposure to second-hand smoke at home during pregnancy. In order to increase the validity of our regression model, some variables were included regardless of their *P*-value. This was the case for swimming pool attendance frequency, which could increase exposure to these groups of compounds (Richardson et al., 2010). Premature neonates tend to have a lower birth weight due to the shorter duration of the pregnancy, and a variable accounting for prematurity was also included in the model regardless of its level of statistical significance. Finally, because a positive association between the concentrations of regulated DBPs and IUGR had been previously suggested (Grellier et al., 2010; Tardiff et al., 2006), THMs and HAAs were kept in our regression model. Due to the simultaneous presence of several DBPs, we measured the correlations between the concentration estimates using Spearman partial correlation coefficient, as part of preliminary analyses. In addition, we also assessed statistical interaction between emerging DBPs and regulated DBPs. Interaction was assessed using adjusted regression models and the terms had to reach statistical significance ($P \leq 0.05$) in order to be kept in the models.

Table 1
Maternal characteristics and risk factors of the 330 cases and 1100 controls participating in the study.

	Cases % (*n*)	Controls % (*n*)
Duration of pregnancy (weeks)		
< 37	6(19)	5(52)
≥ 37	94(311)	95(1048)
Maternal age (years)		
18–25	17(57)	17(186)
26–30	43(142)	46(512)
31–35	30(100)	29(315)
35–43	10(31)	8(87)
Ethnicity		
Caucasian (white)	96(318)	96(1061)
Other	4(12)	4(39)
Highest education level (grade)[a]		
≤ 12th	29(95)	21(226)
> 12th	71(235)	79(872)
Annual household income (Canadian $)		
< 35,000	24(79)	18(195)
35,000–69,000	39(129)	41(454)
≥ 70,000	37(122)	41(451)
Marital status		
Not married	77(255)	75(823)
Married	23(75)	25(277)
Parity		
Nulliparous	67(220)	51(560)
Parous	33(110)	49(540)
Body mass index (kg/m^2) before pregnancy[b]		
< 18.5	9(31)	5(61)
18.5–24.9	69(224)	65(714)
≥ 25.0	20(66)	27(294)
History of chronic disease[c]		
Yes	2(9)	2(20)
Medical problem during pregnancy[d]		
Yes	34(111)	25(273)
Coffee consumption during the last trimester		
Yes	51(166)	47(521)
Alcohol consumption ≥ 1 a week during the third trimester		
Yes	3(9)	4(48)
Smoking (active smoking) during third trimester		
Yes	18(60)	10(112)
Exposure to passive smoking at home during pregnancy[e]		
Yes	16(53)	7(79)
At least 1 recreational drug use during pregnancy		
Yes	5(16)	3(28)
Occupational exposure to lead and solvents during pregnancy[f]		
Yes	15(48)	13(145)
Weekly indoor pool attendance during third trimester		
< 1	88(291)	83(918)
1–2	9(30)	11(117)
> 2	3(9)	6(65)

[a] Level of education was missing for two controls.
[b] Body Mass Index was missing for nine cases and 41 controls.
[c] History of chronic disease included diabetes, hypertension, cardiac disease, kidney disease, cancer, epilepsy, intestinal disease, arthritis and other unspecified chronic diseases.
[d] Medical problem during pregnancy included gestational diabetes, preeclampsia, eclampsia, hypertension, uterine bleeding in first and third trimester. Information was missing for one control.
[e] Exposure to passive smoking at home during pregnancy was missing for one case and two controls.
[f] Occupational exposure to lead and solvents during pregnancy was missing for 54 cases and 134 controls.

3. Results

3.1. Characteristics of participants

Characteristics of participating mothers are described in Table 1. Mothers were mainly Caucasian (white), aged between 26 and 35 years old, with an education level higher than 12th grade (high-school), and unmarried. This last observation is consistent with the results from the 2006 Canadian national census, in which

Table 2
Water exposure of the 330 cases and 1100 controls participating in the study.

	Cases	Controls
Average daily volume (*L*) of cold beverage consumption (SD)	1.2(0.9)	1.1(0.8)
Daily duration (minutes) of showers and baths during third trimester (*n*)		
≤ 15	62(203)	62(682)
> 15	38(127)	38(418)

it was noted that common-law and lone-parent families represented almost 53% of all Quebecer families with children, about 16% more than Canada as a whole (Human Resources and Skills Development Canada, 2007). Nulliparity, smoking, exposure to second-hand smoke, lower body mass index (BMI), lower education level and lower household income were observed more frequently among case mothers (Table 1). Furthermore, the proportion of preeclampsia or hypertension during pregnancy was almost three times higher among case mothers than for controls. Premature neonates accounted for a small proportion of our sample and their distribution was almost identical in both comparison groups. On average, cases had a slightly higher daily water exposure than controls through ingestion (Table 2) and bath duration (11 min on average, versus 10 for the controls).

3.2. DBP tap concentrations in tap water and doses absorbed

The concentrations of total HAs and HANs in tap water estimated at the controls' residences varied between 0.50 and 34.10 μg/L, and 0.12–5.10 μg/L, respectively, with mean values of 9.0 and 1.9 μg/L (Table 3). The total concentrations of THMs and HAAs were, as expected, much higher than HAs and HANs. They varied from 11.0 and 243.8 μg/L for THMs, and from 7.3 to 206.5 μg/L for HAAs, with an estimated mean concentration of 51.8 μg/L and 40.4 μg/L, respectively. When compared to their concentration estimates, the daily-absorbed doses of HAs and HANs saw a wider range and an increased standard deviation (Table A.4. of Supplementary data), which suggests a higher statistical variability. Low, but statistically significant, Spearman partial correlations were observed between concentrations of HAs, HANs, and THMs (see Table A.5. of Supplementary data). An area wide correlation of 0.8 ($P<0.001$) was observed between concentrations of THMs and HAAs, which is consistent the findings from another exposure study led in Spain (Villanueva et al., 2003).

Table 3
HA and HAN concentrations in tap water and associated daily-absorbed doses for the participants.

	Concentration (μg/L)		Absorbed doses (μg/day)	
Disinfection byproducts	**Cases mean (SD)**	**Controls mean (SD)**	**Cases mean (SD)**	**Controls mean (SD)**
Total HAs	8.78(5.67)	9.00(5.74)	9.89 (10.52)	9.14(10.00)
CH	6.36(5.15)	6.52(5.30)	7.13(8.62)	6.67(8.44)
Brominated HAs[a]	0.94(0.74)	0.93(0.70)	1.07(1.43)	0.93(1.09)
Total HANs	1.80(0.99)	1.86(1.02)	2.02(2.08)	1.95(2.15)
DCAN	1.66(1.01)	1.72(1.03)	1.87(2.00)	1.81(2.07)
Brominated HANs[b]	0.13(0.11)	0.13(0.11)	0.15(0.21)	0.13(0.18)
Total THMs[c]	53.0(40.5)	51.8(39.4)	170.8 (159.8)	170.4(170.2)
Total HAAs[d]	41.7(40.2)	40.4(38.8)	36.1(54.6)	31.7(50.0)

Note: arithmetic means are used.

[a] Brominated HAs—sum of bromochloroacetaldehyde and bromodichloroacetaldehyde

[b] Brominated HANs—sum of bromochloroacetonitrile and dibromoacetonitrile.

[c] Total THMs—sum of chloroform, bromodichloromethane, dibromochloromethane, bromoform.

[d] Total HAAs—sum of monochloroacetic, dichloroacetic, trichloroacetic, dibromoacetic, and monobromoacetic acids.

3.3. Association between maternal exposure to DBPs during the third trimester of pregnancy, and association with SGA in neonates

Individual exposure to DBPs during the third trimester of pregnancy was measured by DBP concentrations at the participant's residence, as well as the dose of DBPs absorbed daily by each woman. Odds ratios (ORs) comparing the 4th quartile of exposure to the first three quartiles were obtained by means of conditional logistic regression, and controlling for potential confounders. Table 4 shows the results for univariate and multivariate conditional logistic regression analysis for SGA status in newborns, in association with exposure to total HAs, brominated HAs, CH, total HANs, brominated HANs, and DCAN. No association was observed between SGA and total HA concentration in tap water (OR=1.0; 95% CI [0.7–1.5]) or dose (OR=0.9; 95% CI [0.6–1.3]). However, a small association was found between the dose of brominated HA and SGA (OR=1.4; 95% CI [0.9–2.1]), although the finding was not statistically significant. No association was seen between SGA and total HAN concentration in tap water (OR=0.8; 95% CI [0.6–1.2]) or dose (OR=1.1; 95% CI [0.7–1.6]), nor with brominated HANs and DCAN.

Total HA or HAN exposure, as measured through concentration in tap water or by the daily-absorbed dose, does not appear to lead to statistical interaction with regulated DBPs (Table 5). Although no interaction was found when the compounds were grouped according to their respective class, a statistically significant interaction was found between exposure to CH and regulated DBPs ($P=0.006$) (Table 5). Indeed, a negative association was observed between the CH concentration in tap water and SGA, when the THM and/or HAA concentration in tap water was above current regulation standards for drinking water (OR=0.5; 95% CI [0.2–0.9]). This effect was not observed for participants whose exposure to THMs and/or HAAs was below current standards (OR=1.4; 95% CI [0.9–2.1]). However, a nearly statistically significant interaction ($P=0.053$) was also observed for the association between the total HA concentration in tap water and term SGA. No interaction was observed when exposure was estimated through the daily-absorbed dose (Table 6).

4. Discussion

In this study, no statistically significant association was found between maternal exposure to low concentration of HAs or HANs in tap water at the residence during the third trimester of pregnancy, and SGA in newborns. Moreover, no association was observed when exposure was measured through daily-absorbed doses. Similarly, no statistically significant association was observed when the most prevalent compound of each DBP class was studied separately (CH and DCAN). However, a non statistically significant association was found with brominated HA. Judging by the general lack of statistical significance of the interaction terms, the simultaneous exposure to emerging and regulated DBPs did not seem to increase or antagonize the effect of the latter on the risk of SGA. However, the association between emerging DBPs (HAs and HANs) and SGA generally seemed to decrease when regulated DBPs (THMs and HAAs) were in the higher exposure category, as opposed to baseline.

Table 4
Association between mothers exposure to HAs and HANs during third trimester of pregnancy and SGA in neonates.

	Controls (n)	Cases (n)	Crude OR (95% CI)	OR adjusted for potential confounders (95% CI)
Total HA concentration (μg/L)				
Quartile 1–3 (< 11.30)	822	248	1.0	1.0
Quartile 4 (11.30–34.10)	278	82	1.0 (0.7–1.3)	1.0 (0.7–1.5)
Chloral hydrate concentration (μg/L)				
Quartile 1–3 (< 8.58)	825	246	1.0	1.0
Quartile 4 (8.58–30.31)	275	84	1.0 (0.8–1.4)	1.1 (0.7–1.6)
Brominated HA concentration (μg/L)[a]				
Quartile 1–3 (< 1.33)	826	253	1.0	1.0
Quartile 4 (1.33–3.15)	274	77	0.9 (0.7–1.2)	0.9 (0.6–1.5)
Total HAN concentration (μg/L)				
Quartile 1–3 (< 2.44)	826	256	1.0	1.0
Quartile 4 (≥ 2.44–5.07)	274	74	0.9 (0.7–1.2)	0.8 (0.6–1.2)
Dichloroacetonitrile concentration (μg/L)				
Quartile 1–3 (< 2.29)	826	253	1.0	1.0
Quartile 4 (≥ 2.29–5.06)	274	77	0.9 (0.7–1.2)	0.9 (0.6–1.3)
Brominated HAN concentration (μg/L)[b]				
Quartile 1–3 (< 0.19)	825	251	1.0	1.0
Quartile 4 (≥ 0.19–0.49)	275	79	0.9 (0.7–1.3)	1.0 (0.6–1.7)
Total HA dose (μg/day)				
Quartile 1–3 (< 12.72)	826	238	1.0	1.0
Quartile 4 (12.72–91.50)	274	89	1.1 (0.9–1.5)	0.9 (0.6–1.3)
CH dose (μg/day)				
Quartile 1–3 (< 9.07)	825	237	1.0	1.0
Quartile 4 (9.07–81.60)	275	90	1.1 (0.9–1.5)	1.0 (0.7–1.5)
Brominated HA dose (μg/day)[a]				
Quartile 1–3 (< 1.32)	825	231	1.0	1.0
Quartile 4 (1.32–11.79)	275	96	1.2 (0.9–1.6)	1.4 (0.9–2.1)
Total HAN dose (μg/day)				
Quartile 1–3 (< 2.65)	825	238	1.0	1.0
Quartile 4 (≥ 2.65–16.37)	274	89	1.1 (0.9–1.5)	1.1 (0.7–1.6)
DCAN dose (μg/day)				
Quartile 1–3 (< 2.47)	825	239	1.0	1.0
Quartile 4 (≥ 2.47–16.36)	274	88	1.1 (0.8–1.5)	1.0 (0.7–1.5)
Brominated HAN dose (μg/day)[b]				
Quartile 1–3 (< 0.21)	824	238	1.0	1.0
Quartile 4 (≥ 0.21–1.39)	275	89	1.1 (0.8–1.5)	0.8 (0.5–1.2)

Note: Risk factors included in the adjusted regression model are prematurity, mother's pre-pregnancy BMI, preeclampsia during pregnancy, gestational diabetes, uterine bleeding at the beginning of the pregnancy, nulliparity, mother's height, age, and level of education, marital status, maternal alcohol consumption during the third trimester of pregnancy, exposure to second-hand smoke at home during pregnancy, indoor pool attendance during third trimester of pregnancy, and exposure to THMs and HAAs. Brominated HANs—sum of bromochloroacetonitrile and dibromoacetonitrile.

[a] Brominated HAs—sum of bromochloroacetaldehyde and bromodichloroacetaldehyde.

[b] Brominated HANs—sum of bromochloroacetonitrile and dibromoacetonitrile.

This is the first study to our knowledge evaluating the potential reproductive effect of HA and HAD in humans. Its mostly negative results are reassuring, but the population under study was exposed to very low concentrations of DBPs. Although cases were exposed to slightly lower concentrations of emerging DBPs than the control group, they were on average exposed to a slightly higher daily-dose of DBPs due to their higher water consumption and bath duration. The HA mixture was predominantly composed of CH. The range of HA concentrations in tap water was similar to the findings from a recent exposure study conducted in the same area (Mercier Shanks et al., 2013), and CH mean concentration in tap water fell within the ranges obtained during past national surveys (1.2–8.4 μg/L) (Health Canada, 1995). However, these concentrations were well below guideline health-based values of 100–200 μg/L recommended for CH by Canadian and international health agencies (Santé Canada, 2008; World Health Organization (WHO), 2005). DCAN was the most prevalent HAN in our study and its range of concentrations in tap water was comparable to values reported in a national survey carried out by Health Canada in 1995 (Boorman, 1999; Health Canada, 1995; World Health Organization, 2004), and below the WHO guideline value of 20 μg/L (World Health Organization, 2004). Although THMs and HAAs were the most prevalent DBP classes, their mean concentration was still lower than the Quebec and US standards (80 μg/L for THMs and 60 μg/L for HAAs (Gouvernement du Québec, 2012; United States Environmental Protection Agency, 1998; United States Environmental Protection Agency (USEPA), 2012).

Laboratory studies in rats are suggesting that high exposure to some HAs and HANs could affect reproduction and fetal development (Borzelleca and Carchman, 1982; Christ et al., 1995; Christ et al., 1996; George et al., 1985; Kallman et al., 1984; Klinefelter et al., 1995; Saillenfait et al., 1995; Smith et al., 1987; Smith et al., 1988). In fact, a

Table 5
Association between HA and HAN concentrations in tap water, and term SGA, when the concentration of regulated DBPs at the residence is below or above guideline values.

DBPs Concentration (μg/L)	Controls (*n*)	Cases (*n*)	THM or HAA < current water standards adjusted OR (95% CI)	THM/HAA interaction *P*-value	Controls (*n*)	Cases (*n*)	THM or HAA > current water standards adjusted OR (95% CI)	THM/HAA interaction *P*-value
Total HAs								
Quartile 1–3 (< 11.30)	759	221	1.0		63	27	1.0	
Quartile 4 (11.30–34.10)	185	57	1.2 (0.8–1.8)	$P=0.053$	93	25	0.6 (0.3–1.1)	$P=0.053$
CH								
Quartile 1–3 (< 8.58)	771	220	1.0		54	26	1.0	
Quartile 4 (8.58–30.31)	173	58	1.4 (0.9–2.1)	$P=0.006$	102	26	0.5 (0.2–0.9)	$P=0.006$
Total HANs								
Quartile 1–3 (< 2.44)	780	237	1.0		46	19	1.0	
Quartile 4 (≥ 2.44–5.07)	164	41	0.9 (0.6–1.4)	$P=0.335$	110	33	0.6 (0.3–1.3)	$P=0.335$
DCAN								
Quartile 1–3 (< 2.29)	783	236	1.0		43	17	1.0	
Quartile 4 (≥ 2.29–5.06)	161	42	0.9 (0.6–1.4)	$P=0.491$	113	35	0.7 (0.3–1.5)	$P=0.491$

Note: Risk factors included in the adjusted regression model are prematurity, mother's pre-pregnancy BMI, preeclampsia during pregnancy, gestational diabetes, uterine bleeding at the beginning of the pregnancy, nulliparity, mother's height, age, and level of education, marital status, maternal alcohol consumption during the third trimester of pregnancy, exposure to second-hand smoke at home during pregnancy, indoor pool attendance during third trimester of pregnancy, concentration of THMs and HAAs at participant's tap water. Current water standards are 80 μg/L for THMs and 60 μg/L for HAAs (Gouvernement du Québec, 2012; United States Environmental Protection Agency, 1998).

recent laboratory study aiming to assess cross-generational toxicity in rats showed that although there may not be evidence of maternal toxicity in dams exposed during gestation, some DBPs can cause toxicity in their progeny (Narotsky et al., 2013). However, such adverse effects are generally observed after exposures to relatively higher doses (from 1 to 25 μg/kg-day for TCAN and bromochloroacetonitrile, and from 50 to 55 μg/kg-day for CH (Borzelleca and Carchman, 1982; Christ et al., 1995; Christ et al., 1996; Kallman et al., 1984; Klinefelter et al., 1995; Saillenfait et al., 1995; Smith et al., 1987, 1988)). In the present study, the concentrations and relative doses estimated for our participants were several orders of magnitude lower than the doses animal subjects were exposed to in laboratory studies. Indeed, the average daily-absorbed dose of HAs was 0.15 μg/kg-day in the control group (equivalent of 0.93 μg/kg-day in rats (Center for Drug Evaluation and Research, 2002)), and 0.03 μg/kg-day (equivalent of 0.19 μg/kg-day in rats (Center for Drug Evaluation and Research, 2002)) for HANs.

The small association between brominated HA and SGA should be underlined. Some studies have suggested that brominated compounds had a higher toxicity than their chlorinated counterparts (Nieuwenhuijsen et al., 2000). Although the association obtained for brominated HAs was not statistically significant, its strength is consistent with findings from other studies focusing on the adverse effects of brominated compounds on fetal growth (Horton et al., 2011; Kramer et al., 1992a). Literature on the adverse reproductive and developmental effects of DBPs remains sparse, and results are often inconclusive. Out of all the DBPs included in our adjusted models, only the daily-absorbed dose of HAAs was statistically associated with SGA newborns (OR = 1.5; 95% CI [1.1–2.1]). The strength of this association is in agreement with findings from other studies (Graves et al., 2001; Hinckley et al., 2005; Tardiff et al., 2006) including the one using the global sample from which our participants were selected (OR = 1.4; 95% CI [1.0–1.8]) (Levallois et al., 2012), and highlights the need to consider HAAs as potential confounders related to SGA.

The important diversity of DBPs found in drinking water makes it a favorable environment for interactions to occur between compounds, and very little research has focused on this phenomenon. It has been recommended that environmentally realistic mixtures of DBPs be studied, instead of solely focusing on individual DBPs (Bull et al., 2009; Narotsky et al., 2013). In light of this, we investigated the interaction between emerging and regulated DBPs. The lack of statistical significance obtained from our results suggests that this phenomenon is unlikely between these classes of DBPs, nonetheless a negative interaction was found between the concentrations of chloral hydrate and the regulated compounds ($P=0.006$). However, this observation should be interpreted with caution. First, no interaction was observed between the daily-absorbed doses of these compounds, which are more accurate exposure measures than concentration estimates. Second, laboratory studies in rats have shown that CH could cause developmental toxicity, and epidemiological studies have suggested that maternal exposure to THMs could increase the risk of fetal growth retardation in humans – which casts a doubt on the biological plausibility of this observation. DBPs' effects on SGA are known to be faint (Graves et al., 2001; Grellier et al., 2010; Hoffman et al., 2008; Tardiff et al., 2006) and our participants were exposed to very low levels of contaminants; this interaction could therefore be the result of chance. Nonetheless, the association between emerging DBPs (HAs and HANs) and SGA generally seemed to decrease when regulated DBPs (THMs and HAAs) were in the higher exposure category. This may be explained by the fact that participants in the low exposure category of regulated DBPs were subjected to unequal exposure to THMs and HAAs depending on the level emerging DBPs. Indeed, increasing their exposure to emerging compounds from baseline to the higher exposure category also resulted in a higher prevalence of these risk factors. This situation was not present when participants were in the high exposure category of regulated DBPs. Finally, DBPs are commonly found in drinking water as part of complex mixtures composed of

Table 6
Association between the absorbed dose of HAs and HANs and term SGA, for each level of the participants' absorbed dose of regulated DBPs.

DBPs Absorbed Dose (μg/day)	Controls (*n*)	Cases (*n*)	THM dose < 3rd quartile adjusted OR (95% CI)	Controls (*n*)	Cases (*n*)	THM dose > 3rd quartile adjusted OR (95% CI)	THM interaction *P*-value	Controls (*n*)	Cases (*n*)	HAA dose < 3rd quartile adjusted OR (95% CI)	Controls (*n*)	Cases (*n*)	HAA dose > 3rd quartile adjusted OR (95% CI)	HAA interaction *P*-value
Total HAs														
Quartile 1–3 (< 12.72)	685	196	1.0	141	42	1.0		692	187	1.0	134	51	1.0	
Quartile 4 (12.72–91.50)	141	45	1.0 (0.6–1.6)	133	44	0.8 (0.5–1.5)	*P*=0.604	134	37	1.0 (0.6–1.6)	140	52	0.9 (0.5–1.5)	*P*=0.801
CH														
Quartile 1–3 (< 9.07)	693	194	1.0	132	43	1.0		696	183	1.0	129	54	1.0	
Quartile 4 (9.07–81.60)	133	47	1.2 (0.7–1.8)	142	43	0.8 (0.5–1.4)	*P*=0.290	130	41	1.3 (0.8–2.1)	145	49	0.8 (0.5–1.3)	*P*=0.142
Total HANs														
Quartile 1–3 (< 2.65)	695	201	1.0	130	37	1.0		676	179	1.0	149	59	1.0	
Quartile 4 (≥ 2.65–16.37)	130	40	1.0 (0.7–1.6)	144	49	1.2 (0.7–2.1)	*P*=0.669	150	45	1.2 (0.8–1.9)	124	44	0.9 (0.6–1.6)	*P*=0.490
DCAN														
Quartile 1–3 (< 2.47)	700	202	1.0	125	37	1.0		677	180	1.0	148	59	1.0	
Quartile 4 (≥ 2.47–16.36)	125	39	1.0 (0.6–1.5)	149	49	1.0 (0.6–1.8)	*P*=0.863	149	44	1.1 (0.7–1.7)	125	44	0.9 (0.5–1.5)	*P*=0.525

Note: Risk factors included in the adjusted regression model are prematurity, mother's pre-pregnancy BMI, preeclampsia during pregnancy, gestational diabetes, uterine bleeding at the beginning of the pregnancy, nulliparity, mother's height, age, and level of education, marital status, maternal alcohol consumption during the third trimester of pregnancy, exposure to second-hand smoke at home during pregnancy, indoor pool attendance during third trimester of pregnancy, and daily-absorbed dose of THMs and HAAs.

many different classes of compounds (Simmons et al., 2002), and the possibility of more potent contaminants acting as effect modifiers leading to the negative interaction observed for CH cannot be ignored.

For the same participants, the daily-absorbed doses of emerging DBPs had a higher variability when compared to the concentrations estimated at the residence. This is illustrated by the two-fold increase in standard deviation that was observed for both HAs and HANs (Table 3). This underlines the impact of personal water related habits on individual exposure, and highlights the importance of considering individual multiroute exposure to correctly assess the exposure of participants to such studies. In that regard, we tried, in this study, to manage several limitations often seen in epidemiological studies focusing on drinking water contaminants, and great emphasis was placed on exposure assessment methodology. Firstly, it has been recommended that studies on DBPs take into account potential fluctuations in DBP concentrations in drinking water (Legay et al., 2010b; Rodriguez et al., 2004b; Symanski et al., 2004). The temporal component of these fluctuations was considered through monthly (THMs, HAAs) and bimonthly (HANs, HAs) sampling campaigns, and the geographical location of the each participant's residence used in the strategy applied to estimate DBP concentrations in participant's tap water allowed to consider spatial fluctuations of DBPs. Additionally, some of the correlation estimates between DBP concentrations varied in opposite directions depending on the drinking water distribution system. This could be explained by the variability of parameters influencing the formation or degradation of some DBPs between the distribution systems – which would highlight the importance of estimating DBP exposure on a personal basis, rather than using areawide data. Secondly, the arbitrary assignment of measurements below the DL is a common practice in studies using environmental data, and this approach features inherent frailties (Slymen et al., 1994). This issue was bypassed by modeling values for observations below that threshold through the use of β-substitution (Hewett and Ganser, 2010; Slymen et al., 1994). Thirdly, we reached a large population sample size and a high participation rate, which efficiently mitigated selection bias.

Other strengths of the study should also be underlined. Conducting the interview relatively soon after birth and focusing mainly on the last trimester of pregnancy contributed to recall bias mitigation. 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 upon them, therefore reducing potential information bias. Inhalation and dermal absorption have been considered in our assessment of exposure to drinking water contaminants. Although multiroute assessment using the L-eq methodology is less accurate than a formal PBPK model, we consider its use valuable in situations where such models (or parameters) are unavailable – as it was the case for HANs and HAs at the time of this study. Nonetheless, each pathway's relevance and parameter used in the L-eq model was based on realistic hypotheses.

Although strong emphasis was put on improving exposure assessment, some limitations may have exposure misclassification, which could have led to underestimate the potential risk associated with HANs and HAs exposure. For instance, the sheer number of DBPs present in potable water makes it difficult to isolate the effect of only a handful of compounds. Moreover, the effect of boiling on water concentration was known for only a few emerging DBPs (CH, dichloroacetaldehyde, tribromoacetaldehyde, and DCAN), and inferences had to be drawn in order to account for this treatment method. This was also the case for point-of-use water filtration, the effect of which was only known for CH. Also, with the exception of CH and DCAN, individual factors for dermal absorption and volatilization coefficients were unavailable, and default values had to be inferred. Likewise, swimming pool attendance could increase exposure to these groups of compounds (Richardson et al., 2010; Simard et al., 2013), but its contribution to total exposure could not be assessed as part of our analyses. Instead, the potential effect of pool attendance was controlled for in our multivariate regression model by including a covariate accounting for pool attendance frequency. THMs have previously been used as surrogates for more toxic DBP mixtures (Cantor et al., 2010). The use of THM and HAA concentrations to identify sampling sites to measure HAN and HA concentrations when no sampling site was available for these emerging DBPs is seen as strength in this study. Although this approach has the potential to introduce inaccuracies in the estimation of HAN and HA concentrations, we compared OR measures to those obtained as part of a sensitivity analysis in which we excluded participants whose concentration data was assigned from other sampling sites, and similar results were found. While we recognize the benefits of β-substitution to generate values for data below the LD, approaches based on data modeling can never replace direct measurements and can introduce inaccuracies. However, only a small proportion of the most prevalent DBPs (CH and DCAN) had to be modeled in one of the water distribution systems, and a considerable modification of our results due to the use of of β-substitution is therefore unlikely. Nonetheless, these potential misclassifications are nondifferential. Therefore, the bias they may have introduced is likely to lead to under-estimation of the association between DBP exposure, and term-SGA.

5. Conclusions

In this population, exposure to HAs and HANs did not show a statistically significant association with SGA in newborns. This result may be explained by the very low exposure to HAs and HANs of our participants, along with potential nondifferencial misclassification of exposure measures. However a small, although non statistically significant association with brominated HAs was found. No interaction was observed between emerging and regulated DBPs when exposure was measured through the daily-absorbed dose of these regulated compounds, which is considered a more accurate exposure measurement tool. The approach presented here may provide other researchers with a way to include multiroute exposure in data-poor situations.

Conflicts of interest

The authors declare they have no competing conflicts of interest.

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Research ethics committee approval

This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki)

for experiments involving humans, and was approved by the research ethic committee of the Centre hospitalier universitaire de Québec-Centre hospitalier de l'Université Laval (CHUQ-CHUL) on September 22nd 2010 (CS10-04-008-21).

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Appendix A. Supplementary information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2015.01.005.

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