Association between exposure to drinking water disinfection byproducts and adverse pregnancy outcomes in South Africa

Funanani Mashau, Esper Jacobeth Ncube and Kuku Voyi

ABSTRACT

Currently, there is contradictory evidence for the risk of adverse pregnancy outcomes associated with maternal exposure to disinfection byproducts (DBPs). We examine the association between maternal exposure to trihalomethanes (THMs) in drinking water and adverse pregnancy outcomes, including premature birth, low birth weight (LBW) and small for gestational age (SGA). In total, 1,167 women older than 18 years were enrolled at public antenatal venues in two geographical districts. For each district, we measured the levels of residential drinking water DBPs (measured in THMs) through regulatory data and routine water sampling. We estimated the individual uptake of water of each woman by combining individual water use and uptake factors. Increased daily internal dose of total THMs during the third trimester of pregnancy significantly increased the risk of delivering premature infants (AOR 3.13, 95% CI 1.36–7.17). The risk of premature birth was also positiviely associated with exposure to total THMs during the whole pregnancy (AOR 2.89, 95% CI 1.25–6.68). The risk of delivering an SGA and LBW infant was not associated with maternal exposure to THMs. Our findings suggest that exposure to THMs is associated with certain negative pregnancy outcomes. The levels of THMs in water should be routinely monitored.

Key words | adverse pregnancy outcomes, disinfection byproducts, drinking water, Sub-Saharan Africa, trihalomethanes (THMs)

Funanani Mashau (corresponding author)
Esper Jacobeth Ncube
Kuku Voyi
School of Health Systems and Public health,
Faculty of Health Sciences,
University of Pretoria,
Private Bag x323, Pretoria 0002,
South Africa
E-mail: *mashaufunanani@yahoo.com*

HIGHLIGHTS

- Disinfection byproducts (DBPs) and adverse pregnancy outcomes in South Africa.
- DBPs levels are higher in Sub-Saharan Africa in comparison to the developed countries.
- There is a positive association between DBPs with the risk of delivering premature infants.
- No association between DBPs and small for gestational age.

INTRODUCTION

Water utilities routinely use chlorine-based compounds to disinfect and maintain residual concentrations of pathogenic microorganisms in drinking water distribution systems thus protecting water from microorganism regrowth (El-Attafia & Soraya 2017). The use of chlorine-based compounds to disinfect water causes the formation of undesirable byproducts, commonly referred to as disinfection byproducts (DBPs). DBPs form when chlorine reacts with natural organic matter present in surface waters

doi: 10.2166/wh.2020.214

(Richardson *et al.* 2007). The most commonly studied and quantified DBPs are trihalomethanes (THMs) and haloacetic acids (HAAs), which occur in high concentrations in drinking water. Drinking water utilities in many countries including Southern Africa, the United States and Canada use THMs as a proxy to routinely monitor and control DBPs in drinking water distribution systems. The occurrence and distribution of THMs in drinking water vary according to treatment methods, geographical region or location and season (Richardson *et al.* 2007).

THMs are considered to be potential carcinogens (Richardson *et al.* 2007), and exposure to THMs may be associated with reproductive and fetal developmental toxicity (Christian *et al.* 2002). Given these concerns, the South African National Standards has set the maximum contaminant levels (MCLs) for total THMs in drinking tap water at 300 μg/L (SANS 2015). Although benchmarked with the World Health Organization (WHO) drinking water standards (WHO 2017), South African MCLs are still higher than MCLs set for other countries. For example, the United States Environmental Protection Agency (USEPA) sets the THM safe levels at 100 μg/L (USEPA 2011), while other countries have adopted more strict MCLs for THMs, namely, France (30 μg/L), Italy (30 μg/L), Denmark (15 μg/L) and Germany (10 μg/L) (Rizzo *et al.* 2005).

Numerous epidemiological studies have investigated the association between maternal exposure to THMs in drinking water and adverse pregnancy outcomes (Grazuleviciene *et al.* 2011; Horton *et al.* 2011; Danileviciute *et al.* 2012; Botton *et al.* 2015). Studies have suggested that pregnant women exposed to higher THM concentrations have a greater risk of adverse pregnancy outcomes such as stillbirth, miscarriage, premature delivery/birth (PTD), intrauterine growth retardation (IGR), low birth weight (LBW) and small for gestational age (SGA) (Horton *et al.* 2011; Danileviciute *et al.* 2012; Botton *et al.* 2015). However, findings from these studies have been inconsistent. The associations remain unclear with some studies indicating an increased risk for LBW at term or SGA (Wright *et al.* 2004; Hinckley *et al.* 2005). Exposure to chloroform, a common THM, during pregnancy has been associated with an increased risk for SGA (Grazuleviciene *et al.* 2011). Inconsistent results in these studies may be due to differences in individual water-use activities and geographical variation (Barbone *et al.* 2002; Kaur *et al.* 2004; King *et al.* 2004). In this study, we consider multi-exposure routes related to DBPs.

Exposure to DBPs has been extensively studied in developed countries such as Europe, the United States and Australia, while there are no such studies in Sub-Saharan African countries. In South Africa, specifically, drinking water utilities in 'metropolitan districts' routinely monitor four THMs to demonstrate compliance with national regulations. Drinking water is routinely sampled two to four times a year per sampling point. In South Africa, 'metropolitan districts' have been chlorinating drinking water for more than 100 years. One of the largest 'metropolitan districts' in South Africa sources large volumes of drinking water from other nearby water utilities and blends the water with city-owned sources. For this reason, DBPs, especially THM levels, may vary from the time it was measured at the source to the time it reaches the consumer.

In this prospective cohort study, we investigate the potential health effects of prenatal maternal exposure to drinking water DBPs on fetal outcomes, namely, LBW, SGA and preterm or premature birth (PTB), by following pregnant women in both high-likely exposed and less-likely exposed communities South Africa. We used recommendations on exposure assessment methods from previous studies to collect individual-level information to identify risk factors associated with the adverse pregnancy outcomes.

MATERIALS AND METHODS

Study area and population

The study was conducted in two geographical areas in South Africa, which are served by two different drinking water utilities, referred to as high-likely exposed and less-likely exposed communities. The high-likely exposed community encompassed one of the largest 'metropolitan districts' in South Africa, where water is treated by chlorination as the primary process and chloramination as the secondary process. This is done to afford the necessary disinfectant residual and protect the water against bacterial growth in the distribution network by the time it reaches the Water Services Authority's storage facilities. The water source is not affected by industrial waste discharges. The district

consists of 11 distribution systems (water supply zones) for all reticulation water supplies to residential areas. In this study, only one distribution water system was considered and 10 communities were selected based on being served by the same water supply system. The selected communities had an estimated targeted female population of approximately 910,246 women (StatsSA 2011).

For the less-likely exposed communities, we selected a rural district in South Africa. The district comprises four regions also known as local municipalities. We selected one region for this study based on having more active communal boreholes with unchlorinated groundwater supply systems, supplying residential drinking water. The total household population in the region is approximately 516,031 (StatsSA 2011). The selected communities had an estimated targeted female population of 20,274 women (StatsSA 2011); there were thus fewer study participants in the area.

Participant, recruitment and adverse pregnancy outcomes assessment

This prospective cohort epidemiological study included pregnant women in South Africa. Pregnant women living in the selected geographical districts who were older than 18 years and in their third trimester (24–36 weeks) were invited to participate in the study during visits to public antenatal clinics between February 2017 and May 2018. Eligible women were given a letter containing a statement of consent. The letter also described the study and its procedures. The objectives and concepts of the study and possible risks of participation were clearly explained to the potential participants. The pregnant women were only enrolled in the study after they consented to participate. The study protocol was approved by the Research Ethics Committee, Faculty of Health Sciences, University of Pretoria, South Africa (reference 115/2016). The study was endorsed by the Department of Health and the Department of Water and Sanitation in both districts of South Africa. The study ethics complied with the Declaration of Helsinki (1997).

Initially, 1,500 women across both sites expressed interest in the study. Potential participants were excluded ($N = 312$) if they were (1) younger than 18 years ($N = 63$), (2) residing outside the selected study sites ($N = 12$), (3) did not speak or understand either English or local languages ($N = 4$), (4) were planning to leave the study sites before or just after birth ($N = 54$) and (5) whose scans revealed multiple gestations (twins or triplets). A further 179 women were not willing to be part of the study. Of the remaining 1,188, 21 participants refused to be interviewed, and therefore, the study included 1,167 expectant mothers (study population) across both sites. Thus, 931 (80%) women were recruited from the metropolitan district (high-likely exposed communities) and 235 (20%) were from the rural district (less-likely exposed communities). The study sample was representative of the target population in terms of prenatal care attendance in the public health system, used by more than 80% of pregnant women in both study sites.

Data were collected through face-to-face and telephonic interviews, using a questionnaire as the data collection instrument. A previously validated structured questionnaire from a multi-case-control study on DBPs English version 8 was used to collect the individual data from the pregnant women (Villanueva *et al.* 2006). Additional variables were included according to a validated questionnaire (Kaur *et al.* 2004) to suit the current study. Maternal information was collected through face-to-face interviews with expectant mothers using a structured questionnaire (maternal questionnaire). Data on maternal health history/characteristics were obtained from participant clinical/medical cards/reports. Information from the maternal questionnaire included detailed questions about socio-demographic information, pregnancy, maternal health, women's lifestyle characteristics and water-use habits during pregnancy. Lifestyle characteristics included alcohol consumption, cigarette smoking, intake of coffee and soda, and passive tobacco smoking exposure at home. Season refers to the time of the year when the interview took place, which comprised summer (December, January and February), autumn (March, April and May), winter (June, July and August) and spring (September, October and November).

Maternal health characteristics included body mass index (BMI = weight/height^2), high blood pressure, asthma, HIV and regular diabetes. BMI was based on participants' medical records measured during pregnancy; this was referred to as prenatal BMI. The other health characteristics collected included chronic hypertension, lung disease

and renal disease were based on self-reported information. The water-use activities investigated in this study included intake of bottled water, tap water, bathing and showering habits, and the use of swimming pools. The total amount of water ingested was estimated based on a cup or glass defined in the interview (200 mL cup or glass), tap water (200 mL cup or glass) and boiled water in the form of tea (200 mL cup). These were all based on self-reported information. The amount of time spent bathing and showering were self-reported as average minutes per day. Data on swimming were described as a dichotomous variable (yes/no) for using a swimming pool during pregnancy and minutes spent in the pool. Participants were also asked to permit the research team to review their medical records. History of past and present pregnancies and women's health status were ascertained and validated against medical records.

Data on adverse pregnancy outcomes were self-reported by participants through telephonic interviews and were attained from the measurements of the newborn babies that were perfomed at childbirth, according to the Department of Health's guidelines for maternity care in South Africa (SADoH 2015). The clinician measured the neonate and recorded these measurements in both the individual childbirth card and clinics log register. In this study, information on newborn babies was collected using individual child clinic cards for live births. The WHO guidelines for anthropometric measurements were used, which included variables on infant date of birth, birth weight, length, sex, birth rank, any disabilities observed by mother on a child, gestational age at birth and method of delivery (WHO 2008).

The adverse pregnancy outcomes were assessed using standard definitions. Premature or preterm birth included live births with a gestational age of <37 weeks. Gestational age was estimated using the duration of pregnancy in completed weeks from the first day of the last menstrual period (LMP) and the use of ultrasound scan recorded by clinicians. The clinical file was visited to record this information.

Full-term births were defined as infants born ≥37 weeks completed gestational age, while post-term birth were infants born ≥42 weeks completed gestational age. An SGA infant was defined as an infant with a birth weight below the 10th percentile for his or her gestational age at birth (WHO 2008; SADoH 2015). The 10th percentile cut-point values were obtained from standardized birth weight curves (WHO 2008). Birth weight was coded as continuous in grams. LBW was defined as weight at birth of less than 2,500 g (WHO 2008). Adverse pregnancy outcomes were analyzed first according to the above definitions and then coded as binary variables (1 = case; 0 = non-case).

A total of 1,167 eligible participants were targeted during the follow-up to collect their child's measurements recorded on the child's birth card. The information mentioned above was used to assess adverse pregnancy outcomes. Of the 1,167, 258 (22%) participants across the study sites were lost due to missing contacts or not being available from the contacts given during recruitment. Few participants refused to continue with the study. From 909 participants, 45 were further excluded from the study as they did not meet the inclusion criteria for the adverse pregnancy outcomes assessment. Therefore, this epidemiological study included 864 (74%) study subjects (mother–child pairs) for further adverse pregnancy outcomes analysis. Of these, 696 (80%) were from high-likely exposed communities, and 168 (20%) were from less-likely exposed communities.

THM levels

Routine water sampling was done at the representative water sources (communal boreholes and taps) of less-likely exposed communities. Samples were tested for THMs and other water quality parameters. In this study, four THMs, including, chloroform, bromodichloromethane, dibromochloromethane and bromoform, were tested. Other water contaminants such as nitrate and inorganic chemicals were below MCLs.

In the high-likely exposed communities, data for total trihalomethanes (TTHMs), chloroform, bromodichloromethane, dibromochloromethane and bromoform concentrations, and other water quality parameters were collected from routinely collected samples. The district provided information on district boundaries, raw water sources and the water treatment process, and described the reservoirs that feed into the study communities. The data were checked for errors. Although our cohort included women who were pregnant in 2017, we requested routine THM data from the start of January 2016 to December 2018.

In addition, all available data on free chlorine, residual chlorine, monochloramines, total organic carbon, total chlorine, temperature, turbidity, pH, conductivity and heavy metals were provided for the respective sampling points. On average, water samples were collected 8–12 times annually over the 3-year period (2016–2018). The limit of detection (LOD) was 0.25 μg/L for all the four THMs measured. Multiple values below the LOD were reported from the distribution system, where up to 80% of bromoform values were below the LOD (but occasionally varying from 0.37 to 1.04 μg/L). Dibromochloromethane was occasionally below the LOD of 0.25 μg/L, but chloroform and bromodichloromethane were never below the LOD. Where samples were below the LOD, a value equal to half the LOD was used for that sample point, to calculate total THMs (sum of the four different THMs). Arithmetic means were used to present the results as some of the monitoring sites were intentionally sampled multiple times. Analyses of treated water show that no chemical MCLs were exceeded. No additional data were obtained from the regulator for other DBPs such as HAAs and HNs.

THM modeling

To provide more robust monthly THM estimates for the study period, we predictively modeled the regulatory data (Grazuleviciene *et al.* 2011; Villanueva *et al.* 2011). The raw data were modeled to obtain more robust estimates of THM concentrations for times and places for which data were sparse, and to predict missing values during the study period. Variables were transformed where necessary to obtain a normal distribution. We used a bivariate linear regression to identify the variables influencing THM levels: sampling month and year, and geographical variable (region and sampling points) (Grazuleviciene *et al.* 2011; Villanueva *et al.* 2011). About 202 (70%) records of THM data were used to estimate 86 (30%) records of THM data to give a total of 288 records of THM monthly data. The R^2 values were used to select the final model. The models with the highest R^2 were selected. Separate models for total THMs, chloroform ($CHCl_3$), bromodichloromethane ($CHBrCl_2$), dibromochloromethane ($CHBr_2Cl$) and bromoform ($CHBr_3$) were run. Non-significant variables were discarded, and relevant variables for temporal or geographical variability were tested and retained if they were statistically significant.

Exposure indices

Individual exposures metrics were estimated by linking the mother's residence to the geographical area served by a selected water supply system. Geographical areas were defined according to the residential address code and regions (sampling site) served by the selected water supply system. If a single water supply system served participants, THM values corresponding to the area were assigned to respective participants.

The study was restricted to individuals served by a municipal water supply system only. The individual's residential exposure index and the water-use habits obtained from questionnaire data were combined to assess individual exposure through ingestion, dermal absorption and inhalation of THMs. The personal information on water-use habits included daily ingestion of unfiltered tap water, bathing and showering of the study participants, to create personal indices of THM levels based on the address of residence and regions (sampling site) of the metropolitan, year and month of conception. The model integrated the information on residential THMs levels (μg/L), ingested amounts (L/day), and modification by heating using estimated uptake factors. This was used to derive an integrated index of blood concentration expressed in microgram per day (μg/day).

The values on uptake factors were obtained from studies reporting blood THM levels after drinking, showering and bathing. These were obtained directly from published papers (Backer *et al.* 2000; Lynberg *et al.* 2001; Villanueva *et al.* 2011). In this study, water use and THMs blood concentrations were calculated using liters of water ingested or duration of showering/bathing. Bottled water intake was considered as unchlorinated water in this study. We calculated the proportions of women who ingested the total amount of cold tap water and bottled water (liters per day). The use of swimming pool (yes/no), minutes spent in a pool, minutes spent in showers and minutes spent in baths were calculated as proportions. The arithmetic means, median and percentiles for water use during pregnancy were calculated.

Integrated total THM exposures during the third trimester and the entire period of pregnancy calculated from the regression model were used to quantify the risk of adverse pregnancy outcomes.

Statistical analysis

The THM values were slightly positive skewed; therefore, the values for TTHM and chloroform were log-transformed to normalize the distribution. Logistic regression was used to determine the association between TTHM and chloroform (log-transformed) concentrations and risks of premature birth, LBW and SGA. TTHM and chloroform were included as categorical variables using quartiles as cut points. Multivariate logistic regression modeling was used to explore the relationships between adverse pregnancy outcomes and TTHM after adjusting for the effect of significant covariates.

The potential covariates for adverse pregnancy outcomes were based on biological and statistical consideration (Grazuleviciene *et al.* 2011; Horton *et al.* 2011). In brief, individual data were assessed for potential confounders using univariate analysis. Stepwise hierarchical backwards binary logistic regression was applied. Variables were dropped from the model if their likelihood-ratio (LR) test was statistically significant using a lenient value of alpha of 0.2. The tests were done only to control for potential significant confounders.

Multivariate logistic regression modeling was used to explore the relationships between adverse pregnancy outcomes and TTHM after adjusting for the effect of significant covariates. We included significant covariates that impacted the odds ratio (OR) for TTHM by 10% or more when all of the covariates were included in the model. The adjusted covariates that were examined included but not limited to maternal age (continuous), prenatal BMI (continuous), adverse pregnancy history (yes/no), season, marital status, household income, educational background, alcohol consumption, maternal smoking, passive smoking, and sex of the baby and birth year. Maternal health characteristics included BMI (= weight/height^2), high blood pressure, asthma, HIV status (positive or negative) and regular diabetes.

The probability of exposure given the outcomes (OR) was used to present the results in this study. To indicate the precision of the effect, 95% CIs were calculated. Two-tailed statistical significance was evaluated by using a *p*-value of 0.05. All the analyses were performed using Stata/IC version 14.1 (Stata Corp, USA).

RESULTS

Distribution of maternal characteristics by exposure group

The characteristics of expectant mothers in both the high-likely exposed and the less-likely exposed communities are shown in Table 1. The average age of mothers at enrollment was 27 years for both communities, ranging from 18 to 45 in high-likely and 18 to 43 years in less-likely communities. Overall, the participants were of Black African ethnic origin (99%). Most women had attained high school educational level in both communities (high-likely: 64% and less-likely: 72%). Women with no formal schooling were generally rare in both groups (3–4%). In both groups, women were from low-income households with monthly earnings of less than 2,000–3,000 (RSA Rands) and were unmarried or single at the time of the interview. Prenatal BMI ranged from 11.6 to 52.9 kg/m^2 in high-likely and 17.7 to 68.8 kg/m^2 in less-likely exposed communities.

More women from high-likely exposed communities gave up alcohol consumption during pregnancy (34%) than women in less-likely exposed communities (9%). A greater proportion of women in high-likely exposed communities were exposed to passive smoking (36%) compared with women in less-likely exposed communities (11%). Approximately 68% of women in high-likely exposed communities had a previous pregnancy, while 44% in less-likely exposed communities had previously been pregnant. The prevalence of chronic disease was lower among women in the high-likely exposed communities than in less-likely exposed communities (16 versus 20%). High blood pressure was more prevalent in the less-likely exposed group than in the high-likely exposed group (7 versus 3%).

Levels of THMs and exposure metrics

The primary water supply sources for the high-likely exposed group were surface water, while the less-likely exposed groups sourced water from groundwater sources. In the

Table 1 | Demographic characteristics of mothers in the cohort in high-likely (exposed communities) and less-likely exposed (unexposed) communities ($N = 864$)

	Average TTHM maternal exposure			
	48–114 μg/L		0[e]–0 μg/L	
Maternal characteristics	**Exposed communities ($n = 696$)**		**Unexposed communities ($n = 168$)**	
Continuous variables	**Mean (SD)**	**Min-Max**	**Mean (SD)**	**Min-Max**
Maternal age, years	27.33 (5.40)	18–45	26.86 (6.22)	18–43
Prenatal BMI, (kg/m^2)	27.45 (5.76)	11.6–52.9	28.26 (6.71)	17.7–68.8
Categorical variables	**No.**	**%**	**No.**	**%**
Maternal age, years				
<23	138	19.83	54	32.14
23–26	196	28.16	37	22.02
26–31	210	30.17	30	17.86
>31	152	21.84	47	27.98
Maternal race				
African	692	99.44	168	100
Non-African	4	0.56	0	
Maternal educational level				
No formal schooling	24	3.45	5	2.98
Primary school	42	6.03	4	2.38
High school	442	63.51	121	72.02
Tertiary school	188	27.01	38	22.6
Marital status				
Single	455	65.37	108	64.29
Married or living with a partner	241	34.63	60	35.71
Other	0		0	
Employment during pregnancy				
Yes	184	26.44	20	11.90
No	512	73.56	148	88.09
Monthly household income, Rand				
<2,000	361	51.86	53	31.55
≥3,000	236	33.91	36	21.43
≥6,000	88	12.64	53	31.55
≥12,000	11	1.58	30	17.85
Pregnancy background	**No.**	**%**	**No.**	**%**
Pregnancy before				
Yes	475	68.25	74	44.05
No	221	31.75	94	55.95
Miscarriage or congenital disabilities before				
Yes	64	9.20	17	10.12
No	632	90.80	151	89.88

(*continued*)

Table 1 | continued

	Average TTHM maternal exposure			
	48–114 μg/L		0[e]–0 μg/L	
Maternal characteristics	**Exposed communities (*n* = 696)**		**Unexposed communities (*n* = 168)**	
High blood pressure or hypertension				
Yes	20	2.87	11	6.55
No	676	97.13	157	93.45
Regular diabetes				
Yes	2	0.29	0	
No	694	99.71	168	100
Chronic diseases				
Yes	114	16.38	33	19.64
No	582	83.62	135	80.36
Behaviour				
Maternal alcohol consumption				
Never	416	59.77	149	88.69
Given up during pregnancy	239	34.34	15	8.93
Current	41	5.89	4	2.38
Maternal smoking				
Never	651	93.53	159	94.64
Given up during pregnancy	38	5.46	9	5.36
Current	7	1.01	0	
Passive smoking				
Yes	253	36.35	18	10.71
No	443	63.65	150	89.29

N, total number of study subjects; *n*, number of mothers per study site; SD, standard deviation; %, percentages; 0[e], the value below the LOD/minimal reporting limit.

high-likely exposed region, the estimated TTHM mean values at the area level were 94 μg/L during the third trimester and 72 μg/L for the whole pregnancy. Chloroform was the dominant THM species in the area, contributing approximately 75% of the total concentration of TTHMs. The values for bromoform were below the LOD and not shown. The values for brominated species were significantly low; bromodichloromethane ranged from 15 to 19 μg/L, while dibromochloromethane ranged from 1.6 to 2.0 μg/L, for third trimester and entire pregnancy, respectively (Table 2).

For the less-likely exposed communities, the results for TTHM and THM compounds were all below the LOD (Table 2). The absence of THMs in the area is primarily due to the unchlorinated groundwater supplied to the communities. Thus, the area was not exposed to drinking water DBPs and is further referred to as unexposed communities.

The THM integrated uptake through ingestion, bathing and showering were evaluated in the high-likely exposed communities for the third-trimester gestation (Table 3). The total daily uptake of TTHM during the third trimester ranged from 1.37 to 142.13 μg/day, and the daily uptake of chloroform ranged from 0.99 to 116.59 μg/day. For brominated THM species, the daily uptake was significantly low. Pregnant women who were exposed to high levels of THMs had correspondingly high levels of internal THM uptake. The estimated internal levels of TTHMs were similar for the third trimester and the whole pregnancy.

Table 2 | Average residential levels of TTHMs and THM compounds in drinking water estimated at third trimester and entire pregnancy in the cohort, for high-likely (exposed) and less-likely exposed (unexposed) communities in South Africa, 2016–2018

	Exposed communities		Unexposed communities	
Study site	**Surface water[a]**		**Groundwater[b]**	
Pregnancy time	**Third trimester**	**Entire pregnancy**	**Third trimester**	**Entire pregnancy**
TTHM (μg/L) Mean (SD)	93.57 (18.14)	72.34 (37.41)	0[e]	0[e]
Chloroform (μg/L) Mean (SD)	69.21 (12.77)	55.83 (29.65)	0[e]	0[e]
Bromodichloromethane (μg/L) Mean (SD)	18.37 (1.46)	14.82 (7.37)	0[e]	0[e]
Dibromochloromethane (μg/L) Mean (SD)	1.97 (0.62)	1.59 (0.96)	0[e]	0[e]

0[e], the value below the LOD/minimal reporting limit.
[a]Data were obtained from the district water quality database. Measurements occurred 8–12 times annually (2016–2018). Missing data were imputed with hierarchical linear models.
[b]Routine water samples were collected from representative taps and tested for THMs and other water parameters.

Table 3 | Third-trimester exposure to internal levels of TTHM and THM compounds among women in the high-likely (exposed) communities in South Africa

	Exposure variable					
	Total daily uptake (μg/day)		**Total uptake via water ingestion (μg/day)**		**Via showering/bathing absorbed (μg/day)**	
Compounds	**Mean (SD)**	**Median (range)**	**Mean (SD)**	**Median (range)**	**Mean (SD)**	**Median (range)**
TTHM	38.87 (21.38)	36.21 (1.37–142.13)	0.59 (0.26)	0.60 (0.04–1.30)	36.90 (21.75)	33.89 (0–141.66)
Chloroform	31.18 (17.76)	28.37 (0.99–116.59)	0.53 (0.23)	0.55 (0.03–1.08)	29.51 (17.99)	26.66 (0–116.14)
DCBM	6.93 (3.56)	6.84 (0.35–25.54)	0.03 (0.01)	0.03 (0.00–0.06)	6.67 (3.65)	6.40 (0–25.50)
DBCM	0.75 (0.44)	0.69 (0.03–3.29)	0 (0)	0 (0)	0.73 (0.45)	0.66 (0–3.29)

Data were obtained from the district water quality database. Missing data were calculated using hierarchical linear models. *Note*: Bromoform values were below the LOD/minimal reporting limit.

The daily uptake levels of TTHMs for the entire pregnancy and third trimester of pregnancy were correlated with a correlation coefficient of 0.96, $p < 0.001$. The results for environmental area-level TTHM exposure indicated that the higher the area-level TTHM concentrations, the higher the internal dose (results not shown).

Adverse pregnancy outcomes by exposure group

Data on adverse pregnancy outcomes were collected on live births (864) only and included information on child weight, length, maternal gestational age at birth, child sex and birth rank. The prevalence of adverse pregnancy outcomes is summarized in Table 4. The proportion of female and male infants for both exposed and unexposed communities were the same (46 and 54%, respectively). The exposed and unexposed communities, respectively, had 67 (9%) and 8 (5%) premature births. Infants with SGA were 72 (10%) and 19 (11%) for exposed and unexposed communities, respectively. Babies that weighed less than 2,500 g (LBW) at birth were 69 (10%) and 14 (8%) for exposed and unexposed communities, respectively. Most SGA infants (92%) were full-term births at delivery (≥ 37 weeks of gestational age).

Association between maternal exposure of DBPs and adverse pregnancy outcomes

Tables 5 and 6 show the results for univariate and multivariate conditional logistic regression, while Table 7 only shows multivariate conditional logistic regression. The risk of premature birth associated with TTHM during the third-trimester gestation was statistically significant, with an adjusted odds ratio (AOR) of 3.13, 95% CI 1.36–7.17 and 2.40, 95% CI 1.03–5.63, for second and fourth quartiles, respectively (Table 5). Similarly, the risk for premature birth

Table 4 | Anthropometric characteristics of the livebirth's infants from the cohorts ($N = 864$)

Variables	Exposed communities ($n = 696$) *n* (%)	Unexposed communities ($n = 168$) *n* (%)
Infant sex		
Female	318 (45.69)	77 (45.83)
Male	378 (54.31)	91 (54.17)
Infant weight (in g)		
Mean; SD; range	3,136; 563.83; 1,000–5,400	3,131;493; 1,950–4,900
<2,500	69 (9.91)	14 (8.33)
2,500–2,800	137 (19.68)	19 (11.31)
2,800–3,100	153 (21.98)	58 (34.52)
3,100–3,500	190 (27.30)	44 (26.19)
>3,500	147 (21.12)	33 (19.64)
Infant length (in cm)		
Mean; SD; range	49.92; 5.97; 23–69	48.24; 5.77; 32–64
Infant circumference (in cm)		
Mean; SD; range	34.62; 3.13; 23–62	36.64; 6.32; 26–73
Gestational age at giving birth (in weeks)		
Mean; SD; range	38.23; 1.83; 27–44	39.02; 1.54; 32–42
<37	67 (9.63)	8 (4.76)
37–38	359 (51.58)	36 (21.43)
38–40	204 (29.31)	117 (69.64)
>40	66 (9.48)	7 (10.29)
Childbirth year		
2017	465 (66.81)	115 (68.45)
2018	231 (33.19)	53 (31.55)
Season of childbirth		
Autumn (March–May)	237 (34.05)	24 (14.29)
Spring (September–November)	167 (23.99)	39 (23.21)
Summer (December–February)	31 (4.45)	46 (27.38)
Winter (June–August)	261 (37.5)	59 (35.12)
Childbirth rank		
1	270 (38.79)	83 (49.40)
2	287 (41.24)	39 (23.21)
3	98 (14.08)	20 (11.90)
4	31 (4.45)	19 (11.31)
5	7 (1.01)	5 (2.98)
6	2 (0.29)	1 (0.60)
7	0	1 (0.60)
8	1 (0.14)	0

N, total number of infants in the study; *n*, number of infants born to women per study site; SD, standard deviation; %, percentages.

Table 5 | Internal levels of TTHM (log-transformed) (μg/day) uptake during the third trimester of pregnancy, odds ratios and 95% confidence intervals (CI) for the risk of preterm births, LBW and SGA among the cohort

Outcome	Cases	Non-cases	Crude OR	95% CI	Adjusted OR*	95% CI	*p*-value
Preterm births	**N = 75**						
No exposure†	8	160	Reference		Reference		
<0.972	1	47	0.43	0.1–3.4	0.43	0.05–3.56	0.432
0.972–< 1.367	27	190	2.84	1.1–5.9	3.13[a]	1.36–7.17	0.007
1.367–< 1.581	17	197	1.73	0.8–4.5	2.05	0.85–4.96	0.110
1.581 or more	22	195	2.26	1.0–5.2	2.40[a]	1.03–5.63	0.044
LBW	**N = 82**						
No exposure†	13	155	Reference		Reference		
<0.972	2	46	0.52	0.11–2.38	0.49	0.10–2.28	0.362
0.972–<1.367	22	195	1.35	0.66–2.76	1.31	0.63–2.73	0.472
1.367–<1.581	20	194	1.23	0.60–2.55	1.12	0.53–2.38	0.758
1.581 or more	25	192	1.55	0.77–3.14	1.42	0.69–2.92	0.340
SGA	**N = 91**						
No exposure†	19	149	Reference		Reference		
< 0.972	6	42	1.12	0.42–2.98	0.66	0.21–2.03	0.465
0.972–< 1.367	20	197	0.80	0.41–1.54	0.42[a]	0.19–0.97	0.042
1.367–< 1.581	19	195	0.76	0.39–1.49	0.38[a]	0.17–0.86	0.020
1.581 or more	27	190	1.11	0.60–2.08	0.55	0.25–1.19	0.129

†Reference group.

**Premature birth* estimate was adjusted for maternal age, maternal education, adverse pregnancy history (yes/no), HIV status, marital status and employment. *LBW* estimate was adjusted for maternal age, adverse pregnancy history (yes/no), HIV status, marital status, birth rank and employment. *SGA* estimate was adjusted for maternal age, marital status, birth rank, birth season, employment, passive smoking and alcohol consumption.

[a]$p < 0.05$.

associated with TTHM exposure during the entire pregnancy was statistically significant, with AOR of 2.55, 95% CI 1.09–5.96 and 2.89, 95% CI 1.25–6.68, for second and third quartiles, respectively (Table 6). Moreover, the risk of premature birth associated with chloroform exposure during the third-trimester gestation was statistically significant, with an AOR of 2.99, 95% CI 1.30–6.87 and 2.41, 95% CI 1.03–5.64, for second and fourth quartiles, respectively (Table 7). There was a slight, but not significant, increase in the risk of delivering LBW infants associated with higher internal doses of TTHM and chloroform during the third-trimester gestation and the entire pregnancy.

There was a negative risk of SGA birth associated with TTHM exposure during the third-trimester gestation, with the crude odds ratios of 0.80, 95% CI 0.41–1.54 and 0.76, 95% CI 0.39–1.49, for second and third quartiles, respectively (Table 5). Similarly, the risk of SGA birth was negatively associated with TTHM exposure over the entire pregnancy, for second and third quartiles, respectively (Table 6). There was also a negative association between the risk of SGA birth and chloroform exposure during the third trimester of pregnancy, with a *p*-value of 0.023 and 0.024, for second and third quartiles, respectively (Table 7).

DISCUSSION

In this prospective cohort study, we examined the association between maternal exposure to THMs and the risk of delivering premature, LBW and SGA infants in areas where there is a high likelihood of exposure to DBPs and in areas where exposure to DBPs is less likely. In residential areas, we noted that high concetrations of THMs were associated with higher potential internal doses of THMs

Table 6 | Internal level of TTHM (log-transformed) (μg/day) uptake during the entire pregnancy, odds ratios and 95% confidence intervals (CI) for the risk of preterm births, LBW and SGA among the cohort

Outcome	Cases	Non-cases	Crude OR	95% CI	Adjusted OR*	95% CI	*p*-value
Preterm births	**N = 75**						
No exposure†	8	160	Reference		Reference		
< 0.958	1	47	0.43	0.05–3.49	0.42	0.05–3.52	0.426
0.958–< 1.365	22	194	2.27	0.98–5.23	2.55[a]	1.09–5.96	0.031
1.365–< 1.548	25	191	2.62	1.15–5.96	2.89[a]	1.25–6.68	0.013
1.548 or more	19	197	1.93	0.82–4.52	2.20	0.92–5.22	0.075
LBW	**N = 82**						
No exposure†	13	155	Reference		Reference		
< 0.958	2	46	0.52	0.11–2.38	0.50	0.11–2.35	0.382
0.958–< 1.365	19	197	1.15	0.55–2.40	1.15	0.54–2.44	0.723
1.365–< 1.548	23	193	1.42	0.70–2.90	1.21	0.58–2.52	0.607
1.548 or more	25	191	1.56	0.77–3.15	1.50	0.73–3.08	0.273
SGA	**N = 91**						
No exposure†	19	149	Reference		Reference		
< 0.958	5	43	0.91	0.32–2.58	0.53	0.163–1.73	0.294
0.958–< 1.365	20	196	0.80	0.41–1.55	0.43	0.19–0.99	0.047
1.365–< 1.548	22	194	0.89	0.46–1.70	0.42	0.19–0.94	0.035
1.548 or more	25	191	1.03	0.54–1.93	0.51	0.23–1.12	0.093

†Reference group. *N*, total number per case.

**Premature birth* estimate was adjusted for maternal age, maternal education, adverse pregnancy history (yes/no), HIV status, marital status and employment. *LBW* estimate was adjusted for maternal age, adverse pregnancy history (yes/no), HIV status, marital status, birth rank and employment. *SGA* estimate was adjusted for maternal age, marital status, birth rank, birth season, employment, passive smoking and alcohol consumption.

[a]$p < 0.05$.

among pregnant women. The internal uptake dose of total THMs varied according to the individual water-use habits of participants. In general, internal uptake of total THM was mainly contributed via bathing and showering (95%) as compared with ingestion (5%) of chlorinated tap water. The absorption and inhalation of THMs during bathing and showering might be associated with long bathing durations. Our findings are similar to a previous study (Grazuleviciene *et al.* 2011), where uptake via showering and bathing contributed 92%, while ingestion contributed 8% to internal uptake of total THM.

Higher internal daily uptake of THMs may significantly increase the risk of premature birth, LBW and SGA. In this study, the risk of delivering a premature infant was significantly associated with total THM and chloroform exposure during the third trimester of pregnancy and the entire pregnancy. The risk of delivering an SGA baby seemed to decrease with increased exposure to total THMs and chloroform concentrations. In our study, only women living in larger metropolitan areas, where water was treated using chlorine compounds, were exposed to DBPs, whilst women living in rural areas were not exposed to DBPs at all. We found no association between maternal exposure to total THM and chloroform and the risk of delivering LBW infants. Despite previous studies reporting significant risks of LBW during entire pregnancy exposures and trimester-specific exposures to TTHM (Grazuleviciene *et al.* 2011; Danileviciute *et al.* 2012; Kumar *et al.* 2014), the lack of statistically significant effects in this study may be due to the lack of power in our sample size.

The third trimester of pregnancy plays an essential role in fetal development. Exposure measurements during this period are important in assessing any association between THM exposure and indicators of fetal growth. Hence, we

Table 7 | Internal level of chloroform (log-transformed) (μg/day) uptake during the third trimester of pregnancy, odds ratios and 95% confidence intervals (CI) for the risk of preterm births, LBW and SGA among the cohort

Outcome	Cases	Non-case	Adjusted OR*	95% CI	*p*-value
Preterm births	**N = 75**				
No exposure†	8	160	Reference		
<0.868	1	47	0.44	0.05–3.69	0.453
0.868–<1.254	26	190	2.99[a]	1.30–6.87	0.010
1.254–<1.488	18	198	2.17	0.90–5.19	0.083
1.488 or more	22	194	2.41[a]	1.03–5.64	0.043
LBW	**N = 82**				
No exposure†	13	155	Reference		
<0.868	2	46	0.51	0.11–2.37	0.390
0.868–<1.254	20	196	1.16	0.55–2.45	0.694
1.254–<1.488	21	195	1.19	0.57–2.49	0.651
1.488 or more	26	190	1.50	0.73–3.07	0.269
SGA	**N = 91**				
No exposure†	19	149	Reference		
<0.868	6	42	0.66	0.22–2.01	0.465
0.868–<1.254	18	198	0.38	0.16–0.87	0.023
1.254–<1.488	20	196	0.39	0.17–0.88	0.024
1.488 or more	28	188	0.56	0.26–1.23	0.148

†Reference group. N, total number per case.
*Premature birth estimate was adjusted for maternal age, maternal education, adverse pregnancy history (yes/no), HIV status, marital status and employment. LBW estimate was adjusted for maternal age, adverse pregnancy history (yes/no), HIV status, marital status, birth rank and employment. SGA estimate was adjusted for maternal age, marital status, birth rank, birth season, employment, passive smoking and alcohol consumption.
[a]$p < 0.05$.

analyzed internal THM uptake during the third trimester as well as for the whole pregnancy. We found that internal total THM levels during the third trimester of pregnancy and the entire pregnancy were similar ($p < 0.001$). Our analyses were also limited to chloroform as the main contributor to THM concentration.

The evidence of associations between exposure to drinking water DBPs, specifically THMs, tend to be inconsistent. Several studies have assessed exposure over the whole pregnancy, the third trimester and other times of gestation which could contribute to inconsistent results as fetal development is more sensitive to environmental influences during specific periods of pregnancy. Few studies have assessed exposure during trimester-specific periods of pregnancy (Hoffman *et al.* 2008; Villanueva *et al.* 2011; Rivera-Nunez *et al.* 2012). For instance, exposure to THMs was associated with reduced birth weight and a significantly increased risk of SGA, when exposure was measured during the third trimester of pregnancy (Cao *et al.* 2016). Previously, there was no risk of delivering LBW among women living Crete, where exposure to THMs was remarkably low (Patelarou *et al.* 2011). Other investigators found no association between THMs and premature birth (Lewis *et al.* 2007; Yang *et al.* 2007). Inconsistent risk estimates may be due to differences in study design, exposure assessment methods and exposure levels. In addition, genetic variation in metabolic enzyme gene polymorphisms influencing THM exposure across different populations may also partly contribute to inconsistent results (Danileviciute *et al.* 2012).

To our knowledge, this is the first study to assess the association between exposure to DBPs and adverse pregnancy outcomes in Sub-Saharan Africa. Our study has several strengths, including the inclusion of a group of women who were not exposed to any DBPs. We assessed

maternal exposure to drinking water THMs by including multiple exposure routes and different water-use behaviors to evaluate the internal dose levels, based on residential THM levels during pregnancy through face-to-face interviews. We were thus able to assess potential confounding variables. Our study also had certain limitations. We did not adjust for confounding variables such as residential air pollution exposure and genetic variations that could also affect adverse pregnancy outcomes (Maroziene & Grazuleviciene 2002; Danileviciute *et al.* 2012; Kogevinas *et al.* 2016). We did not measure other DBPs including HAAs and HNs in the water distribution system. We did not analyze the possible influence of brominated THMs species (i.e. bromodichloromethane and dibromochloromethane) on adverse pregnancy outcomes association, because these compounds are found in low concentrations in water systems (Grazuleviciene *et al.* 2011), and therefore not regulated. Notably, brominated species have been associated with an increased risk of LBW. For instance, the internal dose of dibromochloromethane measured over the entire pregnancy was statistically associated with an increased risk of LBW (AOR 2.52, 95% CI 1.00–6.36) (Grazuleviciene *et al.* 2011). Although other water contaminants such as nitrate and inorganic chemicals were below MCLs, their combined effects cannot be ruled out and may have confounded the results.

Lastly, the self-reported characterization of personal water-use activities may be vulnerable to bias. Therefore, other health risk factors may also contribute to adverse pregnancy outcomes. We recommend that epidemiological studies explore other robust measurements of exposure including the use of biomarkers for internal dose. Biomarkers for DBP exposure including blood THMs and urinary TCAA enhance exposure assessments (Smith *et al.* 2013; Cao *et al.* 2016).

CONCLUSIONS

Maternal exposure to THMs showed an increased risk of premature birth. We found no association between THM exposure and the risk of delivering LBW and SGA infants. The concentrations of THMs in the high-likely exposed communities in a large metropolitan area were higher than the MCLs defined in many developed countries. However, the absence of statistically significant results in this study does not determine the absence of health effects on pregnancy outcomes. Similarly, a statistical significance does not always suggest clinical importance. This study assessed any possible associations or risks and did not disprove or prove causality. These findings indicate potential risks, especially in developing countries where MCLs for THMs are higher. Further studies are needed to address this challenge by improving exposure assessments. Using biomarkers to measure THMs intake in prospective cohort studies is warranted to control exposure misclassification. Other study designs such as case-control studies should also be explored.

AUTHOR CONTRIBUTIONS

Conceptualization, F. M., E. J. N. and K. V.; methodology, F. M., E. J. N. and K. V.; software, F. M.; formal analysis, F. M.; investigation, F. M.; resources, F. M.; data curation, F. M.; writing – original draft preparation, F. M.; writing – review and editing, F. M., E. J. N. and K.V.; supervision, E. J. N. and K. V.; project administration, F.M.; all authors have read and agree to the published version of the manuscript.

FUNDING

This work was supported by the South African National Research Foundation (NRF) (Grant number SFH150625121049). The NRF did not play any role in the analyses, writing of the report, interpretation of data or decision to submit the manuscript. The views expressed in this article are those of the authors and do not reflect the views of the NRF.

CONFLICT OF INTEREST

No conflict of interest is declared.

ACKNOWLEDGEMENTS

The authors thank the Department of Health and the Department of Water and Sanitation, South Africa, for permitting us to conduct the study within their facilities. We thank all research assistants, Busisiwe, Dorothy, Lutendo and Basani for their hard work during the study. To all participants, we are eternally grateful. Appreciation is given to the University of Pretoria, Department of Library services for their contribution towards the article processing charge (APC). The manuscript has been edited by a science editor, Dr Cherl Tosh from the University of Pretoria, Faculty of Health Sciences.

DATA AVAILABILITY STATEMENT

All relevant data are included in the paper or its Supplementary Information.

REFERENCES

Backer, L. C., Ashley, D. L., Bonin, M. A., Cardinali, F. L., Kieszak, S. M. & Wooten, J. V. 2000 Household exposures to drinking water disinfection by-products: whole blood trihalomethane levels. *Journal of Exposure Analysis and Environmental Epidemiology* **10** (4), 321–326.

Barbone, F., Valent, F., Brussi, V., Tomasella, L., Triassi, M., Di Lieto, A., Scognamiglio, G., Righi, E., Fantuzzi, G., Casolari, L. & Aggazzotti, G. 2002 Assessing the exposure of pregnant women to drinking water disinfection byproducts. *Epidemiology* **13** (5), 540–544.

Botton, J., Kogevinas, M., Gracia-Lavedan, E., Patelarou, E., Roumeliotaki, T., Iñiguez, C., Santa Marina, L., Ibarluzea, J., Ballester, F. & Mendez, M. A. 2015 Postnatal weight growth and trihalomethane exposure during pregnancy. *Environmental Research* **13** (6), 280–288.

Cao, W. C., Zeng, Q., Luo, Y., Chen, H. X., Miao, D. Y., Li, L., Cheng, Y. H., Li, M., Wang, F., You, L. & Wang, Y. X. 2016 Blood biomarkers of late pregnancy exposure to trihalomethanes in drinking water and fetal growth measures and gestational age in a Chinese cohort. *Environmental Health Perspectives* **124** (4), 536–541.

Christian, M. S., York, R. G., Hoberman, A. M., Frazee, J., Fisher, L. C., Brown, W. R. & Creasy, D. M. 2002 Oral (drinking water) two-generation reproductive toxicity study of dibromoacetic acid (DBA) in rats. *International Journal of Toxicology* **21** (4), 237–276.

Danileviciute, A., Grazuleviciene, R., Vencloviene, J., Paulauskas, A. & Nieuwenhuijsen, M. J. 2012 Exposure to drinking water trihalomethanes and their association with low birth weight and small for gestational age in genetically susceptible women. *International Journal of Environmental Research and Public Health* **9** (12), 4470–4485.

Declaration of Helsinki 1997 Recommendations guiding physicians in biomedical research involving human subjects. *The Journal of the American Medical Association* **277**, 925–926.

El-Attafia, B. & Soraya, M. 2017 Presence and seasonal variation of trihalomethanes (THMs) levels in drinking tap water in Mostaganem Province in northwest Algeria. *Electronic Physician* **9** (5), 43–64.

Grazuleviciene, R., Nieuwenhuijsen, M. J., Vencloviene, J., Kostopoulou-Karadanelli, M., Krasner, S. W., Danileviciute, A., Balcius, G. & Kapustinskiene, V. 2011 Individual exposures to drinking water trihalomethanes, low birth weight and small for gestational age risk: a prospective Kaunas cohort study. *Environmental Health* **10** (1), 32.

Hinckley, A. F., Bachand, A. M. & Reif, J. S. 2005 Late pregnancy exposures to disinfection by-products and growth-related birth outcomes. *Environmental Health Perspectives* **113** (12), 1808–1813.

Hoffman, C. S., Mendola, P., Savitz, D. A., Herring, A. H., Loomis, D., Hartmann, K. E., Singer, P. C., Weinberg, H. S. & Olshan, A. F. 2008 Drinking water disinfection by-product exposure and duration of gestation. *Epidemiology* **19** (5), 738–746.

Horton, B. J., Luben, T. J., Herring, A. H., Savitz, D. A., Singer, P. C., Weinberg, H. S. & Hartmann, K. E. 2011 The effect of water disinfection by-products on pregnancy outcomes in two South Eastern US communities. *Journal of Occupational and Environmental Medicine/American College of Occupational and Environmental Medicine* **53** (10), 1172–1178.

Kaur, S., Nieuwenhuijsen, M. J., Ferrier, H. & Steer, P. 2004 Exposure of pregnant women to tap water-related activities. *Occupational and Environmental Medicine* **61** (5), 454–460.

King, W. D., Dodds, L., Armson, B. A., Allen, A. C., Fell, D. B. & Nimrod, C. 2004 Exposure assessment in epidemiologic studies of adverse pregnancy outcomes and disinfection byproducts. *Journal of Exposure Analysis and Environmental Epidemiology* **14** (6), 466–472.

Kogevinas, M., Bustamante, M., Gracia-Lavedán, E., Ballester, F., Cordier, S., Costet, N., Espinosa, A., Grazuleviciene, R., Danileviciute, A. & Ibarluzea, J. 2016 Drinking water disinfection by-products, genetic polymorphisms, and birth outcomes in a European mother-child cohort study. *Epidemiology* **27** (6), 903–911.

Kumar, S., Forand, S., Babcock, G. & Hwang, S. 2014 Total trihalomethanes in public drinking water supply and birth outcomes: a cross-sectional study. *Maternal and Child Health Journal* **18** (4), 996–1006.

Lewis, C., Suffet, I. H., Hoggatt, K. & Ritz, B. 2007 Estimated effects of disinfection by-products on preterm birth in a population served by a single water utility. *Environmental Health Perspectives* **115** (2), 290–295.

Lynberg, M., Nuckols, J. R., Langlois, P., Ashley, D., Singer, P., Mendola, P., Wilkes, C., Krapfl, H., Miles, E., Speight, V. & Lin, B. 2001 Assessing exposure to disinfection by-products in women of reproductive age living in Corpus Christi, Texas, and Cobb County, Georgia: descriptive results and methods. *Environmental Health Perspectives* **109** (6), 597–604.

Maroziene, L. & Grazuleviciene, R. 2002 Maternal exposure to low-level air pollution and pregnancy outcomes: a population-based study. *Environmental Research* **1** (1), 6.

Patelarou, E., Kargaki, S., Stephanou, E. G., Nieuwenhuijsen, M., Sourtzi, P., Gracia, E., Chatzi, L., Koutis, A. & Kogevinas, M. 2011 Exposure to brominated trihalomethanes in drinking water and reproductive outcomes. *Occupational and Environmental Medicine* **68** (6), 438–445.

Richardson, S. D., Plewa, M. J., Wagner, E. D., Schoeny, R. & DeMarini, D. M. 2007 Occurrence, genotoxicity, and carcinogenicity of regulated and emerging disinfection by-products in drinking water: a review and roadmap for research. *Mutation Research/Reviews in Mutation Research* **636** (1), 178–242.

Rivera-Nunez, Z., Wright, J. M., Blount, B. C., Silva, L. K., Jones, E., Chan, R. L., Pegram, R. A., Singer, P. C. & Savitz, D. A. 2012 Comparison of trihalomethanes in tap water and blood: a case study in the United States. *Environmental Health Perspectives* **120** (5), 661–667.

Rizzo, L., Selcuk, H., Nikolaou, A., Belgiorno, V., Bekbolet, M. & Meric, S. 2005 Formation of chlorinated organics in drinking water of Istanbul (Turkey) and Salerno (Italy). *Global NEST Journal* **7** (1), 95–105.

SANS 241-1 2015 *South African Bureau of Standards Drinking Water – Part 1: Microbiological, Physical, Aesthetic and Chemical Determinands*. SABS Standards Division, Pretoria. Available from: http://www.saba.gov.za.

Smith, R. B., Nieuwenhuijsen, M. J., Wright, J., Raynor, P., Cocker, J., Jones, K., Kostopoulou-Karadanelli, M. & Toledano, M. B. 2013 Validation of trichloroacetic acid exposure via drinking water during pregnancy using a urinary TCAA biomarker. *Environmental Research* **126**, 145–151.

South African Department of Health (SADoH) 2015 *Guidelines for Maternity*. Available from: http://www.doh.gov.za.

Statistics South Africa (StatsSA) Census 2011 Available from: http://www.statssa.gov.za.

USEPA 2011 Water: Drinking water contaminants. In: *National Primary Drinking Water Regulations*. Available from: http://water.epa.gov/.

Villanueva, C. M., Cantor, K. P., Grimalt, J. O., Malats, N., Silverman, D., Tardon, A., Garcia-Closas, R., Serra, C., Carrato, A., Castano-Vinyals, G. & Marcos, R. 2006 Bladder cancer and exposure to water disinfection by-products through ingestion, bathing, showering and swimming in pools. *American Journal of Epidemiology* **165** (2), 148–156.

Villanueva, C. M., Gracia-Lavedan, E., Ibarluzea, J., Santa Marina, L., Ballester, F., Llop, S., Tardon, A., Fernandez, M. F., Freire, C., Goni, F., Basagana, X., Kogevinas, M., Grimalt, J. O., Sunyer, J. & INMA (Infancia y Medio Ambiente) Project 2011 Exposure to trihalomethanes through different water uses and birth weight, small for gestational age, and preterm delivery in Spain. *Environmental Health Perspectives* **119** (12), 1824–1830.

World Health Organization (WHO) 2008 Training course on child growth assessment. *Geneva* **31** (3), 17–25.

World Health Organization (WHO) 2017 *Guidelines for Drinking-Water Quality*, 4th edn. Available from: http://www.who.int (accessed 26 September 2018).

Wright, J. M., Schwartz, J. & Dockery, D. W. 2004 The effect of disinfection by-products and mutagenic activity on birth weight and gestational duration. *Environmental Health Perspectives* **112** (8), 920–925.

Yang, C., Xiao, Z., Ho, S., Wu, T. & Tsai, S. 2007 Association between trihalomethane concentrations in drinking water and adverse pregnancy outcome in Taiwan. *Environmental Research* **104** (3), 390–395.

First received 5 September 2020; accepted in revised form 12 November 2020. Available online 15 December 2020