EXPOSURE TO DRINKING WATER DISINFECTION BY-PRODUCTS AND PREGNANCY HEALTH: IMPACTS ON FETAL GROWTH AND DURATION OF GESTATION

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ABSTRACT

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Exposure to drinking water disinfection by-products and pregnancy health: Impacts on fetal growth and duration of gestation

(Under the direction of Pauline Mendola, Ph.D., Andrew F. Olshan, Ph.D., and David A. Savitz. Ph.D.)

Background: Previous studies suggest that elevated exposure to disinfection by-products (DBPs) may lead to fetal growth restriction. The association between DBP exposure and preterm birth is unclear. This study examined the effects of trihalomethane (THM), haloacetic acid (HAA), and total organic halide (TOX) exposure on the probability of delivering a small-for-gestational age (SGA) infant, mean birth weight and preterm birth. *Methods:* Women were enrolled early in pregnancy (≤ 12 week's gestation) or while planning a pregnancy from three U.S. communities from 2000-2004. Weekly (or biweekly) water samples were collected and analyzed for DBPs. Participant data were collected through interviews, an early ultrasound and birth records. Associations with total THM (TTHM), the sum of five HAAs (HAA5), and TOX were assessed using log-binomial regression for SGA (*n*=1,958) and preterm birth (*n*=2,039) and linear regression for term birth weight (*n*=1,854). A Bayesian analysis was conducted to examine associations between individual DBPs and fetal growth. Discrete-time hazard analysis was used to model the conditional odds of delivery each week in relation to DBPs. *Results:* HAA5 and TOX were not consistently

associated with SGA or term birth weight. The risk ratio (95% confidence interval) associated with an average third trimester TTHM concentration above the regulatory standard (≥ 80 micrograms/liter) was 2.0 (1.1, 3.6). Results of the Bayesian model did not support a consistent association between any particular DBP and fetal growth. Conversely, average second trimester DBP levels were inversely associated with preterm birth: adjusted risk ratios (95% confidence interval) for preterm birth were 0.8 (0.5, 1.3), 0.9 (0.6, 1.4), 0.7 (0.4, 1.1) and 0.5 (0.3, 0.9) for increasing TTHM concentrations and 1.1 (0.8, 1.7), 0.8 (0.5, 1.2), 0.5 (0.3 0.8), and 0.7 (0.4, 1.1) for increasing HAA concentrations. The conditional odds of delivery each week also were decreased with elevated TTHM and HAA5 exposure for gestational weeks' 33-40. *Conclusions:* Results do not suggest an adverse effect of HAA or TOX exposure on fetal growth or an association with TTHM at average residential concentrations below the regulatory standard. In addition, results clearly indicate the probability of preterm birth is not increased with elevated DBP exposure.

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LIST OF ABBREVIATIONS

ART	Assisted reproductive technology
BAA	Bromoacetic acid
BCAA	Bromochloroacetic acid
BDCAA	Bromodichloroacetic acid
BDCM	Bromodichloromethane
CAA	Chloroacetic acid
DBAA	Dibromoacetic acid
DBCAA	Dibromochloroacetic acid
DBCM	Dibromochloromethane
DBP	Disinfection by-product
DCAA	Dichloroacetic acid
DDT	Dichloro-diphenyl-trichloroethane
DOB	Date of birth
EGA	Estimated gestational age
EPA	Environmental Protection Agency
FGR	Fetal growth restriction
HAA	Haloacetic acid
LBW	Low birth weight

LH	Luteinizing hormone
LMP	Last menstrual period
MCL	Maximum contaminant limit
MLE	Maximum likelihood estimation
PCB	Polychlorinated biphenyl
PHAH	Polyhalogenated aromatic hydrocarbons
POE	Point of entry
PPROM	Preterm premature rupture of membranes
PQL	Practical quantification limit
RFTS	Right from the Start
SDWA	Safe Drinking Water Act
SGA	Small-for-gestational-age
TBAA	Tribromoacetic acid
TCAA	Trichloroacetic acid
THM	Trihalomethane
TOX	Total organic halides
UV	Ultraviolet

CHAPTER 1: INTRODUCTION AND SPECIFIC AIMS

1.1 Introduction

Public heath concern over the potential health effects of drinking water disinfection first began in the 1970s after the discovery of chloroform and other trihalomethanes (THMs) in chlorinated drinking water [1]. While initial interest in drinking water disinfection byproduct (DBP) exposure focused on a possible association with cancer, particularly bladder, colon and rectal cancer [2-4], research that is more recent has focused attention on reproductive outcomes such as fetal growth restriction, preterm birth, stillbirth and birth defects [5-8]. Previous epidemiological studies of DBP exposure and restricted fetal growth generally have shown a moderate increased risk of delivering a small-for-gestational-age (SGA) infant among women exposed to elevated levels of total trihalomethanes (TTHM). Conversely, results of studies examining the impact of DBP exposure on preterm birth have been inconsistent and as a whole do not indicate an association between TTHM and preterm birth. Limitations in exposure and outcome assessment may in part explain the null findings of prior preterm birth studies.

The following analyses of the effects of DBP exposure on fetal growth restriction and preterm birth improve upon the methods used in previous work by utilizing weekly (or biweekly) water measures of several DBPs and incorporating information on individual water consumption and use. Data come from *Right from the Start* (RFTS), a prospective cohort study of the effect of DBP exposure on pregnancy health. As part of the RFTS,

approximately 3,000 women planning a pregnancy or newly pregnant (≤ 12 weeks' gestation) were recruited from three geographic regions of the US. Study sites were selected to provide a wide range of DBP exposure, including moderate levels of chlorinated and brominated DBPs and a low exposure site. Data collection involved two primary components: 1) collection of information about RFTS participants and their pregnancies and 2) collection of information on DBP levels in the water systems serving RFTS participants' homes during their pregnancy. Data on DBP exposure and birth outcomes (*i.e.,* birth weight, date of birth, and infant sex) were available for 2,039 RFTS participants who delivered a live infant. The purpose of this study was to estimate the effect of exposure to a variety of THM and haloacetic acid (HAA) species during pregnancy on fetal growth restriction (specific aim 1) and preterm birth (specific aim 2). For specific aim 1, logistic regression was used to estimate the effect of exposure to specific DBP measures during pregnancy on the probability of delivering an SGA infant and linear regression was used to estimate the mean difference in term birth weight in grams associated with increased DBP exposure. For specific aim 2, discrete-time hazard analysis was used to model the odds of delivery during each week conditional on a woman not having delivered in a prior week for specific intervals of pregnancy (*i.e.,* ≤ 32 weeks', 32-36 weeks', 37-40 weeks' and ≥ 41 weeks') while allowing DBP exposure to change over the course of pregnancy. Residential concentrations and personal exposure to total trihalomethanes (TTHM), the regulated sum of haloacetic acids (HAA5), and total organic halides (TOX) were the main exposures of interest for both fetal growth and duration of gestation analyses.

1.2 Specific aim 1

Specific aim 1 of this study was to estimate the effect of drinking DBP exposure during pregnancy on restricted fetal growth. As previously mentioned, elevated exposure to TTHM has been linked to a moderate increased risk of delivering a SGA infant. However, it is unknown whether TTHM itself, a constituent of TTHM (*e.g.,* BDCM), or some other unmeasured DBP for which TTHM serves as a marker is the biologically active contaminant. Toxicological data suggests that brominated THMs and HAAs are more harmful to the fetus than chlorinated THMs. However, few epidemiological studies have been published on individual THM or HAA exposure and restricted fetal growth, and results of these studies are inconsistent (see chapter 2, section 2.4 for more detail). Given the large number of women exposed to DBPs, understanding the association between this environmental exposure and restricted fetal growth is of great public health importance.

Specific aim 1 examined the associations between THM, HAA and TOX exposure and fetal growth as measured by the proportion of infants born SGA and term birth weight in grams. The following research questions were addressed:

- Are elevated residential concentrations of TTHM, HAA5 and/or TOX during pregnancy associated with increased risk of restricted fetal growth as evidenced by increased odds of delivering an SGA infant and/or a decrease in mean term birth weight?
- Is elevated personal exposure to TTHM, HAA5 and/or TOX during pregnancy associated with increased risk of restricted fetal growth as evidenced by increased odds of SGA and/or a decrease in mean term birth weight?

- Is elevated exposure to any of the individual THM and HAA species associated with increased risk of fetal growth restriction? Is there evidence to suggest that HAAs and brominated compounds show a stronger relationship with restricted fetal growth than THMs and chlorinated compounds?

Details of the analytic strategy taken to address these research questions can be found in chapter 3, section 8. Results of the analyses and conclusions are presented in manuscript #1 entitled "Drinking water disinfection by-product exposure and fetal growth" (chapter 5, section 1).

1.2 Specific aim 2

Specific aim 2 of this study was to estimate the effect of DBP exposure during pregnancy on duration of gestation. Several epidemiological studies have examined the association between exposure to TTHM during pregnancy and preterm birth (defined as gestational age < 37 weeks). As a whole, these studies do not indicate an association between TTHM and preterm birth. However, these null findings may be biased due to limitations in exposure assessment and the inability to accurately date pregnancies, both of which could potentially obscure a true association. Preliminary analyses from the RFTS, which used superior exposure assessment methods and improved pregnancy dating compared to previous studies, found a modest but consistent reduction in the probability of preterm birth in relation to elevated DBP exposure (*i.e.* an inverse effect). Analyses herein build on those previous findings to determine whether the observed protective effect is still present using alternative analytic techniques.

Specific aim 2 examined the odds of delivery each week conditional on a woman not having delivered in a prior week using discrete-time hazard analysis with time interactions for ≤ 32 weeks, 33-36 weeks, 37-40 weeks and ≥ 41. Gestational age at birth was derived from first trimester report of last menstrual period (LMP), which was corrected by ultrasound (also obtained during the first trimester) if the two estimates of gestational age differed by more than +/- 7 days. The following research questions were addressed:

- Are elevated residential concentrations of TTHM, HAA5 and/or TOX during pregnancy associated with increased odds of delivery each week during weeks 20-32, 33-36, 37-40 and/or 41-44 of gestation?
- Is elevated personal exposure to TTHM, HAA5 and/or TOX during pregnancy associated with increased odds of delivery each during weeks 20-32, 33-36, 37-40 and/or 41-44 of gestation?

Details of the analytic strategy taken to address these research questions can be found in chapter 3, section 8. Results of the analyses and conclusions are presented in manuscript #2 entitled "Drinking water disinfection by-product exposure and duration of gestation" (chapter 5, section 2). In addition, results of a methodological study conducted to compare estimation of gestational age based on first-trimester report of LMP versus first trimester ultrasound is presented in manuscript #3, entitled "Comparison of gestational age at birth based on last menstrual period and ultrasound during the first trimester" (chapter 5, section 3).

CHAPTER 2: BACKGROUND AND SIGNIFICANCE

2.1 Drinking water disinfection by-products

Public heath concern over the potential health effects of drinking water disinfection first began in the 1970s after the discovery of chloroform and other trihalomethanes (THMs) in chlorinated drinking water [1]. While initial interest in drinking water disinfection by-product (DBP) exposure focused on a possible association with cancer, particularly bladder, colon and rectal cancer [2-4], more recent research has focused attention on reproductive outcomes such as fetal growth restriction, preterm birth, stillbirth and birth defects [5-8]. A brief overview of the formation and regulation of DBPs and a discussion of factors that influence exposure during pregnancy are given below.

2.1.1 Formation of DBPs in drinking water

DBPs form when chemicals added to water for disinfection (*e.g.,* chlorine) react with organic material in the water supplying a distribution system. The formation and concentrations of byproducts in a water system are influenced by source water characteristics (*e.g.,* nature and concentration of organic material in water, temperature, pH, bromine concentration), the type of disinfectant employed (*e.g.,* chlorine alone, chloramine, chlorine dioxide, ozone or ultra-violet [UV] treatment), and the conditions under which the disinfectant is used (*e.g.,* dose and location of disinfectant addition, residual disinfectant concentrations and contact time) [9]. For example, surface water has more organic material

than ground water, resulting in higher DBP levels. Prolonged chlorine contact time generally results in higher, non-uniform THM concentrations in a system because residual chlorine continues to react with organic material in the water as it moves through the distribution system. On the contrary, haloacetic acid (HAA) concentrations generally decrease with increasing residence time within a water system due to biodegradation [10].

Chloramination (combined treatment with free chlorine and ammonia) results in decreased spatial variability and lower overall concentrations of both THM and HAA levels within a distribution system, and therefore, is considered to be a more stable disinfectant method with respect to DBP formation than chlorination alone [11]. DBPs also exhibit temporal variability. In general, higher temperatures during warm seasons (and possibly differences in the nature of organic material present in source water) increase THM levels compared to colder seasons. However, the magnitude of seasonal variation in DBP concentrations may vary from year to year, such that spring concentrations in one year could be comparable to summer concentrations in another year [12].

2.1.2 Regulations of DBPs in drinking water

Over 500 DBP subspecies have been reported in the literature [13]. THMs and HAAs are the most prevalent and routinely monitored [12]. As a result, the majority of toxicological and epidemiological research to date has focused on exposure to a few THM and HAA species [5-7]. Table 1 lists and describes DBPs regulated by the U.S. Environmental Protection Agency (US EPA) Stage 1 Disinfectants and Disinfection Byproducts Rule. Total trihalomethane (also referred to as "TTHM" or "THM4") is the sum of four THM sub-species: chloroform, bromoform, dibromochloromethane (DBDM) and

bromodichloromethane (BCDM). HAA5 is the sum of five HAA sub-species: dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), monochloroacetic acid (MCAA), bromoacetic acid (BAA) and dibromoacetic acid (DBAA).

Water systems servicing greater than 500 households are required to monitor and report levels of these DBPs on a quarterly schedule. Compliance is currently based upon a running annual average of quarterly measures for TTHM and HAA5 over all monitoring sites within a system [14]. The US Environmental Protection Agency (EPA) is now (as of April 2007) in the process of approving and implementing Stage 2 regulations that will require more stringent monitoring of currently regulated DBPs and improve analytic assessment of these contaminants. For example, stage 2 regulations will require that the running annual average DBP concentration at each monitoring site be in compliance rather than the average of all monitoring sites. This will help insure that monitoring points with high concentrations are not obscured by low concentrations at other points monitored within a water system.

Maximum contaminant level (MCL) values presented in table 1 were derived based upon cancer risk assessments and do not take into account potential adverse reproductive outcomes associated with DBP exposure. Epidemiological studies have shown associations between adverse pregnancy outcomes such as restricted fetal growth, stillbirth and birth defects at TTHM levels within the allowable limit set forth by these standards [5-7], suggesting current regulations may not fully protect against adverse pregnancy outcomes. On the other hand, many water distribution systems have already converted from using chlorination to chloramination or another disinfection method to comply with regulatory requirements. Use of these alternative disinfection methods can increase the relative proportion of highly toxic DBPs in drinking water (*e.g.,* iodated DBPs, haloacetamides, halonitromethanes) as THM

and HAA levels decrease [15,16]. Therefore, continued research of the potential adverse reproductive health effects of THM and HAA exposure is necessary to insure regulatory decision making results in adequate protection of the public health.

Table 1. Drinking water disinfection by-products currently regulated by the US EPA under the Stage 1 Disinfectants and Disinfection By-products Rule

Disinfection Byproduct	MCL[a] (µg/liter)	Individual DBPs contributing to measure
Bromate	10	
Chlorite	1000	
Haloacetic acid (HAA5)[b]	60	Dichloroacetic acid (DCAA) Trichloroacetic acid (TCAA) Monochloroacetic acid (MCAA) Bromoacetic acid (BAA) Dibromoacetic acid (DBAA)
Total Trihalomethane (TTHM)[c]	80	Chloroform Bromoform Dibromochloromethane (DBDM) Bromodichloromethane (BCDM)

a Maximum contaminant level (MCL)=highest level of contaminant allowed in drinking water; compliance based on annual system-wide running average for bromate, HAA5 and TTHM, and monthly average for chlorite; b HAA5 is the sum of five haloacetic acids; c TTHM is the sum of four trihalomethanes

2.1.3 Routes of DBP exposure

DBP exposure occurs through multiple routes. Primary sources of exposure include ingestion of contaminated water and inhalation and dermal absorption of DBPs during activities such as showering, bathing and swimming [12]. Consequently, an individual's DBP exposure depends not only on the DBP concentrations in tap water but also on water intake and use. Table 2 lists the most common uses of water by route of exposure. The relative contribution of each of these exposure sources to an individual's overall exposure varies by type of DBP.

Volatile DBPs (*e.g.,* THM) easily aerosolize and can be inhaled or absorbed through the skin. Therefore, the frequency and duration of activities such as showering and bathing, swimming, and other household chores common among pregnant women (*e.g.,* bathing children, washing dishes and clothes, boiling water) have the largest impact on personal exposure. Conversely, exposure to non-volatile DBPs (*e.g.,* HAA) mainly occurs through intake of tap water and tap-water-based beverages and foods [17]. Several factors influence DBP ingestion, including the volume of water consumed, whether water is bottled, boiled or filtered and the efficacy of filtration [18].

Table 2. List of common sources of water exposure by route of exposure

Ingestion	Dermal and Inhalation	Inhalation
Consumption of tap water directly	Washing dishes	Dishwasher
Consumption of tap water-based beverages and foods	Bathing	Boiling water/cooking
	Showering	Washing Machine
	Swimming	Humidifier

2.1.4 Exposure to tap water during pregnancy

Published estimates for the frequency and duration of personal washing (*i.e.,* showering and bathing) during pregnancy vary considerably between studies. Overall, studies indicate that pregnant women are more likely to shower (76.9-97.2%) than take baths (23-70.6%) but spend less time showering (7.8-13.9 minutes/day) than bathing (7.8-28.8 minutes/day) [19-21]. Estimates for the average daily amount of water consumed by pregnant women also varies widely between studies, ranging from 0.8-3.4 liters of tap water per week [19-24]. Differences may in part be due to differences in the study period, location and demographic make-up of study populations. For example, it has been shown that average tap-water consumption varies slightly by region of the US (highest in the south and west,

intermediate in the mid-west and lowest in the north), urbanicity (higher in rural areas compared to urban/suburban areas), race (higher among non-white, non-black women compared to white or black women) and season (highest in the summer, intermediate in the winter and lowest in the spring and autumn) [23,24]. Average self-reported tap water intake during pregnancy among *Right from the Start* (RFTS) participants ranged from 1.3-2.1 liters/day across study sites. In addition, 18% of women in the RFTS study reported bottled water as their primary water source and 30% reported using home filtration devices [18].

2.1.5 Exposure to tap water at work

Given that approximately 70% of women are employed at some point during the 12 months prior to giving birth [25], DBP exposure at work can be an important contributor to overall exposure. Distinguishing between tap-water ingestion at home and work is important because both DBP concentrations in tap water and patterns of tap-water exposure (*e.g.,* amount of water consumed, use of filtration systems) may vary between work and home. For example, 8.3% of RFTS participants reported employment at a location outside the service area of the water system serving their residences. The amount of DBP that a participant was exposed to at work may be different from her exposure level at home. In addition, RFTS participants reported consuming more cold tap-water at home than at work (1.0 liter/day versus 0.6 liter/day, respectively) but approximately the same amount of hot tap-water at both locations (0.08 and 0.07 liter/day, respectively) [26].

2.1.6 Uptake and metabolism of DBPs

Uptake of DBPs can be estimated by measuring the concentration of THMs in the blood or exhaled breath and concentration of HAAs in urine [12]. Using these biomarkers, it has been shown that the internal dose of chloroform due to inhalation and dermal absorption during a 10-minute shower or a half-hour bath is approximately equal to ingesting two liters of tap-water [27]. However, most DBP species have relatively short biological half-lives (*e.g.,* the biological half-life of chloroform in blood is approximately 30 minutes), so biologic markers only reflect recent DBP exposure [12]. Given that these markers are highly sensitive to time since last exposure, their utility in epidemiological studies interested in estimating average DBP exposure over an extended period of time, such as months or years, is less clear. Furthermore, little is known about genetic variation in metabolism of DBPs.

2.1.7 Conclusions

Potential adverse reproductive health effects of DBPs are an important public health concern given the potential widespread exposure of pregnant women to these contaminants. Current regulatory standards are based upon cancer risk assessments and may not be sufficient to protect against adverse pregnancy outcomes. An individual's DBP exposure is dependent on many factors: DBP concentrations in tap water, the uptake of DBPs by ingestion, inhalation and dermal absorption and exposure to other DBP sources, such as swimming. Furthermore, hundreds of DBPs have been identified in drinking water and it is unclear which DBP species are most harmful. Exposure assessment in research studies must be multifaceted to adequately address these aforementioned issues. The RFTS study, which included the collection of weekly (or bi-weekly) measurements of DBP concentrations in tap

water and information on individual tap-water intake and use, is an example of such a study, and thus, provides an excellent opportunity to examine the association between exposure to DBPs during pregnancy and adverse pregnancy outcomes.

2.2 Fetal growth restriction

Fetal growth restriction (FGR) describes a decrease in fetal growth rate that prevents an infant from reaching his/her growth potential at a given age. Growth-restricted fetuses are at increased risk of several perinatal complications, including increased fetal morbidity and mortality, prematurity, fetal compromise during labor, and need for induced labor or cesarean delivery [28-31]. FGR has also been linked to reduced postnatal growth, neurological and developmental disabilities in childhood [32] and several chronic adulthood diseases, such as cardiovascular disease, hypertension and diabetes mellitus [33,34]. Given the life-long adverse health impacts of FGR, prevention of this adverse pregnancy outcome is of great public health concern.

2.2.1 Prevalence of FGR

The prevalence of FGR is generally estimated to be 5% to 7% of pregnancies but can be up to 15% depending on how FGR is defined [35]. Small-for-gestational-age (SGA) is commonly used as a surrogate measure of FGR in epidemiological research studies. The overall prevalence of newborns who were SGA in the Third National Health and Nutrition Examination Survey (NHANES III) was 8.6% of all live births [36]. Infants are categorized as SGA if their birth weight falls below a certain cut-point value derived from standardized birth weight curves (*e.g.,* below the 10^{th} percentile of birth weight according to gestational

age, sex, race and parity-specific birth weight curves derived from US birth certificate data). By definition, FGR implies a pathological process resulting in reduced fetal growth but does not imply an infant will necessarily be SGA. Along those same lines, SGA infants include infants that are small due to growth restriction as well as infants who are small simply due to constitutional factors determined by maternal ethnicity, parity, weight or height. Furthermore, SGA is just one way of assessing the theoretical concept of FGR. Nonetheless, these two terms are often used interchangeably in the literature and both have been associated with increased perinatal morbidity and mortality.

2.2.2 Classification of infants as SGA

Definitions employed to classify infants as SGA vary widely in the literature. First, the percentile cut-point employed (*e.g.,* 5th percentile or 10th percentile) may differ between studies. While it is generally accepted that using a lower percentile cut-point, such as 5%, is more specific for identifying growth-restricted infants, use of lower cut-points is often prohibited by inadequate sample size. Another complication of classifying infants as SGA is that values for percentile cut points can vary up to several hundred grams depending on the geographic location and composition of the population used to derive standard curves, the source of data (hospital or population-based), how gestational age was measured, subject exclusion criteria, and whether standards are controlled for maternal race, parity, and infant sex [37]. Therefore, use of a single national standard for defining SGA has been recommended, presuming that the standard is applicable to the study population at hand [37].

In 1995, Zhang and Bowes published smoothed birth-weight-for-gestational-age curves derived from birth certificates data on the entire US population in 1989 for

combinations of race (black/white), gender (male/female), and parity (primiparous/multiparous) [38]. Gestational age was based on the date of the last menstrual period (LMP) unless the gestational age derived from LMP was < 36 weeks and birth weight for gestational age was greater than expected under the assumption of a normal birth weight distribution. Under the later scenario, the clinical estimate provided on the birth certificate was used. Zhang and Bowes noted that there were marked differences between the curves they derived and previously published curves in which the gestational age was based on ultrasound estimation [39,40]. A limitation of the Zhang et al. paper is that it does not provide birth weight curves for infants born to women of Hispanic origin, whom comprised 22% of live births in the US in 2003 [41]. Application of these standards to Hispanic infants may result in misclassification of SGA status such that the prevalence of SGA is underestimated for preterm infants and overestimated for term and post-term infants [42]. Since 1995, two standardized birth weight curves have been published for infants of Hispanic ethnicity. One of these papers failed to separate infants by parity [42]. The other focuses specifically on Mexican-American infants, and thus, is only appropriate for use in Hispanic populations that are predominately Mexican-American [43].

2.2.3 Risk factors for fetal growth restriction

Fetal growth depends on four principle variables: genetically predetermined growth potential, fetal health, maternal health, and placental function [44]. Restricted fetal growth may occur if any of the later three factors are impaired. Table 3 outlines risk factors associated with fetal growth by fetal, maternal and placental factors. Major maternal factors affecting growth include age, parity, medical conditions (*e.g.,* hypertension), malnutrition, alcohol

abuse and cigarette smoking. Fetal chromosomal abnormalities and congenital malformations are also highly associated with restricted fetal growth, as well multiple gestations and intrauterine infection. Furthermore, any "mismatch" between placental perfusion and fetal oxygenation and nutrition needs can result in growth restriction [45,46].

Table 3. Risk factors for restricted fetal growth

Fetal Factors	Maternal Factors	Placental Factors
Chromosomal abnormalities	Race/ethnicity	Abnormal trophoblastic invasion
Congenital malformations	Young maternal age	Multiple placental infarctions
Multiple gestations	Parity	Umbilical-placental vascular anomalies
Intrauterine Infection[a]	Intrauterine Infection[a]	Abnormal cord insertion
	Undernutrition	Placenta previa
	Low prepregnancy weight	Circumvallate placenta
	Low pregnancy weight gain	Chorioangiomata
	Maternal complications[b]	
	Uterine malformation or masses	
	Emotional and physical stress	
	Cigarette smoking	
	Alcohol intake	
	Illicit or therapeutic drug use	
	Previous stillbirth, spontaneous abortion, SGA infant or preterm birth	
	Family history of FGR	

Abbreviations: SGA= small-for-gestational-age, FGR=restricted fetal growth
a Intrauterine infections includes malaria, parvovirus, cytomegalovirus, rubella, toxoplasmosis, herpes virus and human immunodeficiency virus (HIV)
b Maternal complications include vascular disorders (hypertension, preeclampsia, diabetes mellitus, renal disease, collagen vascular disease), hypercoagulable states (thrombophilia, antiphospholipid antibody syndrome) and persistent hypoxia (residence in high altitude, pulmonary or cardiac disease, severe anemia)
Adapted from Brodsky and Christou (2004), Baschat (2004), and Lin and Santolaya-Forgas (1998) [35,44,47]

2.2.4 Environmental exposures and fetal growth restriction

Given that maternal toxicants such as cigarette smoking and alcohol use can contribute to the development of a growth-restricted fetus [35], it seems plausible that maternal exposure to environmental contaminants might also result in fetal growth restriction. While there are many studies that have examined the association between environmental pollutants and low birth weight, relatively few studies have specifically focused on restricted fetal growth. The major problem with studying low birth weight (LBW) alone is that it does not

distinguish between whether an infant is small because it was growth restricted or it was born preterm. Environmental exposures that have been examined in relation to fetal growth include *in utero* exposure to air pollution [48,49], polyhalogenated aromatic hydrocarbons (PHAHs) such as dichloro-diphenyl-trichloroethane (DDT) and polychlorinated biphenyls (PCBs) [50,51], pesticides [52], and DBPs [5-7]. Most of these studies have shown a null effect, report inconsistent results, or are too few in number to make any conclusions. However, epidemiological studies of DBP exposure and FGR have shown a moderate increased risk of delivering a SGA infant among women exposed to high levels of TTHM (see chapter 2, section 4.2). The RFTS study serves as an excellent opportunity to examine this association further with superior exposure assessment compared to previous studies.

2.3 Preterm birth

Preterm birth, commonly defined as birth before 37 weeks' gestational age, is associated with a number of adverse health outcomes, including physical, cognitive and psychosocial abnormalities, and is the second leading cause of perinatal mortality in the US [53,54]. The high rate of morbidity and mortality following preterm birth, along with the associated high healthcare burden and cost, make preterm birth a very important public health issue [55]. Considerable research efforts have been made to uncover the causes of preterm birth so that women at high risk of delivering preterm can be identified and early delivery can be prevented. However, few modifiable risk factors have been discovered.

2.3.1 Preterm birth proportions and trends

The overall proportion of preterm births in the US has been steadily increasing over the past two decades [41,56], although the trend varies among race/ethnicity groups. A recent report estimated that 12.3% of all live births in the US in 2003 were preterm, representing a 16% increase since 1990 (from 10.6%) and more than 30% increase since 1981 (from 9.4%). Preterm birth increased from 8.5% of live births in 1990 to 11.3% in 2003 among non-Hispanic whites (32.9% relative increase) and from 11.0% to 11.9% among Hispanics during this same time period (8.2% relative increase). Conversely, preterm birth among blacks decreased from 18.9% in 1990 to 17.8% in 2003 (5.8% relative decrease) [41]. Nonetheless, the proportion of preterm birth among non-Hispanic blacks remains considerably higher than those of other race/ethnicity groups. A possible explanation for the increase in preterm birth proportions among whites is an increase in births to older women and women receiving infertility treatment [41], as both older maternal age and assisted reproductive technology (ART) have been associated with increased risk of preterm birth [57]. The decrease in proportion of preterm birth among blacks may in part be due to improvements in prenatal care and management of other risk factors (*e.g.,* cigarette smoking) but the specific factors associated with this decrease remain unclear [58].

2.3.2 Classification of preterm birth

Preterm births can be classified into one of three separate categories according to clinical presentation: 1) idiopathic preterm labor-- labor starting without apparent reason before rupture of the membranes, resulting in preterm delivery, 2) preterm premature rupture of membranes (PPROM)-- spontaneous rupture of the membranes at any time before onset of

labor, resulting in preterm birth and 3) iatrogenic preterm birth-- medically induced preterm delivery (induced labor or cesarean section) due to complications of pregnancy (*e.g.,* fetal distress, maternal bleeding, severe preeclampsia). Some researchers have argued that these categories may represent distinct etiological pathways to preterm birth, particularly spontaneous versus iatrogenic indications, and thus should be considered separately in analyses to avoid attenuation of results due to outcome misclassification [59,60]. Others have argued that the apparent clinical presentation of preterm birth are more likely a function of varying access to medical care and have proposed other classification schemes to separate preterm births into more etiologically homogenous groups for study [61]. In reality, adequate information to classify preterm births by indication and examine groups separately is often not available (*e.g.,* in studies based on vital records).

2.3.3 Estimation of gestational age

Another methodological issue when studying preterm birth is how to most accurately estimate gestational age. Most often gestational age at delivery is calculated using the self-reported date of a woman's last menstrual period (LMP) as an estimated date of conception. However, there are many reasons why LMP may be unreliable: recall of dates may not be accurate, occurrence of post-conception bleeding may be misinterpreted as normal menses, or women with irregular menstrual cycles or delayed ovulation may not have the presumed 15-day interval between menstruation and ovulation [57,62]. An alternative method of estimating gestational age is the use of early ultrasound dating. Because there is generally little variation in fetal growth up to mid-pregnancy, knowing the size of the baby is generally equivalent to knowing the gestational age. However, this assumption may not hold in the

case of early growth restriction, which can occur due to chromosomal abnormalities, congenital malformations, infection or early onset pre-eclampsia [63]. Therefore, early ultrasound dating is often used to correct LMP assignments when the two measurements deviate substantially from each other or the LMP date deviates substantially from that expected given the birth weight of the infant.

2.3.4 Risk factors for preterm birth

Table 4 lists factors that have been associated with preterm birth, including demographic characteristics, other maternal factors and exposures, aspects of the current pregnancy and prior pregnancy history. The strongest predictor of preterm birth is a history of delivering a previous low birth weight or preterm infant [64]. Other common factors that have been consistently associated with a considerable increase in the risk of preterm birth are black race, single marital status, low socio-economic status as measured through education, occupation and family income, inadequate prenatal care, maternal cigarette smoking, use of ART, multiple gestations, gestational bleeding, and cervical and uterine anomalies.

Table 4. Risk factors for preterm birth

Maternal demographics	Other maternal factors/ exposures	Pregnancy history	
		Current	Prior
Black race	Cervical/uterine anomalies	Conceived with ART	Previous LBW/preterm delivery
Single marital status	In utero DES exposure	Multiple gestations	Multi 2nd trimester miscarriages
Low SES status	Cigarette smoking	Placental abnormalities	Parity
Younger or older maternal age	Cocaine use	Gestational bleeding	
	Poor nutrition	Urogenital infection	
	High stress	Inadequate prenatal care	
	Alcohol intake	Conception during summer/fall	
	High caffeine intake	Male infant	
	Low pre-pregnancy weight	Maternal complications[a]	
		Fetal complications[b]	
		Low weight gain	

Abbreviations: SES= socioeconomic status, DES= diethylstilbestrol, ART= assisted reproductive technology, LBW = low birth weight; a Maternal complications include placenta previa, abruptio placentae, cervical incompetence, hypertensive disorders, diabetes, asthma, epilepsy, and hyperthyroidism; b Fetal complications include congenital malformations and growth restriction; Table adapted from Berkowitz and Papiernik (1993) [57]

Several studies have suggested seasonal variation in the occurrence of preterm birth [57]. For example, an analysis using vital records data from Minnesota between 1967-1973 found the proportion of pregnancies delivered preterm during late summer and fall (59 per 1,000 births) was slightly higher than the proportion of pregnancies delivered preterm spring months (55 per 1,000 births) [65]. Similar seasonal patterns were found in the Collaborative Perinatal Project [66] and a study conducted in Japan between 1979-1983 [67]. The seasonal trend in preterm birth may in part be explained by seasonal changes in the rate of maternal infection and maternal nutritional status. Another explanation may be seasonal variation in maternal exposure to environmental toxicants [57].

2.3.5 Environmental exposures and preterm birth

Several studies have been conducted to examine the association between exposure to air pollution and preterm birth. Collectively, these studies suggest a moderate association between ambient levels of particulate matter ≤ 10 micrometers (PM_{10}) and sulfur dioxide

(SO_2) and preterm birth [48,68-71]. Increased risk of preterm birth has also been associated with exposure to environmental tobacco smoke [72] and DDT [50]. Studies examining the effect of DBP exposure during pregnancy and adverse pregnancy outcomes to date do not indicate an association between TTHM and preterm birth; however, these studies may be biased by poor exposure and outcome assessment (see chapter 2, section 4.2). The RFTS study serves as an excellent opportunity to examine this association further using superior exposure assessment compared to previous studies.

2.4 Exposure to DBPs in drinking water and adverse pregnancy outcomes

Over the past decade, many animal and human studies have been published indicating an association between DBP exposure and several adverse pregnancy outcomes such as LBW, FGR, birth defects and stillbirth [5-7]. The mechanism by which DBP exposure may lead to these adverse pregnancy outcomes is not well understood [7]. Rather, it is evidence from *in vitro* and animal research and a few key epidemiological research studies implicating DBPs as reproductive toxicants that have fostered continued interest in the research area. Furthermore, there appears to be some consistency across the adverse pregnancy outcomes that have been associated with DBP exposure. For example, birth defects and fetal growth restriction are both risk factors for stillbirth [73-75], and all three of these outcomes have been linked with DBP exposure. The following section summarizes toxicological and epidemiological research on this topic.

2.4.1 Toxicological research

Toxicological studies of the potential adverse effects of DBPs on reproduction have examined a wide range of outcomes in animals, including developmental disability, structural congenital malformations, growth retardation and fetal loss [7]. Reductions in body weight and pregnancy loss have been the most consistently found adverse effects of exposure. Chlorinated THMs (*e.g.,* chloroform) have generally shown no direct evidence of teratogenicity. However, toxicological data do suggest that brominated THM and HAA exposure may be harmful to the fetus. For example, studies have found an increase in fetal resorption (*i.e.,* fetal loss) in rats after exposure to BDCM [76-78], which may be mediated through alteration of luteinizing hormone (LH) levels [79]. Studies of HAA exposure have also found associations between DCAA and TCAA and craniofacial and cardiovascular malformations [80-82]. More recently, *in vitro* studies have shown that BDCM may inhibit human placental trophoblast differentiation [83,84]. As previously mentioned, abnormal trophoblast invasion may lead to reduced fetal growth.

2.4.2 Epidemiological research

Exposure assessment is arguably the most difficult aspect of studying the effect of DBP exposure on human health and is clearly the greatest limitation of epidemiological studies conducted to date. The following sections discuss the design, results and limitations of epidemiological studies that have examined the association between THM and HAA exposure and reduced birth weight, SGA and/or preterm birth. Although fetal growth restriction and preterm birth are the primary focus of this dissertation, previous studies of DBP exposure on birth weight are also relevant for review given that both fetal growth

restriction and preterm birth result in reduced birth weight. Sections are divided by exposure assessment method and study outcome.

Studies using type of water treatment as an exposure index

Table 5 lists human studies that are based on the comparison of water treatment methods as a surrogate measure of DBP exposure [85-88]. These studies looked at a wide range of outcomes, including preterm birth (<37 weeks gestational age), very preterm birth (<32 weeks gestational age), low birth weight (<2,500 grams), very low birth weight (<1,500 grams) and SGA. Study populations consisted of births that occurred in the late 1980s through the mid-1990s from several different countries. All but one study identified births from birth registries, and all studies ascertained exposure by linking maternal address obtained from birth records with information on the type of water treatment employed by the utility plant servicing her residence. Adjustment for covariates was similar across studies and included maternal age, education, smoking and alcohol intake, infant sex, year of birth, and urbanicity of residence. Collectively, these studies do not indicate a strong association between type of water treatment and adverse live birth outcomes. However, exposure assessment in these studies has several limitations:

- Use of a contextual ecological variable to characterize DBP exposure, like type of water treatment, does not take spatial and temporal variation in DBP concentrations into consideration and provides little information on the types and concentrations of DBPs that may be present.

- Pregnant women often work and/or change residences during pregnancy, so water treatment status determined by maternal residence at birth may not be representative of exposure over the entire pregnancy.
- Modification of exposure through individual variation in uptake of DBPs through the three routes of exposure (consumption, inhalation and dermal absorption) or use of private wells were not considered.

These limitations likely resulted in exposure misclassification and attenuation of the estimated effect. Therefore, it is difficult to make any conclusions about the association between THM and HAA exposure and adverse pregnancy outcomes in the context of these studies.

Studies using routinely collected DBP measurements

Tables 6, 7 and 8 summarize studies that have examined the association between birth weight, SGA, and preterm birth, respectively, using routinely collected DBP measurements [89-101]. Many of these studies looked at more than one birth outcome, and therefore appear in more than one table. For the convenience of the reader, basic study characteristics are repeated in each table. Study results are discussed separately by outcome.

Study characteristics

A total of 13 studies have been conducted to date in the United States (Iowa, New Jersey, North Carolina, Denver, Massachusetts, Arizona and Maryland), Canada (Novia-Scotia and Montreal) and the United Kingdom. The majority of studies employed a

population-based cohort or case-control design in which births were identified from birth records or local hospitals. For exposure estimation, maternal residence at the time of birth was linked with municipal water DBP measurements, which generally provided quarterly estimates of monitored DBP concentrations in the systems serving women's residences. Because routine collection of HAAs did not begin until the late 1990s, early studies were only able to examine the association between THM exposures (most often TTHM) and birth outcomes.

A little over half of the studies attempted to estimate pregnancy window-specific exposure, either focusing solely on third trimester exposure or calculating exposure for multiple windows (*e.g.,* first, second and third trimesters). In addition, several of the more recent studies incorporated various regression modeling techniques to estimate monthly residential DBP concentrations. Only two studies incorporated information on individual water use to estimate personal DBP exposure: Savitz et al. (1995) combined residential DBP concentrations with self-reported consumption of water to estimate "THM dose" [92], and Infante-Rivard (2004) combined information on both maternal water consumption and showering to estimate personal exposure [94]. Adjustment covariates were similar across studies.

Results for birth weight

Previous studies have examined the effect of DBP exposure on birth weight using several birth weight measures, including mean change in birth weight in grams, the probability of a low birth weight infant (< 2,500 grams) and the probability of a very low birth weight infant (<1,500 grams) (table 6). In general, these studies show a moderate yet

consistent decrease in continuous birth weight (-1 to -70 grams) with increasing exposure to TTHM. Only one study examined the association between birth weight in grams and individual THM species (*e.g.,* chloroform and BDCM); the decrease in birth weight associated with exposure was similar across THM measures [89]. No association between HAA exposure and birth weight in grams was indicated in the one study that looked at this association [89]. In addition, the association between low birth weight and very low birth and TTHM exposure was much less consistent across studies than the association with a continuous measure of birth weight in grams.

Results for SGA

Of the birth outcomes studied to date, studies of the reproductive health effects of DBPs provide the greatest support for increased risk of SGA associated with higher exposure (table 7). Reported relative risk estimates in the literature range from 1.0-1.5 for residential TTHM exposure, depending on how categories of TTHM exposure were defined. Of note, studies that have examined exposure to individual THM species (*e.g.,* BDCM) have been much less consistent, and overall do not implicate any particular component of TTHM as responsible for the observed association found with the aggregate THM measure [89,93-95,101]. Results for HAA exposure are also inconsistent, although two out of three studies did find an increased probability of delivering an SGA infant with increased residential HAA5 concentrations, perhaps being driven by DCAA and TCAA concentrations [89,95,101].

Results for preterm birth

Previous studies examining the association between TTHM and preterm birth have generally indicated no association, with estimated relative risks for preterm birth ranging between 0.7-1.2 and showing no notable dose-response trends (table 8). To date, two studies have examined the association between preterm birth and individual TTHM components and both suggest no effects [89,93]. Only one previous study by Wright et al. (2004) has examined the association between HAA exposure and preterm birth and that study did not find an association [89]. Conversely, a moderate yet consistent inverse association between THM residential water concentrations and preterm birth was found in preliminary analyses of the RFTS study and in a recent study by Lewis et al. (2007)[100].

Strengths and limitations of previous studies

Previous studies have several strengths. First, most studies were population-based. Collectively, the studies cover a wide range of geographic locations and demographic characteristics. Second, most studies are large, with several studies involving more than 50,000 births. However, there are also many limitations to previous studies. Most studies relied on birth record data to obtain information on birth outcomes and covariates. US birth certificate data is believed to provide poor information on gestational age among births dated < 37 weeks [102] and underreport exposures such as cigarette smoking and alcohol intake during pregnancy [103], which likely resulted in misclassification of preterm birth and residual confounding by smoking and alcohol use. Furthermore, despite the large overall sample size of most studies, the number of cases in the highest categories of DBP exposure often was still

low, leading to unstable effect estimates. Finally, studies had several limitations with respect to exposure assessment:

- Variation in individual DBP uptake through ingestion, inhalation and dermal absorption, use of bottled water and treatment of water before consumption (filtering or boiling water) was not taken into account in most studies. In the studies that did estimate personal exposure, information on changes in water intake and use over pregnancy was not used.
- Exposure to DBPs at work was not taken into account
- Exposure assessment was limited to DBP species that are routinely measured (TTHM).
- Exposure window-specific estimates (*e.g.,* 1^{st}, 2^{nd} 3^{rd} trimester exposure) could not be estimated for some studies.

Each of these limitations likely contributed to substantial error in exposure assessment and could have biased study results either to or away from the null. Clearly, further research that addresses the limitations outlined above is warranted.

The RFTS study improved upon previous studies in several ways. First, concentrations of several THM and HAA species were collected prospectively, including some HAA species that are not routinely monitored. In addition, weekly (or bi-weekly) DBP measurements were taken to capture the temporal variability in DBP concentrations and allow estimation of window-specific exposures, and pregnant women were prospectively followed, allowing collection of individual-level data during a baseline interview, follow-up

interview at 20 weeks gestation and medical record abstraction. Finally, detailed information on water consumption and use during the perinatal period was collected.

Table 5. Summary of epidemiological studies using contextual surrogates of disinfection by-product exposure and adverse live birth outcomes[a]

Author (year)	Study location	Study Population	Outcome (n)	Exposure Assessment	Adjustment Covariates	Main Results [OR(95% CI)]
Kanitz et al. (1996)	Genoa and Chiavarti, Italy	Deliveries at two local hospitals between 1988 and 1989 (N=676)	PTB (50) LBW (20)	Maternal residence used to ascertain type of water source (Chlorine dioxide, hypochlorite or both treatments *vs.* no treatment)	Maternal age, education, smoking and alcohol intake Sex of infant	Chlorine dioxide *vs.* none Na-hypochlorite *vs.* none Both *vs.* none *PTB* 1.8 (0.7,4.7) 1.1 (0.3,3.7) 1.8 (0.6,5.0) *LBW* 5.9 (0.8,14.9) 6.0 (0.6,12.6) 6.6 (0.9,14.6)
Kallen and Robert (2000)	Sweden	Registered births occurring between 1985 and 1994 in municipalities for which disinfection method remained the same over relevant exposure time (N= 74324)	EPTB[b] PTB[b] VLBW[b] LBW[b] SGA[b]	Maternal residence used to ascertain type of water source (Chlorine dioxide, hypochlorite or both treatments *vs.* no treatment)	Maternal age, parity, education and smoking Year of birth County of residence	Chlorine dioxide *vs.* none Na-hypochlorite *vs.* none *EPTB* 0.95 (0.75,1.09) 1.22 (1.00,1.48) *PTB* 0.96 (0.88,1.04) 1.09 (1.01,1.17) *VLBW* 0.84 (0.65,1.09) 1.11 (0.90,1.36) *LBW* 0.93 (0.84,1.03) 1.15 (1.05,1.26) *SGA* 0.95 (0.84,1.07) 1.07 (0.96,1.19)

Jaakkola et al. (2001)	Norway	Registered births between 1993-1995 (N=137145)	PTB (7886) LBW (6249) SGA [b]	Maternal residence used to ascertain disinfection status (chlorinated vs. non-chlorinated) and organic content (low color vs. high color) of water source	Maternal age and parity Place of birth Urbanicity of municipality	No CL,high *vs.* No CL,Low CL,low *vs.* No CL,Low CL,high *vs.* No CL,low *PTB* 0.92 (0.83,1.03) 0.95 (0.88,1.03) 0.91 (0.84,0.99) *LBW* 1.02 (0.91,1.14) 0.99 (0.90,1.09) 0.97 (0.89,1.06) *SGA* 1.02 (0.89,1.14) 1.00 (0.91,1.11) 1.00 (0.91,1.10)
Yang (2004)	Taiwan	Registered births in 310 municipalities between 1994 and 1996 (N= 182796)	PTB (8251) LBW (8225)	Maternal residence used to ascertain disinfection status (chlorinated vs. non-chlorinated) of water source	Maternal age, marital status and education Sex of infant Urbanicity of Municipality	CL vs. No CL *PTB* 1.05 (0.94,1.18) *LBW* 1.37 (1.20,1.56)

[*]All studies are cross-sectional in design, [b] Missing (n) value indicates the number of cases was not specified in article,Abbreviations: PTB= preterm birth (infants < 37 weeks gestational age at birth), EPTB = early preterm birth (infants < 32 weeks gestational age at birth), LBW = low birth weight (Infants weighing <2,500 grams at birth), VLBW = very low birth weight (Infants weighing <1,500 grams at birth), SGA= Small for gestational age, OR = Odds Ratio, 95% CI= 95 percent Confidence Interval, CL = chlorine

Table 6. Summary of epidemiological studies examining the association between THM exposure and birth weight

Author (year)	Study details	THM Exposure Assessment	Adjustment Covariates	Mean Δ in Birth weight (grams) (95% CI)	LBW[a] or VLBW OR (95% CI)
Kramer et al. (1992)	*Design:* Population-based case-control *Location:* Iowa, USA *Population:* All low birth weight cases delivered between 1989 and 1990 identified from vital records along with five normal weight controls *Sample Size:* 159 preterm births and 795 term births	Maternal residence at time of birth was linked with municipal water THM measurements for 1987 Measurements available for chloroform, bromoform, BDCM, DBCM and TTHM Non-specific time window of exposure	Maternal age, parity, martial status, education and smoking during pregnancy Adequacy of prenatal care	--	Chloroform: 1-9, ≥10 μ/liter vs. ND 1.1 (0.7, 1.6), 1.3 (0.8,2.2) BDCM: 1-9, 10 μ/liter vs. ND 1.0 (0.5, 1.9), 1.1 (0.7,1.5) DBCM: 1-3, 4 μ/liter vs. ND 0.7 (0.5, 1.1), 0.8 (0.4,1.4) Bromoform: Detectable vs. ND 0.9 (0.6,1.5)
Bove et al. (1995)	*Design:* Population-based cohort *Location:* New Jersey, USA *Population:* All live births and fetal deaths identified from vital records that were delivered in 1 of 75 NJ towns between 1985 and 1988 *Sample Size:* 1853 LBW infants, 905 VLBW infants and 52334 live, normal weight and gestational age comparison births	Maternal residence at time of birth was linked with municipal water TTHM measurements for 1984-1988 Monthly estimates were averaged over entire pregnancy period	Maternal age, race, education, parity, history of stillbirth or miscarriage Sex of infant Adequacy of prenatal care A-280 contaminants[b]	TTHM: 20-40, 40-60, 60-80, 80-100, >100 ppb vs. ND 34.8 (58.2,11.4)[c] -51.2 (-38.6,-63.8)[c] -26.6 (-11.9,-41.3)[c] -54.9 (-33.0,-76.8)[c] -70.4 (-23.8,-117.0)[c]	TTHM: >100 ppb vs. ND 1.42 (1.22,1.65)[d]

Savitz et al. (1995)	*Design:* Population-based case-control *Location:* North Carolina, USA *Population:* Low birth weight cases identified from local hospitals between 1988 and 1989 in 2 NC counties and 1988 to 1991 in a third county; controls selected from term, normal weight births immediately following preterm birth matched to cases on race and hospital *Sample Size:* 178 LBW infants and 333 controls	Maternal residence at time of birth was linked with municipal THM measurements THM measure nearest to the 28th week of pregnancy was used to assign residential THM level Also estimated "THM dose" by combining self-reported data on maternal water consumption and residential THM levels: THM dose = (ppb X glasses/day)	Maternal age, race, education, marital status, poverty level, smoking, alcohol consumption and employment Delivery hospital	--	THM: 63.4-82.7, 82.8-168.8 vs. 40.8-63.3 ppb 1.5 (1.0,2.3), 1.3 (0.8,2.1) Per 50 ppb change in THM 0.9 (0.6, 1.4) THM dose: 170.0-330.8, 330.9-1171.0 vs. 44.0-169.9 units 1.0 (0.6,1.5), 0.8 (0.5,1.3) Per 250 unit change in THM dose 1.0 (0.8, 1.2)
Gallagher et al. (1998)	*Design:* population-based cohort *Location:* Denver, CO, USA *Population:* Births between 1990 and 1993 to mothers residing in census blocks served by one of two water systems identified from vital records *Sample Size:* 1244 total births, including 72 LBW infants and 29 term LBW infants	Maternal residence at time of birth was linked with municipal THM measurements for 1990-1993 Residential TTHM levels estimated using hydraulic modeling Focused analyses on third trimester exposure	Maternal smoking, age, parity, education, marital status, employment during pregnancy	--	TTHM: 21-40, 41-60, ≥ 61 vs. 40.8-63.3 ppb *LBW* 1 (0.6,1.8) 0.8 (0.3,1.7) 2.1 (1.0,4.8) *Term LBW* 1.3 (0.5,3.3) 1.2 (0.4,4.0) 5.9 (2.0,17.0)

Dodds et al. (1999)	*Design:* Population-based cohort *Location:* Nova Scotia, Canada *Population:* All live born and stillborn infants >500 gm born between 1988 and 1995 identified from nation-wide perinatal and fetal anomaly databases *Sample Size:* 50755 total births, including 2392 LBW infants and 342 VLBW	Maternal residence at time of birth was linked with municipal THM measurements between 1987 and 1995 Third trimester TTHM exposure was estimated from linear regression model including terms for year, month and facility	Maternal age, parity, smoking, attendance at perinatal classes Neighborhood family income Sex of infant	--	TTHM: 50-74, 75-99, >100 vs. 40.8-63.3 µ/liter *LBW* 1.07 (0.97,1.19) 1.11 (0.97,1.26) 1.04 (0.92,1.18) *VLBW* 1.03 (0.80,1.33) 0.93 (0.65,1.32) 0.89 (0.64,1.23)
Wright, Schwartz and Dockery (2003)	*Design:* Population-based Cross-sectional *Location:* Massachusetts, USA *Population:* Births to women residing in communities that routinely monitored THMs in 1990 identified from birth records and hospital worksheets *Sample Size:* 56513 total births, including 1325 term LBW infants	Maternal residence at time of birth was linked with municipal TTHM measurements; City-specific aggregate TTHM concentrations where used to assign TTHM exposure Examined 1st, 2nd and 3rd trimester and pregnancy average exposure	Maternal age, race, education, parity, smoking, household income, pregnancy history, medical history Gestational age Sex of infant Adequacy of prenatal care	1st trimester TTHM: 60-80, >80 vs. 0-60 µ/liter -4 (-18, 9), -17 (-31,-3) 2nd trimester TTHM: 60-80, >80 vs. 0-60 µ/liter -5 (-19, 9), -23 (-36,-10) 3rd trimester TTHM: 60-80, >80 vs. 0-60 µ/liter -9 (-22, 4), -11 (-24, 2) Pregnancy average TTHM: 60-80, >80 vs. 0-60 µ/liter -1 (-12, 11), -32 (-47, -18)	1st trimester TTHM: 60-80, >80 vs. 0-60 µ/liter 1.13 (0.93,1.38), 0.98 (0.79,1.21) 2nd trimester TTHM: 60-80, >80 vs. 0-60 µ/liter 0.93 (0.75,1.15), 1.14 (0.95,1.38) 3rd trimester TTHM: 60-80, >80 vs. 0-60 µ/liter 1.08 (0.90,1.31), 1.09 (0.91,1.31) Pregnancy average TTHM: 60-80, >80 vs. 0-60 µ/liter 0.97 (0.81, 1.26), 1.05 (0.85, 1.29)

Wright, Schwartz and Dockery (2004)	*Design:* Population-based cohort *Location:* Massachusetts, USA *Population:* Births to women residing in towns with population >10,000 between 1995 and 1998 identified from birth records (109 towns included in THM analyses and 17 towns included in HAA analyses) *Sample Size:* 196000 total births	Maternal residence at time of birth was linked with municipal THM (TTHM, chloroform and BDCM) and HAA (HAA5, trichloroacetic acid, dichloroacetic acid) measurements City-specific aggregate DBP concentrations where used to assign third trimester DBP exposure	Maternal age, race, education, parity, smoking, household income, pregnancy history, medical history Gestational age Sex of infant Adequacy of prenatal care	TTHM: 33-74, 74-163 vs. 0-33 µ/liter -12 (-16,-7), -18 (-26,-10) Chloroform: 26-63, 63-135 vs. 0-26 µ/liter -14 (-19,-9), -18 (-26,-10) BDCM: 5-13, 13-46 vs. 0-5 µ/liter -12 (-17,-8), -12 (-2,-3) HAA: 30-49, 49-58 vs. 4-30 µ/liter 25 (9, 40), 7 (-25, 39) TCAA: 18-27, 27-37 vs. 0-18µ/liter 21 (9, 40), -4 (-35, 27) DCAA: 15-22, 22-24 vs. 2-15µ/liter 15 (-4, 34), 12 (-14, 38)	--
Toledano et al. (2005)	*Design:* Population-based cohort *Location:* United Kingdom *Population:* Births identified from birth registry born to women residing in area served by one of three water companies over specific periods for which water zone boundary information was available: 1997 for Northumbrian, 1992-1997 for United Utilities, 1993-1998 for Severn Trent *Sample Size:* 481255 total live births, including 30572 LBW and 4686 VLBW infants	Maternal residence at birth was linked with water zone data Quarterly, zone-specific TTHM levels were estimated using Bayesian modeling with terms for year, month and facility Estimated exposure for last 93 days of pregnancy (*i.e.,* third trimester for full term infants)	Maternal age Sex of infant Socioeconomic deprivation (measured at small-area level)	--	TTHM: 30-59, ≥60 vs. <30 µ/liter *LBW* 1.05 (0.96,1.15) 1.09 (0.93,1.27) *VLBW* 1.03 (0.96,1.10) 1.05 (0.82,1.34)

Hinckley et al. (2005)	*Design:* Population-based cohort *Location:* Arizona, USA *Population:* All live births and fetal deaths for women whose residence was provided water by one of three facilities from 1998-2002 identified from birth records *Sample Size:* 48119 total births, including 1010 LBW infants and 564 VLBW infants	Maternal residence at birth was linked with utility data by zip Code Quarterly THM and HAA5 measurements were available for 1998-2002 and supplemented with monthly and biweekly measures for some facilities in 2001and 2002 (HAA data only available prior to 2000 for one facility) Monthly DBP levels were imputed when missing using spline regression Third trimester exposure and window-specific exposure (25-28, 29-32, 33-36, 37-40 and 41-44 weeks) was estimated	Maternal age, race, ethnicity, education, parity and smoking Adequacy of prenatal care (Kessner Index)	--	TTHM: 40-53, ≥ 53 vs. ≤ 40 µ/liter 1.06 (0.89, 1.25), 1.11 (0.94, 1.31) Chloroform: 10-16, ≥ 16 vs. ≤ 10 µ/liter 1.18 (1.00, 1.39), 1.04 (0.88, 1.23) BDCM: 13-18, ≥ 18 vs. ≤ 13 µ/liter 1.05 (0.89, 1.24), 1.04 (0.88, 1.23) DBCM: 12-16, ≥ 16 vs. ≤ 12 µ/liter 1.0 (0.84, 1.18), 1.05 (0.89, 1.24) HAA5: 15-19, ≥ 19 vs. ≤ 15 µ/liter 1.26 (0.96, 1.65), 1.25 (0.96, 1.64) DBAA: 4-5, ≥ 5 vs. ≤ 4 µ/liter 1.01 (0.72, 1.41), 1.49 (1.09, 2.04) DCAA: 6-8, ≥ 8 vs. ≤ 6 µ/liter 1.04 (0.75, 1.43), 1.1 (0.80, 1.50) TCAA 4-6, ≥ 6 vs. ≤ 4 µ/liter 0.94 (0.68, 1.30), 1.0 (0.73, 1.37)

Lewis, Suffet and Ritz (2006)	*Design:* Population-based cohort *Location:* Massachusetts, USA *Population:* Births to women residing in 27 communities between August 1991 and December 2001 identified from birth records *Sample Size: 36,529* total term births, including 780 TLBW infants	Maternal residence at time of birth was linked with weekly municipal TTHM measurements; Examined 1st, 2nd and 3rd trimester and pregnancy average exposure Assessed OR-modification by maternal race/ethnicity (Caucasian *vs*. Non-Caucasian)	Maternal age, race/ethnicity, education, marital status, parity, smoking, household income, pregnancy history, medical history Gestational age Sex of infant Adequacy of prenatal care Season of conception Birth season TTHM exposure level in previous trimester	--	1st trimester TTHM: 40-50, 50-60, 60-70, >70 vs. <40 µ/liter 0.82 (0.66,1.03), 0.84 (0.66,1.08), 0.88 (0.66,1.17), 0.87 (0.89,1.04) 2nd trimester TTHM: 40-50, 50-60, 60-70, >70 vs. <40 µ/liter 1.10 (0.81,1.49), 1.08 (0.79,1.49), 1.24 (0.92,1.67), 1.50 (1.07,2.10) 3rd trimester TTHM: 40-50, 50-60, 60-70, >70 vs. <40 µ/liter 0.87 (0.60,1.26), 0.79 (0.56,1.12), 0.84 (0.58,1.21), 0.74 (0.44,1.22) Pregnancy average TTHM: 40-50, 50-60, 60-70, >70 vs. <40 µ/liter 1.07 (0.81,1.42), 0.95 (0.75,1.20), 1.23 (0.92,1.64), N/A

a "A-280 contaminants" are contaminants monitored by the New Jersey Bureau of Safe Drinking Water, including trichloroethylene, tetrachloroethylene, total dichloroethylenes, 1,1,1-trichloroethane, carbon tetrachloride, 1,2-dihcloroethane, and benzene Low birth weight among all births unless otherwise specified;
b Analysis restricted to term birth and 99% Confidence Interval presented
c 50% confidence interval
Abbreviations: Δ= change, LBW= Low birth weight, VLBW= Very low birth weight, THM= Trihalomethane, BDCM = Dichlorobromomethane, DBCM= Dibromochloromethane, TTHM= Total trihalomethane, HAA5 = Haloacetic acid 5 (sum of CAA, DCAA, TCAA, BAA and DBAA), CAA = monochloroacetic acid, DCAA= dichloroacetic acid, TCAA= trichloroacetic acid, BAA= monobromoacetic acid, DBAA= dibromoacetic acid, OR= Odds ratio, 95% CI= 95 percent Confidence Interval, ND= non-detectable, N/A = not available

Table 7. Summary of epidemiological studies examining the association between THM exposure and SGA infant

Author (year)	Study details	THM Exposure Assessment	Adjustment Covariates	Main results (OR [95% CI])
Kramer et al. (1992)	*Design:* Population-based case-control *Location:* Iowa, USA *Population:* All low birth weight cases delivered between 1989 and 1990 identified from vital records along with five normal weight controls *Sample Size:* 187 SGA infants and 795 non-SGA controls	Maternal residence at time of birth was linked with municipal water THM measurements for 1987 Measurements available for chloroform, bromoform, BDCM, DBCM and TTHM Non-specific exposure window	Maternal age, parity, martial status, education and smoking during pregnancy Adequacy of prenatal care	Chloroform: 1-9, ≥ 10 μ/liter vs. ND 1.3 (0.9, 1.8), 1.8 (1.1,2.9 BDCM: 1-9, 10 μ/liter vs. ND 1.2 (0.8, 1.7), 1.7 (0.9,2.9) DBCM: 1-3, 4 μ/liter vs. ND 1.0 (0.7, 1.5), 0.9 (0.1,8.6) Bromoform: Detectable vs. ND 1.1 (0.7,1.6)
Bove et al. (1995)	*Design:* Population-based cohort *Location:* New Jersey, USA *Population:* All live births and fetal deaths identified from vital records that were delivered in 1 of 75 NJ towns between 1985 and 1988 *Sample Size:* 4082 SGA infants and 52334 live, normal weight and gestational age births	Maternal residence at time of birth was linked with municipal water TTHM measurements for 1984-1988 Monthly estimates were averaged over entire pregnancy period	Maternal age, race, education, parity, history of stillbirth or miscarriage Sex of infant Adequacy of prenatal care A-280 contaminants	TTHM: 20-40, 40-60, 60-80, 80-100, >100 ppb vs. ND 0.98 (0.79,1.20)[c] 1.33 (1.20,1.47)[c] 1.11 (0.98,1.25)[c] 1.22 (1.02,1.45)[c] 1.5 (1.04,2.09)[c]
Dodds et al. (1999)	*Design:* Population-based cohort *Location:* Nova Scotia, Canada *Population:* All live born and stillborn infants >500 gm born between 1988 and 1995 identified from nation-wide perinatal and fetal anomaly databases *Sample Size:* 50755 total births, including 4673 SGA infants	Maternal residence at time of birth was linked with municipal THM measurements between 1987 and 1995 Third trimester TTHM exposure was estimated from linear regression model including terms for year, month and facility	Maternal age, parity, smoking, attendance at perinatal classes Neighborhood family income Sex of infant	TTHM: 50-74, 75-99, >100 vs. 40.8-63.3 μ/liter 1.04 (0.97,1.11) 1.01 (0.92,1.11) 1.08 (0.99,1.18)

Wright, Schwartz and Dockery (2003)	*Design:* Population-based Cross-sectional *Location:* Massachusetts, USA *Population:* Births to women residing in communities that routinely monitored THMs in 1990 identified from birth records and hospital worksheets *Sample Size:* 56513 total births, including 5310 term LBW infants	Maternal residence at time of birth was linked with municipal TTHM measurements City-specific aggregate TTHM concentrations where used to assign TTHM exposure First, second and third trimester and pregnancy average exposure were considered	Maternal age, race, education, parity, smoking, household income, pregnancy history, medical history Gestational age Sex of infant Adequacy of prenatal care	1st trimester TTHM: 60-80, >80 vs. 0-60 µ/liter 1.00 (0.89,1.10), 1.09 (0.98,1.21) 2nd trimester TTHM: 60-80, >80 vs. 0-60 µ/liter 0.99 (0.89,1.10), 1.13 (1.03,1.14) 3rd trimester TTHM: 60-80, >80 vs. 0-60 µ/liter 0.98 (0.89, 1.09), 1.03 (0.94, 1.14) Pregnancy average TTHM: 60-80, >80 vs. 0-60 µ/liter 1.00 (0.92,1.09), 1.14 (1.02,1.26)
Wright, Schwartz and Dockery (2004)	*Design:* Population-based cohort *Location:* Massachusetts, USA *Population:* Births to women residing in towns with population >10,000 between 1995 and 1998 identified from birth records (109 towns included in THM analyses and 17 towns included in HAA analyses) *Sample Size:* 196000 total births, including 17359 term SGA infants	Maternal residence at time of birth was linked with municipal THM (TTHM, chloroform and BDCM) and HAA (HAA5, trichloroacetic acid, dichloroacetic acid) measurements City-specific aggregate DBP concentrations where used to assign third trimester DBP exposure	Maternal age, race, education, parity, smoking, household income, pregnancy history, medical history Gestational age Sex of infant Adequacy of prenatal care	TTHM: 33-74, 74-163 vs. 0-33 µ/liter 1.06 (1.02,1.10), 1.13 (1.07,1.20) Chloroform: 26-63, 63-135 vs. 0-26 µ/liter 1.05 (1.02,1.09), 1.11 (1.04,1.17) BDCM: 5-13, 13-46 vs. 0-5 µ/liter 1.1 (1.07,1.14), 1.15 (1.08,1.22) HAA: 30-49, 49-58 vs. 4-30 µ/liter 0.9 (0.81,1.01), 0.97 (0.77,1.23) TCAA: 18-27, 27-37 vs. 0-18 µ/liter 0.87 (0.76,0.99), 0.95 (0.76,1.19) DCAA: 15-22, 22-24 vs. 2-15 µ/liter 0.86 (0.75,0.99), 0.9 (0.75,1.09)

Infante-Rivard (2004)	*Design:* Hospital-based case-control *Location*: Montreal, Canada *Population:* Cases and controls were recruited from one hospital between 1998 and 2000, and matched on gestational week, sex, race and date of birth (usually within 1 week window) *Sample Size:* 493 SGA cases and 472 non-SGA controls	Maternal residence during each trimester of pregnancy was linked with municipal THM (chloroform, bromoform, BDCM, DBCM, TTHM) measurements Residential THM concentrations were combined with self-reported data on maternal consumption and showering to estimate average personal exposure over the course of pregnancy	Maternal race, weight gain during pregnancy, pre-pregnancy BMI, parity, pregnancy history, parity, smoking during pregnancy Sex of infant Gestational age	Chloroform: >23.7 vs. ≤23.7 μ/liter 1.06 (0.63,1.79) Bromoform: >1.22 vs. ≤ 1.22 μ/liter 2.44 (0.19,31.10) BDCM: >6.3 vs. ≤6.3 μ/liter 0.84 (0.50,1.43) DBCM: >3.9 vs. ≤3.9 μ/liter 0.62 (0.27,1.44) TTHM: >29.4 vs. ≤ 29.4 μ/liter 0.97 (0.57,1.62)

Porter et al. (2005)[b]	*Design:* Population-based cohort *Location:* Maryland county; USA *Population:* Births identified from birth records born to mothers whose resided in zip codes corresponding to a water utility's point measurements (four sampling points total) between 1998 to 2002 *Sample Size:* 1114 SGA births and 14201 non-SGA births	Maternal residence at birth was linked with utility company water data; monthly measurements were available for TTHM (bromoform, chloroform, BDCM, DBCM, TTHM) between 1997-2002 and HAA5 (CAA, DCAA, TCAA, BAA, DBAA, HAA5) between 1999-2002 Trimester-specific and pregnancy average DBP exposure was estimated	Maternal age, weight gain, marital status, tobacco use, alcohol use, region of residence Child's race/ethnicity Adequacy of prenatal care	THM: 2^{nd}, 3^{rd}, 4^{th}, 5^{th} vs. 1st quintile 1.18 (0.97,1.44), 1.2 (0.99,1.46), 1.05 (0.86,1.26), 1.17 (0.96,1.24) Chloroform: 2^{nd}, 3^{rd}, 4^{th}, 5^{th} vs. 1st quintile 1.02 (0.84,1.24), 0.96 (0.79,1.16), 0.98 (0.81,1.19), 1.07 (0.88,1.29) Bromoform: 2^{nd}, 3^{rd}, 4^{th}, 5^{th} vs. 1st quintile 1.14 (0.94,1.38), 1 (0.82,1.23), 1.2 (0.99,1.46), 1.01 (0.83,1.23) DBCM: 2^{nd}, 3^{rd}, 4^{th}, 5^{th} vs. 1st quintile 0.95 (0.79,1.15), 0.84 (0.69,1.02), 0.92 (0.76,1.12), 0.9 (0.74,1.09) BDCM: 2^{nd}, 3^{rd}, 4^{th}, 5^{th} vs. 1st quintile 0.92 (0.76,1.12), 1.04 (0.86,1.25), 0.92 (0.76,1.12), 0.98 (0.81,1.19) HAA5: 2^{nd}, 3^{rd}, 4^{th}, 5^{th} vs. 1st quintile 1.29 (1.01,1.66), 1.41 (1.11,1.814), 1.15 (0.89,1.49), 1.34 (1.04,1.71) CAA: 2^{nd}, 3^{rd}, 4^{th}, 5^{th} vs. 1st quintile 0.83 (0.65,1.06), 0.94 (0.75,1.19), 0.95 (0.75,1.20), 1 (0.79,1.26) DCAA: 2^{nd}, 3^{rd}, 4^{th}, 5^{th} vs. 1st quintile 1.14 (0.89,1.46), 1.29 (1.02,1.64), 1.06 (0.83,1.37), 1.27 (0.99,1.61) TCAA: 2^{nd}, 3^{rd}, 4^{th}, 5^{th} vs. 1st quintile 1.3 (1.01,1.65), 1.34 (1.05,1.71), 1.21 (0.94,1.55), 1.2 (0.94,1.54) BAA: 2^{nd}, 3^{rd}, 4^{th}, 5^{th} vs. 1st quintile 0.87 (0.68,1.10), 0.97 (0.77,1.23), 0.95 (0.75,1.21), 1.07 (0.85,1.35) DBAA: 2^{nd}, 3^{rd}, 4^{th}, 5^{th} vs. 1st quintile 0.87 (0.68,1.11), 0.99 (0.78,1.26), 1.1 (0.87,1.39), 1.05 (0.83,1.33)

Hinckley et al. (2005)	*Design:* Population-based cohort *Location:* Arizona, USA *Population:* All live births and fetal deaths for women whose residence was provided water by one of three facilities from 1998-2002 identified from birth records *Sample Size:* 48119 total births, including 4346 SGA infants	Maternal residence at birth was linked with utility data by zip Code Quarterly THM and HAA5 measurements were available for 1998-2002 and supplemented with monthly and biweekly measures for some facilities in 2001and 2002 (HAA data only available prior to 2000 for one facility) Monthly DBP levels were imputed when missing using spline regression Third trimester exposure and window-specific exposure (25-28, 29-32, 33-36, 37-40 and 41-44 weeks) were estimated	Maternal age, race, ethnicity, education, parity and smoking Adequacy of prenatal care (Kessner Index)	TTHM: 40-53, ≥ 53 vs. ≤ 40 µ/liter 0.98 (0.90, 1.07), 1.09 (1.00, 1.18) Chloroform: 10-16, ≥ 16 vs. ≤ 10 µ/liter 1.02 (0.94, 1.11), 1.01 (0.93, 1.10) BDCM: 13-18, ≥ 18 vs. ≤ 13 µ/liter 0.93 (0.85, 1.01), 1.03 (0.95, 1.12) DBCM: 12-16, ≥ 16 vs. ≤ 12 µ/liter 0.96 (0.89, 1.05), 1.01 (0.94, 1.10) HAA5: 15-19, ≥ 19 vs. ≤ 15 µ/liter 1.00 (0.87, 1.15), 1.08 (0.94, 1.23) DBAA: 4-5, ≥ 5 vs. ≤ 4 µ/liter 1.04 (0.88, 1.23), 1.12 (0.95, 1.32) DCAA: 6-8, ≥ 8 vs. ≤ 6 µ/liter 1.15 (0.97, 1.36), 1.28 (1.08, 1.51) TCAA 4-6, ≥ 6 vs. ≤ 4 µ/liter 1 (0.84, 1.18), 1.19 (1.01, 1.41)

[*] 99% Confidence Interval, [b]Quintile cut-points were not reported, main results presented for third trimester exposure

Abbreviations: LBW= Low birth weight, VLBW= Very low birth weight, THM= Trihalomethane, BDCM = Dichlorobromomethane, DBCM= Dibromochloromethane, TTHM= Total trihalomethane, HAA5 = Haloacetic acid 5 (sum of CAA, DCAA, TCAA, BAA and DBAA), CAA = monochloroacetic acid, DCAA= dichloroacetic acid, TCAA= trichloroacetic acid, BAA= monobromoacetic acid, DBAA= dibromoacetic acid, OR= Odds ratio, 95% CI= 95 percent Confidence Interval

Table 8. Summary of epidemiological studies examining the association between THM exposure and preterm birth

Author (year)	Study details	THM Exposure Assessment	Adjustment Covariates	Main Results [OR(95% CI)]
Kramer et al. (1992)	*Design:* Population-based case-control *Location:* Iowa, USA *Population:* All preterm birth cases delivered between 1989 and 1990 identified from vital records along with five term birth controls *Sample Size:* 342 preterm births and 1710 term births	Maternal residence at time of birth was linked with municipal water THM measurements for 1987 Measurements available for chloroform, bromoform, BDCM, DBCM and TTHM Non-specific time window of exposure	Maternal age, parity, martial status, education and smoking during pregnancy Adequacy of prenatal care	Chloroform: 1-9, ≥ 10 µ/liter vs. ND 1.1 (0.8,1.4), 1.1 (0.7, 1.6) BDCM: 1-9, ≥ 10 µ/liter vs. ND 1.1 (0.9,1.5), 1.0 (0.6, 1.5) DBCM: 1-3, ≥ 4 µ/liter vs. ND 1.1 (0.7, 1.4), undefined-no cases Bromoform: Detectable vs. ND 1.1 (0.8,1.4)
Bove et al. (1995)	*Design:* Population-based cohort *Location:* New Jersey, USA *Population:* All live births and fetal deaths identified from vital records that were delivered in 1 of 75 NJ towns between 1985 and 1988 *Sample Size:* 7167 preterm births and 52334 live, normal weight and gestational age comparison births	Maternal residence at time of birth was linked with municipal water TTHM measurements for 1984-1988 Monthly estimates were averaged over entire pregnancy period	Maternal age, race, education, parity, history of stillbirth or miscarriage Sex of infant Adequacy of prenatal care A-280 contaminants	Exact values were not specified but can infer all OR estimates < 1.5 because only estimated ORs ≥ 1.5 were reported in tables and no THM-preterm birth results were presented.
Savitz et al. (1995)	*Design:* Population-based case-control *Location:* North Carolina, USA *Population:* Preterm birth cases identified from local hospitals between 1988 and 1989 in 2 NC counties and 1988 to 1991 in a third county; controls selected from term, normal weight births immediately following preterm birth matched to cases on race and hospital *Sample Size:* 244 preterm births and 333 controls	Maternal residence at time of birth was linked with municipal THM measurements THM measure nearest to the 28th week of pregnancy was used to assign residential THM level Also estimated "THM dose" by combining self-reported data on maternal water consumption and residential THM levels: THM dose = (ppb X glasses/day)	Maternal age, race, education, marital status, poverty level, smoking, alcohol consumption and employment Delivery hospital	THM: 63.4-82.7, 82.8-168.8 vs. 40.8-63.3 ppb 1.2 (0.8,1.8), 0.9 (0.6,1.5) Per 50 ppb change in THM 0.8 (0.6, 1.2) THM dose: 170.0-330.8, 330.9-1171.0 vs. 44.0-169.9 units 1.2 (0.8,1.7), 0.9 (0.6,1.3) Per 250 unit change in THM dose 0.9 (0.8-1.1)

Gallagher et al. (1998)	*Design:* population-based cohort *Location:* Denver, CO, USA *Population:* Births between 1990 and 1993 to mothers residing in census blocks served by one of two water systems identified from vital records *Sample Size:* 1244 total births, including 68 preterm births	Maternal residence at time of birth was linked with municipal THM measurements for 1990-1993 Residential TTHM levels estimated using hydraulic modeling Focused analyses on third trimester exposure	Maternal smoking, age, parity, education, marital status, employment during pregnancy	TTHM: 21-40, 41-60, $\geq$ 61 vs. 40.8-63.3 ppb 1.0 (0.6,1.7), 0.7 (0.3,1.6), 1.0 (0.3,2.8)
Dodds et al. (1999)	*Design:* Population-based cohort *Location:* Nova Scotia, Canada *Population:* All live born and stillborn infants >500 gm born between 1988 and 1995 identified from nation-wide perinatal and fetal anomaly databases *Sample Size:* 50755 total births, including 2689 preterm births	Maternal residence at time of birth was linked with municipal THM measurements between 1987 and 1995 Third trimester TTHM exposure was estimated from linear regression model including terms for year, month and facility	Maternal age, parity, smoking, attendance at perinatal classes Neighborhood family income Sex of infant	TTHM: 50-74, 75-99, >100 vs. 40.8-63.3 μ/liter 0.96 (0.88,1.06), 0.99 (0.88,1.12), 0.97 (0.87,1.09)
Wright, Schwartz and Dockery (2003)	*Design:* Population-based Cross-sectional *Location:* Massachusetts, USA *Population:* Births to women residing in communities that routinely monitored THMs in 1990 identified from birth records and hospital worksheets *Sample Size:* 56513 total births, including 3173 preterm births	Maternal residence at time of birth was linked with municipal TTHM measurements City-specific aggregate TTHM concentrations where used to assign TTHM exposure First, second and third trimester and pregnancy average exposure were considered	Maternal age, race, education, parity, smoking, household income, pregnancy history, medical history Gestational age Sex of infant Adequacy of prenatal care	1st trimester TTHM: 60-80, >80 vs. 0-60 μ/liter 0.96 (0.84,1.10), 1.01 (0.88,1.16) 2nd trimester TTHM: 60-80, >80 vs. 0-60 μ/liter 1.02 (0.89,1.16), 0.9 (0.79,1.03) 3rd trimester TTHM: 60-80, >80 vs. 0-60 μ/liter 0.99 (0.87, 1.13), 0.97 (0.85, 1.11) Pregnancy average TTHM: 60-80, >80 vs. 0-60 μ/liter 1.00 (0.89,1.12), 0.9 (0.77,1.04)

Wright, Schwartz and Dockery (2004)	*Design:* Population-based cohort *Location:* Massachusetts, USA *Population:* Births to women residing in towns with population >10,000 between 1995 and 1998 identified from birth records (109 towns included in THM analyses and 17 towns included in HAA analyses) *Sample Size:* 196000 total births, including 11580 preterm births	Maternal residence at time of birth was linked with municipal THM (TTHM, chloroform and BDCM) and HAA (HAA5, trichloroacetic acid, dichloroacetic acid) measurements City-specific aggregate DBP concentrations where used to assign third trimester DBP exposure	Maternal age, race, education, parity, smoking, household income, pregnancy history, medical history Gestational age Sex of infant Adequacy of prenatal care	TTHM: 33-74, 74-163 vs. 0-33 μ/liter 0.95 (0.91,0.99), 0.88 (0.81,0.94) Chloroform: 26-63, 63-135 vs. 0-26 μ/liter 0.95 (0.91,0.99), 0.9 (0.84,0.97) BDCM: 5-13, 13-46 vs. 0-5 μ/liter 0.89 (0.85,0.93), 0.92 (0.85,0.99) HAA: 30-49, 49-58 vs. 4-30 μ/liter 0.95 (0.83,1.10), 1.03 (0.77,1.39) TCAA: 18-27, 27-31 vs. 0-18 μ/liter 0.91 (0.77,1.07), 1.07 (0.81,1.42) DCAA: 15-22, 22-24 vs. 2-15 μ/liter 0.85 (0.71,1.01), 0.99 (0.79,1.23)
Lewis, Suffet and Ritz (2007)	*Design:* Population-based cohort *Location:* Massachusetts, USA *Population:* Births to women residing in 27 communities between August 1991 and December 2001 identified from birth records *Sample Size:* 37,498 total births, including 2,813 preterm infants	Maternal residence at time of birth was linked with weekly municipal TTHM measurements; Examined 1st, 2nd and 3rd trimester and pregnancy average exposure Assessed OR-modification by maternal race/ethnicity (Caucasian *vs*. Non-Caucasian)	Maternal age, race/ethnicity, education, marital status, parity, smoking, household income, pregnancy history, medical history Gestational age Sex of infant Adequacy of prenatal care Season of conception Birth season TTHM exposure level in previous trimester	1st trimester TTHM: 40-<60, ≥ 60 *vs*.<40 μ/liter 1.02 (0.92,1.13), 1.00 (0.88,1.14) 2nd trimester TTHM: 40-<60, ≥ 60 *vs*.<40 μ/liter 0.87 (0.77,1.99), 0.82 (0.71,0.94) 3rd trimester TTHM: 40-<60, ≥ 60 *vs*.<40 μ/liter 1.00 (0.87,1.15), 1.13 (0.95,1.35) Pregnancy average TTHM: 40-<60, ≥ 60 *vs*.<40 μ/liter 0.92 (0.81,1.02), 0.85 (0.74,0.97)

Abbreviations: THM= Trihalomethane, BDCM = Dichlorobromomethane, DBCM= Dibromochloromethane, TTHM= Total trihalomethane, HAA = Haloacetic acid, OR= Odds ratio, 95% CI= 95 percent Confidence Interval

2.5 Public health significance

Public health interest in the potential adverse health effects due to water DBP exposure is a legitimate concern. Several recent studies have indicated an increased risk of fetal growth restriction among pregnant women exposed to high levels of DBPs. Limitations in exposure assessment may in part explain the inconsistent findings of studies of birth weight and null findings of preterm birth studies. Given the long-term consequences of fetal growth restriction and preterm birth and the fact that most pregnant women are exposed to some amount of DBPs during pregnancy, even a small effect of exposure could have a substantial impact on a population level. Further examination of this association with improved DBP exposure estimation is clearly needed. This proposed analysis of DBP exposure, fetal growth restriction and preterm birth improves upon the methods used in previous work by utilizing weekly (or biweekly) water measures of several DBPs and incorporating information on individual water consumption and use. The author expected to find a stronger estimated effect of DBP exposure (presuming a causal association) than in previous studies given these improvements in exposure assessment.

CHAPTER 3: MATERIAL AND METHODS

3.1 Overview

This study involved analyses of data collected from Phase I of *Right from the Start* (RFTS), a community-based prospective cohort study conducted from 2000-2004 to examine the effect of drinking water disinfection by-product (DBP) exposure on pregnancy health. As part of the RFTS study, women trying to conceive or newly pregnant (≤ 12 weeks' gestation) were recruited from three geographic locations in the US selected to provide a broad exposure range: moderate levels of predominately chlorinated DBPs (hereafter referred to as the "chlorinated DBP site"), moderate levels of predominately brominated DBPs (the "brominated DBP site"), and low levels of all DBPs (the "low DBP site"). In addition, moderate DBP sites were selected because they used chloramination for terminal disinfection rather than free chlorine to insure that spatial variability in DBP concentrations within a site would be minimal.

Approximately 3,000 women were enrolled across all study sites. Data collection involved two primary components: 1) collection of information about RFTS participants and their pregnancy obtained through interviews, an early pregnancy ultrasound, medical record abstraction and vital records matching, and 2) collection of information on DBP levels in the water systems serving RFTS participants' homes during their pregnancy obtained through weekly (or biweekly) sampling of water systems and testing for concentrations of trihalomethanes (THMs), haloacetic acids (HAAs) and total organic halide (TOX).

Information on infant date of birth, birth weight and sex was obtained by medical record abstraction, vital records matching and self-report for 2,039 RFTS participants who delivered a live infant.

The purpose of this study was to estimate the effect of exposure to a variety of THM and HAA species during pregnancy on fetal growth restriction (specific aim 1) and preterm birth (specific aim 2). To address specific aim 1, logistic regression was used to estimate the effect of exposure to specific DBP measures during pregnancy on the probability of delivering an SGA infant and linear regression was used to estimate the mean difference in term birth weight in grams associated with increased DBP exposure. To address specific aim 2, discrete-time hazard analysis was used to model the odds of delivery during each week conditional on a woman not having delivered in a prior week for specific intervals of pregnancy (*i.e.,* $\leq$ 32 weeks', 32-36 weeks', 37-40 weeks', $\geq$ 41 weeks') while allowing DBP exposure to change over the course of pregnancy. The associations with residential concentrations and personal exposure to total trihalomethane (TTHM), the sum of the regulated haloacetic acids (HAA5), and TOX were examined using traditional maximum likelihood estimation (MLE). In addition, Bayesian methods were used to examine the associations between fetal growth outcomes and individual THMs and HAAs, which are highly correlated.

The following sections give a detailed description of participant recruitment, enrollment and follow-up in the RFTS study as well as RFTS data collection methods. In addition, methods for outcome assessment, exposure assessment and data analyses are outlined.

3.2 Selection of RFTS study sites

The three geographic locations studied for RFTS were chosen based upon attributes of the water systems serving the area. The chlorinated DBP site had moderate levels of predominantly chlorinated THMs and HAAs in the water (*e.g.,* chloroform, dichloroacetic acid [DCAA], and trichloroacetic acid [TCAA]). The brominated DBP site had similar total THM and HAA concentrations but speciation was dominated by brominated by-products due to the relatively high concentrations of bromide in the source water (*e.g.,* bromodichloromethane [BDCM], dibromochloromethane [DBCM], bromoacetic acid [BAA], and dibromoacetic acid [DBAA]). The low DBP site had relatively low overall DBP concentrations because source water for the water system comes from deep wells with low organic material concentration. An additional consideration for the two moderate DBP sites (*i.e.,* the chlorinated and brominated DBP sites) was that they used chloramination as a terminal disinfectant, which minimizes spatial variation in DBP concentrations, to facilitate the characterization of THM and HAA exposure. The low DBP site used free chlorine but spatial variation was not a concern because of low DBP levels overall [26].

3.3 Study population

3.3.1 Recruitment and enrollment

As part of the RFTS study, pregnant women ≤ 12 weeks' gestation in pregnancy and women trying to become pregnant were recruited from private and public prenatal care venues, the community at large (*e.g.,* via informational posters and brochures posted in drug stores, bookstores, childcare facilities, coffee shops, fitness centers, retail stores, grocery stores, libraries, beauty salons, worksites, and churches; advertisements placed in

community, worksite, and church publications) and by targeted mailings sent to new home owners and women who had delivered a child within the past three years. Overall, the majority of participants (62%) were enrolled from private and public obstetric practices; however, the relative success of recruitment sources varied by site (*e.g.,* approximately 70% of subjects were recruited from prenatal care practices in the chlorinated and low DBP sites versus only 26% in the brominated DBP site).

Women interested in participating in the study were identified by RFTS staff in different ways. Most commonly, interested women phoned RFTS using the study's advertised 1-800-telephone number. In addition, some prenatal clinics collected contact information for interested subjects and faxed it to the RFTS study office, or forwarded patient calls directly to the study office if women were interested in learning more about the study. Once identified, women were screened over the phone to determine their eligibility to participate. Eligibility criteria were as follows:

- Less than or at 12 weeks' gestation in pregnancy with a positive pregnancy test, or trying to conceive but had not been trying for more than 6 months. (These women were pre-enrolled and followed for a maximum of 6 months).
- Maternal age ≥ 18 years if already pregnant or age 18 to 45 if trying to conceive.
- Residence in the geographic study area served by city water and no intention to move out of the area prior to delivery.
- No assisted reproductive technology used to conceive.
- Intention to carry pregnancy to term.
- Ability to speak, read, and write English or Spanish.

Table 9 gives the enrollment period and water sampling period for each study site. Of note, enrollment and water sampling began much earlier in the chlorinated DBP site than the other study sites. Recruitment at the brominated and low DBP sites was delayed for several reasons. First, a functional protocol was developed at the chlorinated DBP site before attempting to scale up to multiple sites. Additional delays incurred in the process of setting up subcontracts and in obtaining the needed Institutional Review Board (IRB) approvals. Finally, recruitment had to be delayed at brominated DBP site to accommodate the expansion of the water distribution system serving this study site.

Table 9. Enrollment and water sampling time frames

Site	Enrollment period	Length of recruitment period (years)	Water sampling period
Chlorinated	12/2000–2/29/2004	3.3	10/10/2000–2/29/2004
Low	6/2002–3/31/2004	1.8	7/30/2001–8/1/2004
Brominated	9/2002–4/30/2004	1.7	6/3/2002–9/5/2004

Adapted from Savitz et al. (2005) AWWARF report

3.3.2 Participant follow-up

The following sections outline RFTS participant attrition from screening through those eligible for the proposed analyses. Follow-up is first discussed separately for participant interviews and collection of birth outcome information. Then analysis-specific exclusions are given to produce the final sample size for each set of analyses. Finally, select characteristics of women enrolled in the RFTS study are compared to characteristics of both the general population of women giving birth in the three study sites and characteristics of RFTS participants eligible to be included in analyses.

Participant interviews

Figure 1 is a flow chart outlining study participation from screening through follow-up interview. A total of 4,066 women were screened for inclusion. Of those, 3,125 women (2,514 pregnant and 611 trying to conceive at screening) met the inclusion criteria listed above and were enrolled or pre-enrolled into the study. Study participants who were pregnant at screening or converted to pregnant within 6 months after pre-enrollment (252 women were formally enrolled after conceiving) were eligible to complete a baseline interview. Of those eligible women, 2,418 (87%) completed the full baseline interview. An additional 89 (3%) women completed the modified baseline interview (administered to women who reported a pregnancy loss at the beginning of the baseline interview). Women who completed the full baseline interview were re-contacted later in pregnancy to participate in a follow-up interview. Of these women, 2,066 (85%) completed the full follow-up interview and 196 (8%) completed the modified follow-up interview (administered to women who reported a loss).

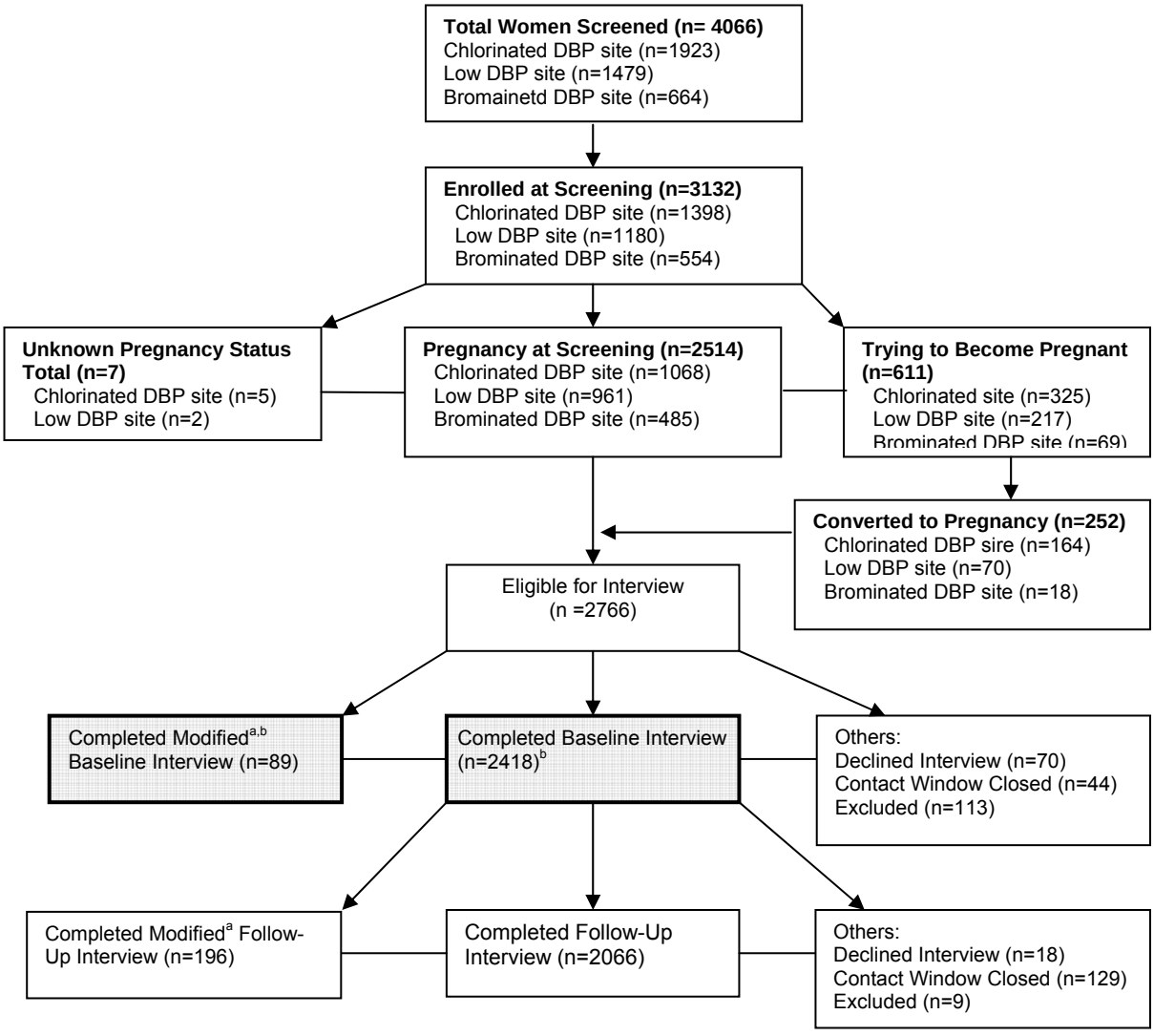
Women were excluded from the study after initial enrollment primarily because they did not become pregnant within 6 months of trying to conceive (n=359). Other participants were excluded because their estimated gestational age at enrollment based on ultrasound was >12 weeks, study staff were unable to reach the participant by telephone for >7 weeks, or the participant moved out of the study area. Participants withdrew from the study for a variety of reasons including not wanting to have the study ultrasound, concerns about their pregnancy or having had a pregnancy loss, lack of time and other life events, or their partner's concern about their participation in the study. Some women also decided that the questions asked in the interview were too personal. Table 10 shows exclusions and dropouts by site.

Table 10. Withdrawals and exclusions by Study Site

n(%)	All Sites (n=3125)	Chlorinated (n=1393)	Low (n=1178)	Brominated (n=554)
Excluded	499 (16.0)	204 (14.6)	209 (17.7)	86 (15.5)
Withdrew	85 (2.7)	38 (2.7)	35 (3.0)	12 (2.2)

Adapted from Savitz et al. (2005) AWWARF report

Figure 1. Flow-chart of study participation in the RFTS study



a Modified interviews are completed by participants who reported a pregnancy loss
b A total of 2,507 women completed the full or modified baseline interview
Figure adapted from Savitz et al. (2005) AWWARF report

Collection of birth outcome information

Table 11 summarizes documented pregnancy outcomes of women who completed the full or modified baseline interview (*n*=2,507) shown in the highlighted boxes of figure 1. Among these women, 347 (13.8%) had pregnancies that ended in a loss (*i.e.,* spontaneous abortions, induced abortions, stillbirth, or ectopic, tubal or molar pregnancies) and 2,070 (82.6%) had pregnancies that ended in a live birth. The outcome status of 90 pregnancies (3.6%) could not be determined because medical records for the participant could not be located or were not released to RFTS study staff, the participant could not be matched with vital records and RFTS staff were not able to re-contact the participant by mail or phone to inquire about the pregnancy outcome directly from the participant.

Table 11. Pregnancy outcome for women completing baseline interview by study site

n (%)	All Sites	Site 1	Site 2	Site 3
Spontaneous Abortion[a]	306 (12.2)	143 (12.4)	100 (10.9)	63 (14.5)
Induced Abortion	19 (0.8)	9 (0.9)	5 (0.5)	5 (1.2)
Stillbirth[b]	12 (0.5)	7 (0.6)	4 (0.4)	1 (0.2)
Ectopic, tubal or molar pregnancy	10 (0.4)	1 (0.1)	5 (0.5)	4 (0.9)
Live birth	2070 (82.6)	947 (82.3)	768 (83.5)	355 (81.4)
Missing	90 (3.6)	44 (3.8)	38 (4.1)	8 (1.8)

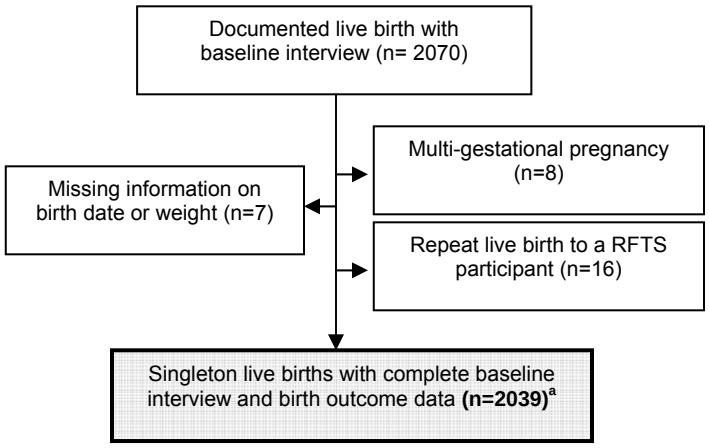
[a] defined as pregnancy loss at <20 weeks gestation; b defined as pregnancy loss at ≥20 weeks gestation
Adapted from Savitz et al. (2005) AWWARF report

Other exclusions

Figures 2, 3, and 4 outline specific exclusions made for the duration of gestation analyses (specific aim 2, presented in manuscript #2), fetal growth analyses (specific aim 1, presented in manuscript #1), and gestational age comparison analysis (presented in manuscript #3), respectfully. For fetal growth and duration of gestation analyses, pregnancies were excluded if missing information on infant's date of birth (DOB) or birth weight (*n*=7), reducing the sample to 2,063 (99.7% of 2,070 documented live births with

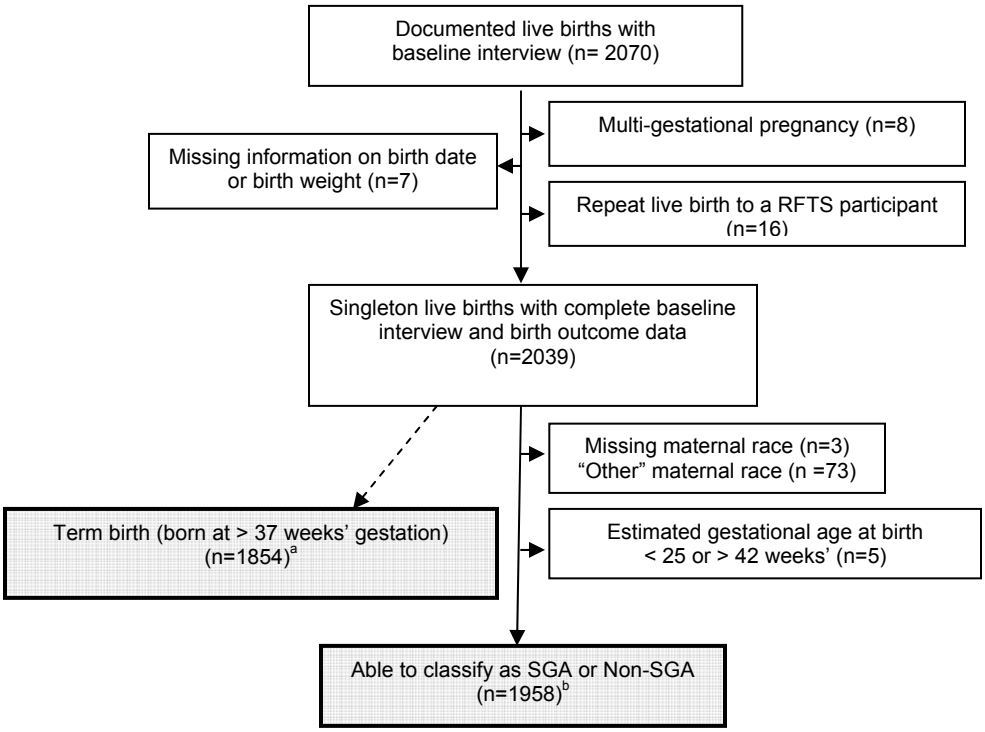
complete baseline interview). This information was obtained from medical records for 886 pregnancies (42.9%), vital records for 1,167 pregnancies (56.6%), and self-reports for 10 pregnancies (0.5%). Among the 2,063 pregnancies, eight multigestional pregnancies (*i.e.,* twins) were excluded. In addition, 56 of the remaining 2,055 pregnancies were repeat pregnancies to women who re-enrolled in the RFTS study. Forty of these pregnancies were to women whose first RFTS pregnancy ended in a loss or had missing outcome information (*i.e.,* not included in the 2,055 live births detailed above) and were retained in the live birth analyses. The remaining 16 pregnancies are a second live birth to a RFTS participant and excluded to retain independence of observations, resulting in a final sample of 2,039 for duration of gestation analyses (figure 2).

Figure 2. Flow-chart of exclusions for duration of gestation analyses



a 5 women missing data on showering and bathing (and thus, missing first and second trimester average TTHM personal exposure), 4 women missing data on tap water consumption (and thus, missing first and second trimester personal HAA5 and TOX exposure), 65 women missing DBP measurements during third trimester (and thus, 65 missing third trimester average TTHM, HAA5 and TOX residential concentrations) and one additional woman missing follow-up data on bathing and showering and tap water consumption (and thus, 66 missing third trimester average TTHM, HAA5 and TOX personal exposure)

Figure 3. Flow-chart of exclusions for fetal growth restriction analyses



a 5 women missing data on showering and bathing (and thus, missing first and second trimester average TTHM personal exposure), 4 women missing data on tap water consumption (and thus, missing first and second trimester personal HAA5 and TOX exposure), 54 women missing DBP measurements during third trimester (and thus, 54 missing third trimester average TTHM, HAA5 and TOX residential concentrations and personal exposure)

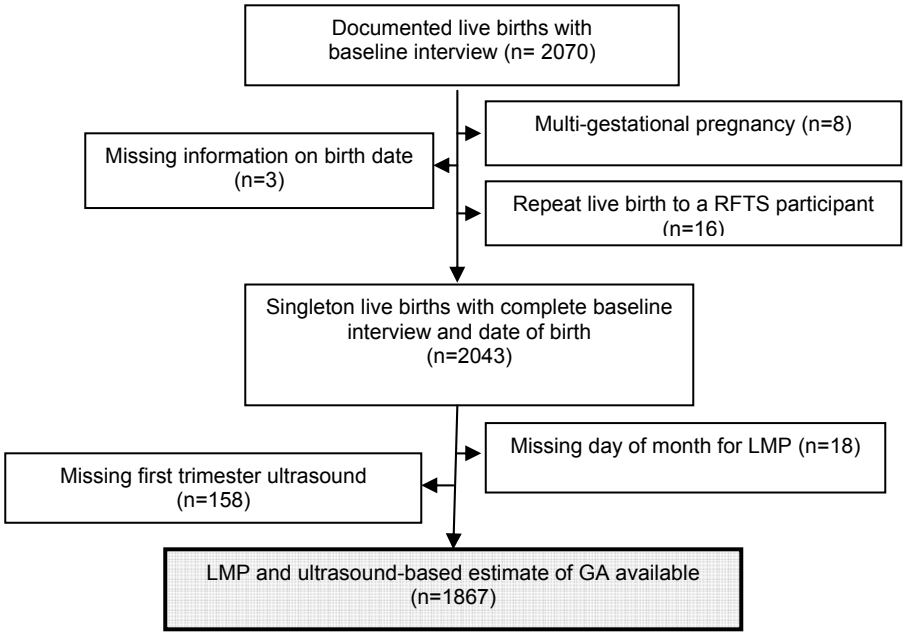
b 5 women missing data on showering and bathing (and thus, missing first and second trimester average TTHM personal exposure), 4 women missing data on tap water consumption (and thus, missing first and second trimester personal HAA5 and TOX exposure), 64 women missing DBP measurements during third trimester (and thus, 64 missing third trimester average TTHM, HAA5 and TOX residential concentrations) plus one additional woman missing data on bathing and showering and tap water consumption (and thus, 65 missing third trimester average TTHM, HAA5 and TOX personal exposure)

In addition to exclusions outlined above to obtain a group of singleton live births with complete baseline interview and birth outcome data for duration of gestation analyses, SGA status could not be assigned for three births missing information on maternal race, 73 births with a reported maternal race of "Indian", "Asian/Pacific islander", or "Other", and five births with an estimated gestational age at birth <25 or > 42 weeks' gestation, reducing the final sample size for SGA models to 1,958 births (figure 3). Term mean birth weight models

were restricted to 1,854 of the 2,039 singleton live births with complete baseline interview and birth outcome data that were born at ≥ 37 weeks'.

The analysis comparing gestational age at birth based on last menstrual period (LMP) versus first trimester ultrasound included 1,867 singleton live births with complete baseline interview, LMP (month and day of month) and ultrasound data (figure 4). Again, 347 (12.5 %) pregnancies that ended in a loss, 90 (3.3 %) pregnancies lost to follow-up, eight (0.3 %) multi-gestational pregnancies, 16 (0.6 %) repeat live births to a RFTS participant, and three (0.07 %) pregnancies missing infant birth date (0.07 %) were excluded. Additional exclusions were made for pregnancies with incomplete LMP date (*n*=18; 0.6 %) and pregnancies with no ultrasound data (*n*=158; 5.7 %).

Figure 4. Flow-chart of exclusions for gestational age estimates comparison analysis



Abbreviations: LMP = last menstrual period

3.3.3 Comparison of general, study, and analysis populations

Although RFTS attempted to recruit a cross-section of women from the participating geographic areas, the population that agreed to join the study was not random and likely not representative of the general population. Therefore, RFTS obtained and analyzed vital records from the state health departments of study sites to assess the degree to which participating women differ from their counterparts who lived in the area and gave birth over the same time period as the study (table 12). Participants from chlorinated DBP site were similar to the total population with respect to age, but more highly educated, more likely to be non-Hispanic White and less likely to be Hispanic, and more likely to be nulliparous. Participants from low DBP site were slightly less likely to be 18 or 19 years old at the start of pregnancy, more likely to be non-Hispanic White than Black or Hispanic, more likely to be nulliparous, and more highly educated than the total population of the area. Participants from the brominated DBP site were more likely to be Hispanic and less likely to be non-Hispanic White or Black, and more likely to be nulliparous than the total population, but similar with respect to education and age. Participants from low DBP site were slightly less likely to be 18 or 19 years old at the start of pregnancy, more likely to be non-Hispanic White than Black or Hispanic, more likely to be nulliparous, and more highly educated than the total population of the area [26].

Table 12. Demographic characteristics of RFTS participants and the general population

Maternal Characteristics	Chlorinated DBP sire: n (percent)		Brominated DBP site: n (percent)		Low DBP site: n (percent)	
	General population	RFTS study population	General population	RFTS study population	General population	RFTS study population
Age at pregnancy start						
18 – 19 years	354 (6.2)	52 (4.77)	366 (10.9)	40 (9.46)	1474 (11.5)	57 (6.34)
20 – 34 years	4623 (80.5)	890 (81.58)	2663 (79.3)	349 (82.51)	10204 (79.3)	743 (82.65)
≥ 35 years	764 (13.3)	149 (13.66)	329 (9.8)	34 (8.04)	1187 (9.2)	99 (11.01)
Race/ethnicity						
White, non-Hispanic	2669 (46.6)	718 (65.81)	1760 (52.7)	153 (36.26)	4412 (34.3)	477 (53.12)
Black, non-Hispanic	1658 (29.0)	290 (26.58)	607(18.2)	100 (23.70)	7144 (55.6)	375 (41.76)
Hispanic	1113 (19.4)	30 (2.75)	848 (25.4)	158 (37.44)	890 (6.9)	21 (2.34)
Other, non-Hispanic	287 (5.0)	53 (4.86)	123 (3.7)	11 (2.61)	410 (3.2)	25 (2.78)
Parity						
Nulliparous	2388 (41.6)	586 (53.71)	1129 (34.3)	184 (43.50)	4432 (34.5)	423 (47.05)
Parous	3348 (58.4)	505 (46.29)	2160 (65.7)	239 (56.5)	8411 (65.5)	476 (52.95)
Education						
≤ 12 years	2128 (37.1)	201 (18.42)	1834 (54.8)	232 (54.85)	6276 (50.5)	282 (31.4)
13 – 15 years	1049 (18.3)	200 (18.33)	704 (21.0)	107 (25.3)	2855 (23.0)	211 (23.5)
≥ 16 years	2564 (44.7)	690 (63.24)	811 (24.2)	84 (19.86)	3287 (26.5)	405 (45.1)

Adapted from Savitz et al. (2005) AWWARF report

Table 13 presents demographic characteristics of women enrolled in RFTS compared to women eligible for duration of gestation analyses. These two groups are similar with respect to maternal age at enrollment, estimated gestational age and parity. Both groups are ethnically diverse. However, White women were more likely and Black women were less likely to be retained in the analysis populations. In addition, women included in analyses are more highly educated than women originally enrolled into the RFTS. As noted earlier, women originally enrolled into the RFTS study sample were excluded from analysis for multiple reasons: 1) women were excluded or withdrew from the study after initial enrollment (including enrolled while trying to conceive that never became pregnant), 2) pregnancy ended in a loss or pregnancy outcome status is missing, 4) complete information on infant DOB and birth weight was not obtained or 5) pregnancy was multigestational.

Table 13. Demographics of women enrolled in RFTS and women included in duration of gestation analyses

Characteristic	Enrolled women (n = 3,132)	Women in analysis (n=2,039)
Mean age at enrollment (years)	28.34	28.2
Mean estimated gestational age at enrollment (days)	56.26	55.2
Race/ethnicity, n (%)		
African-American	1,102 (35.19)	614 (30.14)
White	1,732 (55.30)	1,229 (60.33)
Asian/Pacific Islander	58 (1.85)	43 (2.11)
Other	228 (7.28)	151 (7.41)
Hispanic origin	276 (8.81)	185 (9.08)
Education, n (%)		
≤ 12 years	1,014 (32.38)	573 (28.12)
13-15 years	679 (21.68)	440 (21.59)
≥ 16 years	1,439 (45.95)	1,025 (50.29)
Parity, n (%)		
0	1,425 (45.51)	991 (48.60)
1	1,067 (34.07)	673 (33.01)
≥ 2	640 (20.42)	375 (18.39)

Adapted from Savitz et al. (2005) AWWARF report

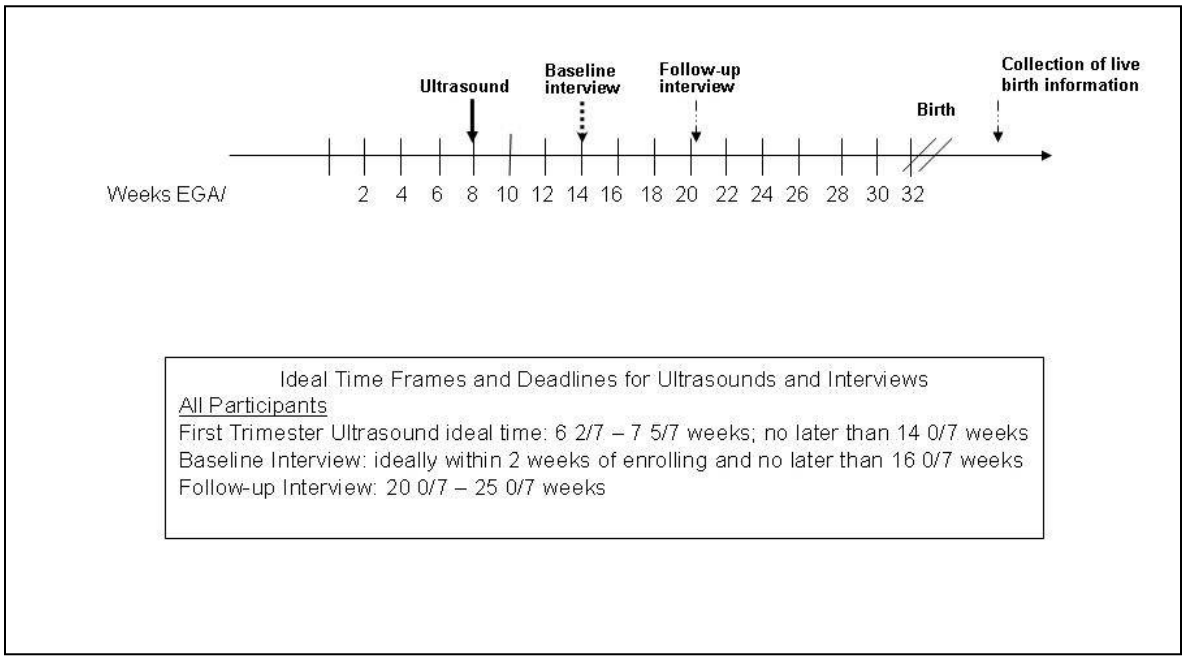
3.4 Data collection

Data collection in RFTS involved two primary components: 1) collection of individual level information about RFTS participants and their pregnancy obtained through interviews, an early pregnancy ultrasound, medical record abstraction and vital records matching, and 2) collection of information on DBP concentrations in the water distribution systems serving the three study sites while RFTS participants were pregnant. The following sections discuss these components in detail.

3.4.1 Collection of individual information on RFTS participants

Figure 2 summarizes the sources and timing of individual level data collection over the course of RFTS, beginning with the screening interview through collection of birth outcome information. These sources of data are described in detail below.

Figure 5. Flow diagram of data collection



Screening interview

A 5-minute telephone screening interview was conducted with interested women, at which time information necessary to establish eligibility was collected (*e.g.,* maternal date of birth, residential address, and LMP). In addition, if a woman was found eligible and agreed to enroll in the RFTS study, staff completed a 5 to 10-minute interview at screening to collect personal information about the participant. This included information on race/ethnicity, marital status, and education level.

First trimester ultrasound

First trimester endovaginal ultrasounds were conducted by clinical sonographers required to have ARDMS® certification, use state-of-the-art equipment as assessed by a study investigator (KH), conduct and document manufacturer recommended machine calibration, and have three or more years experience in pelvic and obstetric diagnostic sonography. In addition, sonographers participated in study-specific training. Measurements of the gestational sac, yolk sac, fetal pole, and fetal heart rate were fully comparable with those required for clinical pregnancy dating. A still image was reviewed by trained staff prior to entry of ultrasound data, and a 20% quality sample was reviewed by a clinician skilled in first trimester sonography (KH). All ultrasounds were performed at or before 13 weeks' completed gestation (mean= 9 weeks, median = 8 weeks).

Baseline telephone interview

The baseline telephone interview was completed 1 to 2 weeks after enrollment and no later than 16 completed weeks' gestation. A contract research organization (Battelle) conducted the baseline interviews. The baseline interview took on average 45 minutes to complete. Phone numbers and best times to call were obtained during the screening interview and provided to Battelle. The interview covered the following topics:

- Demographic information: social, household, and income information
- Recent/Current employment
- Health behaviors
- Water exposure

- Menstrual history
- Previous pregnancy history, time to conception, current pregnancy history
- Physical and sexual abuse
- Vitamin and mineral supplement use

If a participant had a pregnancy loss prior to completing the baseline interview, she completed a modified version of the baseline interview. If a participant did not complete the baseline interview by 16 completed weeks' gestation, she was not contacted to complete the follow-up interview [26].

Follow-up telephone interview

The follow-up interview was completed with participants starting at 20 weeks' gestation. RFTS attempted to complete the follow-up interview during week 20 when possible, and all follow-up interviews were completed no later than 25 weeks' gestation. Battelle also conducted the follow-up interview, which lasted 30 minutes on average. This interview covered the following topics:

- Changes in water use habits and health behaviors
- More information on previous pregnancy history and current pregnancy history, including pregnancy-related symptoms and information on prenatal care/delivery choices
- Maternal medical history
- Paternal characteristics

A participant completed the modified follow-up interview if she had a pregnancy loss before she was called to complete the follow-up interview [26].

Collection of live birth outcome information

Information on birth outcomes was collected from three sources: medical records, vital records and participant self-report. For pregnancies ending in a live birth between 2001 and 2003, RFTS staff first attempted to obtain key information on pregnancy outcome from vital records (*i.e.,* date of delivery, birth weight and infant sex). For those women who gave birth in 2004 and for whom vital records could not be successfully matched, RFTS requested hospital discharge summaries and prenatal care records to abstract birth outcome information. Information abstracted from medical records included:

- Infant date of birth (DOB), birth weight and gender
- Apgar scores at 1 and 5 minutes
- Congenital anomalies
- Delivery methods
- Indication for preterm birthFinally, self-reported information on live birth outcomes

was also obtained verbally from some participants during a follow-up telephone call or from a short 1-page questionnaire mailed to participants, which the participant then completed and mailed back to the RFTS office. Of note, outcome information is available from multiple sources for some participants (*e.g.,* medical records and self-report). In this case, information was taken from medical records first, vital records second and participant self-report last.

3.4.2 Collection of data on DBP concentrations

The following section describes how data on DBP concentrations was collected and analyzed. In addition, results are presented from a small validation study to confirm the lack of spatial variation in THM and HAA concentrations at the chlorinated and brominated DBP sites.

Determining sampling points

Utility companies were visited by a RFTS team member at the beginning of the study to review the water treatment facilities (including the method of terminal disinfection), analyze the service area and distribution system, select possible sampling locations, and collect samples at a number of locations for DBP analysis. Using information collected from the initial sampling trip, a representative sampling location was chosen for each utility for the remainder of the study. Because Site 3 had several booster chlorination stations serving a large portion of its population, two sampling locations were chosen at the brominated DBP site: 1) the treatment plant point of entry (POE) to the distribution system and 2) a second location on the downstream side of a booster station. The amount of chlorine applied at the booster station was relatively minor (0.3 to 0.5 mg/liter), so it was expected that the added free chlorine would be converted by residual free ammonia in the water to combined chlorine with little additional formation of DBPs [26].

Collection of water samples

As part of the RFTS study, weekly water samples were collected at the representative locations for the chlorinated and brominated DBP site. Samples were collected every other week at the low DBP site. Residual chlorine concentrations and temperature were also measured at the time of DBP sample collection. The chlorinated DBP site utility system switched from combined chlorine to free chlorine for one month each year (March) to control potential microbial re-growth and biofilm problems. To account for the anticipated spatial variation in DBP levels during the one-month conversion, samples for DBP analysis were collected weekly at up to 10 locations in the distribution system. The brominated DBP sire utility also converted to free chlorine for a period of several weeks during October 2003. Again, samples were collected weekly at a number of locations in the distribution system including the representative sample locations to account for the anticipated spatial variation in DBP levels [26].

Collection of water samples was performed by field personnel in accordance with a specified protocol. Key features of the protocol are listed below:

- Sample collection vials were washed, labeled, and reagents added prior to shipment to study sites.
- Identification labels indicating the sampling location, target analyte, reagents added were placed on all vials; samplers also recorded the date/time of sample collection and their initials on the label.
- Chain of Custody documentation and return overnight shipping labels were included with each shipment of vials.

- Weekly THM and HAA samples at moderate DBP sites and bi-weekly sample at the low DBP site were collected in quadruplicate in order to provide duplicate samples for analysis and for matrix spike analyses.
- Samples were collected near mid-day on Thursday at the chlorinated DBP site, Tuesday at the low DBP site, and Wednesday at the brominated DBP site from a cold-water tap that had been run for at least five minutes prior to sample collection.
- The samples were returned by overnight delivery to the Drinking Water Research Center laboratories of UNC where they were inspected and stored in a refrigerator at $4^{o}C$.
- A tracking database which included information on sampling date, target analyte, outgoing shipment date, date received back at UNC, extraction date, instrument analysis date, quantification date, and quality control review status was kept at the University of North Carolina.

Please see appendix 1, "Water Sampling Methodology" excerpted from Savitz et al. (2005) for the full protocol.

Analysis of THM concentrations

THM samples were analyzed within a 14-day holding time of the sample collection date using a 5890 series II gas chromatograph (Agilent Technologies, Palo Alto, CA) equipped with an electron capture detector. A modified version of EPA Method 551.1 [104] was utilized to extract each of the THM4 species from the aqueous samples (see appendix 1 for full details). The practical quantification limit (PQL) for all THMs was 0.1

micrograms/liter. Linear calibration for each THM species was in the range of 1.0-150 micrograms/liter. The acceptable relative percent difference for THM analysis duplicates was <10% and the matrix spike recovery had to be in the range 80-120%. Any samples not meeting these criteria were flagged and examined further for analytical or instrumentation errors [26].

Analysis of HAA concentrations

HAA samples were analyzed within a 21-day holding time using a 5890 series II gas chromatograph (Agilent Technologies, Palo Alto, CA) equipped with an electron capture detector. The method used for extraction of all nine HAA species was developed by Brophy et al. [105] and based upon EPA method 552 [106] and Standard Method 6251B [107] (see appendix 1 for full details). The coefficient of variation (% CV) was calculated for the surrogate area counts of all analytical samples. The PQL was 1.0 or 2.0 micrograms/liter, depending on the HAA, and the maximum calibration standard utilized was 150 micrograms/liter. Analysis and quantification of the calibration standards and aqueous samples was based on replicate precision of duplicate samples having a relative percent difference of less than 25 percent [26].

Analysis of TOX concentrations

TOX analysis was performed using a model AD-2000 Adsorption Module and TOX Analyzer (Tekmar Dohrmann, Cincinnati, Ohio). Samples of 250 milliliters were acidified to pH < 2 with 2 milliliters of concentrated sulfuric acid (H_2SO_4), loaded into an adsorption module, dispensed through two granular activated carbon columns, and subsequently rinsed

with potassium nitrate to remove retained inorganic chloride. The carbon was then combusted at 850°C to volatilize organic halogens, which were then analyzed by micro-coulometric detection. Preceding and following each batch of samples, a "nitrate blank" was also analyzed to determine the contribution of background organic halogen from the reagents, carbon, and carrier gases. TOX concentrations (in micrograms chlorine/liter) were calculated by adding organic halogen for the combustion of top and bottom columns of samples (in micrograms chlorine), subtracting the average of nitrate blank concentrations, and then dividing by volume (in milliliters) of sample absorbed.

Table 14. Distributions of DBP concentrations by study site

	DBP concentration (µg/liter)				
Location	n	Mean	Median	Maximum	Minimum
Chlorinated DBP Site					
THM4	177	63.3	60.7	149	24.7
$CHCl_3$	177	45.6	43.5	124	14.7
$CHBrCl_2$	177	13.8	12.5	33.3	6.8
THM-Br	177	17.8	16.2	43.5	9.0
HAA5	177	33.2	31.9	62.2	12.1
HAA9	177	43.2	41.5	78.9	15.4
HAA-Br	177	10.8	10.2	28.7	1.9
Brominated DBP site					
THM4	108	58.9	57.8	165.0	26.6
$CHCl_3$	108	11.5	10.0	52.7	3.0
$CHBrCl_2$	108	19.0	18.3	51.7	7.1
THM-Br	108	47.4	44.9	112.3	21.4
HAA5	108	21.5	20.1	53.1	13.2
HAA9	108	45.8	44.7	98.9	30.4
HAA-Br	108	32.0	31.4	55.7	20.4
Low DBP site					
THM4	157	4.2	3.6	15.9	1.4
$CHCl_3$	157	BMRL	BMRL	2.4	BMRL
$CHBrCl_2$	157	1.5	1.1	6.5	BMRL
THM-Br	157	3.9	3.4	13.5	1.4
HAA5	157	BMRL	BMRL	3.1	BMRL
HAA9	157	3.5	3.3	6.5	BMRL
HAA-Br	157	BMRL	BMRL	6.4	BMRL

BMRL=below the minimum reporting level (*i.e.,* "non-detects")
Table adapted from Savitz et al. 2005 AWWARF report

Measured THM and HAA concentrations

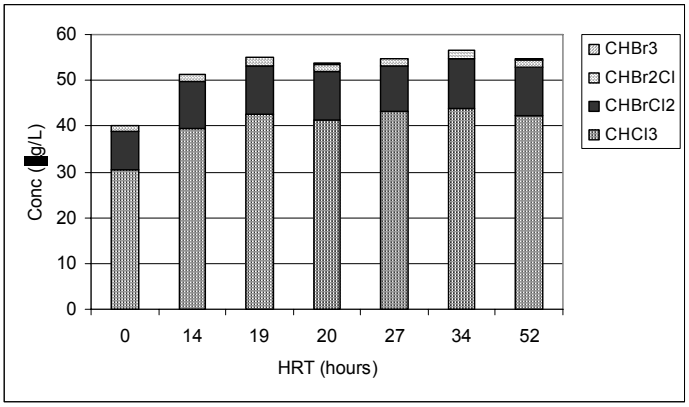
Table 14 presents the mean, median, maximum and minimum concentrations of select THM and HAA species over the respective periods when water sampling was conducted at each site. Overall concentrations of TTHM and HAA5 were similar at the chlorinated and brominated DBP sites; however, relative concentrations of chlorinated and brominated THM and HAA species varied markedly between. THM and HAA concentrations were much lower at the low DBP site than at moderate DBP sites. Of note, marked seasonal variation in THM levels was observed in the chlorinated DBP site and to a lesser extent at the brominated DBP site, with peak concentrations occurring in summer months and lower concentrations in winter months [26].

Validation of sampling strategy

The proposed sampling strategy described above was confirmed by validation studies conducted at chlorinated and brominated DBP sites. Water samples were collected from six sampling locations within each water distribution system on the same day. Apart from concentrations at the point of entry (POE) to the distribution system, measurements of TTHMs at the chlorinated DBP site were all similar, ranging from 51 to 57 micrograms/liter (figure 3). The POE value (labeled HRT = 0 in figure 3) is lower than the others because the sample was taken before the ammonia was fully mixed into the finished water. TTHM levels were also similar at the brominated DBP site, ranging 89 to 99 micrograms/liter (figure 4). These results, which were repeated on two other occasions at the chlorinated DBP site and one other occasion for the brominated DBP site, confirm that there was very little spatial variation in THM concentrations in the water distribution systems serving the moderate DBP

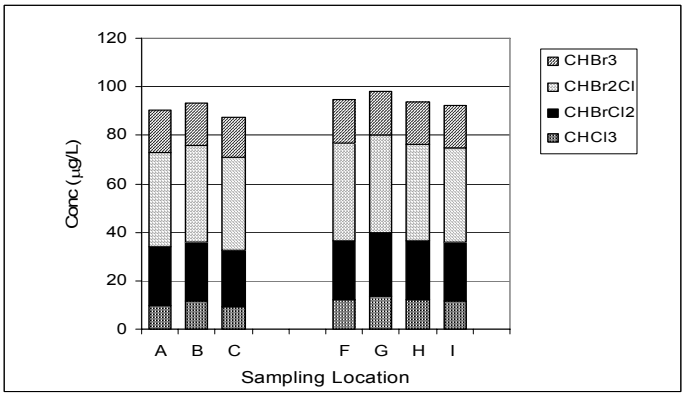
sites. Similar consistency in HAA concentrations was found on multiple occasions at the moderate DBP sites (results not shown) [26].

Figure 6. Spatial variability of THM species at the chlorinated DBP site, February 2003



Abbreviations: Conc = concentrations, HRT = hydraulic residence time
Adapted from Savtiz et al. (2005) AWWARF report

Figure 7. Spatial variability of THM species at the brominated DBP site, June 2003



Abbreviations: Conc = concentrations
Adapted from Savtiz et al. (2005) AWWARF report

3.5 Outcome assessment

The following sections describe how fetal growth restriction (specific aim 1) and duration of gestation (specific aim 2) were assessed for analyses. The method used to date pregnancies is given and justified. Definitions for SGA, term birth weight and gestational age also are presented.

3.5.1 Estimation of gestational age

Infant DOB is available from medical records, vital records and participant self-report and was combined with LMP estimates to calculate estimated gestational age (EGA) at delivery (*i.e.,* EGA at delivery in days = DOB - LMP). Two sources for estimating date of conception were available: 1) participant-reported LMP collected during a screening interview conducted at or before 12 weeks' gestation and 2) early ultrasound dating conducted before 14 weeks' gestation (assumes LMP occurred 14 days prior to date of conception). Given that both estimates of conception were collected early in pregnancy, the concordance between gestational age estimates derived from these two sources (henceforth referred to as LMP-based and ultrasound-based estimates) should be high, particularly among pregnancies ending in a live birth. As previously outlined in section 3.3.2, a total of 1,867 documented singleton live birth were available with complete information on self-reported LMP, a first trimester ultrasound, and date of birth. The mean difference in number of days between LMP and ultrasound-based estimates of gestational age is -0.9 ± 7.7 days (mean ± standard deviation), with a median discrepancy of 0 days. Eighty-eight percent of births have an estimated gestational age from ultrasound within 1 week (*i.e.,* plus or minus 7 days) of the

estimate derived from LMP. Additional results are provided in manuscript #3 (chapter 5, section 3).

Given that use of self-reported LMP was found to be an accurate method of estimating gestational age for most births, LMP-based estimates were used when LMP and ultrasound-based estimates were within +/- 7 days or if ultrasound data was missing. This was done to help preserve comparability with previous DBP studies and maintain compatibility with birth weight percentile cut-points used for SGA classification (see section 3.5.2 below.

3.5.2 Assessment of restricted fetal growth

Two outcomes were used to assess the impact of THM and HAA exposure during pregnancy on restricted fetal growth (specific aim 1): small for gestational age (SGA) and term birth weight in grams. SGA was chosen because it is a conventional measure for identifying more severe growth restriction and has been consistently associated with DBP exposure in the literature. Main analyses included all infants (both preterm and term births). In addition, analyses were run restricting to term births, which are often viewed as a "cleaner" group for assessing effects on fetal growth, to assess whether the inclusion of preterm SGA infants substantially influenced results.

Term birth weight was chosen because it allows examination of the effect of DBP exposure on birth weight as a continuum while minimizing variation in birth weight due to differences in gestational age at birth. Low birth weight (LBW) was also considered as an alternative measure; however, use of LBW is complicated by the relationship between

growth restriction and preterm delivery, both of which contribute to low birth weight. Thus, LBW was not examined.

Categorization of infants as SGA

An SGA infant was defined as an infant with a birth weight below the tenth percentile according to gestational age (in weeks, ranging from 25 to 42 weeks), infant gender, maternal race/ethnicity (non-Hispanic White, Non-Hispanic Black, or Hispanic), and parity (primiparous or mulitparous) specific birth weight curves. Tenth percentile cut-point values were obtained from standardized birth weight curves derived by Zhang and Bowes (1995) for non-Hispanic Black women [38] and by Overpeck et al (1999) for non-Hispanic White women and Hispanic women [43]. Estimated gestational age was converted from days into weeks of gestation using the calculation: EGA (weeks) = integer [(EGA in days - 1) /7]. Information on infant gender, maternal race/ethnicity and parity was obtained from interviews. All women included in analyses had complete information on infant gender and parity. Subjects missing complete information on maternal race/ethnicity (n=3), a maternal race of "Indian", "Asian/Pacific islander", or "Other" (n=73) or estimated gestational age < 25 or > 42 weeks' gestation (n=5) were excluded from SGA analyses (figure 3).

Assigning term birth weight

Term birth weight analyses were restricted to infants born ≥ 37 weeks completed gestational age (n=1854), and birth weight was coded continuously in grams. Infant birth weight was obtained from medical records, vital records and/or participant self-report. Birth

weight information was taken from the medical record first, vital records second and participant self-report last if more than one source of information was available for a participant. Birth weight was converted to grams if reported in pounds (lbs) and ounces (oz).

3.5.3 Assessment of reduced duration of gestation

Time from LMP until delivery (gestational age in weeks) was used to assess the impact of THM and HAA exposure during pregnancy on duration of gestation (specific aim 2) using a discrete hazard model. This measure was chosen because it allows estimation of odds ratios for delivery during multiple intervals of pregnancy (*e.g.,* ≤ 32 weeks, 33-36 weeks, 37-40 weeks and ≥ 41 weeks) in one model so that a spectrum of preterm severity can be considered simultaneously. The intervals ≤ 32 weeks, 32-36 weeks, 37-40 weeks and ≥ 41 were chosen because they roughly represent very preterm, moderately preterm, term and post-term births, respectively. Another option would be to dichotomize births into preterm and non-preterm (*e.g.,* <37 weeks versus ≥ 37 weeks). This measure is not ideal because it masks variability in severity of prematurity among infants categorized as preterm while over-emphasizing a difference between deliveries occurring shortly before and after 37 weeks' gestation. However, preterm birth was examined in an ancillary analysis for manuscript #3 to help in the interpretation of discrete hazard analyses and comparison with previous studies.

3.6 Exposure assessment

Several approaches can be taken to assign DBP exposure. Incorporation of available information on personal water consumption and use may lead to more accurate estimation of

an individual's exposure. However, it also requires the assumptions that behavioral information is accurately reported and is correctly integrated into exposure assessment. Two exposure metrics were examine in this study to address this concern: 1) average DBP concentrations for a study site over specific windows of pregnancy, henceforth referred to as "residential DBP concentrations" and 2) estimated personal DBP exposure (described in detail below in section 3.6.3) over the same time windows of pregnancy. The first metric estimates DBP concentrations in tap water serving a woman's home (and possibly her workplace if employed at a location within the study site) during pregnancy and ignores modification in exposure due to individual variation in water consumption and use. The second metric estimates a woman's individual DBP exposure during pregnancy given residential DBP concentrations and her personal water exposure patterns (specifically water consumption, filtering and boiling; showering and bathing). These two exposure metrics were estimated for several different THM and HAA species and for several different exposure windows of interest. The following sections described exposure assessment in more detail.

3.6.1. Selection of main exposures to be examined

THM and HAA species examined in this study are listed below in table 15. The association between aggregate DBP measures (TTHM, HAA5, and TOX) and pregnancy outcomes (SGA, term birth weight, and duration of gestation) were assessed using traditional maximum likelihood estimation (MLE) methods. These THM and HAA aggregate measures were chosen because they represent DBP measures currently regulated, and TOX provides a

crude measure of overall DBP exposure. The association between fetal growth outcomes and individual THMs and HAAs were examined simultaneously using a Bayesian approach.

Table 15. THM and HAA species to be considered in analyses

Maximum Likelihood Estimation	Bayesian Analyses			
TTHM	Chloroform	CAA	BCAA	BAA
HAA5	BDCM	DCAA	BDCAA	DBAA
TOX	DBCM	TCAA	DBCAA	TBAA
	Bromoform			

Abbreviations: TTHM=total trihalomethanes, BDCM=bromodichloromethane, DBCM= dibromochloromethane, HAA5= sum of five regulated haloacetic acids, CAA= chloroacetic acid, DCAA= dichloroacetic acid, TCAA= trichloroacetic acid, BCAA = bromochloroacetic acid, BDCAA = bromodichloroacetic acid, DBCAA = dibromochloroacetic acid, BAA= bromoacetic acid, DBAA= dibromoacetic acid, TBAA = tribromoacetic acid, and TOX = total organic halide

3.6.2 Calculation of window-specific residential DBP concentrations

The most relevant time period for a potential adverse effect of DBPs on pregnancy health is unclear. Possible exposure windows for restricted fetal growth analysis include the first, second and third trimester and the entire period of pregnancy. Third trimester exposure (exposure during the latter part of pregnancy) was initially examined given that window-specific averages are highly correlated and examining third trimester exposure would preserve comparability with several recent studies that only reported results for third trimester exposure. However, after further considerations, first and second trimester average exposures were examined as an ancillary analysis for manuscript #2.

Weekly exposure and average exposure over a 6-week running period (both allowing exposure to change) were examined in duration of gestation analyses as well as second trimester average exposure (exposure fixed). Use of weekly exposure allowed examination of the effect of concurrent exposure on timing of delivery. Conversely, the 6-week running average exposure (*i.e.,* average level over the current week and 5 proceeding weeks of

pregnancy) and second-trimester average exposure allowed examination of a more delayed effect of DBP exposure on duration of gestation. The last 6-week running average exposure also was used assessment of the impact of average DBP exposure near the end of pregnancy but avoid bias that could be introduced by examining third trimester or total pregnancy exposure [108].

The mean DBP concentration of all weekly measurements covered by each time window of interest was used to estimate window-specific residential DBP concentrations. Weekly DBP measurements below the PQL (*i.e.,* below 0.1 μg/liter for THMs and 1.0 or 2.0 μg/liter for HAAs) were set to zero. Exposure windows were defined by gestational weeks relative to LMP: third trimester = 27 weeks' gestation until birth, and second trimester = 13 to 26 weeks' gestation. Window-specific residential DBP concentrations were then used to estimate window-specific personal DBP exposure as described below.

3.6.3 Calculation of personal DBP exposure

Information on individual water use was collected during the baseline interview and follow-up interview as part of the RFTS study and was integrated with residential DBP concentrations to estimate personal DBP exposure. The estimation of integrated personal DBP exposure from residential DBP concentrations and self-reported water exposure was implemented in three main steps: 1) adjustment of residential THM and HAA concentrations for water treatment, 2) estimation of the amount of HAAs ingested daily, 3) estimation of the amount of THMs inhaled/absorbed through the skin daily. Of note, only exposure through ingestion were considered for HAAs (steps 1 and 2), as exposure to HAAs primarily occurs through intake of tap water and tap-water-based beverages [17]. Conversely, only step 3 was

considered for THMs, as exposure to parent THM compounds primarily occurs through inhalation and dermal absorption. Steps 1 through 3 are explained in detail below.

Step 1- adjusting THM and HAA residential concentrations for heating and filtration

Two main water treatment activities that can alter DBP concentrations in tap water before ingestion were considered: thermal treatment (*e.g.,* heating water in the microwave or a kettle) and point of use filtration (*e.g.,* filtering water using a home filtration system or filtration pitcher). As part of the RFTS study, a series of experiments was conducted to calculate correction factors to adjust residential DBP levels if a woman reported boiling and/or filtering her water [26]. Thermal correction factors for individual THM and HAA species in chlorinated and chloraminated water are also available from a study by Krasner and Wright [109]. These correction factors were applied to residential DBP concentrations to estimate the amount of DBPs ingested under eight different combinations of heating (cold/hot) and filtration (no filtration/faucet filtration/pitcher filtration/filtration of unknown type). A table of conversions factors by treatment and DBP exposure can be found in appendix 2.

Step 2- estimate amount of HAA exposure due to ingestion

Women were asked about their typical tap water consumption in detail during baseline and follow-up interviews. Briefly, information was collected at baseline on the number of glasses of tap water (or tap water-based drinks) typically consumed per day, the usual size of glasses, whether frequency of consumption had changed over the past 4 months,

and if so, how many glasses were previously consumed per day and when consumption changed. All women were asked these questions separately for cold and hot tap water consumption. These questions were also asked separately for home and work if a woman reported working at a location outside of the study site. In addition, information was collected on the frequency and type of water filtration system a woman used to treat water before consumption. At follow-up interview, women were again asked about the typical number and size of glasses of cold and hot tap water they consumed per day at work and home. Please see appendix 3 and 4 for the complete sequence of questions asked at baseline and follow-up interview, respectively.

To estimate the average daily amount of DBPs ingested (ounces per day), adjusted DBP concentrations estimated in step 1 were combined with interview information to estimate the amount of DBP ingested under each of the eight different water treatment scenarios. The following assumptions were made:

- The volume of cold/hot water contained in small, medium and large glasses/cups was equal to the mid-range of ounces given to describe size categories during interview.
- Self-reports of filtering "all or nearly all", "most", "some", "very little" and "none" of water corresponded to filtering 100%, 75%, 40%, 20% and 0%, respectively, of all cold and hot water that was ingested.

Treatment-specific values were then summed to derive daily ingested amounts in units of "micrograms/day". If a woman reports a change in tap-water ingestion over the period of pregnancy, a time-weighted average was calculated for all periods during which a change was reported to have occurred. For changes reported between baseline and follow-up interview, that change was assumed to have occurred halfway through the period between

interviews. If no change was reported, this value was simply the reported average daily amount. Also, bottled water was assumed to have no DBP content and did not contribute to the estimated amount of DBPs ingested, which is supported by a small study conducted by RFTS researchers that found most brands of bottled water contain little to no DBP contaminants [26].

Step 3- estimate amount of THM exposure due to showering and bathing

To quantify exposure through absorption and inhalation from showering and bathing, data on residential THM levels was integrated with self-reported information on the average duration and frequency of showering and bathing using an uptake factor that links duration and water concentration into an absorbed dose. Information on the frequency and length of time typically spent showering and bathing was collected at baseline and follow-up interview and was converted to the average minutes per day engaged in each. Uptake factors of 0.001538 micrograms and 0.001321 micrograms of THMs in blood per minute per microgram were used for showering and bathing, respectively. These uptake factor values were obtained from previous studies that measured blood THMs in relation to known duration of bathing and showering in water of known THM concentration [26,110].

Of note, inhalation and absorption of THMs also occurs through swimming, washing dishes and clothes, bathing children, and other activities such as washing hands and flushing the toilet. Furthermore, the amount of THM exposure via inhalation is influenced by home ventilation. However, incorporating all of these DBP sources into exposure assessment is not feasible, as exposure pathways are very complex and toxicokinetic studies of exposure routes are either non-existent or do not provide results that can be easily incorporated into exposure

assessment. Therefore, only showering and bathing were considered in estimating exposure through inhalation and dermal absorption.

3.7 Covariate assessment

Covariate information is available from RFTS telephone interviews, medical record abstraction and vital record matching. Potential confounders were defined as moderate to strong risk factors for restricted fetal growth and/or preterm birth according to the literature that may also be associated with DBP exposure (*e.g.,* demographic variables that vary in distribution by study site or are potentially associated with water exposure) but are not thought to be on the causal pathway between exposure and outcome. Covariates are listed below in table 16 along with coding schemes used in analyses. In addition to confounder assessment, maternal age, race/ethnicity and swimming during pregnancy (yes/no) were assessed as potential effect measure modifiers in both the fetal growth and gestational age analyses. Of note, most coding schemes outlined in table 16 were previously implemented in preliminary analyses conducted for the RFTS end-of-grant report [26] and used in this study to preserve uniformity across publications. The appropriateness of coding schemes was confirmed in univariate analyses.

Several studies have shown that the proportion of births delivered preterm is higher during late summer and fall compared to spring months [65-67]. Likewise, DBP concentrations are generally higher during warm seasons compared to colder seasons [12]. Seasonal variation in preterm birth could in part reflect seasonal variation in DBP concentrations assuming a casual association. On the other hand, an erroneous association between DBP exposure and

preterm birth may arise due to parallel temporal variability in the prevalence of preterm birth and DBP concentrations, making adjustment for season of conception necessary.

Table 16. Covariates to be considered as potential confounders in analyses.

Covariate description	Coding
Maternal Age (range: 18 to 45)	Categorical variables grouped into 5 year increments (<25, 25-30, 30-35 or >=35) and/or a continuous variable using quadratic term
Race/ethnicity	Categorical variable (white non-Hispanic, black non-Hispanic, Hispanic or other)
Marital status	Dichotomous variable (unmarried or married)
Highest attained education level	Categorical variable (high school only, high school plus some college or college degree +)
Annual Household Income (range:≤ $5,000/year to >$ 80,000/year)	Categorical variable (cut points will be chosen based upon distribution among study subjects)
Employment	Dichotomous variable (unemployed or employed)
Body mass index (BMI)	Categorical variable (underweight, normal weight, overweight, obese)
Smoking during pregnancy	Dichotomous variable (non-smoker, <10 cigarettes per day or ≥10 cigarettes per day)
Alcohol use during pregnancy	Dichotomous variable (yes/no)
Caffeine consumption[a]	Categorical variable (0, 1-150, 151-300, or >300 mg/day)
Number of previous live births (parity)	Dichotomous variable (nulliparous/multiparous)
Infant Sex[b]	Dichotomous variable (male/female)

a Only included in gestational age analyses (specific aim 2)
b Only included in term birth weight analyses (specific aim 1)

To assess whether adjustment for season in aim #2 analyses was needed, the ability of season of LMP or season of birth to predict the proportion of infants born preterm (*i.e.,* before 37 weeks' completed gestation) was tested. Season was coded into four groups: winter (January, February and March), spring (April, May and June), summer (July, August

and September) and fall (October, November December), and entered into the model using indicator variable coding. For both season of LMP and season of birth, none of the individual indicator terms for season were statistically significant at an alpha level = 0.05 nor were Wald Chi-square tests significant for an overall seasonal effect. Accordingly, it was decided not to control for season in duration of gestation analyses.

Because study sites were selected based upon having distinct distributions of DBP concentrations in the water, any risk factor for adverse pregnancy outcome that varies in distribution between sites may confound the association between DBP exposure and that outcome. These risk factors may extend beyond what can be adequately controlled for by the list of covariates above in table 16. Furthermore, THM and HAA levels may serve as markers for other unmeasured, toxic DBPs rather than increasing risk themselves. The occurrence of unmeasured DBPs relative to measured DBPs likely varies by site. Therefore, residual confounding and/or effect modification by study site is of significant concern. To address this issue, site-specific analyses were run to examine the extent to which results vary by study site. Women from the low DBP site have a small range of low exposure levels, making analyses restricted to these women of less interest. Relatively few women were recruited from the brominated DBP site (total number live births = 320, number of SGA infants = 28, number of preterm infants = 48), so effect estimates estimated from an analyses restricted to these women would be highly imprecise. Therefore, two sets of MLE analyses were conducted: one using all women and one restricted to women from the chlorinated DBP site.

3.8 Data analysis

3.8.1 Univariate analysis

The univariate distribution of all variables included in analyses was examined, including variables involved in constructing outcome measures, exposure variables and covariates of interest. For categorical variables, the frequency and percent of observations at each level of the covariate was calculated, including missing values. For continuous variables, descriptive statistics (*e.g.,* mean, median, standard deviation and percentile values) were calculated and the frequency and percent of observations with missing values was assessed.

Out-of-range values that are known to be impossible were set to missing. In particular, gestational age and birth weight values were examined individually and jointly to check for implausible values. A gestational age at birth outside the range of 20 to 45 weeks or birth weight outside the range of 125 to 6,000 grams was considered implausible and resulted in exclusion of that observation. In addition, an "expert opinion" rule developed by Alexander et al. (1996) was employed to identify and exclude live births with implausible values of birth weight for gestational age [111]. While several rules are available, this particular rule was chosen because it is the least conservative with respect to excluding live births too small for gestational age (*i.e.,* least likely to exclude questionable infants with low birth weights given their gestational age) and is relatively simple to implement [112]. Constructed variables (*e.g.,* SGA status, first trimester personal TTHM exposure) were created after data cleaning was complete. Exposure variables and covariates that did not exhibit sufficient variability to support multivariate analysis (*i.e.,* maternal alcohol use and smoking) were

dropped from subsequent modeling. Participants missing information on the outcome, exposure or important covariates were also excluded from those specific analyses.

3.8.2 Bivariate analysis

Pairwise associations between outcomes, exposures and covariates of interest were examined prior to regression modeling. The following bivariate analyses were conducted:

- Cross-tabulations of SGA status with quantiles of exposure (collapsed over and stratified by covariate categories).
- Cross-tabulations of SGA status with covariates.
- Calculation of descriptive statistics for term birth weight and gestational age at delivery (*i.e.,* mean, median, and standard deviation) by exposure quantiles (collapsed over and stratified by covariate categories).
- Calculation of descriptive statistics for term birth weight and gestational age at delivery by covariate categories.
- Cross-tabulations of exposure quantiles with covariate categories and calculation of descriptive statistics for exposure by covariate levels.

In addition, correlation coefficients between residential concentrations of different DBP species, exposure metric estimates (residential versus personal) and exposure window estimates were examined. Graphical techniques such as side-by-side histograms and scatter plots were employed when warranted to get a visual impression of pairwise associations.

3.8.3 Analytic plan for specific aim #1:

Traditional MLE analyses

To estimate the effect of drinking water DBP exposure during pregnancy on restricted fetal growth, logistic regression was used to estimate the effect of exposure to specific DBP measures during pregnancy on the probability of delivering an SGA infant. Linear regression was used to estimate the difference in mean term birth weight (in grams) associated with exposure to DBP measures during pregnancy. As outlined in section 3.6, aggregate DBP measures (TTHM, HAA5, and TOX) were examined in MLE analyses. Two exposure metrics (residential DBP concentrations and personal DBP exposure) and three exposure windows (1st trimester, 2nd trimester, 3rd trimester) were considered for each DBP measure.

Multiple coding schemes for DBP exposures could be employed given that DBP exposures will be estimated on a continuous scale. Exposure could be coded categorically using quantiles of exposure (the conventional coding scheme) or coded continuously using flexible splines. While categorizing exposure produces more easily interpretable results and facilitates comparison with previous studies, splines can give a better idea of the dose-response relationship between DBP exposure and fetal growth. Therefore, residential DBP concentrations were initially coded continuously using restricted quadratic splines with knots at quantile values. Model estimates were then used to plot the predicted outcome response (*i.e.,* probability of delivering a small-for-gestational-age [SGA] infant, mean birth weight or probability of delivery by pregnancy intervals) by residential DBP concentration to get a visual impression of the dose-response relationship. Since spline-based dose-response plots did not strongly oppose coding residential DBP concentrations into quantiles (*i.e.,* the plots do not show substantial change in predicted risk within quantile categories), models using

quantile categories of exposure, with the low exposure site used as the referent, were run to produce more easily interpretable results and facilitate comparison with previous studies.

The amount of error introduced into exposure assessment while estimating personal DBP exposure is unknown, and it is unclear how much confidence should be given to the exact numeric value estimated for personal exposure. Nonetheless, the author felt confident that proposed algorithm for estimating personal DBP exposure would roughly sort women into those with relatively "high", "intermediate" or "low" exposure. Therefore, the association between personal DBP exposure estimates and adverse pregnancy outcomes were examined using quantile coding only.

For SGA models, the number of quantile levels (two or three) that exposures at the moderate exposure sites were chosen so that approximately 20 cases were in each index exposure category. Quartiles were used in term birth weight models. In addition, residential TTHM levels were examined at the current maximum contaminant limit (MCL) (*i.e.,* residential TTHMs ≥ 80 *vs.* < 80 micrograms/liter). The MCL for HAA5 could not be assessed because too few RFTS participants were exposed to levels ≥ 60 micrograms/liter.

Bayesian analyses

As expected, individual THM and HAA levels were highly correlated in this study. Modeling each exposure in a separate risk model could lead to spurious associations due to confounding by other correlated DBPs, so a single model that controls for all individual THMs and HAAs is desirable. However, adjustment for multiple DBP exposures using standard MLE may fail to provide plausible estimates given that exposures are highly

correlated [113]. Alternatively, Bayesian analytic techniques allow simultaneous modeling of highly correlated exposures in a single model. In addition, prior distributions can be specified to "borrow" information across sets of individual DBPs that may have a common underlying biologic mechanism (*e.g.,* HAAs or brominated DBP compounds)[113].

A fully Bayesian analysis was conducted to examine the association between fetal growth measures and third trimester average residential concentrations of individual THMs and HAAs. Logistic and linear regression models were constructed for SGA and term birth weight, respectively, and DBP concentrations were entered into the model using quantile categories. DBP exposures were coded categorically as described above for MLE analyses. In addition, like the conventional MLE analyses, generalized linear models were constructed for SGA (link=logit) and term birth weight (link=identity).

The generalized structure of the model can be written as follows:

$$g\left(E\left[y_i \mid x_{ij}, \beta_j\right]\right) \sim \sum_{j=1}^{k} \beta_j x_{ij}$$

$$\left[\beta_j \mid \theta, \phi_j^2\right] \sim N\left(\sum_{l=1}^{p} \theta_l z_{jl}, \phi_j^2\right)$$

$$\left[\theta_l\right] \sim N(\mu_l, \omega_l^2)$$

$$\left[\phi_j\right] \sim \text{uniform}(0, r)$$

Here, the response of subject i (y_i ; i = 1 to n, where n is the number of study subjects) is conditional on her DBP exposure values (x_{ij}) and the effect of DBP exposures (β_j ; j =1 to p, where p is the number of DBP exposures). The prior distribution for β_j is specified as a normal distribution with prior mean = $\sum_{l=1}^{p} \theta_l z_{lj}$, which is the function of l

covariates representing substantive information that may in part explain the effect of the DBP exposure j (*e.g.,* DBP class, number of brominated halogens) and corresponding coefficients which may have their own specified prior distribution = $\theta_l \sim N(\mu_l, \omega_l^2)$ [113]. The variance of the normal distribution prior for β_j is specified as ϕ_j^2. In a fully-Bayesian approach, which was used herein, a prior distribution is also placed on ϕ_j^2. Recently, Bayesian statisticians have turned away from using an inverse gamma distribution as a non-informative prior for ϕ_j^2 (or on the precision parameter $\tau = 1 / \phi_j^2$), and instead, place priors on the standard deviation of β_j, represented by ϕ_j.

For this study, two scenarios were considered for the specification of the prior mean: 1) no effect of DBP exposures (*i.e.,* μ_j=0 for all *j*) and 2) the effect of an individual DBP compound is a function of DBP class and bromination status (*i.e.,* $\mu_j = \mu_k$, where μ_k ~N(0,10) and represents the mean of the combined effect of DBP class and bromination status). This latter prior specification of the mean results in shrinkage of the effect for non-brominated THMs (*i.e.,* chloroform), non-brominated HAAs, brominated THMs, and brominated HAAs towards each other, to the extent that the data support a similar effect within groups, and allows "borrowing" of information within groups. For prior specification of the variance of effects of DBP exposures, R was set at 0.70 for the SGA analysis (mean value of φ = 0.35) and 100 (mean value of φ = 50) for the term birth weight analysis. In a semi-Bayesian approach with fixed *R*, these mean values would corresponds to a 95% range in risk ratios (RR) for SGA of 0.5 to 2.0 and 95% range in mean difference in birth weight of -100 to 100 grams, respectively.

Marchov Chain Monte Carlo (MCMC) was implemented to obtain posterior distributions, including the mean effect for each DBP category and an associated 95% posterior interval (PI), which can be interpreted as an interval that has a high probability (95%) of containing the unknown quantity of interest [114]. Three chains were simulated, with 5,000 iterations run for each chain. The first 2,500 iterations of each chain were discarded as "burn-in", and the remaining iterations were thinned by keeping every 7th simulation drawn to avoid dependence of iterations from the same chain[114], resulting in a total of 1,074 simulations saved.

For simplicity, the above model does not explicitly show adjustment for confounding variables but these variables were taken into consideration in Bayesian analyses. Three sets of Bayesian analyses were conducted: one using all women, one restricted to women from the chlorinated DBP site and one restricted to women from the brominated DBP site. Unlike the MLE analyses, the Bayesian analyses could be restricted to the brominated DBP site and still provide reasonably stable results.

Assessing effect measure modification

Maternal age, race/ethnicity and swimming during pregnancy were evaluated as potential effect measure modifiers. Maternal age and race/ethnicity were chosen because it seems biologically plausible that the effect of DBP exposure may vary by age of the mother and/or across race and ethnicity groups. Modification by swimming during pregnancy is of interest as one might hypothesis that exposure to DBPs (particularly chlorinated THMs) while swimming in a chlorinated pool would far surpass exposure incurred through tap water

alone, making an observable effect of DBP exposure via tap-water exposure alone less likely among swimming mothers.

The presence of odds ratio modification was assessed by both visual inspection and statistical testing. Stratum-specific effect estimates for each potential effect measure modifier were calculated and graphed to get a visual impression of interaction. Statistical significance of modification was assessed by constructing DBP-covariate interaction terms and retaining the terms if the *p*- value for the joint effect of all terms was < 0.10. The set of interaction terms for each potential effect modifier were assessed separately to avoid over-specification of the model.

Assessing confounding

Covariates identified from the literature as potential confounders are listed in table 16 (section 4.7). Confounding was first examined using a backwards elimination approach starting with a full model that included all covariates and the DBP exposure of interest. Covariates that resulted in < 10 percent change in one or more of the estimates for DBP exposure were then dropped from the model until a final reduced model was obtained. Very few covariates were retained in the model as "confounders" according to this method of confounder selection. Nonetheless, full models were not notably less precise than the reduced models. Given that impacts on precision were minimal but residual confounding by study site was a great concern, it was ultimately decided to adjust for all risk factors identified from the literature as risk factors for fetal growth restriction that may be independently associated with DBP exposure but not on the causal pathway between exposure and disease according to directed acyclic graph analysis[115]. All variables in table

16 met this criterion except maternal alcohol use and smoking, which were infrequently reported across sites, and infant birth weight. In addition, site-specific analyses were re-run to assess the potential for residual confounding by site.

Power calculations for SGA analyses

Table 17 presents results of preliminary power calculations conducted to determine the power of this study to detect odds ratios of varying magnitude for SGA. A sample size of 450 participants per DBP exposure quartile (or, a total of 900 women for each exposure contrast) was assumed for the comparison of women in an "exposed" quartile (*e.g.,* $\geq 75^{th}$ percentile) to women in the referent quartile (*i.e.,* $< 25^{th}$ percentile). Similarly, samples sizes of 600 and 360 were used for tertile and quintile contrasts, respectively. For comparing women exposed to residential THM4 concentrations ≥ 80 versus < 80 micrograms/liter, it was assumed that approximately 260 women would be "exposed" and 1540 would be "unexposed". In all calculations, it was assumed the "unexposed" prevalence of SGA infant was 0.06, which was the prevalence of SGA infant found among all RFTS births in preliminary analyses.

Table 17. Power calculations for SGA analysis [a]

	Power (%) for contrast			
OR	Quartiles	Tertiles	Quintiles	TTHM MCL (80 µg/liter)
1.2	11	11	8	13
1.4	29	30	20	33
1.6	52	56	37	58
1.8	75	78	56	78
1.9	83	86	65	85
2.0	90	92	73	90
2.2	97	98	86	97

a Alpha = 0.05, Prevalence of SGA infant among "unexposed" = 0.06
b total sample size of 900 for contrast between an "exposed" quartile (2nd, 3rd, or 4th quartile) and the lower, "unexposed" quartile (1st quartile), 1200 for tertile contrast and 720 for quintile contrast.
c total sample size of 1800 for contrast between THM4 ≥ 80 versus < 80 µg/liter

According to preliminary power calculations, there was adequate power (≥ 80%) to detect an OR ≥ 1.9 for all exposure contrasts of interest except when using quintiles. The study was underpowered to detect ORs of ≤ 1.5, which is approximately the range of OR estimates reported by previous studies. However, there were several issues to consider when interpreting these preliminary calculations:

- An overall sample size of 1800 births was assumed in power calculations to account for the fact that some observations may be dropped due to incomplete information on outcome, exposure or covariates. It was proposed that the final complete case sample size might actually be greater, which would improve power. This was not the case.
- Power calculations did not take into account adjustment for confounding or stratification by effect measure modifiers, which may influence power.
- A constant probability of SGA infants was assumed across study sites to simplify calculations but probabilities in fact varied slightly between sites.
- A stronger estimated effect of DBP exposure than that found in previous studies was expected (if causal) given the improvements in proposed exposure methods.
- Power would be higher for modeling DBP exposure continuously.

Post-hoc assessment of power via examination of estimated 95% confidence intervals (see chapter 4, section 4.1) indicate that power was less than ideal in this study but within the range predicted by preliminary power calculations. As such, the inability to detect moderate effects of DBP exposure on the probability of delivering an SGA infant must be taken into account when interpreting results.

Power calculations for term birth weight analyses

Table 18 presents preliminary power calculations for detecting a difference in mean term birth weight when comparing women with a DBP exposure in an upper quintiles of exposure (*e.g.,* ≥ 80th percentile) to women with an exposure level in the lowest quintile (<20th percentile). A sample size of 670 infants was used to calculate power for the quintile contrast. This number was derived by multiplying the expected number of term infants in the study sample (n=1675) by the percentage of term infants expected to fall within the two exposure quintiles being compared (40%). In addition, the standard deviation (SD) for DBP exposure category (coded 0 or 1) was set at 0.5 and root mean square error (RMSE) at 455 for all calculations (derived from preliminary analyses).

Table 18**.** Power calculations for difference in mean term birth weight [a,b]

Absolute difference in mean birth weight	Power(%)
10	5
25	10
50	29
80	62
100	81
150	98
200	99

a Alpha = 0.05, σ(x) = 0.5 and σ(y.x) =455 ; b total sample size fixed at 670 term infants for each exposure contrast, assuming 40% of subjects fall into "exposed" (2nd, 3rd, 4th or 5th quintile) or "unexposed" (1st quintile) category for comparison at hand.

According to preliminary power calculations, there was adequate power (≥ 80%) to detect a mean difference in term birth weight of approximately 100 grams or greater. However, the study was underpowered to detect differences of -1 to -70 grams, which is the range of differences found for residential TTHM exposure in previous studies. It is also important to note that these power calculations did not take into account adjustment for confounding or stratification by effect measure modifiers. Ultimately, *Post-hoc* assessment of power via examination of estimated 95% confidence intervals (see chapter 4, section 4.3) indicate that

power was less than ideal in this study but within the range predicted by preliminary power calculations. As such, the inability to detect moderate effects of DBP exposure on the distribution of birth weight among term infants must be taken into account when interpreting results.

3.8.4 Analytic plan for specific aim #2

Discrete hazard regression with a logit link and time interactions was used to estimate the effect of DBP exposure during pregnancy on duration of gestation by modeling the effect of DBP exposure on the odds of delivery each week conditional on a woman not having delivered in a prior week [116]. This model is analogous to a partially unconstrained continuation log odds model because categorical time interactions between DBP exposure and pregnancy intervals of ≤ 32 weeks', 32-36 weeks', 37-40 weeks', ≥ 41 weeks' will be included in the model. This model can be written as follows:

$$\text{logit}(h(t_{ij})) = z_{ij}'\alpha + x_{ij}'\beta_K$$

In this model, $h(t_{ij}) = \Pr(T_i = j \mid T_i \geq j, x_{ij})$ is the probability that the week of pregnancy delivery for subject *i* (indicated by T_i) is equal to week *j*, given that subject *i* did not deliver in a week preceding week *j*. The $\text{logit}(h(t_{ij}))$ is the log odds of that probability (*i.e.,* a discrete hazard model using a logit link). The vector x_{ij} represents a DBP concentration summary (*e.g.,* vector of indicator variables for quantile categories of the DBP exposure of interest) for subject *i* at pregnancy week *j*. The β_k's describe the association between DBP exposure and the log odds of delivery during pregnancy intervals k=1,2 3, and 4 (≤ 32 weeks, 32-36 weeks, 37-40 weeks, and ≥ 41 weeks, respectively. The vector product $z_{ij}'\alpha$ represents week-specific

intercepts, which will account for the varying baseline probability of delivery as pregnancy progresses, and the association between potential confounders of interest and the log odds of delivery.

The partially unconstrained continuation log odds model has several advantages. First, it avoids having to dichotomize infants into preterm and term births (*e.g.,* <37 weeks *vs.* ≥ 37 weeks). Second, the model allows estimation of an odds ratio for the effect of exposure during each pregnancy interval (*i.e.,* allows the effect of exposure to vary over the course of pregnancy). As a result, an effect of exposure early in gestation, when there are fewer births, is not dominated by the effect of exposure at later weeks, when the number of births is greater. Finally, this model facilitates easy incorporation of time-varying exposures. Gestational intervals ≤ 32 weeks, 32-36 weeks, 37-40 weeks and ≥ 41 weeks were chosen because these intervals represent meaningful groups (very preterm, moderately preterm, term and post-term births, respectively) and there are a reasonable number of births during each interval to support statistical analyses.

Coding of DBP exposures and assessment of effect modification and confounding

As outlined in section 3.6, aggregate DBP measures examined in duration of gestation analyses were TTHM, HAA5 and TOX. Two exposure metrics (residential DBP concentrations and personal DBP exposure) and three exposure "windows" (second trimester, weekly, and 6-week sliding average exposure) were considered for each DBP measure. Coding of DBP exposures was identical to that outlined for specific aim 1. Assessment of effect measure modification and confounding was the same as that outlined for specific aim 1.

Power calculations

Table 19 presents preliminary power calculations for duration of gestation analyses. Because there is no computer software program available to calculate power for a discrete hazard analysis, the power to detect ORs of varying magnitude for each gestational interval ($\leq$ 32 weeks, 32-36 weeks, 37-40 weeks and $\geq$ 41 weeks) was approximated using power calculation software for traditional time-to-event methods (specifically, a two group test of equal exponential survival with no dropouts). These calculations assumed a constant exponential rate of birth over the period of follow-up, which is a reasonable assumption within the pregnancy intervals examined. For the first pregnancy interval, a sample size of 450 participants was assumed at the beginning of the interval in each DBP exposure quartile and a 2% probability of delivery among the "unexposed". For the second, third and last pregnancy interval, initial sample sizes of 440, 405 and 60 participants were assumed per DBP exposure quartile and interval-specific delivery probabilities of 8%, 85% and 100% among the unexposed.

Table 19. Power calculations for duration of gestation analyses[a,b,c]

Pregnancy Interval							
≤ 32 weeks		33-36 weeks		37-40 weeks		≥ 41 weeks	
OR	Power (%)	OR	Power (%)	OR	Power (%)	OR	Power (%)
1.5	15	1.5	45	1.1	24	1.5	49
2.0	40	1.8	79	1.2	67	1.8	81
2.5	65	1.9	86	1.3	93	1.9	87
3.0	82	2.0	91	1.4	99	2.0	92
3.5	91	2.2	97	1.5	99	2.2	97

a Alpha = 0.05.
b Contrast between an "exposed" quartile (2nd, 3rd, or 4th quartile) and the referent quartile (1st quartile), 1200 for tertile contrast and 720 for quintile contrast.
c Initial sample sizes per quartile for the first, second, third and last pregnancy interval were set at 450, 440, 405 and 60 participants.

According to preliminary power calculations, there was adequate power (≥ 80%) to detect an odds ratio for delivery of 1.3 or higher for the pregnancy interval 37-40 weeks, an odds ratio of 1.8 or higher for the pregnancy intervals 33-36 and ≥ 41 weeks, and an odds ratio of 3.0 or higher for the interval ≤ 32 weeks. Of note, the initial sample sizes for subsequent pregnancy intervals were calculated under the simplifying assumption that an equal number of births would occur in each exposure category in the proceeding interval; however, this would not be the case if exposure influences the probability of delivery in the preceding interval. Furthermore, these power calculations did not take into account adjustment for confounding or stratification by effect measure modifiers. *Post-hoc* assessment of power via examination of estimated 95% confidence intervals (see chapter 4, section 5.1) indicate that power was better than predicted by preliminary power calculations.

3.9 Software use

Data cleaning was conducted using SAS 8.2 (SAS Institute, Inc., Cary, NC) and Stata 9.2 (Statcorp, College Station, TX). Univariate, bivariate and MLE analyses were conducted

using Stata. Bayesian analyses were conducted using R (R Development Core Team, Vienna, Austria)[117] and WinBUGS 1.4.2 (2007 MRC Biostatistics Unit, Cambridge, UK)[118].

3.10 Required Approvals

The Public Health IRB at the University of North Carolina at Chapel Hill determined that this dissertation does not constitute human subjects research as defined under federal regulations, and therefore does not require IRB approval (Study #: 06-0082).

CHAPTER 4: GENERAL RESULTS

4.1 Study population characteristics

Table 20 presents the distributions of maternal demographic and health behavior variables, pregnancy-related variables, and tap water exposure variables for women included in duration of gestation analyses (*n*=2,039). General descriptive statistics were calculated among this group of women because they also serve as the base for women included in SGA and term birth weight analyses. The description "women eligible for inclusion in live birth analyses" is used to refer to this group of women in subsequent text, tables and figures.

A considerably higher number of women were missing data on annual household income (number missing = 82) and body mass index (BMI) (number missing = 51) compared to other covariates, but the percentage of missing data for all variables was still under 5%. In addition, a number of women did not report information on swimming in a pool and/or Jacuzzi use at follow-up interview (n= 169). For these women, pool or Jacuzzi use at follow-up was assumed to be the same as that reported at baseline when creating the final indicator variable for pool or Jacuzzi use anytime during gestation (yes/no) shown below in table 20. Very few women (< 5%) reported alcohol use or smoking during pregnancy or reported "Other" maternal race/ethnicity (*i.e.,* "Indian", "Asian/Pacific islander", or "Other").

Table 20. Descriptive statistics describing the distribution of variables to be used in live birth analyses among women eligible for inclusion in live birth analyses, 2000-2004 (n=2,039)

Variable	Categorical coding		Continuous coding						
					Percentile Values			Range	
	N (*n* missing)	%	Mean	SD	25%	50%	75%	Min	Max
MATERNAL DEMOGRAPHICS									
Reported household Income ($/year)									
<5,000	64	3.3							
5,001-10,000	108	5.5							
10,001-15,000	141	7.2							
15,001-20,000	143	7.3							
20,001-30,000	181	9.2				NA			
30,001-40,000	188	9.6							
40,001-60,000	347	17.7							
60,001-80,000	321	16.4							
> 80,000	465	23.8							
Missing	(81)								
Annual Household Income Category ($/year)									
<30,000	637	32.5							
30,001-60,000	535	27.3				NA			
60,001-80,000	321	16.4							
>80,000	465	23.8							
Missing	(81)								
Body Mass Index (kg/m^2)									
< 19.8	232	11.7							
19.8-25.9	1,016	51.1							
26.0-29.9	333	16.8	25.8	6.4	21.3	24.1	28.5	15.1	64.0
> 29.9	407	20.5							
Missing	(51)								
Caffeine intake (mg/day)									
0	519	25.5							
1-150	468	23.0							
151-300	387	19.0	301.1	429.9	0	153.8	396.1	0	4801.1
> 300	665	32.6							
Employment									
Employed	608	29.8				NA			
Unemployed	1,430	70.2							
Missing	(1)								
Maternal Age (years)									
< 25	599	29.4							
25-59	657	32.2							
30-35	564	27.7	28.2	5.3	24.1	28.3	32.1	17.8	44.7
>= 35	219	10.7							
Maternal alcohol use									
Yes	2,007	98.4				NA			
No	32	1.6							
Maternal education level									
≤ HS	573	28.1							
Some college	440	21.6	14.6	2.6	12.0	16.0	16.0	3.0	22.0
4+ years college	1,025	50.3							
Missing	(1)								

Self-reported marital status									
Single	588	28.9							
Married	1,390	68.2							
Separated	33	1.6				NA			
Divorced	26	1.3							
Widowed	1	0.1							
Missing	(1)								
Maternal marital status									
married	1,390	68.2				NA			
not married	648	31.8							
Missing	(1)								
Maternal race									
White	1,229	60.3							
Black	614	30.1				NA			
Indian	5	0.3							
Asian	43	2.1							
Other	146	7.2							
Missing	(2)								
Hispanic ethnicity									
Yes	1,853	90.9				NA			
No	185	9.1							
Missing	(1)								
Maternal Race/ethnicity									
Non-Hispanic White	1,169	57.4							
Non-Hispanic Black	609	29.9				NA			
Hispanic	185	9.1							
Other	73	3.6							
Missing	(3)								
Maternal Smoking									
Smoker	1,940	95.1				NA			
Non-smoker	99	4.9							
Study Site									
Chlorinated	929	45.6							
Brominated	349	17.1				NA			
Low	791	37.3							
PREGNANCY RELATED VARIABLES									
Self-reported LMP	2021	NA	11/21/02	NA				10/20/00	3/18/04
Missing	(18)								
Certainty in LMP									
very sure	1,368	68.6							
pretty sure	398	20.0				NA			
somewhat sure	156	7.8							
very uncertain	72	3.6							
Missing	(45)								
Estimated Gestational age at delivery									
LMP	2021 (18)	NA	274.1	15.4	269	276	283	152	315
Ultrasound	1881 (158)	NA	273.5	13.7	269	276	281	155	307
LMP corrected by ultrasound	2039	NA	273.4	13.9	269	276	282	152	310
Infant Birth Weight	2,039	NA	3380.4	589.4	3085.7	3400.0	3742.9	428.6	5228.6

Infant sex									
female	994	49.0				NA			
male	1045	51.0							
Number of previous live births (parity)									
0	993	48.6							
1	674	33.0	0.8	1.0	0	1	1	0	9
≥ 2	375	18.4							
VARIABLES RELATED TO PERSONAL DBP EXPOSURE (baseline)									
Reported swimming in pool or Jacuzzi currently at baseline									
No	1402	68.8				NA			
Yes	637	31.2							
Portion of water filtered at home									
None	144	70.9							
Some	26	1.3							
half	69	3.4				NA			
most	93	4.6							
all	406	19.9							
missing	(1)								
Portion of water filtered at work									
None	1493	73.2							
Some	234	11.5							
half	153	7.5				NA			
most	65	3.2							
all	94	4.6							
Consumption of cold tap water at home (ounces/day)	2037 (2)	NA	43.7	39.8	13.4	35.3	64.0	0.0	336.0
Consumption of hot tap water at home (ounces/day)	2039	NA	3.8	8.7	0.0	0.0	3.6	0.0	91.0
Total consumption of tap water at home (ounces/day)	2037 (2)	NA	47.5	41.6	16.0	40.3	66.0	0.0	336.0
Consumption of cold tap water at work (ounces/day)	2038 (1)	NA	13.2	18.8	0.0	2.6	23.7	0.0	188.2
Consumption of hot tap water at work (ounces/day)	2038 (1)	NA	1.5	4.5	0.0	0.0	0.0	0.0	74.9

Total consumption of tap water at work (ounces/day)	2037 (2)	NA	14.8	20.1	0.0	5.2	24.0	0.0	188.2
Total consumption of cold tap water (ounces/day)	2037 (2)	NA	57.0	48.4	16.0	48.0	80.0	0.0	336.0
Total consumption of hot tap water (ounces/day)	2038 (1)	NA	5.3	11.4	0.0	0.0	7.0	0.0	156.0
Total tap water consumption (ounces/day)	2036 (1)	NA	62.3	50.3	21.0	56.0	91.0	0.0	340.0
Total time spent showering (minutes/day) at baseline	2038 (1)	NA	16.7	15.7	10.0	15.0	20.0	0	270.0
Total time spent bathing (minutes/day) at baseline	2036 (3)	NA	5.8	15.4	0	0	5.7	0	270.0
Total time spent showering (minutes/day) at follow-up	2039	NA	14.2	13.5	8.0	10.0	17.1	0	180.0
Total time spent bathing (minutes/week) at follow-up	2038 (1)	NA	5.2	14.0	0	0	4.3	0	190.0

Abbreviations: DOB= date of birth, HS = high school, LMP= last menstrual period, NA= not applicable

Table 21 presents the distributions of study population characteristics (*i.e.,* final "cleaned" variables used in regression models as confounders and/ or effect measure modifiers) by study site. Women from the brominated disinfection by-product (DBP) site were more likely to be Hispanic, overweight, and parous, less likely to be employed during pregnancy or married, and tended to be younger, less educated, and have a lower income than women from the chlorinated and low DBP sites. Although women from the chlorinated and low DBP sites were much more similar, women from the chlorinated site were still slightly

older, more educated, had higher income and were more likely to be non-Hispanic White than those from the low DBP site. In addition, women at the chlorinated site were more likely to report swimming in a pool or Jacuzzi during pregnancy than women from the brominated or low sites. The distribution of daily caffeine intake was similar across sites.

Table 21. Participant characteristics by site among women eligible for inclusion in live birth analyses, 2000-2004

	Chlorinated DBP site (n=929)		Brominated DBP site (n=349)		Low DBP site (n=761)	
Covariate	N	Col %	N	Col %	N	Col %
Maternal Age (years)						
< 25	195	21.0	168	48.1	236	31.0
25-29	294	31.7	114	32.7	249	32.7
30-35	321	34.6	47	13.5	196	25.8
≥ 35	119	12.8	20	5.7	80	10.5
Maternal Race/ethnicity						
Non-Hispanic White	623	67.1	125	35.9	421.0	55.5
Non-Hispanic Black	234	25.2	78	22.4	297.0	39.1
Hispanic	29	3.1	138	39.7	18	2.4
Other	43	4.6	7	2.0	23	3.0
Missing	0		1		2	
Highest education level obtained						
High school or less	157	16.9	186	53.3	230	30.3
Some college	172	18.5	95	27.2	173	22.8
College degree or more	600	64.6	68	19.5	357	47.0
Missing	0		0		1	
Annual household income ($)						
<30,000	200	22.3	200	60.2	237	32.5
30,001-60,000	263	29.4	73	22.0	199	27.3
60,001-80,000	162	18.1	31	9.3	128	17.5
>80,000	271	30.3	28	8.4	166	22.7
Missing	33		17		31	
Employed during pregnancy						
Non-employed	262	28.2	131	37.5	215	28.3
Employed	667	71.8	218	62.5	545	71.7
Missing	0		0		1	
Marital status						
Married	696	74.9	185	53.2	509	66.9
Not married	233	25.1	163	46.8	252	33.1
Missing	0		1		0	
Pre-pregnancy BMI (kg/m^2)						
<19.8	122	13.4	27	8.3	83	11.1
19.8-25.9	500	54.7	151	46.3	365	48.8
26.0-29.9	139	15.2	59	18.1	135	18.1
>29.9	153	16.7	89	27.3	165	22.1
Missing	15		23		13	

Daily caffeine intake (mg/day)						
0	256	27.6	81	23.2	182	23.9
1-150	198	21.3	79	22.6	191	25.1
151-300	154	16.6	76	21.8	157	20.6
>300	321	34.6	113	32.4	231	30.4
Parity						
Nulliparous	493	53.1	148	42.4	350	46.0
Parous	436	46.9	201	57.6	411	54.0
Pool or Jacuzzi use						
No	605	65.1	257	73.6	540	71.0
Yes	324	34.9	92	26.4	221	29.0

Abbreviations: BMI = body mass index, DBP= disinfection by-product

4.2 Distributions of birth outcomes

Among all participants eligible for outcome-specific analyses, 5.8 % (113 out of 1,854 included in SGA analyses) delivered an infant that was small-for-gestational-age (SGA) and 9.1% (185 of 2,039 included in preterm birth analyses) delivered preterm. The mean birth weight among term births (*n*= 1854) was 3480.1 grams (standard deviation = 470.4). Table 22 presents the proportion of SGA infants, term mean birth weight, and proportion of preterm infants by study site and other maternal characteristics. The proportion of SGA infants was higher at the brominated DBP site (8.2%) compared to the chlorinated and low DBP sites (4.8% and 5.9%, respectively). Mean birth weight among term births was higher at the chlorinated site compared to the brominated and low DBP sites. The proportions of births born preterm also varied by site (6.1% at the chlorinated DBP site, 12.6% at the brominated DBP site, and 11.0% at the low DBP site). The breakdown of live birth outcomes by other maternal characteristics followed expected patterns of association. Crude associations between birth outcomes and DBP exposures are provided in section 4.4.

Table 22. Distribution of live birth outcomes by maternal characteristics among women eligible for inclusion in analyses of live birth outcomes, 2000-2004

	Women included in SGA analyses (n=1,958)		Women included in term birth weight analyses (n=1,854)		Women included in preterm birth analyses (n=2,039)	
Covariate	N	% SGA	N	Mean birth weight	N	% preterm
Study site						
Chlorinated DBP site	883	4.8	872	3530.5	929	6.1
Brominated DBP site	340	8.2	305	3406.3	349	12.6
Low DBP site	735	5.9	677	3448.3	761	11.0
Maternal Age (years)						
< 25	579	7.4	534	3361.9	599	10.9
25-29	631	5.7	603	3480.9	657	8.2
30-35	543	4.1	523	3567.0	564	7.3
≥ 35	205	5.9	194	3568.3	219	11.4
Maternal Race/ethnicity						
Non-Hispanic White	1168	4.9	1082	3560.4	1169	7.4
Non-Hispanic Black	605	7.4	533	3316.4	609	12.5
Hispanic	185	5.9	169	3499.1	185	8.6
Other	0	.	68	3444.7	73	6.8
Highest education level obtained						
High school or less	561	8.9	500	3366.5	573	12.7
Some college	423	5.4	398	3454.8	440	9.5
College degree or more	973	4.1	955	3550.1	1025	6.8
Annual household income ($)						
<30,000	610	6.9	561	3385.8	637	11.9
30,001-60,000	511	6.7	497	3505.8	535	7.1
60,001-80,000	310	4.8	303	3495.6	321	5.6
>80,000	450	3.1	428	3593.0	465	8.0
Employed during pregnancy						
Non-employed	580	6.6	551	3514.1	608	9.4
Employed	1377	5.4	1303	3465.6	1430	8.9
Marital status						
Married	1334	4.7	1290	3534.6	1390	7.2
Not married	623	8.0	563	3353.5	648	13.1
Pre-pregnancy BMI (kg/m^2)						
<19.8	220	8.6	214	3362.9	232	7.8
19.8-25.9	978	5.1	934	3487.9	1016	8.1
26.0-29.9	317	5.7	311	3490.1	333	6.6
>29.9	398	4.8	349	3539.1	407	14.3
Daily caffeine intake (mg/day)						
0	496	4.4	472	3514.2	519	9.1
1-150	453	5.1	430	3471.4	468	8.1
151-300	371	5.9	346	3453.1	387	10.6
>300	638	7.2	606	3475.0	665	8.9
Parity						
Nulliparous	947	7.1	890	3429.0	991	10.2
Parous	1011	4.5	964	3527.2	1048	8.0
Pool or Jacuzzi use						
No	1339	5.5	1260	3467.1	1402	10.1
Yes	619	6.3	594	3507.6	637	6.8

Abbreviations: BMI = body mass index, DBP= disinfection by-product, SGA= small-for-gestational-age

4.3 Distributions of disinfection by-product exposures

4.3.1 Residential DBP concentrations

Table 23 presents the mean and standard deviation of second trimester average concentrations for aggregate and individual DBP measures by study site. As expected, total trihalomethane (TTHM) concentrations were similar between the chlorinated and brominated DBP sites. While concentrations of the sum of five haloacetic acids (HAA5) and total organic halides (TOX) were elevated at both of the moderate exposure sites, the chlorinated site had slightly higher concentrations of HAA5 and slightly lower concentrations of TOX compared to the brominated DBP site (table 2). In addition, the brominated DBP site had much higher concentrations of the brominated DBP compounds and much lower concentrations of non-brominated compounds compared to the chlorinated DBP site, with the exception of bromodichloromethane (BDCM), chloroacetic acid (CAA), bromochloroacetic acid (BCAA) and bromodichloroacetic (BDCAA), which were found in relatively comparable concentrations between the two moderate exposure sites. Over all, DBP concentrations at the low exposure site were much less than concentrations found at the two moderate exposure sites. Means and standard deviations for DBP concentrations were essentially the same when restricted to births included in the SGA analyses alone and term births alone and when examining first and third trimester average DBP concentrations.

Table 23. Second trimester average residential DBP concentrations[a, b] across study sites among women eligible for inclusion in live birth analyses, 2000-2004

DBP (µg/liter)	Chlorinated DBP site (n=929)	Brominated DBP site (n=349)	Low DBP site (n=761)
Trihalomethanes			
Chloroform	46.7 (13.3)	13.7 (3.3)	0.2 (0.2)
BDCM	15.1 (4.4)	21.1 (2.9)	1 (0.2)
DBCM	4.4 (2.1)	23.1 (6.5)	1.4 (0.2)
Bromoform	0.2 (0.2)	5.7 (3.9)	0.7 (0.1)
TTHM[c]	66.4 (15.8)	63.6 (11.8)	3.3 (0.6)
Haloacetic Acids			
CAA	2.8 (1.1)	1.7 (0.9)	0 (0.1)
DCAA	18.7 (3.5)	7.1 (1.8)	0 (0)
TCAA	13.6 (5)	5.3 (1.8)	0 (0.1)
BCAA	4.6 (1.3)	8.9 (1.3)	0.8 (0.7)
BDCAA	4.6 (1.4)	8.2 (0.7)	0 (0)
DBCAA	1.2 (0.6)	5.6 (1.2)	0.4 (0.6)
BAA	0.1 (0.1)	0.7 (0.5)	0 (0)
DBAA	0.7 (0.5)	6.2 (2.6)	0 (0.1)
TBAA	0.2 (0.3)	2.7 (0.9)	0.2 (0.4)
HAA5[d]	35.9 (8.6)	21.1 (2.5)	0.08 (0.1)
TOX	173.8 (16.3)	195.3 (16.7)	17.7 (2.0)

a Mean (standard deviation)
b Weekly DBP concentrations below the practical quantitation limit (PQL) were set to zero for calculation of second trimester average residential DBP concentrations
Abbreviations: DBP= disinfection by-product, BDCM= bromodichloromethane, DBCM = dibromochloromethane, TTHM = total trihalomethane, CAA= chloroacetic acid, DCAA=dichloroacetic acid, TCAA=trichloroacetic acid, BCAA= bromochloroacetic acid, BDCAA= bromodichloroacetic acid, DBCAA= dibromochloroacetic acetic acid, BAA= bromoacetic acid, DBAA= dibromoacetic acid, TBAA= tribromoacetic acid, HAA5 = sum of five haloacetic acids, TOX= total organic halides.
c TTHM is the sum of chloroform, BDCM, DBCM and bromoform
d HAA5 is the sum of CAA, DCAA, TCAA, BAA, DBAA

Figures 5, 6 and 7 are plots of weekly TTHM, HAA5 and TOX concentrations, respectively, from gestational week 20 until birth (or until water sampling ended) for 30 women randomly selected from the three study sites (10 women from each site). As in table 23, TTHM concentrations are comparable between the two moderate exposure sites, but HAA5 concentrations are lower at the brominated DBP site compared to the chlorinated site. Furthermore, TTHM and HAA5 concentrations appear to be less stable overtime at the brominated DBP, at least among this particular sample of women. For each site, variability in aggregate DBP exposures between and within women overtime appears similar.

Figure 8. Weekly residential concentrations of total trihalomethane (TTHM) from gestational week 20 until birth among 30 women randomly selected from the group of women eligible for inclusion in live birth outcome analyses.

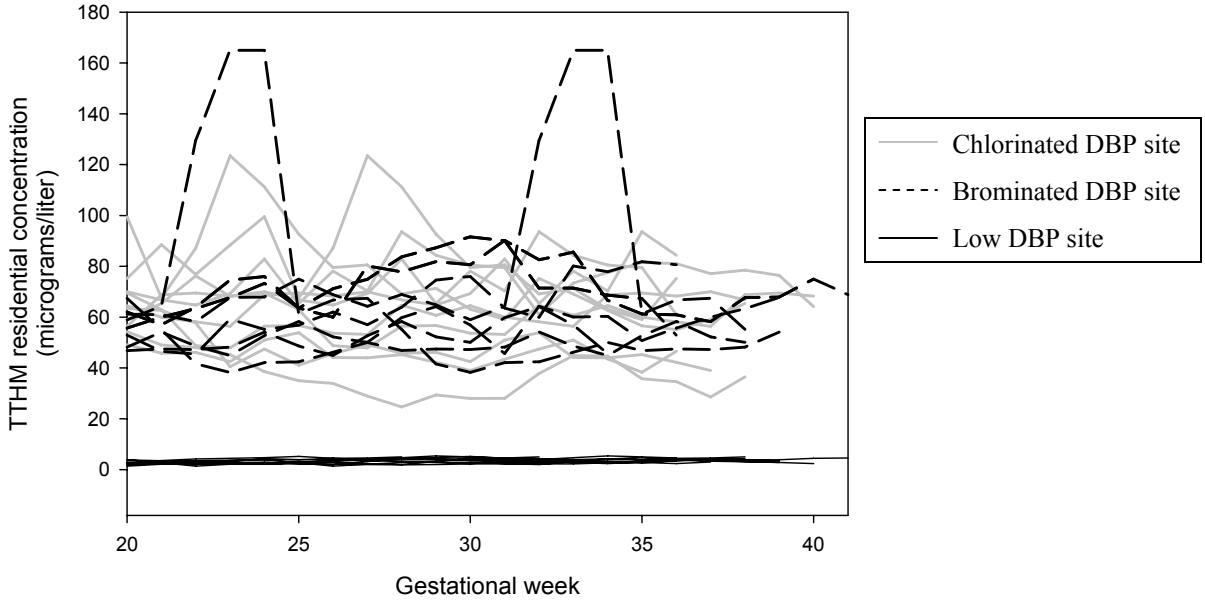


Figure 9. Weekly residential concentrations of the sum of five haloacetic acids (HAA5) from gestational week 20 until birth among 30 women randomly selected from the group of women eligible for inclusion in live birth outcome.

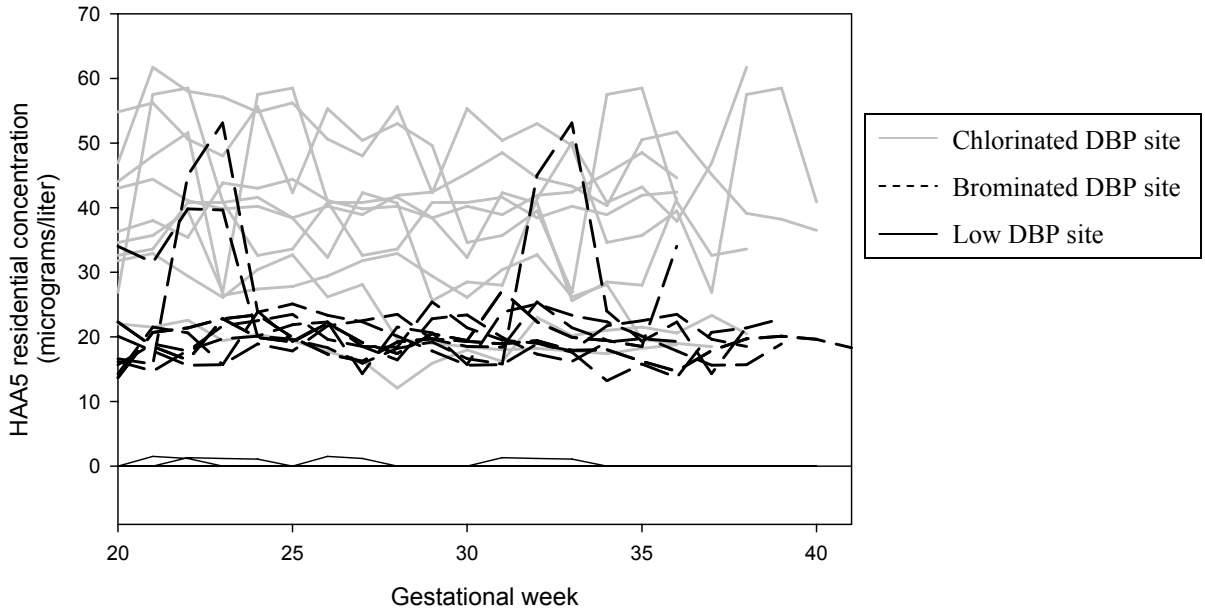
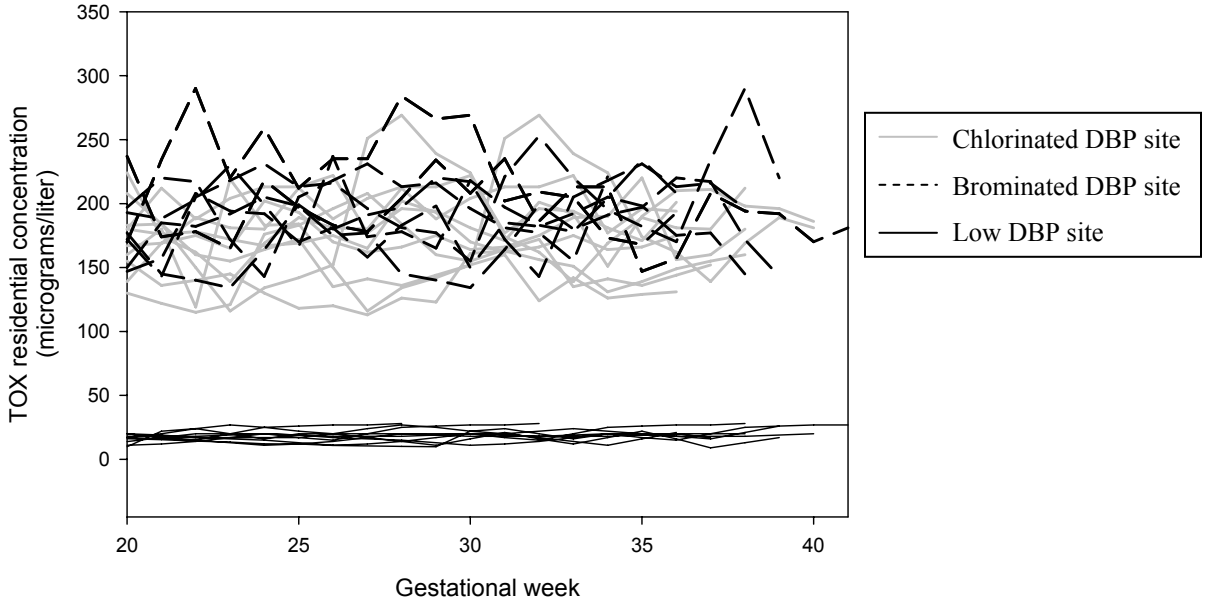


Figure 10. Weekly residential concentrations of total organic halide (TOX) from gestational week 20 until birth among 30 women randomly selected from the group of women eligible for inclusion in live birth outcome analyses.



4.3.2 Personal DBP exposure

Table 24 present the percentage of women falling within categories of personal TTHM, HAA5 and TOX exposure by trimester (first, second and third) and study site. Cut-points for exposure categorization were derived from second trimester average exposure estimates among all women eligible for live birth outcome analyses (*i.e.,* combined over study sites). Overall, personal TTHM exposure appeared to go down slightly over gestation where as personal exposure to HAA5 and TOX appeared to go up across study sites. Personal TTHM exposure distributions were similar at the chlorinated and brominated DBP sites, but the low exposure site remained the predominant "low exposure" referent TTHM group. Conversely, there was much more overlap in HAA5 and TOX personal exposure

distributions across study sites at the lower end of exposure ranges but few or no women from the low exposure site in the highest category of exposures. This would suggest that residential and personal metrics for TTHM rank women more similarly than residential and personal metrics for HAA5 and TOX when examining the total population of women eligible for analyses. None-the-less, the major factor influencing variability in personal DBP exposure across study sites continues to be residential DBP concentrations.

Table 3. Distribution of second trimester average personal TTHM, HAA5, and TOX exposure by study site among women eligible for inclusion in live birth analyses, 2000-2004

	Chlorinated DBP site[a] (n=929)			Brominated DBP site[b] (n=349)			Low DBP site[c] (n=761)		
	Trimester (col. %)			Trimester (col. %)			Trimester (col. %)		
	First	Second	Third	First	Second	Third	First	Second	Third
TTHM exposure through showering & bathing (µg absorbed /day)									
0.02-0.09	0.1	0.3	2.3	0	0	8.6	64.69	66.5	69.8
0.1-0.8	19.8	22.5	23.4	15.9	14	10.4	35.05	33.2	30
0.9-1.5	39.9	43.1	41.8	32	31	31.1	0.26	0.3	0.27
1.6-27.1	40.2	34.1	32.4	52.2	55	50	0	0.0	0
(Missing)	(1)	(1)	(28)	(2)	(2)	(11)	(2)	(2)	(27)
HAA5 exposure through tap-water consumption (µg consumed /day)									
0	10.78	5.9	8.56	32.7	20	28.6	58.84	63.1	84.1
0.01-16.1	9.05	9.6	7.67	19.8	32	23.3	39.58	36.7	15.9
16.2-54.4	38.9	38	36.56	35.8	34	35.7	1.19	0.1	0
54.7-369.1	41.27	46	47.22	11.8	14	12.4	0.4	0.1	0
(Missing)	(1)	(1)	(29)	(0)	(0)	(10)	(3)	(3)	(27)
TOX exposure through tap-water intake (µg/day)									
0-25.8	12.07	8.6	10.33	33	26	28.9	50.26	44.9	43.3
25.9-75	9.59	9.8	7.78	10.3	11	6.5	44.2	49.7	48.8
75.1-253.5	40.19	39	39.56	27.2	30	28.6	5.54	5.4	7.9
253.6-1827	38.15	42	42.33	29.5	33	36	0	0.0	0
(Missing)	(1)	(1)	(29)	(0)	(0)	(10)	(3)	(3)	(27)

Abbreviations: TTHM = trihalomethane, HAA5 = sum of five haloacetic acids, TOX = total organic halides

a 1 woman from the chlorinated DBP site was missing data on showering and bathing needed to assign first and second trimester average TTHM personal exposure; 1 woman was missing data on tap water consumption needed to assign first, second and third trimester average HAA5 and TOX personal exposure; and an additional 28 women were missing residential DBP concentrations during third trimester needed to assign third trimester average TTHM, HAA5 and TOX personal exposure

b 2 women from the brominated DBP site were missing data on showering and bathing needed to assign first and second trimester average TTHM personal exposure; one of those women was also missing data on showering and bathing needed to assign third trimester average TTHM personal exposure; and an additional 10 women were missing residential DBP concentrations during third trimester needed to assign third trimester average TTHM, HAA5 and TOX personal exposure

c 2 women from the low DBP site were missing data on showering and bathing needed to assign first and second trimester average TTHM personal exposure; 3 women were missing data on tap water consumption needed to assign first and second trimester average HAA5 and TOX personal exposure; and an additional 27 women were missing residential DBP concentrations during third trimester needed to assign third trimester average TTHM, HAA5 and TOX personal exposure

4.4 Results of fetal growth analyses

Results of SGA and term birth weight analyses, addressing specific aim #1 of this dissertation, are summarized in tables below. A brief description precedes each table or figure and any notable findings are highlighted. For all analyses, results for the total study

population are presented first and then followed by the analogous results restricted to the chlorinated site alone.

4.4.1 Associations between DBPs and SGA for all sites

Tables 24-26 present results from SGA models for TTHM, HAA5 and TOX, respectively, combined over study sites. Models were run separately for each trimester and exposure metric (residential versus personal). In addition, models were re-run restricting to infants born after 37 week's gestation ("term SGA"). Overall, estimated RRs comparing quartiles of moderate DBP exposure to the low exposure group did not suggest a consistent association with TTHM, HAA5, or TOX residential levels or personal exposure estimates for any trimester. However, the estimated probability of delivering an SGA infant among women with an average third trimester residential TTHM concentration ≥ 80 micrograms/liter was twice as high as the probability of delivering an SGA infant among women with an average concentration < 80 micrograms/liter (RR [95% confidence interval] = 2.0 [1.1, 3.6]). Similar results were found when results were restricted to term births. Effect measure modification by maternal age, race/ethnicity or swimming during pregnancy was not found (*p*-values for the joint effect of interaction terms ranged from 0.3-0.9).

Dose-response curves for the probability of delivering an SGA infant by third trimester average residential concentrations of TTHM, HAA5 and TOX also did not indicate any consistent pattern of associations (figures 7, 8, and 9, respectively). Similar curves were found when linear spline, restricted quadratic spline and categorical coding of residential concentrations were used.

Table 24. Association between TTHM exposure and the probability of delivering an SGA infant among all women included in SGA analyses from all study sites, 2000-2004

Residential TTHM Concentration (µg/liter)	SGA (n=1,958) # SGA	# Non-SGA	Unadjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]	Term SGA only (n=1,780) # SGA	# Non-SGA	Unadjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]
1st-trimester average								
2.2-4.6	43	692	1.	1.	31	623	1.	1.
33.1-55	21	339	1.00 (0.60,1.65)	1.14 (0.67, 1.97)	15	305	0.99 (0.54,1.81)	1.20 (0.63, 2.26)
55-66.3	16	256	1.01 (0.58,1.75)	1.19 (0.67, 2.12)	16	234	1.35 (0.75,2.42)	1.62 (0.88, 2.99)
66.4-74.8	18	239	1.20 (0.70,2.04)	1.21 (0.67, 2.16)	16	225	1.40 (0.78,2.51)	1.49 (0.79, 2.79)
74.9-108.8	15	319	0.77 (0.43,1.36)	0.82 (0.44, 1.52)	14	301	0.94 (0.51,1.74)	1.05 (0.54, 2.04)
p for trend test[c]			0.8	0.9			0.6	0.3
≥ 80 *vs.* <80[d]	9/104	202/1,643	0.72 (0.37,1.39)	0.65 (0.31,1.37)	9/83	195/1,493	0.84 (0.43, 1.64)	0.77 (0.36, 1.63)
2nd-trimester average								
1.4-5.4	43	692	1.	1.	31	623	1.	1.
24.7-54.8	17	290	0.95 (0.55,1.63)	1.01 (0.55, 1.84)	15	265	1.13 (0.62,2.06)	1.25 (0.64, 2.44)
55.1-65.4	20	289	1.11 (0.66,1.85)	1.26 (0.74, 2.16)	16	264	1.21 (0.67,2.17)	1.35 (0.73, 2.49)
66.6-74.6	15	289	0.84 (0.48,1.49)	0.82 (0.43, 1.55)	13	269	0.97 (0.52,1.83)	1.04 (0.52, 2.06)
74.9-165	18	285	1.02 (0.60,1.73)	1.20 (0.69, 2.08)	17	267	1.26 (0.71,2.24)	1.61 (0.90, 2.90)
p for trend test[c]			0.9	0.7			0.6	0.2
≥ 80 *vs.* <80[d]	8/105	166/1,679	0.78 (0.39,1.58)	0.83 (0.40,1.73)	7/85	158/1,530	0.81 (0.38, 1.71)	0.98 (0.47, 2.06)
3rd-trimester average								
2.1-5.3	41	667	1.	1.	30	602	1.	1.
28.8-54.8	19	258	1.18 (0.70,2.00)	1.22 (0.69, 2.16)	19	245	1.52 (0.87,2.64)	1.61 (0.89, 2.93)
55.1-66.3	15	330	0.75 (0.42,1.34)	0.80 (0.43, 1.50)	11	308	0.73 (0.37,1.43)	0.83 (0.41, 1.70)
66.4-74.7	16	256	1.01 (0.58,1.78)	1.22 (0.68, 2.19)	13	233	1.11 (0.59,2.10)	1.46 (0.76, 2.78)
75.1-133.2	18	274	1.06 (0.62,1.82)	1.28 (0.73, 2.26)	16	250	1.27 (0.70,2.29)	1.51 (0.81, 2.80)
Missing	4	60			3	50		
p for trend test[c]			0.9	0.5			0.7	0.3
≥ 80 *vs.* <80[d]	12/97	108/1,677	1.83 (1.03,3.24)	2.00 (1.09,3.61)	11/78	100/1,538	2.05 (1.13, 3.75)	2.09 (1.11, 3.94)

TTHM exposure through showering and bathing (µg/day)								
1st-trimester average								
0-0.09	25	446	1.	1.	16	404	1.	1.
0.1-0.8	24	467	0.92 (0.53,1.59)	0.87 (0.49, 1.56)	21	426	1.23 (0.65,2.33)	1.23 (0.62, 2.42)
0.9-1.5	26	438	1.06 (0.62,1.80)	1.00 (0.55, 1.79)	22	414	1.32 (0.71,2.49)	1.33 (0.68, 2.61)
1.6-31.2	37	490	1.32 (0.81,2.16)	1.27 (0.75, 2.15)	32	440	1.78 (0.99,3.20)	1.83 (0.98, 3.41)
Missing	1	4			1	4		
2nd-trimester average								
0.1-0.09	25	466	1.	1.	18	424	1.	1.
0.1-0.8	29	460	1.16 (0.69,1.96)	1.10 (0.62, 1.92)	22	414	1.24 (0.67,2.28)	1.21 (0.63, 2.33)
0.9-1.5	24	465	0.96 (0.56,1.66)	0.98 (0.55, 1.76)	22	439	1.17 (0.64,2.15)	1.17 (0.61, 2.22)
1.6-27.1	34	450	1.38 (0.84,2.28)	1.35 (0.79, 2.32)	29	407	1.63 (0.92,2.90)	1.73 (0.95, 3.18)
Missing	1	4			1	4		
3rd-trimester average								
0-0.09	30	511	1.	1.	20	458	1.	1.
0.1-0.8	28	419	1.13 (0.69,1.86)	1.24 (0.71, 2.16)	24	384	1.41 (0.79,2.51)	1.57 (0.83, 2.97)
0.9-1.5	18	444	0.70 (0.40,1.24)	0.99 (0.55, 1.80)	16	420	0.88 (0.46,1.67)	1.19 (0.61, 2.31)
1.6-24.5	33	410	1.34 (0.83,2.17)	1.63 (0.98, 2.73)	29	375	1.72 (0.99,2.99)	2.03 (1.13, 3.67)
Missing	4	61			3	51		

a Unadjusted model.
b Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
c Chi-square test (H_0: $\beta_{DBP} = 0$) for a single, continuous residential DBP concentration term (*i.e.,* linear term); p-value rounded to 1 significant figure
d # SGA and non-SGA presented as number ≥ 80 µg/liter over number < 80 µg/liter.
Abbreviations: RR = risk ratio, CI= confidence interval

Table 25. Association between HAA5 exposure and the probability of delivering an SGA infant among all women included in SGA analyses from all study sites, 2000-2004

	SGA (n=1,958)				Term SGA only (n=1,780)			
Residential HAA5 Concentration (µg/liter)	# SGA	# Non-SGA	Unadjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]	# SGA	# Non-SGA	Unadjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]
1st-trimester average								
0-0.9	43	692	1.	1.	31	623	1.	1.
17.9-22	17	267	1.02 (0.59,1.76)	1.23 (0.68, 2.21)	15	243	1.23 (0.67,2.23)	1.51 (0.79, 2.87)
22.1-31.5	30	338	1.39 (0.89,2.18)	1.53 (0.94, 2.49)	25	305	1.60 (0.96,2.66)	1.94 (1.13, 3.34)
31.6-40.4	11	272	0.66 (0.35,1.27)	0.80 (0.42, 1.55)	9	257	0.71 (0.34,1.48)	0.86 (0.41, 1.80)
40.4-52.8	12	276	0.71 (0.38,1.33)	0.72 (0.36, 1.43)	12	260	0.93 (0.49,1.78)	0.98 (0.48, 2.00)
p for trend test[c]			0.3	0.5			0.7	0.9
2nd-trimester average								
0-1.5	43	692	1.	1.	31	623	1.	1.
12.1-22	28	283	1.54 (0.97,2.43)	1.81 (1.09, 3.00)	23	251	1.77 (1.05,2.98)	2.21 (1.25, 3.91)
22.1-31.5	14	289	0.79 (0.44,1.42)	0.86 (0.46, 1.63)	13	266	0.98 (0.52,1.85)	1.11 (0.56, 2.21)
31.6-40.3	15	291	0.84 (0.47,1.49)	0.88 (0.48, 1.64)	13	275	0.95 (0.51,1.79)	1.13 (0.58, 2.20)
40.7-62.2	13	290	0.73 (0.40,1.34)	0.88 (0.48, 1.62)	12	273	0.89 (0.46,1.70)	1.05 (0.54, 2.02)
p for trend test[c]			0.2	0.6			0.6	0.9
3rd-trimester average								
0-0.6	41	667	1.	1.	30	602	1.	1.
16-21.8	30	366	1.31 (0.83,2.06)	1.35 (0.80, 2.25)	26	331	1.53 (0.92,2.55)	1.71 (0.97, 3.02)
22.1-31.5	12	192	1.01 (0.54,1.90)	1.28 (0.67, 2.45)	11	179	1.22 (0.62,2.39)	1.60 (0.80, 3.22)
31.6-40.3	12	234	0.84 (0.45,1.58)	0.94 (0.49, 1.82)	9	220	0.83 (0.40,1.72)	1.00 (0.48, 2.09)
40.6-56.4	14	326	0.71 (0.39,1.29)	0.90 (0.49, 1.65)	13	306	0.86 (0.45,1.62)	1.08 (0.57, 2.06)
Missing	4	60			3	50		
p for trend test[c]			0.2	0.8			0.6	0.8

HAA5 exposure through tap-water intake (μg/day)								
1st-trimester average								
0	35	597	1.	1.	28	541	1.	1.
0.01-16.1	31	408	1.28 (0.80,2.04)	1.53 (0.92, 2.53)	21	369	1.09 (0.63,1.90)	1.35 (0.75, 2.45)
16.2-54.4	30	446	1.14 (0.71,1.83)	1.47 (0.88, 2.47)	27	409	1.26 (0.75,2.10)	1.76 (1.00, 3.08)
54.7-369.1	17	390	0.75 (0.43,1.33)	0.94 (0.51, 1.70)	16	365	0.85 (0.47,1.56)	1.08 (0.57, 2.05)
Missing	0	4			0	4		
2nd-trimester average								
0	43	538	1.	1.	34	486	1.	1.
0.2-16.1	22	436	0.65 (0.39,1.07)	0.58 (0.33, 1.01)	15	391	0.57 (0.31,1.02)	0.54 (0.28, 1.05)
16.1-54.7	30	427	0.89 (0.57,1.39)	0.99 (0.61, 1.60)	27	391	0.99 (0.61,1.61)	1.18 (0.70, 1.98)
54.7-511.4	18	440	0.53 (0.31,0.91)	0.61 (0.35, 1.06)	16	416	0.57 (0.32,1.01)	0.70 (0.38, 1.26)
Missing	0	4			0	4		
3rd-trimester average								
0	48	712	1.	1.	36	639	1.	1.
0.2-16.1	16	240	0.99 (0.57,1.71)	1.10 (0.61, 1.99)	13	222	1.04 (0.56,1.92)	1.26 (0.66, 2.42)
16.1-54.7	26	402	0.96 (0.61,1.53)	1.08 (0.65, 1.77)	25	370	1.19 (0.72,1.95)	1.41 (0.83, 2.39)
54.7-511.4	19	430	0.67 (0.40,1.12)	0.82 (0.48, 1.40)	15	406	0.67 (0.37,1.21)	0.86 (0.47, 1.57)
Missing	4	61			3	51		

a Unadjusted model.
b Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
c Chi-square test (H_0: $\beta_{DBP} = 0$) for a single, continuous residential DBP concentration term (*i.e.,* linear term) ; p-value rounded to 1 significant figure
Abbreviations: RR = risk ratio, CI= confidence interval

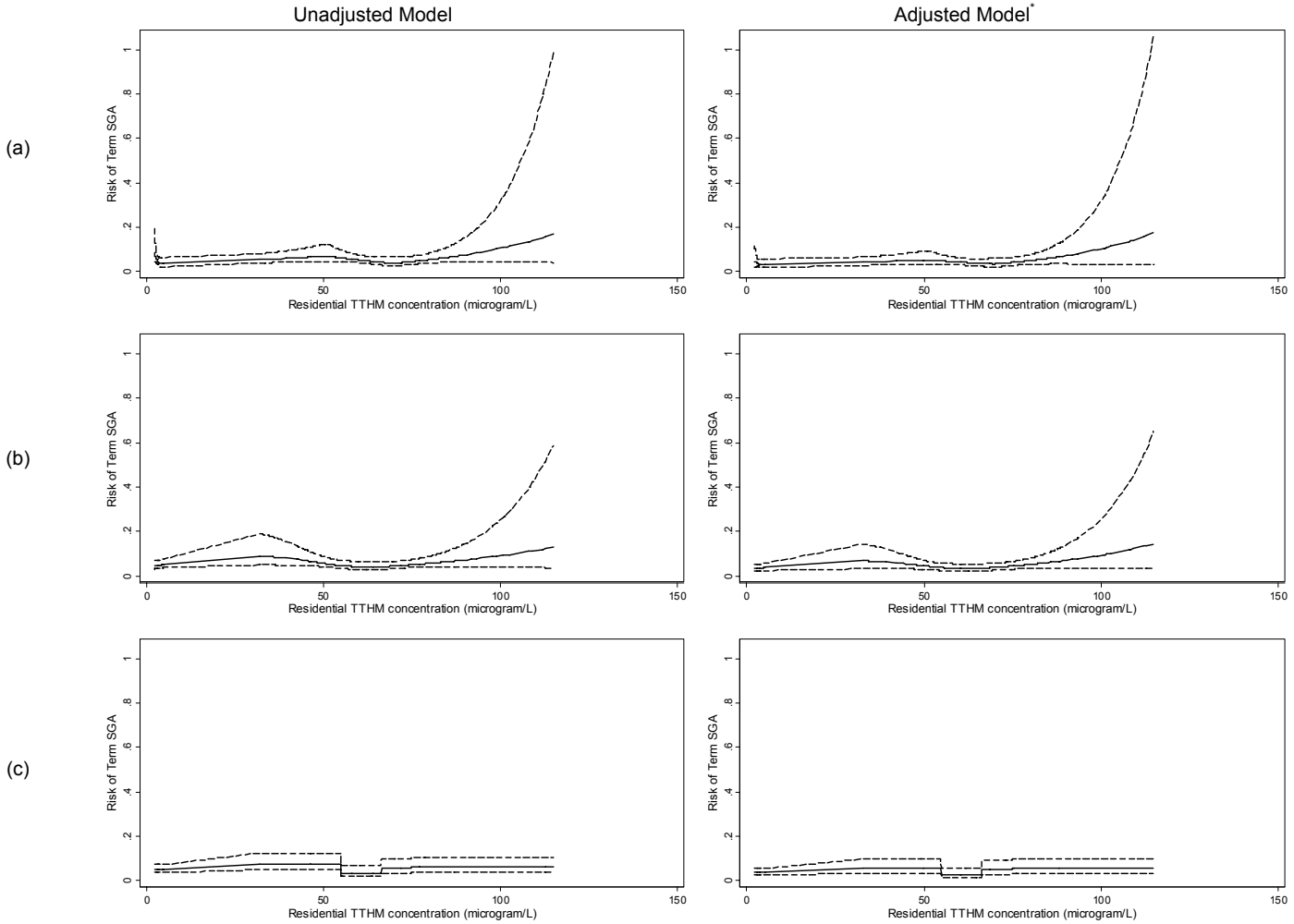
Table 26. Association between TOX exposure and the probability of delivering an SGA infant among all women included in SGA analyses from all study sites, 2000-2004

Residential TOX Concentration (µg/liter)	SGA (n=1,958) # SGA	# Non-SGA	Unadjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]	Term SGA only (n=1,780) # SGA	# Non-SGA	Unadjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]
1st-trimester average								
14.3-22.4	43	692	1.	1.	31	623	1.	1.
136.7-169.6	18	338	0.86 (0.51,1.48)	0.97 (0.55, 1.72)	14	311	0.91 (0.49,1.68)	1.08 (0.57, 2.07)
169.6-177.7	18	315	0.92 (0.54,1.58)	1.10 (0.63, 1.92)	15	285	1.05 (0.58,1.92)	1.24 (0.66, 2.33)
177.7-192.6	18	261	1.10 (0.65,1.88)	1.12 (0.62, 2.00)	17	247	1.36 (0.77,2.41)	1.53 (0.83, 2.83)
192.8-235.2	16	239	1.07 (0.62,1.87)	1.17 (0.64, 2.14)	15	222	1.34 (0.73,2.43)	1.54 (0.80, 2.94)
p for trend test[c]			1.0	0.7			0.4	0.2
2nd-trimester average								
9-28	43	692	1.	1.	31	623	1.	1.
104-169	13	290	0.73 (0.40,1.34)	0.74 (0.38, 1.43)	12	272	0.89 (0.46,1.71)	0.90 (0.44, 1.83)
170-177	23	286	1.27 (0.78,2.07)	1.52 (0.91, 2.55)	21	267	1.54 (0.90,2.63)	1.87 (1.06, 3.31)
178-192	13	293	0.73 (0.40,1.33)	0.77 (0.40, 1.49)	11	272	0.82 (0.42,1.61)	0.98 (0.48, 2.00)
192.8-290	21	284	1.18 (0.71,1.95)	1.34 (0.78, 2.30)	17	254	1.32 (0.75,2.35)	1.62 (0.89, 2.98)
p for trend test[c]			1.0	0.6			0.7	0.2
3rd-trimester average								
10.9-25.5	41	667	1.	1.	30	602	1.	1.
121.7-169.5	16	302	0.87 (0.50,1.52)	0.95 (0.52, 1.74)	15	287	1.05 (0.57,1.91)	1.17 (0.62, 2.23)
170-177.5	16	250	1.04 (0.59,1.82)	1.28 (0.71, 2.31)	13	237	1.10 (0.58,2.07)	1.46 (0.76, 2.81)
177.8-192.5	13	288	0.75 (0.41,1.37)	0.78 (0.40, 1.52)	11	265	0.84 (0.43,1.65)	0.95 (0.46, 1.93)
192.7-250.2	23	278	1.32 (0.81,2.16)	1.49 (0.87, 2.53)	20	247	1.58 (0.91,2.73)	1.83 (1.02, 3.30)
Missing	4	60			3	50		
p for trend test[c]			0.8	0.4			0.4	0.1

TOX exposure through tap-water intake (μg/day)								
1st-trimester average								
0-25.8	44	541	1.	1.	33	490	1.	1.
25.9-75	15	426	0.45 (0.26,0.80)	0.48 (0.26, 0.90)	10	387	0.40 (0.20,0.80)	0.44 (0.21, 0.93)
75.1-252.9	27	466	0.73 (0.46,1.16)	0.95 (0.58, 1.56)	24	429	0.84 (0.50,1.40)	1.14 (0.66, 1.95)
253.6-1302.9	27	408	0.83 (0.52,1.31)	0.93 (0.57, 1.52)	25	378	0.98 (0.59,1.63)	1.15 (0.67, 1.97)
Missing	0	4			0	4		
2nd-trimester average								
0-25.8	34	456	1.	1.	26	412	1.	1.
25.9-75	28	460	0.83 (0.51,1.34)	0.84 (0.50, 1.43)	21	414	0.81 (0.46,1.42)	0.92 (0.50, 1.70)
75.1-253.5	26	462	0.77 (0.47,1.26)	0.90 (0.53, 1.53)	24	428	0.89 (0.52,1.53)	1.15 (0.64, 2.06)
253.6-1827	25	463	0.74 (0.45,1.22)	0.84 (0.49, 1.43)	21	430	0.78 (0.45,1.37)	0.99 (0.54, 1.81)
Missing	0	4			0	4		
3rd-trimester average								
0-25.8	33	453	1.	1.	25	410	1.	1.
25.9-75	25	407	0.85 (0.52,1.41)	0.82 (0.48, 1.42)	18	372	0.80 (0.45,1.45)	0.87 (0.46, 1.65)
75.1-253.6	27	464	0.81 (0.49,1.33)	0.91 (0.53, 1.54)	26	431	0.99 (0.58,1.69)	1.17 (0.66, 2.08)
253.6-1827	24	460	0.73 (0.44,1.22)	0.83 (0.48, 1.41)	20	424	0.78 (0.44,1.39)	0.96 (0.52, 1.77)
Missing	4	61			3	51		

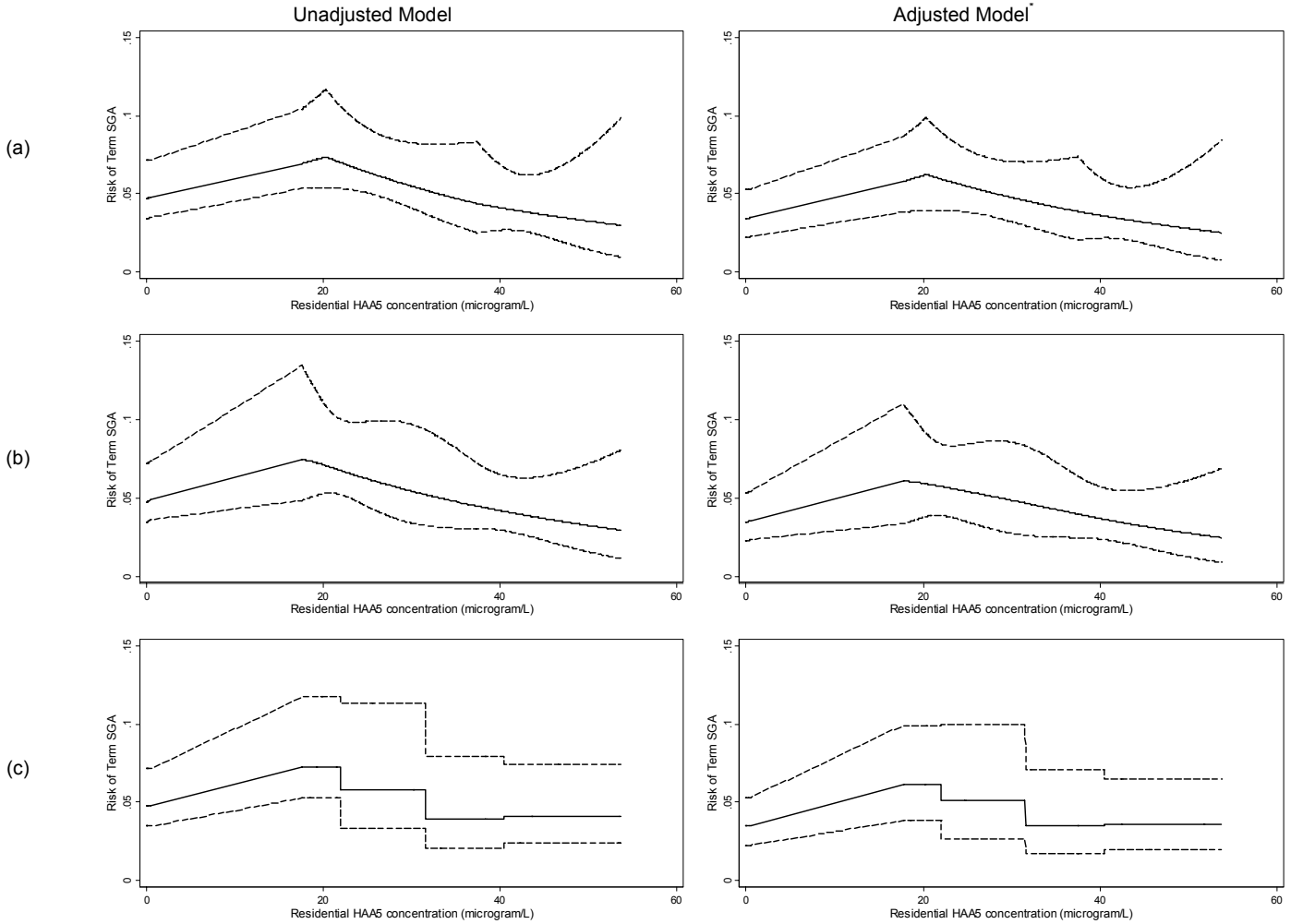
a Unadjusted model.
b Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
c Chi-square test (H_0: $\beta_{DBP} = 0$) for a single, continuous residential DBP concentration term (*i.e.,* linear term); p-value rounded to 1 significant figure.
Abbreviations: RR = risk ratio, CI= confidence interval

Figure 11. Predicted risk of term SGA by average residential TTHM concentration during the third trimester of pregnancy among all women included in SGA analyses from all study sites, 2000-2004



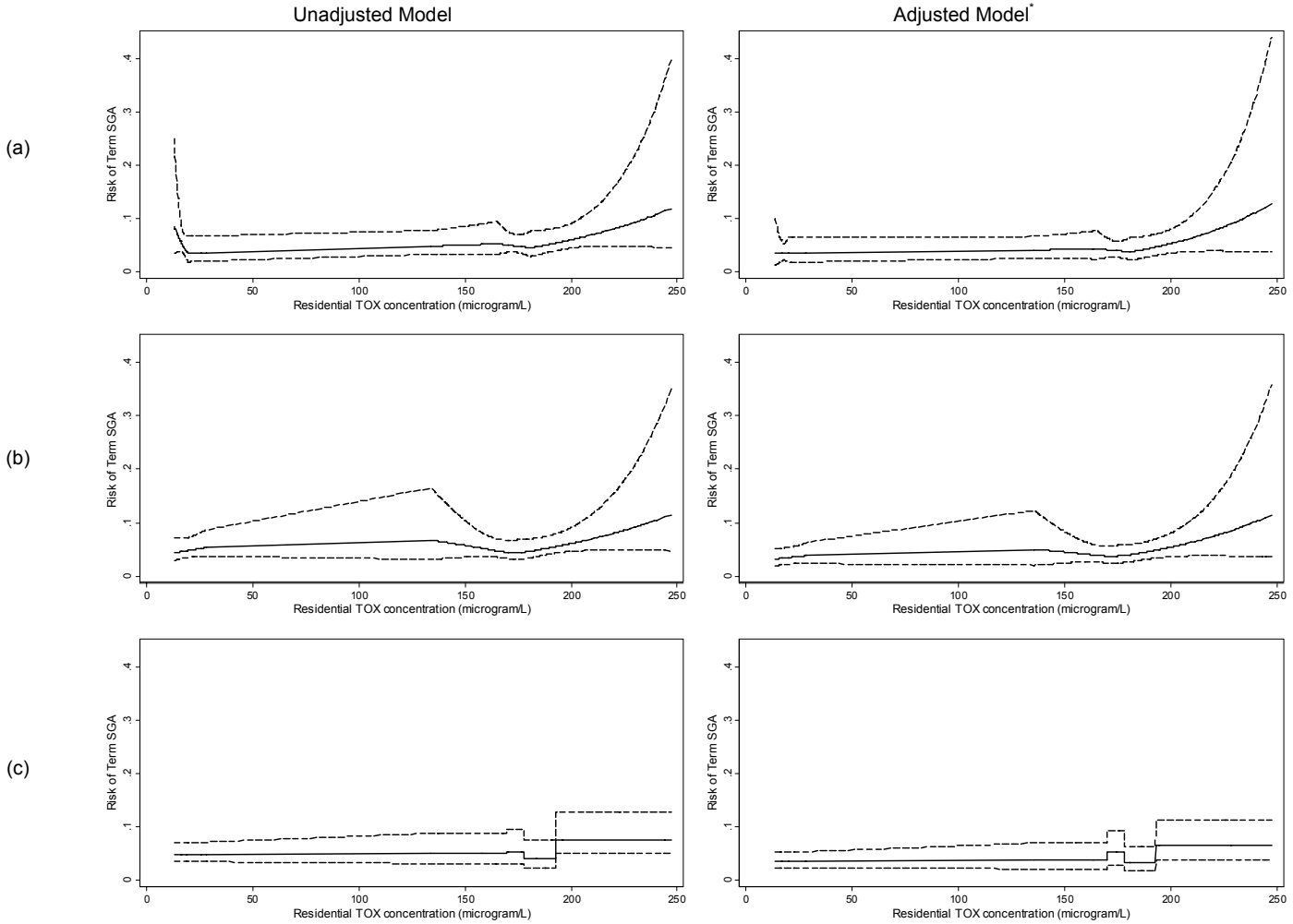
*Predicted risk adjusted for (averaged over) maternal age, race/ethnicity, household income, employment status, education level, marital status, pre-pregnancy BMI, and caffeine intake; (a) TTHM coded as linear spline; (b) TTHM coded as restricted quadratic spline, (c) TTHM coded as quartiles using indicator variables; dashed line is pointwise 95% confidence interval

Figure 12. Predicted risk of term SGA by average residential HAA5 concentration during the third trimester of pregnancy among all women included in SGA analyses from all study sites, 2000-2004



*Predicted risk adjusted for (averaged over) maternal age, race/ethnicity, household income, employment status, education level, marital status, pre-pregnancy BMI, and caffeine intake; (a) HAA5 coded as linear spline; (b) HAA5 coded as restricted quadratic spline, (c) HAA5 coded as quartiles using indicator variables; dashed line is pointwise 95% confidence interval

Figure 13. Predicted risk of term SGA by average residential TOX concentration during the third trimester of pregnancy among all women included in SGA analyses from all study sites, 2000-2004



*Predicted risk adjusted for (averaged over) maternal age, race/ethnicity, household income, employment status, education level, marital status, pre-pregnancy BMI, and caffeine intake; (a) TOX coded as linear spline; (b) TOX coded as restricted quadratic spline, (c) TOX coded as quartiles using indicator variables; dashed line is pointwise 95% confidence interval

4.4.2 Associations between DBPs and SGA at the chlorinated DBP site

Tables 27-29 present results from SGA models for TTHM, HAA5 and TOX, respectively, restricted to the chlorinated DBP site. Again, models were run separately for each trimester and exposure metric (residential versus personal), and with and without restricting to infants born after 37 week's gestation ("term SGA"). Findings were similar to those found when examining all study sites combined, except for personal exposure to HAA5 and TOX, which showed an inverse trend. However, when residential concentrations of HAA5 were examined stratified by women who reported consuming ≥ 5 glasses of tap water per day (the median number of glasses of tap water consumed per day reported among all women) versus < 5 glasses per day, no modification of the effect of HAA5 residential concentrations was found. It is possible that women who reported drinking greater amounts of bottled water and filtered water (and thus, have lower HAA5 and TOX personal exposure estimates) also tend to engage in other healthy behaviors and have better pregnancy outcomes. If so, this could explain the inverse association found when examining personal exposure metrics for HAA5 and TOX.

Table 27. Association between TTHM exposure and the probability of delivering an SGA infant among women included in SGA analyses from the chlorinated DBP site, 2000-2004

	SGA (n= 883)				Term SGA (n=828)			
Residential TTHM Concentration (µg/liter)	# SGA	# Non-SGA	Unadjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]	# SGA	# Non-SGA	Unadjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]
1st trimester average								
33.9-60.2	16	277	1.	1.	13	255	1.	1.
60.3-73.7	13	251	0.90 (0.44,1.84)	0.90 (0.42, 1.93)	11	235	0.92 (0.42,2.02)	1.05 (0.46, 2.38)
74-111.3	13	313	0.73 (0.36,1.49)	0.65 (0.30, 1.42)	13	301	0.85 (0.40,1.81)	0.82 (0.36, 1.86)
p-value for trend[c]			0.4	0.2			0.6	0.5
≥ 80 *vs.* <80[d]	6/36	174/667	0.65 (0.28, 1.52)	0.58 (0.23, 1.45)			0.72 (0.30, 1.69)	0.64 (0.25, 1.62)
2nd trimester average								
33.1-60.2	14	282	1.	1.	12	263	1.	1.
60.4-73.9	16	281	1.14 (0.57,2.29)	1.26 (0.60, 2.63)	14	267	1.14 (0.54,2.42)	1.26 (0.56, 2.81)
74-108.8	12	278	0.87 (0.41,1.86)	0.94 (0.42, 2.06)	11	261	0.93 (0.42,2.06)	1.10 (0.48, 2.52)
p-value for trend[c]	7/35	143/698	0.7	1.0			0.7	0.8
≥ 80 *vs.* <80[d]			0.98 (0.44, 2.16)	0.97 (0.41, 2.28)			0.92 (0.39, 2.16)	1.11 (0.47, 2.60)
3rd trimester average								
31.9-60.2	17	317	1.	1.	15	307	1.	1.
60.3-73.7	10	273	0.69 (0.32,1.49)	0.72 (0.32, 1.61)	8	256	0.65 (0.28,1.51)	0.71 (0.30, 1.67)
74-114.8	13	226	1.07 (0.53,2.16)	1.25 (0.60, 2.62)	12	207	1.18 (0.56,2.46)	1.32 (0.61, 2.86)
Missing	2	25			2	21		
p-value for trend[c]	8/32	93/723	0.9	0.7			0.7	1.0
≥ 80 *vs.* <80[d]			1.87 (0.89, 3.94)	1.91 (0.87, 4.16)			1.91 (0.86, 4.26)	1.76 (0.76, 4.08)

TTHM exposure through showering and bathing (μg/liter)								
1st trimester average								
0-0.9	8	235	1.	1.	8	225	1.	1.
1-1.5	12	286	1.22 (0.51,2.94)	1.29 (0.51, 3.25)	9	271	0.94 (0.37,2.39)	1.07 (0.41, 2.80)
1.6-31.2	22	319	1.96 (0.89,4.33)	1.86 (0.76, 4.56)	20	294	1.86 (0.83,4.14)	1.61 (0.65, 3.99)
Missing	0	1			0	1		
2nd trimester average								
0.1-0.9	9	286	1.	1.	8	272	1.	1.
1-1.5	19	278	2.10 (0.96,4.56)	2.32 (0.97, 5.54)	17	265	2.11 (0.93,4.81)	1.87 (0.77, 4.55)
1.6-27.1	14	276	1.58 (0.70,3.60)	1.69 (0.65, 4.39)	12	253	1.58 (0.66,3.82)	1.33 (0.50, 3.58)
Missing	0	1			0	1		
3rd trimester average								
0-0.9	14	306	1.	1.	13	293	1.	1.
1-1.5	8	257	0.69 (0.29,1.62)	0.78 (0.33, 1.88)	6	241	0.57 (0.22,1.48)	0.55 (0.21, 1.45)
1.6-16.1	18	253	1.52 (0.77,3.00)	1.74 (0.83, 3.65)	16	236	1.49 (0.73,3.05)	1.41 (0.66, 3.01)
Missing	2	25			2	21		

a Unadjusted model.
b Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
c Chi-square test (H_0: $\beta_{DBP} = 0$) for a single, continuous residential DBP concentration term (*i.e.,* linear term); p-value rounded to 1 significant figure.
d # SGA and non-SGA presented as number ≥ 80 μg/liter over number < 80 μg/liter.
Abbreviations: RR = risk ratio, CI= confidence interval

Table 28. Association between HAA5 exposure and the probability of delivering an SGA infant among women included in SGA analyses from the chlorinated DBP site, 2000-2004

	SGA (n= 883)				Term SGA (n=828)			
Residential HAA5 Concentration (µg/liter)	# SGA	# Non-SGA	Unadjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]	# SGA	# Non-SGA	Unadjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]
1st trimester average								
17.5-32.4	21	311	1.	1.	18	292	1.	1.
32.5-40.7	10	268	0.57 (0.27,1.19)	0.57 (0.26, 1.24)	8	253	0.53 (0.23,1.19)	0.51 (0.21, 1.21)
40.8-53.2	11	262	0.64 (0.31,1.30)	0.64 (0.31, 1.35)	11	246	0.74 (0.35,1.53)	0.74 (0.35, 1.57)
p-value for trend[c]			0.3	0.3			0.5	0.6
2nd trimester average								
18.7-32.4	16	276	1.	1.	13	259	1.	1.
32.5-40.7	13	286	0.79 (0.39,1.62)	0.71 (0.32, 1.54)	12	270	0.89 (0.41,1.92)	0.89 (0.39, 2.04)
40.8-52.8	13	279	0.81 (0.40,1.66)	0.90 (0.43, 1.87)	12	262	0.92 (0.43,1.97)	1.06 (0.48, 2.35)
p-value for trend[c]			0.4	0.6			0.5	0.8
3rd trimester average								
17.6-32.4	14	267	1.	1.	13	253	1.	1.
32.6-40.7	13	236	1.05 (0.50,2.19)	1.07 (0.49, 2.35)	10	222	0.88 (0.39,1.97)	0.92 (0.40, 2.13)
40.8-53.9	13	313	0.80 (0.38,1.67)	0.91 (0.42, 1.97)	12	295	0.80 (0.37,1.72)	0.91 (0.41, 2.02)
Missing	2	25			2	21		
p-value for trend[c]			0.3	0.6			0.3	0.7

HAA5 exposure through tap-water intake (μg/liter)								
1st trimester average								
0-35.2	17	323	1.	1.	14	299	1.	1.
35.5-69.2	16	259	1.16 (0.60,2.26)	1.19 (0.59, 2.42)	14	248	1.19 (0.58,2.46)	1.17 (0.55, 2.50)
69.8-349.5	9	258	0.67 (0.31,1.49)	0.64 (0.27, 1.51)	9	243	0.80 (0.35,1.81)	0.75 (0.31, 1.81)
Missing	0	1			0	1		
2nd trimester average								
0-35.2	21	270	1.	1.	19	251	1.	1.
35.4-69.7	12	282	0.57 (0.28,1.13)	0.46 (0.22, 0.96)	10	267	0.51 (0.24,1.08)	0.37 (0.17, 0.81)
69.8-369.1	9	288	0.42 (0.20,0.90)	0.35 (0.16, 0.77)	8	272	0.41 (0.18,0.91)	0.33 (0.14, 0.74)
Missing	0	1			0	1		
3rd trimester								
0-35.2	19	267	1.	1.	17	250	1.	1.
35.6-69.5	10	255	0.57 (0.27,1.20)	0.59 (0.27, 1.28)	9	241	0.57 (0.26,1.24)	0.53 (0.24, 1.19)
69.8-418.4	11	293	0.54 (0.26,1.12)	0.52 (0.24, 1.10)	9	278	0.49 (0.22,1.09)	0.45 (0.20, 1.03)
Missing	2	26			2	22		

a Unadjusted model.
b Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
c Chi-square test (H_0: $\beta_{DBP} = 0$) for a single, continuous residential DBP concentration term (*i.e.,* linear term); p-value rounded to 1 significant figure.
Abbreviations: RR = risk ratio, CI= confidence interval

Table 29. Association between TOX exposure and the probability of delivering an SGA infant among women included in SGA analyses from the chlorinated DBP site, 2000-2004

	SGA (n= 883)				Term SGA (n=828)			
Residential TOX Concentration (µg/liter)	# SGA	# Non-SGA	Unadjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]	# SGA	# Non-SGA	Unadjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]
1st trimester average								
136.8-169.2	17	307	1.	1.	13	284	1.	1.
169.4-178.3	14	266	0.95 (0.48,1.90)	1.07 (0.53, 2.18)	13	246	1.15 (0.54,2.43)	1.26 (0.59, 2.70)
178.6-223	11	268	0.75 (0.36,1.58)	0.65 (0.29, 1.46)	11	261	0.92 (0.42,2.03)	0.78 (0.33, 1.82)
p-value for trend[c]			0.7	0.5			1.0	0.9
2nd trimester average								
136.7-169.1	13	280	1.	1.	12	262	1.	1.
169.4-178.3	17	281	1.29 (0.64,2.60)	1.41 (0.66, 3.01)	15	265	1.22 (0.58,2.57)	1.32 (0.59, 2.96)
178.5-220.5	12	280	0.93 (0.43,2.00)	1.01 (0.45, 2.30)	10	264	0.83 (0.37,1.90)	1.02 (0.44, 2.39)
p-value for trend[c]			0.4	0.5			0.5	0.8
3rd trimester average								
134.1-169.2	15	295	1.	1.	14	281	1.	1.
169.4-178.3	14	237	1.15 (0.57,2.34)	1.24 (0.59, 2.62)	11	226	0.98 (0.45,2.11)	1.10 (0.50, 2.42)
178.5-224.8	11	284	0.77 (0.36,1.65)	0.87 (0.40, 1.89)	10	263	0.77 (0.35,1.71)	0.83 (0.37, 1.88)
Missing	2	25			2	21		
p-value for trend[c]			0.2	0.6			0.2	0.5

TOX exposure through tap-water intake (μg/liter)								
1st trimester average								
0-143.8	19	322	1.	1.	16	299	1.	1.
145.1-304.6	9	269	0.58 (0.27,1.26)	0.64 (0.29, 1.45)	8	255	0.60 (0.26,1.38)	0.63 (0.27, 1.50)
307-1349.6	14	249	0.96 (0.49,1.87)	0.87 (0.42, 1.78)	13	236	1.03 (0.50,2.10)	0.89 (0.41, 1.91)
Missing	0	1			0	1		
2nd trimester average								
0-143.9	20	270	1.	1.	18	250	1.	1.
144.6-306.6	11	287	0.54 (0.26,1.10)	0.46 (0.22, 1.00)	10	272	0.53 (0.25,1.12)	0.41 (0.19, 0.91)
307-1225.5	11	283	0.54 (0.26,1.11)	0.48 (0.23, 1.02)	9	268	0.48 (0.22,1.06)	0.42 (0.18, 0.94)
Missing	0	1			0	1		
3rd trimester								
0-144.3	18	259	1.	1.	16	243	1.	1.
144.7-306.2	12	270	0.65 (0.32,1.33)	0.58 (0.27, 1.22)	10	256	0.61 (0.28,1.32)	0.46 (0.21, 1.03)
308.2-1370.8	10	286	0.52 (0.24,1.11)	0.45 (0.20, 0.98)	9	270	0.52 (0.23,1.16)	0.42 (0.19, 0.97)
Missing	2	26			2	22		

a Unadjusted model.
b Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
c Chi-square test (H_0: $\beta_{DBP} = 0$) for a single, continuous residential DBP concentration term (*i.e.,* linear term); p-value rounded to 1 significant figure.
Abbreviations: RR = risk ratio, CI= confidence interval

4.4.3 Association between DBPs and term birth weight for all study sites

Tables 30-31 present results from term birth weight models for TTHM, HAA5 and TOX, respectively, combined over study sites. Models were run separately for each trimester and exposure metric (residential versus personal). Estimated changes in mean birth weight among term births associated with moderate DBP exposure compared to the low exposure group did not suggest a consistent association with TTHM, HAA5, or TOX residential levels or personal exposure estimates for any trimester. The estimated decrease in term birth weight associated with an average third trimester residential TTHM concentration ≥ 80 versus < 80 micrograms/liter (mean difference in grams = -55.5 [-143.7, 31.9]) was consistent but less pronounced than the association found for SGA. Effect measure modification by maternal age, race/ethnicity or swimming during pregnancy was not found (*p*-values for the joint effect of interaction terms ranged from 0.1-0.9). Dose-response curves for mean term birth weight by third trimester average residential concentrations of TTHM, HAA5 and TOX also did not indicate any consistent pattern of associations (figures 10, 11, and 12, respectively).

Table 30. Association between TTHM exposure and mean term birth weight among women included in term birth weight analyses, 2000-2004

Residential TTHM Concentration (µg/liter)	N (n= 1,854)	Term Birth Weight (grams) Unadjusted Mean change (95% CI)[a]	Adjusted Mean change (95% CI)[b]
1st-trimester average			
2.2-4.6	677	0.	0.
33.1-55	334	30.1 (-31.5, 91.66)	-10.0 (-72.3, 52.3)
55-66.3	258	66.2 (-1.1, 133.62)	34.4 (-32.7, 101.5)
66.4-74.8	253	6.5 (-61.4, 74.32)	-21.3 (-88.6, 46.0)
74.9-108.8	332	90.8 (29.1, 152.51)	58.6 (-3.0, 120.1)
p for trend test[c]		0.01	0.2
≥ 80 vs. <80[d]	214/1640	45.0 (-22.0, 112.1)	36.1 (-30.4, 102.5)
2nd-trimester average			
1.4-5.4	677	0.	0.
24.7-54.8	295	63.8 (-0.5, 128.11)	31.2 (-33.2, 95.5)
55.1-65.4	288	65.0 (0.1, 129.87)	31.2 (-33.3, 95.8)
66.6-74.6	294	46.1 (-18.3, 110.45)	29.7 (-35.2, 94.6)
74.9-165	300	26.1 (-37.8, 90.08)	-22.4 (-85.7, 40.9)
p for trend test[c]		0.08	0.8
≥ 80 vs. <80[d]	175/1679	-4.2 (-77.5, 69.1)	-35.6 (-107.1, 35.9)
3rd-trimester average			
2.1-5.3	655	0.	0.
28.8-54.8	281	19.6 (-45.7, 84.96)	-7.1 (-72.3, 58.0)
55.1-66.3	335	90.2 (28.7, 151.74)	52.2 (-9.7, 114.1)
66.4-74.7	255	64.3 (-3.4, 131.97)	33.1 (-35.1, 101.3)
75.1-133.2	275	34.9 (-31.0, 100.72)	3.8 (-62.8, 70.4)
Missing	53		
p for trend test[c]		0.04	0.5
≥ 80 vs. <80[d]	117/1684	-43.9 (-132.1, 44.4)	-55.9 (-143.7, 31.9)
TTHM exposure through showering & bathing (µg/day)			
1st-trimester average			
0-0.09	439	0.	0.
0.1-0.8	458	-80.8 (-142.3, -19.4)	-26.0 (-87.3, 35.2)
0.9-1.5	455	16.6 (-45.0, 78.1)	-4.6 (-65.6, 56.4)
1.6-31.2	497	-59.5 (-119.7, 0.8)	-7.0 (-68.8, 54.9)
Missing	5		
2nd-trimester average			
0-0.09	458	0.	0.
0.1-0.8	453	-25.3 (-86.4, 35.8)	13.7 (-46.8, 74.2)
0.9-1.5	480	20.2 (-40.0, 80.5)	3.2 (-56.0, 62.5)
1.6-27.1	458	-35.7 (-96.6, 25.3)	8.1 (-54.4, 70.7)
Missing	5		
3rd-trimester average			
0-0.09	497	0.	0.
0.1-0.8	425	-45.7 (-106.6, 15.2)	-38.8 (-99.1, 21.6)
0.9-1.5	457	53.7 (-6.0, 113.4)	7.2 (-51.9, 66.3)
1.6-24.5	421	-14.2 (-75.2, 46.8)	4.8 (-57.0, 66.7)
Missing	54		

a Unadjusted model.
b Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
c Chi-square test (H_0: $\beta_{DBP} = 0$) for a single, continuous residential DBP concentration term (*i.e.,* linear term), p-value rounded to 1 significant figure.
d Numbers for N are number in exposure group ≥ 80 / number in exposure group < 80 µg/liter
Abbreviations: RR = risk ratio, CI= confidence interval

Table 31. Association between HAA5 exposure and mean term birth weight among women included in term birth weight analyses, 2000-2004

Residential HAA5 Concentration (µg/liter)	N (n= 1,854)	Term Birth Weight (grams) Unadjusted Mean change (95% CI)[a]	Adjusted Mean change (95% CI)[b]
1st-trimester average			
0-0.9	677	0.	0.
17.9-22	268	-1.4 (-67.7, 64.81)	-26.9 (-96.1, 42.3)
22.1-31.5	345	-9.0 (-69.7, 51.71)	-57.5 (-118.7, 3.6)
31.6-40.4	280	120.7 (55.4, 185.87)	78.6 (14.0, 143.2)
40.4-52.8	284	100.8 (35.9, 165.66)	72.3 (8.0, 136.5)
p for trend test[c]		<0.001	0.02
2nd-trimester average			
0-1.5	677	0.	0.
12.1-22	282	-3.2 (-68.4, 62.08)	-31.5 (-100.9, 37.8)
22.1-31.5	294	35.6 (-28.7, 99.88)	4.4 (-59.9, 68.6)
31.6-40.3	300	74.0 (10.1, 137.83)	33.4 (-30.5, 97.3)
40.7-62.2	301	90.2 (26.5, 154.01)	48.4 (-14.7, 111.6)
p for trend test[c]		0.001	0.08
3rd-trimester average			
0-0.6	655	0.	0.
16-21.8	367	-9.1 (-68.6, 50.52)	-36.9 (-99.5, 25.7)
22.1-31.5	205	98.6 (25.3, 171.85)	68.0 (-5.5, 141.5)
31.6-40.3	244	54.2 (-14.5, 122.78)	12.0 (-56.5, 80.5)
40.6-56.4	330	95.8 (34.1, 157.54)	59.0 (-2.9, 120.9)
Missing	53		
p for trend test[c]		0.001	0.08
HAA5 through tap-water consumption (µg/liter)			
1st-trimester average			
0	594	0.	0.
0.01-16.1	402	-7.4 (-66.7, 52.0)	-25.7 (-84.5, 33.1)
16.2-54.4	454	51.4 (-5.9, 108.7)	-7.6 (-65.0, 49.9)
54.7-369.1	400	105.2 (45.8, 164.7)	57.3 (-2.4, 117.0)
Missing	4		
2nd-trimester average			
0	539	0.	0.
0.2-16.1	422	-26.9 (-86.6, 32.8)	-31.7 (-90.7, 27.4)
16.1-54.7	437	38.8 (-20.3, 98.0)	10.2 (-48.7, 69.1)
54.7-511.4	452	96.0 (37.4, 154.6)	52.9 (-5.9, 111.8)
Missing	4		
3rd-trimester average			
0	701	0.	0.
0.2-16.1	243	-21.6 (-90.0, 46.9)	-34.9 (-103.2, 33.4)
16.1-54.7	417	30.3 (-26.6, 87.1)	10.1 (-46.2, 66.5)
54.7-511.4	439	96.4 (40.5, 152.4)	61.9 (5.5, 118.4)
Missing	54		

a Unadjusted model

b Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.

c Chi-square test (H_0: $\beta_{DBP} = 0$) for a single, continuous residential DBP concentration term (*i.e.,* linear term), p-value rounded to 1 significant figure.

d Numbers for N are number in exposure group ≥ 80 / number in exposure group < 80 µg/liter

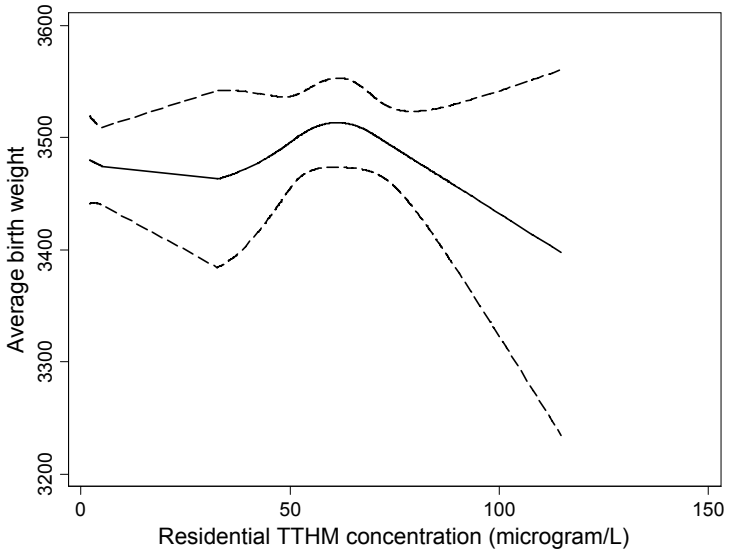
Abbreviations: RR = risk ratio, CI= confidence interval

Table 32. Association between TOX exposure and mean term birth weight among women included in term birth weight analyses, 2000-2004 (n= 1,854).

Residential TOX Concentration (µg/liter)	Term Birth Weight (grams) N (n= 1,854)	Unadjusted Mean change (95% CI)[a]	Adjusted Mean change (95% CI)[b]
1st-trimester average			
14.3-22.4	677	0.	0.
136.7-169.6	340	57.1 (-4.2, 118.38)	18.8 (-42.2, 79.7)
169.6-177.7	315	78.7 (15.8, 141.53)	34.9 (-27.6, 97.5)
177.7-192.6	278	22.7 (-43.0, 88.33)	-14.0 (-79.7, 51.7)
192.8-235.2	244	34.5 (-34.3, 103.33)	25.6 (-44.3, 95.4)
p for trend test[c]		0.04	0.5
2nd-trimester average			
9-28	677	0.	0.
104-169	300	93.5 (29.6, 157.40)	69.8 (6.5, 133.1)
170-177	300	36.5 (-27.5, 100.36)	-11.9 (-75.5, 51.8)
178-192	295	42.5 (-21.8, 106.81)	17.3 (-47.0, 81.7)
192.8-290	282	26.2 (-39.1, 91.51)	-15.2 (-82.2, 51.9)
p for trend test[c]		0.07	0.7
3rd-trimester average			
10.9-25.5	655	0.	0.
121.7-169.5	322	101.7 (39.5, 163.99)	62.1 (-0.1, 124.4)
170-177.5	259	31.1 (-36.1, 98.27)	-19.9 (-87.1, 47.3)
177.8-192.5	292	78.7 (14.3, 143.04)	64.1 (-0.1, 128.4)
192.7-250.2	273	-7.5 (-73.5, 58.37)	-39.9 (-108.6, 28.9)
Missing	53		
p for trend test[c]		0.07	0.6
TOX exposure through tap-water consumption (µg/liter)			
1st-trimester average			
0-25.8	543	0.	0.
25.9-75	414	12.3 (-47.8, 72.3)	0.5 (-59.0, 60.1)
75.1-252.9	470	65.9 (7.9, 123.8)	14.8 (-43.4, 73.0)
253.6-1302.9	423	81.7 (22.0, 141.4)	39.7 (-20.3, 99.6)
Missing	4		
2nd-trimester average			
0-25.8	454	0.	0.
25.9-75	453	33.9 (-27.2, 95.1)	19.7 (-40.7, 80.2)
75.1-253.5	471	72.5 (12.0, 133.0)	33.7 (-26.7, 94.2)
253.6-1827	472	98.2 (37.7, 158.6)	63.8 (2.7, 124.8)
Missing	4		
3rd-trimester average			
0-25.8	455	0.	0.
25.9-75	405	42.1 (-20.8, 105.0)	24.9 (-37.4, 87.2)
75.1-253.6	477	50.5 (-9.8, 110.9)	19.7 (-40.5, 79.8)
253.6-1827	463	86.2 (25.4, 147.0)	53.7 (-7.9, 115.3)
Missing	54		

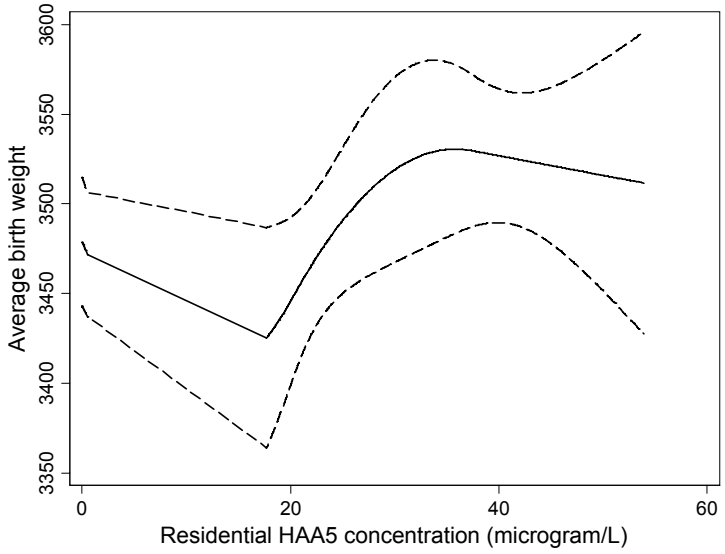
a Unadjusted model.
b Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
c Chi-square test (H_0: $\beta_{DBP} = 0$) for a single, continuous residential DBP concentration term (*i.e.,* linear term), p-value rounded to 1 significant figure.
d Numbers for N are number in exposure group ≥ 80 / number in exposure group < 80 µg/liter
Abbreviations: RR = risk ratio, CI= confidence interval

Figure 14. Estimated mean birth weight among terms by average third trimester residential TTHM concentration among women included in term birth weight analyses, 2000-2004



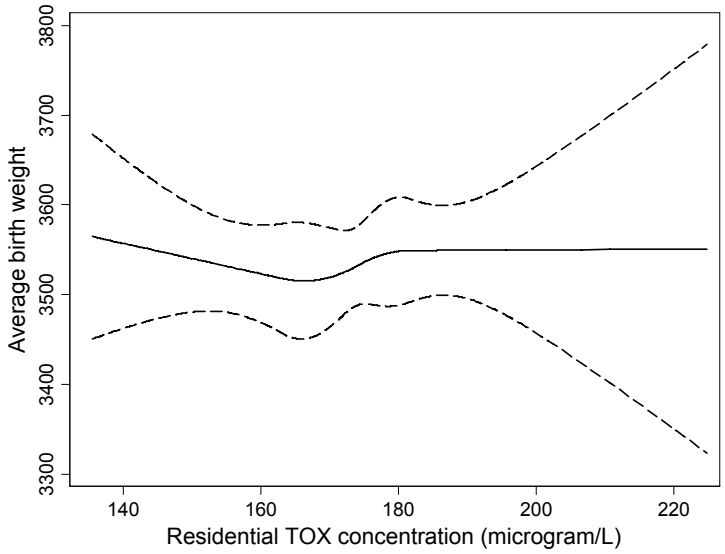
Model adjusted for and averaged over gestational age at birth, maternal age, race/ethnicity, household income, employment status, education level, marital status, pre-pregnancy BMI and caffeine intake. Third trimester average TTHM exposure was coded using restricted quadratic splines and missing for 53 of 1,854 term births. Dashed line represents the 95% pointwise confidence interval. Abbreviations: TTHM = total trihalomethane.

Figure 15. Estimated mean birth weight among terms by average third trimester residential HAA5 concentration among women included in term birth weight analyses, 2000-2004



Model adjusted for and averaged over gestational age at birth, maternal age, race/ethnicity, household income, employment status, education level, marital status, pre-pregnancy BMI and caffeine intake. Third trimester average HAA5 exposure was coded using restricted quadratic splines and missing for 53 of 1,854 term births. Dashed line represents the 95% pointwise confidence interval. Abbreviations: HAA5= sum of five haloacetic acids.

Figure 16. Estimated mean birth weight among terms by average third trimester residential TOX concentration among women included in term birth weight analyses, 2000-2004



Model adjusted for and averaged over gestational age at birth, maternal age, race/ethnicity, household income, employment status, education level, marital status, pre-pregnancy BMI and caffeine intake. Third trimester average TOX exposure was coded using restricted quadratic splines and missing for 53 of 1,854 term births. Dashed line represents the 95% pointwise confidence interval. Abbreviations: TOX = total organic halide.

4.4.4. Association between DBPs and term birth weight at the chlorinated DBP site

Tables 33-34 present results from term birth weight models for TTHM, HAA5 and TOX, respectively, restricted to the chlorinated DBP site. Models were run separately for each trimester and exposure metric (residential versus personal). Estimated changes in mean birth weight among term births associated with moderate DBP exposure compared to the low exposure group did not suggest a consistent association with TTHM, HAA5, or TOX residential levels or personal exposure estimates for any trimester. The estimated decrease in term birth weight associated with an average third trimester residential TTHM concentration ≥ 80 versus < 80 micrograms/liter (mean difference in grams = -96.9 [-198.5, 4.6]) was more pronounced than when examining all study sites combined.

Table 33. Association between TTHM exposure and mean term birth weight among women included in term birth analyses from the chlorinated DBP site, 2000-2004

Residential TTHM Concentration (µg/liter)	N (n= 872)	Term Birth Weight (grams) Unadjusted Mean change (95% CI)[a]	Adjusted Mean change (95% CI)[b]
1st-trimester average			
33.8-57.4	211	0.	0.
57.5-66.5	208	49.5 (-43.0, 141.9)	52.4 (-40.0, 144.7)
66.5-77	223	1.1 (-89.8, 92.0)	-6.3 (-97.2, 84.5)
77-111.3	230	53.5 (-36.7, 143.8)	66.6 (-24.1, 157.2)
p for trend test[c]		0.4	0.3
≥ 80 vs. <80[d]	185/687	20.9 (-57.5, 99.3)	36.8 (-41.5, 115.1)
2nd-trimester average			
33.1-57.1	218	0.	0.
57.4-66.5	215	11.6 (-79.4, 102.6)	2.3 (-88.2, 92.9)
66.6-76.8	215	5.1 (-85.9, 96.1)	13.1 (-78.1, 104.3)
77-108.8	224	-44.4 (-134.5, 45.7)	-62.4 (-151.6, 26.7)
p for trend test[c]		0.5	0.2
≥ 80 vs. <80[d]	153/719	-53.0 (-137.2, 31.2)	-70.3 (-153.6, 13.1)
3rd-trimester average			
31.8-57.4	239	0.	0.
57.5-66.5	259	23.0 (-61.8, 107.7)	16.0 (-68.0, 99.9)
66.6-77	201	15.5 (-74.9, 105.9)	2.0 (-87.5, 91.5)
77-114.8	150	-23.4 (-121.8, 75.0)	-9.1 (-108.7, 90.5)
Missing	23		
p for trend test[c]		0.6	0.5
≥ 80 vs. <80[d]	99/750	-88.3 (-189.1, 12.4)	-96.9 (-198.5, 4.6)
TTHM exposure through showering & bathing (µg/day)			
1st-trimester average			
0-0.09	194	0.	0.
0.1-0.8	181	46.4 (-50.7, 143.4)	33.0 (-64.0, 130.1)
0.9-1.5	246	-38.4 (-128.5, 51.8)	-45.6 (-136.8, 45.5)
1.6-31.2	250	-133.9 (-223.7, -44.1)	-66.0 (-160.9, 28.8)
Missing	1		
2nd-trimester average			
0.1-0.09	220	0.	0.
0.1-0.8	219	-38.6 (-128.5, 51.4)	-28.9 (-118.7, 60.8)
0.9-1.5	220	-57.0 (-146.9, 32.8)	-57.1 (-147.0, 32.8)
1.6-27.1	212	-138.8 (-229.5, -48.1)	-48.5 (-147.7, 50.7)
Missing	1		
3rd-trimester average			
0-0.09	245	0.	0.
0.1-0.8	220	4.1 (-83.5, 91.6)	-10.6 (-97.9, 76.8)
0.9-1.5	189	25.6 (-65.7, 116.8)	11.3 (-79.3, 101.8)
1.6-24.5	195	-73.1 (-163.6, 17.3)	-3.0 (-98.4, 92.3)
Missing	23		

a Unadjusted model.
b Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
c Chi-square test (H_0: $\beta_{DBP} = 0$) for a single, continuous residential DBP concentration term (*i.e.,* linear term), p-value rounded to 1 significant figure.
Abbreviations: RR = risk ratio, CI= confidence interval

Table 34. Association between HAA5 exposure and mean term birth weight among women included in term birth analyses from the chlorinated DBP site, 2000-2004

Residential HAA5 Concentration (µg/liter)	Term Birth Weight (grams) N (n= 872)	Unadjusted Mean change (95% CI)[a]	Adjusted Mean change (95% CI)[b]
1st-trimester average			
17.5-29.7	243	0.	0.
29.8-37.8	249	11.3 (-74.1, 96.6)	6.4 (-79.1, 91.9)
37.9-42.2	162	43.2 (-52.8, 139.2)	35.6 (-59.4, 130.7)
42.2-53.2	218	67.8 (-20.5, 156.1)	75.5 (-12.5, 163.6)
p for trend test[c]		0.08	0.05
2nd-trimester average			
18.7-29.7	215	0.	0.
29.7-37.9	218	-10.9 (-101.9, 80.2)	-1.7 (-92.5, 89.1)
37.9-42.2	223	13.5 (-77.1, 104.0)	5.8 (-85.0, 96.6)
42.2-52.8	216	10.9 (-80.4, 102.2)	0.7 (-90.0, 91.3)
p for trend test[c]		0.6	0.7
3rd-trimester average			
17.6-29.7	237	0.	0.
29.8-37.9	181	-37.7 (-131.0, 55.5)	-60.1 (-152.5, 32.4)
37.9-42.2	172	-41.8 (-136.4, 52.8)	-50.2 (-143.6, 43.2)
42.2-53.9	259	-5.1 (-89.9, 79.8)	-7.0 (-91.8, 77.7)
Missing	23		
p for trend test[c]		0.9	0.8
HAA5 through tap-water consumption (µg/liter)			
1st-trimester average			
0-0	261	0.	0.
2.1-35.3	212	79.0 (-8.2, 166.2)	75.1 (-42.5, 192.6)
35.4-69.3	211	98.1 (10.8, 185.5)	69.4 (-46.1, 184.9)
69.7-349.6	187	95.6 (5.3, 186.0)	110.6 (-4.7, 225.9)
Missing	1		
2nd-trimester average			
0-0	213	0.	0.
0.1-35.3	219	68.7 (-22.2, 159.6)	40.5 (-109.9, 191.0)
35.3-69.7	220	78.9 (-11.9, 169.7)	90.6 (-57.2, 238.3)
69.7-369.1	219	85.8 (-5.1, 176.7)	120.8 (-27.6, 269.2)
Missing	1		
3rd-trimester average			
0-0	224	0.	0.
2.7-35.2	198	36.4 (-55.6, 128.3)	15.4 (-113.1, 143.9)
35.5-69.5	189	54.1 (-39.0, 147.2)	54.5 (-71.5, 180.5)
69.8-418.5	237	65.2 (-22.6, 153.1)	73.9 (-51.4, 199.2)
Missing	24		

a Unadjusted model.
b Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
c Chi-square test (H_0: $\beta_{DBP} = 0$) for a single, continuous residential DBP concentration term (*i.e.,* linear term), p-value rounded to 1 significant figure.
Abbreviations: RR = risk ratio, CI= confidence interval

Table 35. Association between TOX exposure and mean term birth weight among women included in term birth analyses from the chlorinated DBP site, 2000-2004

Residential TOX Concentration (μg/liter)	Term Birth Weight (grams) N (n= 872)	Unadjusted Mean change (95% CI)[a]	Adjusted Mean change (95% CI)[b]
1st-trimester average			
136.7-165.6	224	0.	0.
165.7-173.8	221	-61.3 (-151.0, 28.3)	-57.5 (-147.1, 32.2)
173.8-180.8	195	9.5 (-83.2, 102.2)	-10.7 (-103.5, 82.0)
180.9-223.1	232	9.2 (-79.4, 97.8)	21.2 (-67.7, 110.0)
p for trend test[c]		0.3	0.2
2nd-trimester average			
136.7-165.4	218	0.	0.
165.7-173.8	213	15.0 (-76.3, 106.3)	9.0 (-82.2, 100.1)
173.8-180.7	227	-16.4 (-106.3, 73.4)	-16.0 (-105.2, 73.3)
180.9-220.6	214	-4.3 (-95.5, 86.8)	-21.0 (-111.5, 69.5)
p for trend test[c]		0.9	0.8
3rd-trimester average			
134.1-165.6	248	0.	0.
165.7-173.8	174	-17.6 (-111.0, 75.8)	-33.9 (-126.9, 59.0)
173.9-180.9	211	-44.9 (-133.4, 43.5)	-32.4 (-120.4, 55.7)
180.9-224.8	216	0.2 (-87.7, 88.1)	8.5 (-79.6, 96.5)
Missing	23		
p for trend test[c]		1.0	1.0
TOX exposure through tap-water consumption (μg/liter)			
1st-trimester average			
0-108.5	268	0.	0.
109.1-215.7	204	52.8 (-35.0, 140.7)	23.2 (-65.4, 111.9)
216.2-369.7	209	33.0 (-54.3, 120.2)	27.9 (-60.2, 116.0)
369.8-1349.7	190	71.5 (-18.2, 161.1)	71.6 (-19.4, 162.5)
Missing	1		
2nd-trimester average			
0-108.3	216	0.	0.
108.8-216.1	214	45.6 (-45.6, 136.8)	43.2 (-47.6, 134.0)
216.2-369.7	221	37.2 (-53.3, 127.6)	42.1 (-49.3, 133.5)
369.8-1225.5	220	71.8 (-18.8, 162.4)	91.7 (-1.5, 185.0)
Missing	1		
3rd-trimester average			
0-108.5	216	0.	0.
109-216	210	28.6 (-62.8, 120.0)	47.5 (-42.9, 137.9)
217.3-369.4	203	7.4 (-84.8, 99.6)	15.1 (-77.8, 108.0)
370.7-1370.8	219	52.9 (-37.5, 143.4)	88.2 (-4.0, 180.5)
Missing	24		

a Unadjusted model.
b Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
c Chi-square test (H_0: $\beta_{DBP} = 0$) for a single, continuous residential DBP concentration term (*i.e.,* linear term), p-value rounded to 1 significant figure.
Abbreviations: RR = risk ratio, CI= confidence interval

4.4.5 Associations between individual DBPs and fetal growth measures

Table 36 and 37 show estimated associations between individual trihalomethanes (THMs) and haloacetic acids (HAAs) with fetal growth outcomes (probability of SGA infant and term birth weight, respectively) among all study sites combined. For each set of analyses, separate maximum likelihood estimation (MLE) models were created for each of the individual DBPs to serve as a reference when examining results from the fully adjusted Bayesian models. Conversely, a single model including all individual THMs and HAAs were constructed for Bayesian analyses. Results from both the Bayesian model specifying a vague prior mean and the model specifying shrinkage by DBP class and bromination categories are shown. All models were adjusted for maternal characteristics.

As previously discussed, distributions of the predominantly chlorinated (*e.g.,* chloroform) and predominately brominated (*e.g.,* bromoform) compounds overlapped very little (if at all) between the chlorinated and brominated DBP sites. As such, comparisons of exposure categories for these individual DBPs are completely confounded by study site. Therefore, while several of the MLE estimates for the brominated THMs were elevated in analyses, it is unclear whether these associations truly reflect a relationship with brominated THMs or are simply an artifact of confounding by site. Results of the Bayesian model specifying a vague prior mean did not implicate any particular DBP, and results of the Bayesian analyses with shrinkage by DBP class and bromination were contradictory to that found from MLE models.

Table 36. Associations between third trimester average exposure to residential concentrations of individual THMs and HAAs and the odds of delivering an SGA infant among women included in SGA analyses, 2000-2004[a]

			MLE models[b]	Bayesian Models[c]	
				Model 1	Model 4
DBP	*n* SGA	*n* Non-SGA	OR (95% CI)	OR (95% CI)	OR (95% CI)
Chloroform					
0-0.1	28	451	1	1	1
0.1-16.5	33	442	1.4 (0.8,2.5)	1.1 (0.7,1.6)	1.6 (0.5,6.0)
16.5-47.2	27	441	1.2 (0.6,2.1)	1.1 (0.7,1.8)	1.6 (0.4,7.4)
>47.2	21	451	1.0 (0.5,1.8)	1.0 (0.7,1.6)	1.5 (0.4,6.7)
BDCM					
0-1.1	28	448	1	1	
1.1-12.1	26	448	1.1 (0.6,2.1)	1.1 (0.8,1.8)	1.2 (0.6,2.2)
12.1-17.8	18	448	0.8 (0.4,1.5)	1.0 (0.6,1.3)	1.1 (0.4,2.0)
>17.8	37	441	1.8 (1.0,3.1)	1.1 (0.7,1.6)	1.3 (0.6,2.7)
DBCM					
0-1.5	29	448	1	1	
1.5-3.2	22	453	1.0 (0.6,1.9)	1.1 (0.7,1.8)	1.2 (0.6,2.2)
3.2-6.8	20	446	0.8 (0.4,1.6)	1.0 (0.6,1.5)	1.1 (0.4,1.8)
>6.8	38	438	1.8 (1.0,3.1)	1.0 (0.7,1.6)	1.3 (0.5,2.7)
Bromoform					
0-0.1	18	454	1	1	
0.1-0.6	31	436	1.9 (1.0,3.6)	1.2 (0.9,2.2)	1.5 (0.8,3.0)
0.6-0.9	25	451	1.5 (0.8,2.9)	1.1 (0.7,1.6)	1.3 (0.7,2.7)
>0.9	35	444	2.1 (1.1,4.1)	1.0 (0.7,1.5)	1.3 (0.6,2.7)
CAA					
0	37	612	1	1	
>0-2.3	40	587	1.2 (0.7,2.1)	1.1 (0.7,1.8)	1.8 (0.8,4.1)
>2.3	32	586	1.1 (0.6,1.9)	1.0 (0.7,1.8)	1.8 (0.7,4.1)
DCAA					
0	41	667	1	1	
>0-17.5	39	557	1.1 (0.7,1.9)	0.9 (0.5,1.3)	1.2 (0.4,3.0)
>17.5	29	561	1.1 (0.6,1.8)	1.1 (0.8,2.2)	2.0 (0.8,5.5)
TCAA					
0	41	667	1	1	
>0-10.2	43	552	1.4 (0.8,2.3)	1.1 (0.8,2.0)	1.8 (0.8,5.0)
>10.2	25	566	0.8 (0.5,1.5)	0.9 (0.5,1.2)	1.2 (0.4,3.0)
BCAA					
0	41	667	1	1	1
>0-5	24	567	0.8 (0.4,1.3)	1.0 (0.6,1.5)	0.6 (0.2,1.2)
>5	44	551	1.5 (0.9,2.5)	1.1 (0.7,1.8)	0.7 (0.3,1.3)
BDCAA					
0-1.3	33	443	1	1	1
1.3-3.7	19	450	0.5 (0.3,1.0)	0.9 (0.5,1.2)	0.6 (0.3,1.0)
3.7-6.2	19	453	0.7 (0.4,1.2)	1.0 (0.6,1.5)	0.6 (0.3,1.2)
>6.2	38	439	1.4 (0.8,2.4)	1.1 (0.7,1.8)	0.8 (0.4,1.6)
DBCAA					
0	37	439	1	1	1
>0-1.4	26	679	0.5 (0.3,0.8)	0.8 (0.4,1.1)	0.5 (0.2,0.9)
>1.4	46	667	0.9 (0.6,1.5)	1.0 (0.7,1.6)	0.7 (0.4,1.3)
BAA					
0	67	1,297	1	1	1
>0	42	488	1.7 (1.1,2.8)	1.1 (0.8,1.8)	0.8 (0.5,1.8)
DBAA					
0	44	692	1	1	1
>0-1	21	552	0.7 (0.4,1.2)	0.9 (0.6,1.2)	0.7 (0.3,1.1)
>1	44	541	1.4 (0.9,2.4)	1.0 (0.7,1.6)	0.7 (0.3,1.5)
TBAA					
0	53	815	1	1	1

>0-0.6	22	487	0.7 (0.4,1.3)	0.9 (0.5,1.2)	0.7 (0.4,1.1)
>0.6	34	483	1.1 (0.6,1.8)	1.0 (0.6,1.3)	0.7 (0.4,1.1)

a N= 1,894; seven births born before 27 weeks' gestation and 57 births that were < 27 weeks' in gestation when water sampling ended (64 births total) are not included in third trimester average models

b Maximum likelihood estimation models were constructed separately for each individual THM and HAA; all models were adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake

c Two fully-Bayesian models were constructed using different prior specifications for the effect of DBP exposures: model 1 specified $\beta_j \sim N(0,\varphi^2)$, model 2 specified $\beta_j \sim N(\mu_k,\varphi_k^2)$ where k is an indictor for DBP class and bromination (non-brominated THM, non-brominated HAA, brominated TTHM, brominated HAA); models adjusted for all other DBPs listed in the table and maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake

Abbreviations: SGA, small-for-gestational-age, MLE = maximum likelihood estimation, OR= odds ratios, CI = confidence interval, DBP= disinfection by-product, BDCM= bromodichloromethane, DBCM = dichloromethane, CAA= chloroacetic acid, DCAA=dichloroacetic acid, TCAA=trichloroacetic acid, BCAA= bromochloroacetic acid, BDCAA= Bromochloroacetic acid, DBCAA= dibromochloroacetic acetic acid, BAA= bromoacetic acid, DBAA= dibromoacetic acid, TBAA= tribromoacetic acid

Table 37. Associations between third trimester average exposure to residential concentrations of individual THMs and HAAs and mean birth weight among term infants born to women included in the analysis of exposure to drinking water DBPs and term birth weight, 2000-2004[a]

			Bayesian Models[c]	
		MLE models[b]	Model 1	Model 2
DBP	*n*	Δ in grams (95% CI)	Δ in grams (95% CI)	Δ in grams (95% CI)
Chloroform				
0-0.1	438	0	0	0
0.1-16.5	442	-64.8 (-127.5, -2.0)	-13.0 (-54.0, 16.7)	-25.4 (-91.0, 23.6)
16.5-47.2	465	25.5 (-35.4, 86.5)	4.1 (-31.0, 38.1)	9.0 (-38.0, 83.5)
>47.2	456	51.7 (-9.8, 113.1)	10.5 (-23.0, 55.0)	26.4 (-22.0, 111.4)
BDCM				
0-1.1	437	0	0	0
1.1-12.1	464	4.2 (-56.5, 64.9)	-5.4 (-41.0, 23.3)	-3.9 (-52.0, 24.7)
12.1-17.8	461	41.0 (-20.6, 102.6)	2.9 (-36.0, 36.5)	0.6 (-39.0, 43.2)
>17.8	439	-37.9 (-103.1, 27.3)	1.3 (-33.0, 51.3)	1.7 (-37.0, 61.3)
DBCM				
0-1.5	438	0	0	
1.5-3.2	451	34.0 (-26.7, 94.7)	8.6 (-21.0, 47.9)	7.6 (-19.0, 73.2)
3.2-6.8	476	51.7 (-8.9, 112.4)	8.5 (-21.0, 49.7)	4.3 (-27.0, 61.0)
>6.8	436	-54.4 (-120.0, 11.2)	-5.7 (-44.0, 33.4)	-3.6 (-63.0, 45.0)
Bromoform				
0-0.1	475	0	0	0
0.1-0.6	445	-35.6 (-96.0, 24.7)	1.8 (-28.0, 33.6)	0.6 (-37.0, 37.7)
0.6-0.9	449	-92.8 (-152.8, -32.7)	-10.6 (-53.0, 17.3)	-7.9 (-63.0, 18.8)
>0.9	432	-99.1 (-164.8, -33.3)	2.0 (-30.0, 49.3)	2.7 (-37.0, 51.5)
CAA				
0	604	0	0	0
>0-2.3	584	-6.5 (-60.6, 47.6)	-3.2 (-36.0, 27.2)	-0.8 (-42.0, 37.0)
>2.3	613	39.7 (-13.2, 92.7)	6.3 (-25.0, 42.0)	1.4 (-33.0, 60.3)
DCAA				
0	655	0	0	0
>0-17.5	563	-10.1 (-64.9, 44.6)	1.6 (-36.0, 42.3)	0.7 (-48.0, 51.0)
>17.5	583	41.4 (-11.3, 94.1)	0.5 (-40.0, 38.2)	-0.9 (-59.0, 39.2)
TCAA				
0	655	0	0	0
>0-10.2	563	-13.0 (-67.9, 41.9)	-3.2 (-44.0, 31.8)	-1.3 (-54.0, 37.8)
>10.2	583	43.8 (-8.9, 96.5)	3.3 (-35.0, 39.9)	0.6 (-47.0, 45.0)
BCAA				
0	655	0	0	0
>0-5	587	63.1 (10.8, 115.4)	11.6 (-21.0, 48.7)	7.6 (-28.0, 59.8)
>5	559	-38.4 (-93.8, 16.9)	-10.3 (-50.0, 22.6)	-8.4 (-64.0, 32.7)
BDCAA				
0-1.3	441	0	0	0
1.3-3.7	456	-1.0 (-61.7, 59.6)	-2.2 (-37.0, 28.9)	-2.3 (-57.0, 36.0)
3.7-6.2	463	58.7 (-2.2, 119.5)	10.4 (-21.0, 50.6)	7.9 (-31.0, 61.7)
>6.2	441	-89.1 (-153.6, -24.5)	-18.6 (-69.0, 10.4)	-20.3 (-100.0, 12.9)
DBCAA				
0	442	0	0	0
>0-1.4	693	27.1 (-28.6, 82.8)	4.0 (-27.0, 38.5)	4.3 (-26.0, 54.2)
>1.4	666	19.6 (-37.8, 77.0)	4.5 (-29.0, 47.5)	4.5 (-33.0, 71.7)
BAA				
0	1298	0	0	0
>0	503	-75.5 (-127.1, -23.9)	-8.6 (-46.0, 26.0)	-8.0 (-59.0, 34.6)
DBAA				
0	681	0	0	0
>0-1	576	43.7 (-7.9, 95.3)	3.9 (-33.0, 35.1)	0.4 (-44.0, 41.9)
>1	544	-51.7 (-107.2, 3.8)	-12.7 (-60.0, 21.8)	-12.2 (-79.0, 21.0)
TBAA				
0	836	0	0	0

>0-0.6	497	19.5 (-31.9, 71.0)	4.1 (-31.0, 39.4)	2.5 (-33.0, 45.8)
>0.6	468	-56.1 (-113.0, 0.9)	-5.4 (-42.0, 30.0)	-2.4 (-51.0, 38.4)

a N=1801; 53 births that were < 27 weeks' in gestation when water sampling ended are not included in third trimester average models
b Maximum likelihood estimation models were constructed separately for each individual THM and HAA; all models were adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake
c Four fully-Bayesian models were constructed using different prior specifications for the effect of DBP exposures: model 1 specified $\beta_j \sim N(0,\varphi^2)$, model 2 specified $\beta_j \sim N(\mu_k,\varphi_k^2)$ where k is an indictor for DBP class and bromination (non-brominated THM, non-brominated HAA, brominated TTHM, brominated HAA); models adjusted for all other DBPs listed in the table and maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake
Abbreviations: SGA, small-for-gestational-age, MLE = maximum likelihood estimation, Δ= change, CI = confidence interval, DBP= disinfection by-product, BDCM= bromodichloromethane, DBCM = dichloromethane, CAA= chloroacetic acid, DCAA=dichloroacetic acid, TCAA=trichloroacetic acid, BCAA= bromochloroacetic acid, BDCAA= Bromochloroacetic acid, DBCAA= dibromochloroacetic acetic acid, BAA= bromoacetic acid, DBAA= dibromoacetic acid, TBAA= tribromoacetic acid

Bayesian analyses also were run separately for the chlorinated (table 38) and brominated (table 39) DBP sites to avoid the potential for residual confounding by study site. Results of the MLE analyses restricted to the chlorinated DBP site suggested that elevated exposure to bromoform, dibromochloromethane (DBCM) and bromoacetic acid (BAA) was associated with increased probability of delivering an SGA infant. Estimated associations for these DBPs from the Bayesian analysis were attenuated after adjustment for other DBPs and shrinking by DBP class and bromination status, and 95% CIs for all effect estimates included values below the null value, indicating that a null or protective effect of DBPs was within the probable range. RRs for SGA from the Bayesian analysis using a vague prior were all within the range of 0.9.-1.2, with wide 95% CIs (data not shown). A similar pattern of associations was found for term birth weight.

In contrast, results of the MLE analyses restricted to the brominated DBP site suggested that elevated exposure to predominately chlorinated DBPs (*i.e.,* chloroform, chloroacetic acid [CAA], dichloroacetic acid [DCAA], trichloroacetic acid [TCAA], and bromochloroacetic acid [BCAA]) was associated with increased probability of delivering an SGA infant and decreased term birth weight, albeit effect estimates were highly unstable given the small number of participants from this study site (table 38). Estimated effects for CAA, DCAA and BCAA remained elevated in the Bayesian analysis for SGA, but a respective decrease in mean birth weight for the DBPs was not found. Again, 95% CIs for all effect estimates included the null value, and results of Bayesian analysis using a vague prior did not indicate an association between either fetal growth measure and any individual THM or HAA.

Table 38. Estimated effects of third trimester average concentrations of individual THMs and HAAs on fetal growth measures among women included in the analysis of exposure to drinking water DBPs and fetal growth restriction from the chlorinated DBP site, 2000-2004[a,b]

			SGA		Term birth weight (in grams)	
	n SGA	*n* Non-SGA	MLE model OR (95% CI)[c]	Bayesian Model OR (95% PI)[d]	MLE model Mean Δ (95% CI)[c]	Bayesian Model Mean Δ (95% PI)[d]
Chloroform						
19.9-44.2	14	267	1	1	0	0
44.3-49	14	274	1.4 (0.6, 3.1)	2.0 (0.5, 8.2)	41.6 (-40.3, 123.6)	11.8 (-29.5, 96.0)
49.1-94.0	12	275	1.1 (0.5, 2.6)	1.8 (0.4, 8.2)	27.3 (-57.1, 111.6)	4.5 (-44.5, 75.0)
BDCM						
8.2-11.8	14	274	1	1	0	0
11.9-14.1	10	273	0.9 (0.4,2.2)	1.5 (0.7,3.0)	26.0 (-56.3, 108.3)	2.4 (-39.0, 56.0)
14.2-28.5	16	269	1.5 (0.7,3.5)	1.3 (0.6,2.7)	-43.6 (-126.7, 39.4)	-3.3 (-72.7, 40.0)
DBCM						
1.1-3.2	11	281	1	1	0	0
3.3-4.4	11	269	0.8 (0.3,2.1)	1.5 (0.6,2.7)	4.1 (-77.7, 85.9)	3.9 (-30.8, 65.0)
4.5-9.1	18	266	2.0 (0.9,4.4)	1.6 (0.8,3.7)	-51.5 (-135.7, 32.8)	-1.2 (-54.0, 53.0)
Bromoform						
0.0-0	8	278	1	1	0	0
0.1-0.2	13	275	1.5 (0.6,3.9)	1.5 (0.8,3.0)	41.7 (-40.4, 123.8)	5.7 (-26.0, 67.0)
0.3-0.9	19	263	2.9 (1.2,7.0)	1.8 (0.9,4.1)	-32.4 (-116.9, 52.1)	-2.4 (-62.3, 46.0)
CAA						
0.0-2.2	13	273	1	1	0	0
2.3-3.2	11	273	1.1 (0.5,2.7)	0.9 (0.5,2.0)	11.3 (-70.8, 93.3)	0.1 (-42.1, 42.0)
3.3-5.6	16	270	1.6 (0.7,3.7)	0.9 (0.4,1.8)	-18.3 (-103.3, 66.7)	-0.8 (-43.7, 39.0)
DCAA						
10.2-17.3	15	269	1	1	0	0
17.4-20.8	14	267	1.2 (0.5,2.7)	0.9 (0.5,2.0)	1.9 (-81.6, 85.4)	-0.7 (-40.3, 37.0)
20.9-26.9	11	280	0.9 (0.4,2.2)	0.9 (0.5,2.2)	23.2 (-59.8, 106.2)	-0.6 (-45.7, 46.0)
TCAA						
5.3-11	16	268	1	1	0	0
11-17.2	14	272	0.9 (0.4,1.9)	0.7 (0.3,1.3)	4.0 (-80.7, 88.7)	1.5 (-33.4, 54.0)
17.3-24.1	10	276	0.6 (0.3,1.5)	0.9 (0.4,1.8)	1.9 (-81.2, 84.9)	-2.3 (-53.9, 35.0)
BCAA						
0.4-3.7	16	274	1	1	0	0
3.8-4.5	8	274	0.5 (0.2,1.2)	0.7 (0.3,1.5)	49.1 (-33.2, 131.5)	8.9 (-25.7, 75.0)
4.6-11.7	16	268	1.2 (0.5,2.5)	0.9 (0.4,1.8)	-27.8 (-110.8, 55.2)	-4.3 (-62.3, 42.0)
BDCAA						
1.6-3.7	13	270	1	1	0	0
3.8-5	13	275	1.4 (0.6,3.3)	1.0 (0.5,2.2)	53.2 (-30.3, 136.6)	10.3 (-20.2, 76.0)
5.1-7.5	14	271	1.3 (0.6,3.1)	0.9 (0.4,1.8)	-33.5 (-116.2, 49.2)	-8.5 (-67.9, 27.0)
DBCAA						
0.0-0.8	11	270	1	1	0	0
0.9-1.6	15	272	1.5 (0.6,3.5)	1.0 (0.5,2.2)	10.4 (-72.5, 93.3)	0.4 (-42.9, 50.0)
1.7-2.4	14	274	1.6 (0.7,3.9)	1.2 (0.6,3.0)	33.9 (-49.9, 117.8)	3.0 (-35.0, 62.0)
BAA						
0	25	621	1	1	0	0
0.0-0.5	15	195	1.9 (0.9,3.9)	1.2 (0.6,2.7)	-73.9 (-152.8, 4.9)	-5.3 (-59.8, 33.0)
DBAA						
0.0-0.3	16	274	1	1	0	0
0.4-0.9	7	272	0.5 (0.2,1.2)	0.7 (0.3,1.5)	19.5 (-63.6, 102.7)	4.4 (-35.1, 61.0)
1-2.1	17	270	1.1 (0.5,2.3)	0.9 (0.4,1.8)	-37.0 (-121.3, 47.3)	-4.2 (-55.5, 42.0)
TBAA						
0	19	365	1	1	0	0
0.0-1.8	21	451	1.0 (0.5,2.0)	0.8 (0.4,1.5)	25.8 (-42.6, 94.3)	4.0 (-33.4, 59.0)

a N = 856 for SGA analysis; two births born before 27 weeks' gestation and 25 births that were < 27 weeks' in gestation when water sampling ended (27 births total) are not included in third trimester average SGA models

b N = 849 for term birth weight analysis; 23 births that were < 27 weeks' in gestation when water sampling ended are not included in third trimester average term birth weight models

c Maximum likelihood estimation models were constructed separately for each individual THM and HAA; all models were adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake
d Fully-Bayesian models specified $\beta_j \sim N(\mu_k, \varphi^2)$ where k is an indictor for DBP class and bromination (non-brominated THM, non-brominated HAA, brominated THM, brominated HAA); models adjusted for other DBPs listed in the table and maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
Abbreviations: SGA= small-for-gestational-age, MLE = maximum likelihood estimation, OR= odds ratios, CI = confidence interval, PI= posterior interval, DBP= disinfection by-product, BDCM= bromodichloromethane, DBCM = dibromochloromethane, CAA= chloroacetic acid, DCAA=dichloroacetic acid, TCAA=trichloroacetic acid, BCAA= bromochloroacetic acid, BDCAA= bromodichloroacetic acid, DBCAA= dibromochloroacetic acetic acid, BAA= bromoacetic acid, DBAA= dibromoacetic acid, TBAA= tribromoacetic acid

Table 39. Estimated effects of third trimester average concentrations of individual THMs and HAAs on fetal growth measures among women included in the analysis of exposure to drinking water DBPs and fetal growth restriction from the brominated DBP site, 2000-2004[a,b]

			SGA		Term birth weight (in grams)	
	n SGA	*n* Non-SGA	MLE model OR (95% CI)[‡]	Bayesian Model OR (95% PI)[§]	MLE model Mean Δ (95% CI)[‡]	Bayesian Model Mean Δ (95% PI)[§]
Chloroform						
6.4-11.5	4	104	1	1	0	0
11.6-15.6	15	96	4.9 (1.5,15.8)	3.9 (0.6,24.8)	-87.4 (-215.8, 41.1)	-9.9 (-115.0, 61.0)
15.7-22.1	9	102	2.4 (0.7,8.4)	3.5 (0.6,23.8)	59.3 (-70.8, 189.3)	11.7 (-64.0, 129.0)
BDCM						
15.8-20.1	8	101	1	1	0	0
20.2-22.9	8	103	1.0 (0.3,2.7)	0.8 (0.3,2.1)	55.1 (-74.3, 184.4)	8.4 (-62.0, 108.0)
23-29.2	12	98	1.6 (0.6,4.1)	0.9 (0.4,2.5)	49.1 (-81.0, 179.1)	-2.3 (-95.0, 73.0)
DBCM						
15.2-19.3	14	95	1	1	0	0
19.4-26	8	103	0.5 (0.2,1.2)	0.7 (0.3,1.6)	170.9 (42.5, 299.4)	32.6 (-28.0, 169.0)
26.1-38.7	6	104	0.3 (0.1,0.9)	0.7 (0.3,1.8)	142.8 (14.3, 271.2)	7.3 (-62.0, 118.0)
Bromoform						
0.8-2.4	12	98	1	1	0	0
2.5-11.5	7	102	0.6 (0.2,1.6)	0.8 (0.3,2.0)	145.9 (16.4, 275.3)	18.5 (-45.0, 137.0)
11.6-15.1	9	102	0.7 (0.3,1.7)	0.9 (0.3,2.4)	76.1 (-53.0, 205.2)	-1.0 (-94.0, 83.0)
CAA						
0.4-0.8	7	102	1	1	0	0
0.9-1.8	9	101	1.3 (0.5,3.7)	1.1 (0.4,2.4)	-134.0 (-265.2, -2.8)	-15.4 (-124.0, 41.0)
1.9-4.0	12	99	1.9 (0.7,5.3)	1.3 (0.5,3.6)	-105.9 (-234.6, 22.8)	1.2 (-74.0, 84.0)
DCAA						
2.7-6.5	6	103	1	1	0	0
6.6-7.8	14	98	3.0 (1.1,8.3)	1.4 (0.6,3.2)	-56.7 (-184.5, 71.2)	-5.6 (-101.0, 64.0)
7.9-10.3	8	101	1.5 (0.5,4.6)	1.1 (0.4,2.6)	49.7 (-82.6, 182.0)	13.5 (-46.0, 130.0)
TCAA						
1.8-4	6	103	1	1	0	0
4.1-5.7	10	101	1.8 (0.6,5.4)	1.2 (0.5,2.7)	-39.7 (-170.1, 90.7)	-2.4 (-92.0, 82.0)
5.8-9.1	12	98	2.6 (0.9,7.4)	1.3 (0.5,3.5)	-43.0 (-173.1, 87.0)	-3.6 (-99.0, 67.0)
BCAA						
7.0-7.8	6	103	1	1	0	0
7.9-8.4	11	99	2.2 (0.8,6.3)	1.4 (0.7,3.4)	-94.4 (-224.5, 35.8)	-4.3 (-77.0, 44.0)
8.5-9.9	11	100	2.0 (0.7,5.6)	1.4 (0.6,3.6)	-67.2 (-198.3, 63.9)	-1.1 (-76.0, 58.0)
BDCAA						
6.1-7.8	7	102	1	1	0	0
7.9-9.4	10	101	1.5 (0.5,4.1)	1.1 (0.4,2.5)	20.4 (-108.2, 148.9)	8.8 (-34.0, 99.0)
9.5-11.5	11	99	1.7 (0.6,4.7)	1.4 (0.6,3.9)	34.5 (-97.3, 166.3)	-4.5 (-78.0, 48.0)
DBCAA						
2.5-4.3	10	99	1	1	0	0
4.4-5.8	12	99	1.4 (0.5,3.4)	1.2 (0.5,2.9)	21.0 (-108.3, 150.3)	0.4 (-64.0, 69.0)
5.9-8.2	6	104	0.5 (0.2,1.6)	1.2 (0.5,3.1)	71.6 (-58.0, 201.2)	-0.3 (-61.0, 71.0)
BAA						
0.0-0.4	12	99	1	1	0	0
0.5-1.2	7	102	0.5 (0.2,1.4)	0.9 (0.4,1.8)	-39.1 (-169.2, 91.1)	-3.8 (-77.0, 50.0)
1.3-2.1	9	101	0.7 (0.3,1.7)	1.7 (0.8,5.1)	-12.5 (-143.6, 118.6)	0.5 (-70.0, 70.0)
DBAA						
2.3-4.4	13	98	1	1	0	0
4.5-7.2	10	100	0.8 (0.3,1.9)	1.3 (0.6,3.4)	12.3 (-117.7, 142.4)	0.2 (-56.0, 69.0)
7.3-11.4	5	104	0.3 (0.1,0.9)	1.1 (0.4,2.6)	62.3 (-69.0, 193.6)	2.2 (-57.0, 73.0)
TBAA						
1.5-2.6	8	102	1	1	0	0
2.7-3	14	97	1.9 (0.7,4.8)	1.7 (0.6,4.8)	-57.4 (-186.4, 71.6)	-8.8 (-86.0, 36.0)
3.1-5.2	6	103	0.7 (0.2,2.0)	1.3 (0.5,3.4)	-14.3 (-145.0, 116.4)	-3.4 (-95.0, 51.0)

a N = 330 for SGA analysis; two births born before 27 weeks' gestation and 8 births that were < 27 weeks' in gestation when water sampling ended (10 births total) are not included in third trimester average SGA models

b N = 297 for term birth weight analysis; eight births that were < 27 weeks' in gestation when water sampling ended are not included in third trimester average term birth weight models
c Maximum likelihood estimation models were constructed separately for each individual THM and HAA; all models were adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake
d Fully-Bayesian models specified $\beta_j \sim N(\mu_k, \varphi^2)$ where k is an indictor for DBP class and bromination (non-brominated THM, non-brominated HAA, brominated THM, brominated HAA); models adjusted for other DBPs listed in the table and maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
Abbreviations: MLE = maximum likelihood estimation, OR= odds ratios, CI = confidence interval, CI = credible interval, DBP= disinfection by-product, BDCM= bromodichloromethane, DBCM = dibromochloromethane, CAA= chloroacetic acid, DCAA=dichloroacetic acid, TCAA=trichloroacetic acid, BCAA= bromochloroacetic acid, BDCAA= bromodichloroacetic acid, DBCAA= dibromochloroacetic acetic acid, BAA= bromoacetic acid, DBAA= dibromoacetic acid, TBAA= tribromoacetic acid

4.5 Results of duration of gestation analyses

Results of the time-to-birth analyses, addressing specific aim #2 of this dissertation, are summarized below. A brief description precedes each table or figure and any notable findings are highlighted. For all analyses, results for the total study population are presented first and then followed by the analogous results restricted to the chlorinated site alone. Additionally, supplementary tables of preterm birth results are provided in appendix 5.

4.5.1 Associations between time-to-birth and DBP exposure for all study sites

Tables 40-42 present estimated odds ratios for associations between aggregate DBP measures and the conditional odds of delivery each week stratified by gestational periods (≤ 32, 33-36, 37-40 and ≥ 41 weeks). Results are also presented graphically in figure 14. The odds of delivery each week, conditional on not having delivered in a previous week, were decreased for women in the higher categories of average second trimester residential TTHM and HAA5 concentrations compared to women in the lowest group for gestational weeks 33-40. Odds ratios (ORs) over this period ranged from 0.5-0.9 for residential TTHM concentrations and 0.4 to 1.3 for residential HAA5 concentrations.

ORs for 20-32 weeks and 41-44 weeks were imprecise, as evidenced by wide confidence intervals, due to the small number of infants born during these periods. Results suggest that the conditional probability of birth each week was increased with higher DBP exposure over the 41-44 weeks period (ORs ranged from 2.1-7.3); however, these findings should be interpreted with caution. In addition to poor precision, the majority of births during the 41-44 weeks' period occurred at 41 or 42 weeks' (98%) and later births (at 43 or 44 weeks') are likely due to errors in gestational age estimation.

Conditional ORs estimates for personal TTHM and HAA5 exposure showed a pattern of association similar to residential concentrations for 37-40 weeks and 41-44 weeks but were inconsistent for 33-36 weeks. Estimated ORs from models examining 6-week sliding average exposure and weekly exposure did not differ substantially from those shown in figure 2. Effect measure modification by maternal age, maternal race/ethnicity or swimming during pregnancy was not indicated (*p*-values for joint effect of interaction terms ranged form 0.1-0.7).

Table 40. Association between TTHM exposure and the conditional probability if delivery each week (gestational weeks 20 to 44) stratified by gestational period among women included in duration of gestation analyses, 2000-2004.

	Unadjusted Model								Fully-adjusted Model[a]			
	Gestational Period (weeks')								Gestational Period (weeks')			
	≤ 32		33-36		37-40		≥ 41		≤ 32	33-36	37-40	≥ 41
Residential TTHM level (μg/liter)	n[b]	OR (95% CI)	n[b]	OR (95% CI)	n[b]	OR (95% CI)	n[b]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
2nd-trimester average												
2.2-4.6	15	1	69	1	636	1	41	1	1	1	1	1
33.1-55	3	0.47 (0.14,1.63)	24	0.80 (0.50,1.29)	258	0.74 (0.61,0.90)	37	2.31 (0.78,6.84)	0.38 (0.09,1.68)	0.92 (0.56,1.50)	0.73 (0.59,0.89)	2.31 (0.77,6.96)
55-66.3	6	0.96 (0.37,2.47)	24	0.81 (0.51,1.30)	252	0.72 (0.60,0.88)	36	4.97 (1.06,23.38)	1.16 (0.44,3.05)	0.85 (0.51,1.41)	0.77 (0.63,0.95)	4.40 (0.92,21.03)
66.4-74.8	4	0.64 (0.21,1.92)	20	0.67 (0.40,1.11)	247	0.71 (0.58,0.87)	47	4.40 (1.19,16.28)	0.78 (0.26,2.41)	0.65 (0.37,1.14)	0.75 (0.61,0.92)	4.28 (1.14,16.11)
74.9-108.8	5	0.79 (0.29,2.18)	15	0.49 (0.28,0.87)	254	0.68 (0.56,0.83)	46	4.31 (1.16,15.98)	0.77 (0.25,2.37)	0.47 (0.25,0.88)	0.75 (0.61,0.93)	4.06 (1.08,15.27)
Weekly concentration												
1.4-5.4	15	1	69	1	636	1	41	1	1	1	1	1
24.7-54.8	1	0.15 (0.45,1.15)	17	0.48 (0.28,0.83)	283	0.68 (0.56,0.82)	43	3.38 (0.98,11.67)	0.18 (0.02,1.43)	0.55 (0.31,0.97)	0.72 (0.58,0.88)	3.09 (0.88,10.82)
55.1-65.4	7	1.15 (0.02,2.89)	21	0.62 (0.37,1.02)	247	0.65 (0.53,0.8)	49	4.56 (1.42,14.64)	1.21 (0.45,3.28)	0.61 (0.35,1.05)	0.68 (0.55,0.84)	4.15 (1.27,13.54)
66.6-74.6	2	0.52 (0.46,2.33)	18	0.99 (0.58,1.69)	158	0.76 (0.60,0.97)	27	2.96 (0.75,11.62)	0.65 (0.14,2.95)	1.16 (0.67,2.01)	0.79 (0.62,1.02)	2.77 (0.70,11.04)
74.9-165	7	1.13 (0.12,2.84)	22	0.75 (0.46,1.24)	219	0.64 (0.52,0.79)	38	6.10 (1.26,29.48)	1.21 (0.44,3.27)	0.67 (0.38,1.18)	0.67 (0.54,0.84)	5.92 (1.21,29.02)
6-week average												
2.1-5.3	15	1	69	1	636	1	41	1	1	1	1	1
28.8-54.8	1	0.16 (0.02,1.24)	16	0.50 (0.29,0.88)	265	0.69 (0.56,0.84)	38	2.63 (0.85,8.13)	0.18 (0.02,1.42)	0.55 (0.31,0.96)	0.73 (0.60,0.90)	2.44 (0.78,7.64)
55.1-66.3	3	0.53 (0.15,1.88)	16	0.5 (0.29,0.88)	257	0.68 (0.56,0.83)	51	5.78 (1.54,21.75)	0.60 (0.17,2.13)	0.53 (0.30,0.93)	0.70 (0.57,0.87)	5.52 (1.45,21.08)
66.4-74.7	4	0.87 (0.28,2.66)	26	1.17 (0.73,1.87)	158	0.58 (0.46,0.74)	29	5.13 (1.08,24.42)	0.97 (0.31,3.03)	1.16 (0.72,1.89)	0.61 (0.48,0.77)	4.87 (1.01,23.44)
75.1-133.2	9	1.43 (1.61,3.34)	20	0.65 (0.39,1.08)	227	0.73 (0.59,0.89)	39	4.19 (1.08,16.27)	1.60 (0.67,3.81)	0.60 (0.35,1.03)	0.76 (0.61,0.94)	4.34 (1.10,17.11)

TTHM exposure through showering & bathing (μg/day)												
2nd-trimester average												
0.02-0.09	12	1	38	1	433	1	25	1	1	1	1	1
0.1-0.8	6	0.50 (0.19,1.32)	50	1.32 (0.86,2.03)	406	0.80 (0.67,0.96)	47	4.15 (1.23,13.94)	0.38 (0.12,1.20)	1.30 (0.83,2.05)	0.79 (0.65,0.95)	3.72 (1.09,12.68)
0.9-1.5	4	0.33 (0.11,1.03)	25	0.63 (0.38,1.05)	405	0.70 (0.58,0.84)	75	4.38 (1.52,12.63)	0.38 (0.12,1.21)	0.73 (0.43,1.23)	0.74 (0.61,0.89)	4.00 (1.36,11.74)
1.6-27.1	11	0.92 (0.40,2.08)	39	1.02 (0.65,1.61)	398	0.76 (0.63,0.91)	60	4.23 (1.38,12.98)	0.98 (0.42,2.33)	0.93 (0.56,1.53)	0.79 (0.65,0.96)	3.51 (1.12,10.97)
Weekly concentration												
0-0.09	8	1	41	1	354	1	21	1	1	1	1	1
0.1-0.8	6	0.73 (0.25,2.12)	36	0.80 (0.51,1.26)	356	0.84 (0.69,1.02)	44	9.25 (1.84,46.63)	0.52 (0.16,1.72)	0.80 (0.49,1.30)	0.87 (0.71,1.07)	8.61 (1.69,43.84)
0.9-1.5	7	0.85 (0.31,2.34)	23	0.50 (0.30,0.85)	346	0.67 (0.55,0.82)	58	4.43 (1.50,13.09)	0.76 (0.26,2.21)	0.57 (0.33,0.97)	0.70 (0.57,0.86)	4.25 (1.41,12.79)
1.6-29.3	9	1.11 (0.43,2.87)	39	0.89 (0.57,1.39)	352	0.76 (0.62,0.92)	63	5.75 (1.84,17.98)	1.07 (0.40,2.85)	0.82 (0.50,1.34)	0.79 (0.64,0.97)	5.17 (1.62,16.47)
6-week average												
0-0.09	9	1	40	1	362	1	26	1	1	1	1	1
0.1-0.8	8	0.92 (0.35,2.38)	40	0.97 (0.62,1.52)	340	0.76 (0.62,0.93)	42	8.66 (1.79,41.87)	0.61 (0.20,1.82)	0.91 (0.57,1.47)	0.77 (0.63,0.95)	8.28 (1.70,40.42)
0.9-1.5	3	0.33 (0.09,1.22)	22	0.5 (0.29,0.85)	372	0.72 (0.59,0.88)	59	8.32 (2.19,31.59)	0.35 (0.09,1.30)	0.58 (0.34,0.98)	0.76 (0.62,0.93)	8.05 (2.09,30.95)
1.6-29.3	10	1.11 (0.45,2.74)	38	0.91 (0.58,1.43)	342	0.71 (0.58,0.87)	61	3.36 (1.28,8.84)	1.08 (0.43,2.73)	0.81 (0.49,1.33)	0.73 (0.59,0.90)	3.00 (1.12,8.06)

a Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.

b Number of births attributed to exposure category during the gestational period.

Abbreviations: OR = conditional odds ratio, CI= confidence interval

Table 41. Association between HAA5 exposure and the conditional probability if delivery each week (gestational weeks 20 to 44) stratified by gestational period among women included in duration of gestation analyses, 2000-2004.

	Unadjusted Model								Fully-adjusted Model[a]			
	Gestational Period (weeks')								Gestational Period (weeks')			
	≤ 32		33-36		37-40		≥ 41		≤ 32	33-36	37-40	≥ 41
Residential HAA5 level (μg/liter)	n[b]	OR (95% CI)	n[b]	OR (95% CI)	n[b]	OR (95% CI)	n[b]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
2nd-trimester average												
0-0.9	15	1	69	1	636	1	41	1	1	1	1	1
17.9-22	3	0.47 (0.14,1.63)	36	1.24 (0.82,1.87)	261	1.03 (0.84,1.25)	21	--[c]	0.61 (0.17,2.14)	1.32 (0.84,2.07)	1.08 (0.87,1.35)	--[c]
22.1-31.5	3	0.48 (0.14,1.65)	21	0.7 (0.43,1.16)	250	0.66 (0.54,0.80)	44	2.38 (0.87,6.51)	0.39 (0.09,1.73)	0.81 (0.49,1.36)	0.71 (0.58,0.87)	2.13 (0.76,5.96)
31.6-40.4	4	0.63 (0.21,1.92)	14	0.46 (0.26,0.82)	251	0.64 (0.52,0.77)	49	3.03 (1.04,8.89)	0.58 (0.17,2.04)	0.43 (0.23,0.83)	0.67 (0.55,0.83)	2.83 (0.95,8.47)
40.4-52.8	8	1.27 (0.54,3.00)	12	0.39 (0.21,0.73)	249	0.62 (0.51,0.75)	52	7.22 (1.55,33.62)	1.52 (0.63,3.69)	0.43 (0.22,0.82)	0.67 (0.55,0.82)	6.69 (1.41,31.65)
Weekly concentration												
0-1.5	15	1	69	1	636	1	41	1	1	1	1	1
12.1-22	1	0.14 (0.02,1.09)	34	0.95 (0.62,1.45)	271	0.82 (0.67,1.00)	34	5.3 (1.08,26.07)	0.18 (0.02,1.40)	1.01 (0.64,1.61)	0.88 (0.71,1.10)	4.41 (0.88,22.00)
22.1-31.5	4	0.88 (0.29,2.69)	15	0.65 (0.37,1.15)	198	0.72 (0.57,0.89)	34	3.03 (0.91,10.12)	0.80 (0.22,2.88)	0.73 (0.40,1.32)	0.75 (0.59,0.94)	3.01 (0.89,10.20)
31.6-40.3	2	0.45 (0.10,1.99)	12	0.52 (0.28,0.98)	176	0.54 (0.43,0.68)	40	4.9 (1.32,18.18)	0.56 (0.12,2.52)	0.53 (0.27,1.05)	0.56 (0.44,0.70)	4.30 (1.14,16.26)
40.7-62.2	10	1.50 (0.66,3.43)	17	0.49 (0.28,0.84)	262	0.62 (0.51,0.76)	49	4.03 (1.19,13.62)	1.67 (0.69,4.04)	0.48 (0.27,0.88)	0.67 (0.54,0.83)	3.90 (1.14,13.35)
6-week average												
0-0.6	15	1	69	1	636	1	41	1	1	1	1	1
16-21.8	3	0.4 (0.11,1.4)	38	0.98 (0.65,1.49)	309	0.86 (0.71,1.05)	32	5.35 (1.11,25.83)	0.46 (0.13,1.65)	1.01 (0.66,1.55)	0.95 (0.77,1.17)	4.49 (0.92,21.96)
22.1-31.5	1	0.25 (0.03,1.93)	10	0.56 (0.29,1.10)	142	0.63 (0.49,0.81)	31	2.83 (0.85,9.43)	0.29 (0.04,2.26)	0.54 (0.27,1.10)	0.64 (0.49,0.82)	2.80 (0.83,9.51)
31.6-40.3	5	1.04 (0.37,2.92)	18	0.71 (0.42,1.21)	175	0.6 (0.48,0.75)	37	6.11 (1.27,29.41)	1.15 (0.41,3.28)	0.75 (0.44,1.28)	0.63 (0.50,0.79)	6.13 (1.26,29.79)
40.6-56.4	8	1.24 (0.51,3.01)	12	0.34 (0.18,0.64)	281	0.59 (0.48,0.71)	57	3.95 (1.30,11.99)	1.39 (0.57,3.41)	0.36 (0.19,0.67)	0.62 (0.51,0.75)	3.78 (1.23,11.69)

HAA5 exposure through tap-water consumption (μg/day)												
2nd-trimester average												
0	14	1	49	1	500	1	39	1	1	1	1	1
0.01-16.1	7	0.63 (0.25,1.56)	49	1.26 (0.84,1.89)	390	0.97 (0.81,1.16)	32	7.85 (0.96,63.81)	0.40 (0.13,1.22)	1.17 (0.75,1.81)	0.95 (0.79,1.15)	7.32 (0.89,60.38)
16.2-54.4	5	0.45 (0.16,1.24)	35	0.88 (0.56,1.36)	374	0.78 (0.65,0.94)	63	4.15 (1.28,13.47)	0.50 (0.18,1.41)	0.99 (0.62,1.57)	0.81 (0.67,0.98)	3.95 (1.19,13.09)
54.7-369.1	7	0.63 (0.25,1.55)	19	0.47 (0.27,0.79)	380	0.64 (0.54,0.77)	72	2.57 (1.02,6.47)	0.71 (0.28,1.77)	0.53 (0.30,0.92)	0.65 (0.54,0.79)	2.41 (0.93,6.26)
Weekly concentration												
0	14	1	49	1	500	1	39	1	1	1	1	1
0.2-16.1	7	0.88 (0.26,3.04)	49	0.7 (0.37,1.32)	390	0.78 (0.60,1.02)	32	4.40 (0.53,36.4)	0.76 (0.17,3.39)	0.64 (0.30,1.34)	0.84 (0.64,1.11)	3.64 (0.43,30.81)
16.1-54.7	5	0.47 (0.16,1.41)	35	0.53 (0.33,0.84)	374	0.77 (0.65,0.92)	63	5.71 (1.22,26.74)	0.59 (0.19,1.82)	0.56 (0.34,0.92)	0.80 (0.66,0.97)	5.48 (1.16,25.99)
54.7-511.4	7	0.82 (0.34,1.99)	19	0.54 (0.34,0.85)	380	0.62 (0.52,0.74)	72	2.08 (0.86,5.00)	1.05 (0.42,2.64)	0.64 (0.40,1.03)	0.64 (0.53,0.77)	1.98 (0.80,4.90)
6-week average												
0	16	1	78	1	618	1	48	1	1	1	1	1
0.2-16.1	3	0.87 (0.25,3.00)	13	0.76 (0.42,1.39)	118	0.77 (0.59,1.00)	19	4.58 (0.56,37.63)	0.75 (0.17,3.34)	0.66 (0.33,1.35)	0.82 (0.62,1.09)	4.07 (0.49,33.98)
16.1-54.7	5	0.58 (0.21,1.60)	27	0.62 (0.40,0.97)	348	0.85 (0.72,1.02)	52	6.4 (1.39,29.41)	0.74 (0.26,2.08)	0.73 (0.46,1.16)	0.89 (0.74,1.07)	6.36 (1.37,29.53)
54.7-511.4	6	0.70 (0.27,1.79)	22	0.47 (0.29,0.76)	333	0.60 (0.50,0.72)	68	2.03 (0.85,4.90)	0.90 (0.34,2.36)	0.54 (0.32,0.89)	0.62 (0.51,0.75)	1.85 (0.75,4.58)

a Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.

b Number of births attributed to exposure category during the gestational period.

c Non-estimable parameter (all 21 pregnancies in HAA5 category delivered at 41 weeks)

Abbreviations: OR = conditional odds ratio, CI= confidence interval

Table 42. Association between TOX exposure and the conditional probability if delivery each week (gestational weeks 20 to 44) stratified by gestational period among women included in duration of gestation analyses, 2000-2004.

	Unadjusted Model								Fully-adjusted Model[a]			
	Gestational Period (weeks')								Gestational Period (weeks')			
	≤ 32		33-36		37-40		≥ 41		≤ 32	33-36	37-40	≥ 41
Residential TOX level (µg/liter)	n[b]	OR (95% CI)	n[b]	OR (95% CI)	n[b]	OR (95% CI)	n[b]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
2nd-trimester average												
14.3-22.4	15	1	69	1	636	1	41	1	1	1	1	1
136.7-169.6	2	0.32 (0.07,1.38)	17	0.56 (0.33,0.96)	258	0.64 (0.53,0.78)	42	2.61 (0.89,7.67)	0.38 (0.09,1.70)	0.67 (0.39,1.16)	0.66 (0.54,0.81)	2.54 (0.85,7.62)
169.6-177.7	5	0.79 (0.29,2.18)	16	0.53 (0.30,0.91)	245	0.58 (0.48,0.71)	55	7.42 (1.59,34.62)	0.77 (0.25,2.35)	0.55 (0.31,0.99)	0.63 (0.51,0.77)	6.64 (1.40,31.54)
177.7-192.6	5	0.80 (0.29,2.19)	19	0.63 (0.38,1.06)	250	0.71 (0.58,0.86)	45	2.76 (0.94,8.12)	0.79 (0.26,2.41)	0.60 (0.34,1.07)	0.75 (0.61,0.92)	2.50 (0.83,7.49)
192.8-235.2	6	0.95 (0.37,2.46)	31	1.06 (0.69,1.63)	258	1.01 (0.83,1.23)	24	6.55 (0.80,53.31)	1.20 (0.45,3.16)	1.11 (0.69,1.77)	1.09 (0.88,1.35)	6.11 (0.74,50.41)
Weekly concentration												
9-28	15	1	69	1	636	1	41	1	1	1	1	1
104-169	6	0.69 (0.26,1.83)	15	0.31 (0.18,0.55)	350	0.62 (0.52,0.75)	75	6.27 (1.88,20.90)	0.86 (0.32,2.32)	0.36 (0.20,0.64)	0.66 (0.55,0.80)	6.01 (1.78,20.34)
170-177	3	1.38 (0.39,4.85)	10	0.88 (0.45,1.74)	100	0.78 (0.59,1.05)	17	5.73 (0.68,48.14)	1.12 (0.25,5.07)	1.05 (0.53,2.10)	0.87 (0.64,1.17)	5.83 (0.69,49.52)
178-192	2	0.47 (0.10,2.07)	15	0.77 (0.43,1.37)	171	0.65 (0.52,0.82)	29	5.26 (1.11,25.01)	0.59 (0.13,2.66)	0.87 (0.48,1.58)	0.68 (0.53,0.87)	4.54 (0.94,21.92)
192.8-290	6	0.79 (0.30,2.07)	38	1.01 (0.67,1.53)	286	0.73 (0.60,0.88)	36	2.21 (0.77,6.37)	0.81 (0.28,2.33)	0.92 (0.58,1.47)	0.74 (0.60,0.91)	1.96 (0.67,5.76)
6-week average												
10.9-25.5	15	1	69	1	636	1	41	1	1	1	1	1
121.7-169.5	2	0.3 (0.07,1.33)	17	0.48 (0.28,0.82)	276	0.62 (0.51,0.75)	41	3.23 (0.94,11.14)	0.34 (0.08,1.53)	0.52 (0.30,0.90)	0.65 (0.53,0.79)	3.03 (0.86,10.62)
170-177.5	4	1.16 (0.38,3.56)	10	0.59 (0.30,1.17)	143	0.64 (0.50,0.81)	31	5.37 (1.13,25.57)	1.31 (0.42,4.07)	0.62 (0.31,1.22)	0.68 (0.53,0.87)	5.23 (1.08,25.27)
177.8-192.5	4	0.58 (0.19,1.77)	23	0.66 (0.40,1.07)	273	0.69 (0.56,0.84)	55	4.7 (1.43,15.47)	0.66 (0.21,2.04)	0.64 (0.39,1.06)	0.72 (0.59,0.88)	4.35 (1.31,14.52)
192.7-250.2	7	1.24 (0.49,3.1)	28	0.96 (0.61,1.51)	215	0.77 (0.62,0.95)	30	3.44 (0.89,13.21)	1.38 (0.54,3.52)	0.94 (0.59,1.51)	0.80 (0.64,1.00)	3.38 (0.87,13.17)

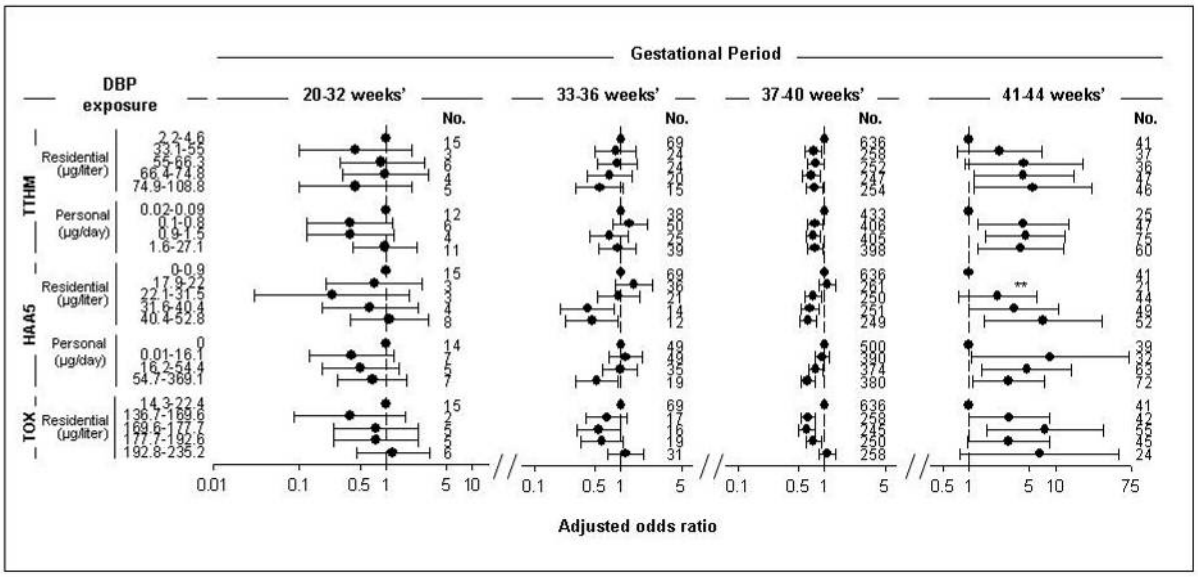
TOX exposure through tap-water consumption (µg/day)													
2nd-trimester average													
0-25.8	12	1	43	1	421	1	33	1	1	1	1	1
25.9-75	8	0.66 (0.27,1.62)	47	1.08 (0.71,1.65)	416	0.91 (0.76,1.10)	37	5.11 (1.07,24.4)	0.53 (0.19,1.43)	0.93 (0.59,1.47)	0.92 (0.76,1.11)	4.66 (0.95,22.76)
75.1-252.9	5	0.41 (0.15,1.17)	33	0.74 (0.46,1.17)	403	0.72 (0.59,0.86)	68	6.13 (1.63,23.12)	0.37 (0.12,1.16)	0.68 (0.41,1.12)	0.75 (0.62,0.91)	6.33 (1.64,24.36)
253.6-1302.9	8	0.66 (0.27,1.62)	29	0.65 (0.40,1.05)	404	0.69 (0.57,0.82)	68	2.36 (0.96,5.80)	0.74 (0.30,1.85)	0.74 (0.45,1.20)	0.69 (0.57,0.84)	2.21 (0.86,5.63)
Weekly concentration												
0-25.8	13	1	42	1	364	1	31	1	1	1	1	1
25.9-75	3	0.28 (0.08,0.97)	33	0.88 (0.55,1.39)	312	0.98 (0.80,1.20)	28	4.22 (0.87,20.36)	0.20 (0.04,0.89)	0.85 (0.51,1.42)	0.97 (0.79,1.20)	3.76 (0.76,18.53)
75.1-253.5	8	0.62 (0.26,1.50)	32	0.72 (0.45,1.16)	353	0.76 (0.62,0.92)	66	9.19 (1.92,43.94)	0.52 (0.19,1.38)	0.78 (0.47,1.30)	0.81 (0.66,0.99)	9.19 (1.90,44.55)
253.6-1827	6	0.47 (0.18,1.25)	32	0.71 (0.44,1.13)	380	0.74 (0.61,0.90)	60	2.23 (0.90,5.53)	0.54 (0.20,1.44)	0.83 (0.51,1.37)	0.74 (0.60,0.91)	2.10 (0.82,5.38)
6-week average												
0-25.8	13	1	45	1	376	1	35	1	1	1	1	1
25.9-75	4	0.36 (0.12,1.11)	39	1.04 (0.67,1.61)	321	1.07 (0.87,1.31)	30	4.73 (0.99,22.46)	0.30 (0.08,1.05)	0.89 (0.55,1.44)	1.06 (0.86,1.30)	4.48 (0.93,21.68)
75.1-253.6	6	0.49 (0.19,1.29)	24	0.51 (0.31,0.85)	351	0.76 (0.62,0.92)	61	17.47 (2.17,140.72)	0.36 (0.12,1.13)	0.52 (0.30,0.89)	0.79 (0.65,0.97)	17.73 (2.18,144.35)
253.6-1827	7	0.55 (0.22,1.38)	32	0.69 (0.43,1.09)	369	0.73 (0.60,0.88)	61	2.18 (0.92,5.12)	0.62 (0.24,1.59)	0.75 (0.46,1.22)	0.72 (0.59,0.88)	2.07 (0.85,5.03)

a Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.

b Number of births attributed to exposure category during the gestational period.

Abbreviations: OR = conditional odds ratio, CI= confidence interval

Figure 17. Association between second trimester average drinking water disinfection by-products (DBP) exposure and the conditional odds of delivery each week (gestational weeks' 20-44) stratified by gestational period among women included in the analysis of exposure to drinking water DBPs and duration of gestation, 2000-2004



Residential concentrations of total trihalomethane (TTHM), the sum of five haloacetic acids (HAA5) and total organic halides presented in µg/liter; personal exposure to TTHM through showering and bathing presented in µg absorbed/day and to HAA5 through tap water consumption as µg consumed/day; models adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake; ** = non-estimable because all infants in exposure category delivered at 41 weeks' gestation.

4.5.2 Associations between time-to-birth and DBP exposure at the chlorinated DBP site

Tables 43-45 present estimated odds ratios for associations between aggregate DBP measures and the conditional odds of delivery each week restricted to women from the chlorinated DBP site alone. Time interactions were included for gestational periods ≤ 36 weeks', 37-40 weeks', and ≥ 40 weeks'. Findings were similar to those found for all study sites combined.

Table 43. Association between TTHM exposure and the conditional probability of delivery each week (gestational weeks' 20 to 44) stratified by gestational period among women included in duration of gestation analyses from the chlorinated DBP site, 2000-2004.

	Unadjusted Model						Fully-adjusted Model[a]		
	Gestational Period (weeks')						Gestational Period (weeks')		
	≤ 36		37-40		≥ 41		≤ 36	37-40	≥ 41
Residential TTHM level (µg/liter)	n[b]	OR (95% CI)	n[b]	OR (95% CI)	n[b]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
2nd-trimester average									
33.1-60.3	21	1	248	1	41	1	1	1	1
60.4-74	16	0.80 (0.42,1.53)	236	0.87 (0.69,1.09)	58	2.61 (0.86,7.93)	0.84 (0.44, 1.61)	0.86 (0.67, 1.09)	2.25 (0.72, 7.02)
74-108.8	17	0.91 (0.49,1.70)	241	0.98 (0.78,1.23)	48	3.42 (0.89,13.06)	0.73 (0.37, 1.44)	1.00 (0.78, 1.26)	2.91 (0.75, 11.38)
Weekly concentration									
24.7-60.2	14	1	310	1	59	1	1	1	1
60.7-73.4	20	2.11 (1.09,4.06)	190	1.09 (0.86,1.37)	46	1.84 (0.62,5.50)	2.25 (1.13, 4.48)	1.05 (0.82, 1.34)	1.57 (0.51, 4.85)
75-148.6	18	1.90 (0.96,3.75)	173	1.02 (0.81,1.30)	36	3.17 (0.67,15.11)	1.94 (0.94, 4.00)	1.03 (0.81, 1.33)	3.15 (0.65, 15.30)
6-week average									
28.8-60.2	10	1	263	1	54	1	1	1	1
60.8-73.8	25	2.71 (1.33,5.51)	237	1.02 (0.82,1.28)	49	3.28 (0.86,12.43)	2.42 (1.17, 5.00)	0.99 (0.78, 1.26)	2.98 (0.77, 11.55)
74.7-133.2	17	2.34 (1.10,4.97)	173	1.02 (0.80,1.31)	38	4.32 (0.93,20.22)	2.08 (0.96, 4.52)	1.02 (0.79, 1.32)	4.41 (0.92, 21.03)
TTHM exposure through showering & bathing (µg/day)									
2nd-trimester average									
0.08-0.9	15		257		37				
1-1.5	15	1.01 (0.49,2.08)	236	0.88 (0.70,1.11)	58	3.13 (0.93,10.52)	1.12 (0.54, 2.33)	0.90 (0.71, 1.14)	3.33 (0.96, 11.59)
1.6-27.1	27	1.88 (0.99,3.54)	231	0.87 (0.69,1.09)	52	2.38 (0.78,7.29)	1.87 (0.95, 3.67)	0.96 (0.74, 1.23)	2.40 (0.76, 7.62)
Weekly concentration									
0-0.9	13		247		50				
1-1.5	18	1.77 (0.86,3.62)	205	0.98 (0.77,1.25)	37	1.85 (0.56,6.16)	1.97 (0.94, 4.11)	0.99 (0.78, 1.27)	1.74 (0.51, 5.98)
1.6-20.6	24	2.17 (1.10,4.28)	218	0.99 (0.78,1.25)	54	2.22 (0.75,6.56)	2.17 (1.05, 4.49)	1.07 (0.83, 1.39)	2.33 (0.75, 7.19)
6-week average									
0-0.9	13		241		49				
1-1.5	15	1.36 (0.64,2.87)	219	1.09 (0.86,1.37)	38	3.36 (0.70,16.16)	1.46 (0.68, 3.15)	1.09 (0.85, 1.39)	3.47 (0.70, 17.09)
1.6-16.6	27	2.40 (1.23,4.67)	210	0.98 (0.77,1.24)	55	1.65 (0.62,4.41)	2.41 (1.19, 4.90)	1.04 (0.80, 1.34)	1.77 (0.64, 4.95)

a Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
b Number of births attributed to exposure category during the gestational period.
Abbreviations: OR = conditional odds ratio, CI= confidence interval

Table 44. Association between HAA5 exposure and the conditional probability of delivery each week (gestational weeks' 20 to 44) stratified by gestational period among women included in duration of gestation analyses from the chlorinated DBP site, 2000-2004.

	Unadjusted Model						Fully-adjusted Model[a]		
	Gestational Period (weeks')						Gestational Period (weeks')		
	≤ 36		37-40		≥ 41		≤ 36	37-40	≥ 41
Residential HAA5 level (µg/liter)	n[b]	OR (95% CI)	n[b]	OR (95% CI)	n[b]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
2nd-trimester average									
18.7-32.4	20	1	240	1	48	1	1	1	1
32.5-40.7	16	0.83 (0.43,1.59)	242	0.99 (0.78,1.24)	52	2.32 (0.77,6.96)	0.61 (0.30, 1.23)	0.98 (0.77, 1.25)	1.93 (0.63, 5.92)
40.7-52.8	18	0.99 (0.53,1.85)	243	1.06 (0.84,1.33)	47	4.61 (0.97,21.96)	0.90 (0.48, 1.70)	1.10 (0.86, 1.39)	3.94 (0.81, 19.17)
Weekly concentration									
12.1-32.5	18	1	266	1	35	1	1	1	1
32.6-40.7	10	0.97 (0.45,2.06)	161	0.96 (0.74,1.23)	48	2.91 (0.80,10.58)	0.78 (0.35, 1.74)	0.91 (0.70, 1.18)	2.58 (0.68, 9.82)
40.8-62.2	24	1.44 (0.78,2.63)	246	1.01 (0.81,1.27)		1.96 (0.58,6.61)	1.27 (0.68, 2.36)	1.00 (0.79, 1.27)	1.77 (0.51, 6.10)
6-week average									
16-32.4	13	1	223	1	48	1	1	1	1
32.7-40.7	23	2.16 (1.10,4.24)	184	1.01 (0.79,1.3)	40	4.32 (0.92,20.36)	1.99 (1.00, 3.95)	1.00 (0.77, 1.29)	4.21 (0.88, 20.15)
41-56.4	16	1.14 (0.55,2.36)	266	1.05 (0.84,1.32)	53	2.21 (0.73,6.75)	0.94 (0.44, 2.02)	1.04 (0.82, 1.32)	1.77 (0.57, 5.56)
HAA5 exposure through tap-water consumption (µg/day)									
2nd-trimester average									
0-35.3	22	1	239	1	48	1	1	1	1
35.3-69.7	16	0.74 (0.39,1.39)	243	0.96 (0.76,1.21)	48	4.18 (0.87,19.99)	0.87 (0.44, 1.70)	0.93 (0.73, 1.18)	4.32 (0.88, 21.18)
69.7-369.1	16	0.73 (0.39,1.37)	242	0.89 (0.71,1.12)	51	1.58 (0.59,4.24)	0.91 (0.47, 1.76)	0.85 (0.66, 1.08)	1.43 (0.51, 4.03)
Weekly concentration									
0-35.3	18	1	240	1	46	1	1	1	1
35.3-69.7	14	0.75 (0.38,1.49)	197	0.99 (0.78,1.26)	41	2.29 (0.59,8.93)	0.72 (0.35, 1.49)	0.99 (0.77, 1.27)	2.32 (0.57, 9.38)
69.7-511.4	20	0.91 (0.49,1.69)	233	0.91 (0.72,1.14)	54	1.68 (0.64,4.46)	1.01 (0.53, 1.92)	0.87 (0.68, 1.11)	1.46 (0.52, 4.09)
6-week averages									
0-35.3	19	1	233	1	48	1	1	1	1
35.3-69.7	16	0.97 (0.51,1.85)	199	0.91 (0.72,1.16)	44	3.71 0.77,17.8)	1.08 (0.55, 2.13)	0.92 (0.71, 1.18)	3.77 (0.77, 18.56)
69.7-511.4	17	0.79 (0.41,1.50)	238	0.91 (0.72,1.15)	50	1.36 (0.53,3.49)	0.91 (0.46, 1.80)	0.88 (0.69, 1.13)	1.15 (0.42, 3.11)

a Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
b Number of births attributed to exposure category during the gestational period.
Abbreviations: OR = conditional odds ratio, CI= confidence interval

Table 13. Association between TOX exposure and the conditional probability of delivery each week (gestational weeks' 20 to 44) stratified by gestational period among women included in duration of gestation analyses from the chlorinated DBP site, 2000-2004.

	Unadjusted Model						Fully-adjusted Model[a]		
	Gestational Period (weeks')						Gestational Period (weeks')		
	≤ 36		37-40		≥ 41		≤ 36	37-40	≥ 41
Residential TOX level (µg/liter)	n[b]	OR (95% CI)	n[b]	OR (95% CI)	n[b]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
2nd-trimester average									
136.7-169.2	19	1	249	1	41	1	1	1	1
169.3-178.4	16	0.93 (0.49,1.79)	240	0.87 (0.69,1.09)	55	4.15 (1.09,15.82)	0.78 (0.39, 1.54)	0.87 (0.68, 1.11)	3.34 (0.86, 13.06)
178.4-220.6	19	1.06 (0.57,2.01)	236	1.03 (0.82,1.3)	51	3.04 (0.91,10.12)	0.93 (0.49, 1.79)	1.10 (0.86, 1.40)	2.72 (0.80, 9.23)
Weekly concentration									
104-169	13	1	323	1	73	1	1	1	1
170-178	8	2.51 (1.05,5.97)	73	1.04 (0.75,1.45)	18	3.34 (0.39,28.22)	2.30 (0.92, 5.76)	1.02 (0.72, 1.43)	3.52 (0.41, 30.45)
179-269	31	2.52 (1.36,4.67)	277	0.92 (0.75,1.14)	50	1.2 (0.45,3.21)	2.40 (1.26, 4.57)	0.89 (0.72, 1.10)	1.03 (0.37, 2.87)
6-week average									
121.7-169	14	1	257	1	38	1	1	1	1
169.5-178.3	13	1.46 (0.7,3.05)	169	0.97 (0.75,1.24)	42	2.57 (0.77,8.53)	1.22 (0.57, 2.63)	0.96 (0.74, 1.25)	2.44 (0.71, 8.41)
178.5-237.3	25	1.61 (0.85,3.05)	247	0.87 (0.7,1.09)	61	3.85 (1.2,12.39)	1.41 (0.73, 2.73)	0.84 (0.66, 1.07)	3.81 (1.15, 12.60)
TOX exposure through tap-water consumption (µg/day)									
2nd-trimester average									
0-143.9	22	1	239	1	46	1	1	1	1
144.6-306.7	15	0.65 (0.34,1.23)	242	0.99 (0.79,1.25)	52	3.04 (0.8,11.55)	0.78 (0.40, 1.54)	1.05 (0.82, 1.33)	3.25 (0.83, 12.71)
307-1225.5	17	0.7 (0.37,1.3)	243	0.89 (0.7,1.12)	49	1.48 (0.55,3.98)	0.88 (0.46, 1.69)	0.87 (0.68, 1.11)	1.25 (0.44, 3.56)
Weekly concentration									
0-144.6	16	1	227	1	50	1	1	1	1
144.6-306.6	19	1.03 (0.54,1.96)	213	1 (0.78,1.27)	46	2.65 (0.7,10.05)	1.09 (0.55, 2.16)	1.04 (0.81, 1.34)	2.82 (0.72, 11.03)
306.7-1823.4	17	0.89 (0.46,1.72)	230	0.88 (0.69,1.11)	45	1.34 (0.5,3.61)	0.99 (0.49, 1.97)	0.85 (0.66, 1.10)	1.12 (0.39, 3.16)
6-week average									
0-144.6	19	1	222	1	45	1	1	1	1
144.6-306.3	15	0.73 (0.38,1.42)	224	1.06 (0.83,1.34)	50	4.37 (0.91,20.94)	0.84 (0.42, 1.69)	1.10 (0.86, 1.41)	4.67 (0.95, 22.91)
306.8-1823.4	18	0.81 (0.43,1.51)	224	0.87 (0.69,1.11)	47	1.35 (0.53,3.49)	0.94 (0.48, 1.82)	0.84 (0.65, 1.08)	1.15 (0.42, 3.13)

a Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.
b Number of births attributed to exposure category during the gestational period.
Abbreviations: OR = conditional odds ratio, CI= confidence interval

CHAPTER 5: MANUSCRIPTS

5.1 Manuscript 1: Drinking water disinfection by-product exposure and fetal growth.

Abstract

Background: Previous studies suggest that elevated exposure to total trihalomethanes (TTHM) may lead to fetal growth restriction. We examined the effects of exposure to trihalomethanes (THMs), haloacetic acids (HAAs) and total organic halide (TOX) on the probability of delivering a small-for-gestational-age (SGA) infant and term birth weight. **Methods:** Women early in pregnancy (≤ 12 week's gestation) or planning a pregnancy were enrolled into a prospective pregnancy study conducted in three U.S. communities from 2000-2004. Weekly water samples were collected and analyzed for DBPs. Participant data were collected through interviews, an early ultrasound and birth records. Associations between aggregate DBP measures (TTHM, HAAs, TOX) and fetal growth were assessed using log-binomial regression for SGA (*n*=1,958) and linear regression for term birth weight (*n*=1,854). A fully-Bayesian analysis was conducted to examine joint associations between individual DBPs and fetal growth in a single model. **Results:** HAAs and TOX were not associated with SGA or term birth weight. The estimated probability of delivering an SGA infant for an average third trimester residential TTHM concentration ≥ 80 micrograms/liter was twice as high as the probability for an average concentration < 80

micrograms/liter (Risk Ratio [95% confidence interval] = 2.0 [1.1, 3.6]). Results of the Bayesian model did not support a consistent association between any particular THM or HAA and SGA or term birth weight. **Conclusions:** Our results do not suggest an adverse effect of HAA or TOX exposure on fetal growth. An association with TTHM was seen for average residential concentrations above the current regulatory standard.

5.1.1 Introduction

Over the past two decades, toxicological and epidemiological studies have suggested that drinking water disinfection by-product (DBP) exposure during pregnancy may increase the risk of adverse pregnancy outcomes such as pregnancy loss, birth defects, and fetal growth restriction[5-7]. In particular, epidemiological studies have found a moderate increased risk of delivering a small-for-gestational-age (SGA) infant among women exposed to high levels of total trihalomethanes (TTHM) compared to women in the lowest exposure group, reporting relative risks in the range of 1.0-1.5 [89,90,94,95,97,98,101]. TTHM also has been associated with decreased mean birth weight and an increased risk of delivering a low birth weight (LBW) infant [89-92,94-99].

The mechanism by which TTHM exposure may lead to reduced fetal growth is not well understood [7]. TTHM is an aggregate measure of four individual trihalomethanes (THMs), chloroform, bromodichloromethane (BDCM), dibromochloromethane (DBCM) and bromoform, that is regulated by the US Environmental Protection Agency (EPA)[14]. The concentration of TTHM within a distribution system is generally correlated with the concentrations of other DBPs, but the magnitude of correlation between DBPs may vary from system to system. Therefore, it is unclear whether findings of previous epidemiological

studies indicate that THMs as a whole or a specific constituent of TTHM (*e.g.,* BDCM) are biologically active, or alternatively, TTHM is serving as a marker for another drinking water contaminant. Toxicological data suggests that brominated THMs and haloacetic acids (HAAs) are probably more harmful to the fetus than chlorinated THMs[7], but relatively few epidemiological studies of DBPs and fetal growth restriction have examined individual THMs [89,93-95,101] or HAA exposure[89,95,101]. Results of these studies as a whole have not implicated any particular constituent of TTHM as being more or less harmful and have been inconsistent for HAA exposure.

Previous epidemiological studies of DBP exposure and pregnancy health are limited by poor exposure assessment. The majority of these studies obtained information on DBP concentrations retrospectively from regulatory databases, which may not have provided sufficient data to capture spatial and/or temporal variability in DBP concentrations within the distribution systems serving the population under study [119,120]. Furthermore, most previous studies were not able to account for individual variation in tap water uptake through ingestion, inhalation and dermal absorption, which can influence an individual's actual exposure to DBPs and lead to exposure assessment error [18,24,121].

This study had two objectives. The first was to examine the association between aggregate DBP measures and measures of fetal growth, specifically the proportion of infants born SGA and mean birth weight among term births, using improved exposure data that allow inter-individual variability to be estimated more accurately than in previous studies. The second was to examine the effect of exposure to individual THMs and HAAs on fetal growth measures simultaneously using Bayesian analytic techniques to account for the high

correlation between DBP concentrations. To the authors' knowledge, this is the most extensive study of DBP exposure and fetal growth that has been conducted to date.

5.1.2 Material and Methods

Study design and population

Women from three US communities were recruited into a prospective cohort study early in pregnancy (≤ 12 weeks' gestation) or while planning to become pregnant from 2000 to 2004. Communities were chosen to insure a wide range of DBP exposure across study sites: moderate levels of predominately chlorinated DBPs (hereafter referred to as the "chlorinated DBP site"), moderate levels of predominately brominated DBPs (the "brominated DBP site"), and low levels of all DBPs (the "low DBP site"). Moderate DBP sites were also selected because they used chloramination for terminal disinfection rather than free chlorine, which minimizes spatial variability in DBP concentrations within a site [122,123]. Additional details on study design and recruitment have been published elsewhere [26,124,125].

A total of 2,766 pregnancies (68% of all women screened) were enrolled. For this study, 259 pregnancies with missing or incomplete baseline interviews, 237 pregnancies that ended in a loss, 90 pregnancies lost to follow-up, seven pregnancies missing information on date of birth or birth weight, eight multi-gestational pregnancies and 16 repeat live births to a study participant were excluded, resulting in a total of 2,039 pregnancies (74% of those enrolled) eligible for fetal growth analyses. In addition, SGA status could not be assigned for three births missing information on maternal race, 73 births with a reported maternal race of "Indian", "Asian/Pacific islander", or "Other", and five births with an estimated gestational

age at birth <25 or > 42 weeks' gestation, reducing the final sample size for SGA models to 1,958 births. Term mean birth weight models were restricted to 1,854 live births born at ≥ 37 weeks' gestation. Women eligible for fetal growth analyses were similar to all enrolled participants with respect to maternal age, estimated gestational age at enrollment, and parity, but were slightly more likely to be White and to have completed ≥ 16 years of education.

Measurement of DBP concentrations

Details of water sample collection, shipment and analysis have been published elsewhere[26]. Briefly, weekly water samples were collected from each study site at a single location that was verified to accurately represent DBP concentrations throughout the water distribution system [26]. Additional samples were collected during one month each year when the chlorinated and brominated sites converted to free chlorine for system flushing and averaged to estimate system wide levels. Concentrations of four individual THMs and nine HAAs (listed in table 2) and total organic halide (TOX) were measured in micrograms/liter using standard methods[104-107]. Individual THMs were summed to calculate the concentration of TTHM. In addition, the US EPA regulated sum of five HAAs was calculated (*i.e.,* the sum of chloroacetic acid [CAA], dichloroacetic acid [DCAA], trichloroacetic acid [TCAA], bromoacetic acid [BAA], and dibromoacetic acid [DBAA] concentrations)[14], henceforth referred to as "HAA5". DBP concentrations below the practical quantitation limit for each analytic method (*i.e.,* 0.1 µg/liter for all four THM species and 1.0 or 2.0 µg/liter for HAA species) were set to zero.

Characterization of DBP exposure

Two exposure metrics were considered for TTHM and HAA5: 1) residential concentrations (*i.e.,* concentrations in the water distribution system serving a woman's residence) and 2) personal exposure. Personal TTHM and HAA5 were estimated by combining residential concentrations of TTHM and HAA5 with detailed information on tap water consumption, showering and bathing habits collected during telephone interviews conducted at baseline (by 16 weeks' gestation) and follow-up (between 20-25 weeks' gestation). Algorithms used to estimate personal exposure have been previously published [26,125]. Briefly, personal TTHM exposure was estimated by integrating residential THM concentrations and self-reported information on average duration and frequency of showering and bathing into an absorbed dose (μg/day) using uptake factors derived from toxicokinetic studies[126,127]. Personal HAA exposure was estimated by first adjusting residential HAA concentrations for boiling and filtering [26,109] and then combining adjusted HAA concentrations with self-reported information on the number and size of glasses of cold/hot filtered/unfiltered tap water drinks typically consumed per day. The personal HAA exposure estimate represents average daily intake of HAAs (μg/day). Exposure to individual THMs and HAAs and TOX were examined using residential concentrations alone.

Assessment of fetal growth parameters

Data used for fetal growth assessment (*i.e.,* infant date of birth, birth weight and gender) were obtained from medical records for 43.0% of live births, vital records for 56.5%, and participant self-report for only 0.5%. SGA was defined as an infant with a birth weight below the tenth percentile for his or her gestational age at birth (between 25 to 42 weeks),

gender, maternal race/ethnicity (non-Hispanic White, Non-Hispanic Black, or Hispanic), and maternal parity (nulliparous or parous) based upon previously published standardized birth weight curves [38,43]. Maternal race/ethnicity and parity were self-reported at telephone interview. Gestational age at birth was derived from first trimester report of last menstrual period (LMP), which was corrected by ultrasound (also obtained during the first trimester) if the two estimates of gestational age were different by more than 7 days.

Statistical Analysis

The association between aggregate DBP measures (TTHM, HAA5 and TOX) and the probability of delivering a SGA infant was examined using log binomial regression. The association with average term birth weight was examined using linear regression, restricting to pregnancies born at ≥ 37 weeks' gestation. Trimester-specific average DBP exposures (first, second and third) were estimated and considered in separate models. First trimester was defined as 0 to 12 weeks, second trimester as 13 to 26 weeks, and third trimester as 27 weeks until birth.

Restricted quadratic splines were used to model the dose-response in probability of an SGA birth and mean term birth by residential DBP concentrations, which was then plotted and visually inspected to determine if quantile categorization of exposure was appropriate. Residential DBP concentrations among the moderate exposure sites also were divided into quartiles using cut-points derived from second-trimester average DBP distributions, and the low exposure site served as the referent. In addition, the US EPA regulatory standard for residential TTHM level (80 micrograms/liter) was examined. Too few women had average HAA5 levels above the US EPA standard (60 micrograms/liter) to be examined. Personal

DBP exposure estimates were examined using categorical coding only, as the authors believe this exposure metric is most useful for roughly separating women into "high", "moderate" and "low" exposure groups when considering the amount of error potentially introduced through self-reported data on water use and consumption.

Individual THM and HAA levels were highly correlated in this study. Modeling each exposure in a separate risk model could lead to spurious associations due to confounding by other correlated DBPs, so a single model that controls for all individual THMs and HAAs is desirable. However, adjustment for multiple DBP exposures using standard maximum likelihood estimation (MLE) may fail to provide plausible estimates given that exposures are highly correlated [113]. Alternatively, Bayesian analytic techniques allow simultaneous modeling of highly correlated exposures in a single model. In addition, prior distributions can be specified to "borrow" information across sets of individual DBPs that may have a common underlying biologic mechanism (*e.g.,* HAAs or brominated DBP compounds)[113].

A fully Bayesian analysis was conducted to examine the association between fetal growth measures and third trimester average residential concentrations of individual THMs and HAAs. Logistic and linear regression models were constructed for SGA and term birth weight, respectively, and DBP concentrations were entered into the model using quantile categories. Prior distributions were specified for the effect of DBP exposures (*i.e.,* $\beta_j \sim$ Normal$[\mu_j,\varphi^2]$, where j represents individual DBP compounds) and the variance of the effect of DBP exposures (*i.e.,* the standard deviation was specified as $\varphi \sim$ uniform$[0,R]$). Two scenarios were considered for the specification of the prior mean: 1) no effect of DBP exposures (*i.e.,* $\mu_j=0$ for all j) and 2) the effect of an individual DBP compound is a function of DBP class and bromination status (*i.e.,* $\mu_j= \mu_k$, where $\mu_k \sim$N(0,10) and represents the mean

of the combined effect of DBP class and bromination status). This latter prior specification of the mean results in shrinkage of the effect for non-brominated THMs (*i.e.,* chloroform), non-brominated HAAs, brominated THMs, and non-brominated HAAs towards each other, to the extent that the data support a similar effect within groups, and allows "borrowing" of information within groups. For prior specification of the variance of effects of DBP exposures, the upper bound for the variance, R, was set at 0.70 for the SGA analysis (mean value of $\varphi = 0.35$) and 100 (mean value of $\varphi = 50$) for the term birth weight analysis. In a semi-Bayesian approach with fixed *R*, these mean values would correspond to a 95% range in risk ratios (RR) for SGA of 0.5 to 2.0 and 95% range in mean difference in birth weight of -100 to 100 grams, respectively. Markov chain Monte Carlo methods (MCMC) in the software package WinBUGS (2007 MRC Biostatistics Unit, Cambridge, UK) were used obtain posterior distributions, including the posterior mean for the effect for each DBP category and an associated 95% credible interval (CI), which can be interpreted as an interval that has a high probability (95%) of containing the unknown quantity of interest [114]. Three chains were simulated, with 5,000 iterations run for each chain. The first 2,500 iterations of each chain were discarded as "burn-in", and the remaining iterations were thinned by keeping every 7th simulation drawn to avoid dependence of iterations from the same chain[114], resulting in a total of 1,074 simulations saved.

For MLE and Bayesian models, confounders were identified from the literature as risk factors for fetal growth restriction that may be independently associated with DBP exposure but not on the causal pathway between exposure and disease according to directed acyclic graph analysis[115]. Effect measure modification by maternal age (< 25, 25-29, 30-35, $\geq$ 35 years of age), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic and

other) and swimming during pregnancy (yes/no) was assessed in MLE models by constructing DBP-covariate interaction terms, which were retained if the *p*- value for the joint effect of all terms was < 0.10. Variables identified as effect measure modifiers in MLE analyses, if any, were incorporated into Bayesian analyses. MLE analyses were conducted using Stata (College Station, TX) and Bayesian analyses were conducted using R (Vienna, Austria)[117] and WinBUGS software (Cambridge, England)[118].

5.1.3 Results

Examining the descriptive statistics by site, the proportion of SGA infants was higher at the brominated DBP site (8.2%) compared to the chlorinated and low DBP sites (4.8% and 5.9%, respectively). Mean birth weight among term births was higher at the chlorinated site compared to the brominated and low DBP sites (table 45).

TTHM concentrations were similar between the chlorinated and brominated DBP sites, but the chlorinated site had slightly higher concentrations of HAA5 and slightly lower concentrations of TOX compared to the brominated DBP site (table 46). As expected, the brominated DBP site had much higher concentrations of the brominated DBP compounds and much lower concentrations of non-brominated compounds compared to the chlorinated DBP site, with the exception of BDCM, CAA, BCAA and BDCAA. These DBPs were found in relatively comparable concentrations between the two moderate exposure sites. Overall, DBP concentrations at the low exposure site were much less than concentrations found at the two moderate exposure sites. Means and standard deviations for DBP concentrations were essentially the same as those presented in table 46 when calculations were restricted strictly to women included in the SGA and term birth weight analyses.

Analyses of aggregate DBP measures

Spline modeling of aggregate DBP measures did not suggest a dose-response in the probability of delivering an SGA infant in relation to TTHM, HAA5 or TOX residential concentrations (data not shown). Although elevated effects for the lowest quartile of moderate residential HAA5 exposure during the second trimester and the highest quartile of personal THM exposure during the third trimester were found, estimated RRs for SGA comparing quartiles of moderate DBP exposure to the low exposure group overall did not suggest consistent patterns of association with increasing TTHM, HAA5, or TOX residential levels or increasing personal TTHM and HAA5 exposure (table 47). The estimated probability of delivering an SGA infant among women with an average third trimester residential TTHM concentration ≥ 80 micrograms/liter was twice as high as the probability of delivering an SGA infant among women with an average concentration < 80 micrograms/liter (RR [95% confidence interval] = 2.0 [1.1, 3.6]). Effect measure modification by maternal age, race/ethnicity or swimming during pregnancy was not found.

A dose-response in mean birth weight among term live births in relation to TTHM, HAA5, or TOX was not suggested by spline modeling of residential concentrations (data not shown) or by estimated changes in mean birth weight when comparing upper quartiles of DBP exposure to the low exposure group for residential concentrations and personal exposure estimates (table 48). A few statistically significant increases and decreases in birth weight were observed, (*e.g.,* first trimester HAA5 residential concentrations), but patterns of associations were not consistent. The estimated decrease in term birth weight associated with an average third trimester residential TTHM concentration ≥ 80 versus < 80 micrograms/liter

(mean difference in grams = -55.9 [-143.7, 31.9]) was less pronounced than the association found for SGA. Effect measure modification by maternal age, race/ethnicity or swimming during pregnancy was not found.

Analyses of individual DBPs

As previously mentioned, examination of the distributions of individual DBPs by study site revealed that the range of concentrations at each site overlapped very little for most THMs and HAAs. Therefore, Bayesian analyses were run separately for the chlorinated and brominated DBP sites to avoid the potential for residual confounding by study site. MLE models were also constructed separately for each DBP to serve as a reference when examining results from the fully adjusted Bayesian models.

Results of the MLE analyses restricted to the chlorinated DBP site suggested that elevated exposure to bromoform, DBCM and BAA was associated with increased probability of delivering an SGA infant (table 49). Estimated associations for these DBPs from the Bayesian analysis were attenuated after adjustment for other DBPs and shrinking by DBP class and bromination status, and 95% CIs for all effect estimates included values below the null value, indicating that a null or protective effect of DBPs was within the probable range. RRs for SGA from the Bayesian analysis using a vague prior were all within the range of 0.9.-1.2, with wide 95% CIs (data not shown). A similar pattern of associations was found for term birth weight.

In contrast, results of the MLE analyses restricted to the brominated DBP site suggested that elevated exposure to predominately chlorinated DBPs (*i.e.,* chloroform, CAA, DCAA, TCAA, and BCAA) was associated with increased probability of delivering an SGA

infant and decreased term birth weight, albeit effect estimates were highly unstable given the small number of participants from this study site (table 50). Estimated effects for chloroform remained elevated in the Bayesian analysis for SGA, but a respective decrease in mean birth weight for the DBPs was not found. Again, 95% CIs for all effect estimates included the null value, and results of Bayesian analysis using a vague prior did not indicate an association between either fetal growth measure and any individual THM or HAA (data not shown).

5.1.4 Discussion

Findings of our study do not suggest an adverse effect of TTHM or HAA5 exposure on fetal growth at residential concentrations below the current regulatory standards or when examining estimated personal exposure to TTHM or HAA5. We also did not find an association with TOX residential concentrations. An increased probability of delivering an SGA infant was found when comparing women with average third trimester TTHM residential concentrations ≥ 80 micrograms/liter to women with average levels < 80 micrograms/liter. This finding suggests that the increased risk of fetal growth restriction associated with elevated residential TTHM concentrations occurs only at levels above the current US EPA regulatory standard, albeit very few women experienced average TTHM levels ≥ 80 micrograms/liter in our study.

Findings for site-specific analyses of individual THMs and HAAs are less clear. Results from the chlorinated DBP site suggest that THMs, particularly the brominated species, may be associated with increased risk of delivering an SGA infant. Conversely, results from the brominated DBP site suggest that chlorinated HAAs may be associated with

both increased risk of SGA and decreased mean birth weight among term births. However, concentrations of the individual DBPs implicated at each site for the most part are not comparable to concentrations at the other site, except for CAA and BDCM. In addition, 95% CI from the Bayesian analysis underscore that a null or protective effect of all THMs and HAAs in relation to fetal growth restriction is also probable given our prior assumptions and the data at hand. Therefore, we do not feel our study provides strong support that any particular DBP (or set of DBPs) is associated with fetal growth restriction.

Previous studies have examined the effect of TTHM exposure on fetal growth using several different outcome measures, including mean change in birth weight in grams, the probability of a LBW (< 2,500 grams) or very LBW (<1,500 grams) infant, and the probability of a SGA infant. In general, these studies suggest that elevated TTHM levels in drinking water may be associated with a moderate decrease in continuous birth weight (-1 to -70 grams) and increased risk of SGA (RRs of 1.0-1.5). Few studies have examined individual THM species or HAA exposure [89,93-95,101]. Findings of these studies have been much less consistent, and overall do not implicate any particular component of TTHM as responsible for the observed association found with this aggregate THM measure. Results from studies examining HAA exposure have also been inconsistent.

A major strength of our study is the concurrent measurement of DBP concentrations over the course of pregnancy, including some HAAs that are not routinely regulated by the US EPA. Weekly DBP measurements (or bi-weekly at the low exposure site) were collected to capture the temporal variability in DBP concentrations and allowed estimation of window-specific average exposures based on more measurements (generally 6-13) made at regular intervals rather than the typical case of one day of monitoring during a 3-month period.

Furthermore, our water sampling strategy was validated to accurately represent levels throughout the water distribution systems serving study participants' homes [26]. As a result, assignment of trimester average residential DBP concentrations should be quite accurate.

An additional strength of our study is that pregnant women were prospectively followed. This allowed collection of self-reported data on maternal demographics and health behaviors that may confound the association between DBP exposure and fetal growth as well as the collection of a first trimester ultrasound and medical record abstraction to provide accurate information on gestational age and birth weight. In addition, data on tap water consumption, showering and bathing, and other tap water use was collected and used to estimate personal DBP exposure and account for intra-individual variability in water exposure. The majority of previous studies relied on birth certificate data to obtain information on pregnancy outcomes and potential confounders, and only two studies have incorporated information on individual water use to estimate personal DBP exposure [92,94], although like our study, personal exposure did not show a stronger association than residential concentration with respect to fetal growth outcomes.

Given these improvements in exposure and outcome assessment and our ability to better control for known risk factors for fetal growth restriction, we expected to find stronger effects of TTHM exposure than previously reported if TTHM is truly associated with fetal growth restriction. However, we did not find an association with TTHM at concentrations below the regulatory cut-point, as has been suggested by previous studies. One possible explanation is differences in the population of women under study. Unlike previous studies, our study population represents a group of women who knew they were pregnant in the first trimester and volunteered to participate in a prospective pregnancy study. We compared

maternal characteristics of pregnancies enrolled in the RFTS study to all births identified from vital records in the same geographic location over the same time period in a previous report and found that our study participants were similar to the general population with respect to age but where more likely to be highly educated (≥ 16 years of education), non-Hispanic White, and nulliparous when compared to the general population[26]. In addition, the sample size of our study was considerably lower than most previous studies, which ultimately resulted in low precision of effect estimates, particularly when stratifying by study site.

By selecting study sites with different distributions of DBP concentrations, we created a range of reliable DBP measures (high/literow, chlorinated/brominated) that would not be possible studying a single geographic region. No other study of DBPs and reproductive health has examined such a broad range of DBP exposure. However, the underlying population characteristics of our three study sites are very different, and factors associated with study participation (*e.g.,* maternal age, race/ethnicity, education) also varied by site. As a result, women who participated from each site have different demographic profiles and show an overall difference in the proportion of infants born SGA and mean birth weight. We adjusted TTHM, HAA5 and TOX analyses for the major risk factors for fetal growth restriction that varied in distribution between sites to control for potential confounding between study sites, and only performed site-specific analyses for individual THMs and HAAs. In addition, we ran aggregate DBP analyses stratifying by study site to confirm that the pattern of results were similar across study sites but less precise (data not shown). For example, RRs (95% CI) for SGA comparing average third trimester TTHM concentrations ≥ 80 micrograms/liter versus < 80 micrograms/liter) were 1.9 (1.0, 3.7)

excluding the low DBP site, 1.9 (0.9, 4.2) restricting to the chlorinated DBP site alone, and 1.7 (0.6, 5.0) restricting to the brominated DBP site alone. While the resiliency of this finding across study sites is impressive, it should be noted that there were few SGA cases in the high exposure group (eight at the chlorinated DBP site and four at the brominated DBP site), so these RR estimates are very unstable.

Fetal growth restriction describes a decrease in fetal growth rate that prevents an infant from reaching his/her growth potential at a given age. We used SGA as a surrogate for fetal growth restriction because it is conventionally used to identify more severe growth restriction in epidemiological research and has been examined in previous DBP studies. However, not all infants that are "small" at birth are growth restricted and vice versa. Researchers often restrict SGA analyses to term infants to obtain a "cleaner" group of infants to assess fetal growth restriction. We found similar results when we restricted analyses to infants born at ≥ 37 weeks' completed gestation (data not shown).

In conclusion, our study is the most extensive study of DBP exposure and fetal growth restriction conducted to date. Our results do not suggest an adverse effect of residential TTHM or HAA5 levels within the regulatory limits on fetal growth, but we did find an increased probability of delivering an SGA infant at exposure levels above the regulatory standard for TTHM (≥ 80 micrograms), which was consistent across study sites. Although the brominated THMs (at the chlorinated DBP site) and non-brominated HAAs (at the chlorinated DBP site) showed a positive association with SGA in MLE analyses, none of the individual THMs or HAAs examined were associated with fetal growth restriction after adjustment for other DBPs.

5.1.5 References

Table 45. Characteristics of women included in the analyses of exposure to drinking water DBPs and fetal growth restriction, 2000-2004

	SGA analysis (n=1,958)			Tem birth weight analysis (n=1,854)	
		SGA (*n*=113)	Non-SGA (*n*=1,845)		Birth weight (grams)
	N	Col. %	Col. %	N	Mean (s.d.)
Study site					
Chlorinated	883	45.6	37.2	305	3530 (482)
Brominated	340	16.9	24.8	677	3406 (460)
Low DBP site	735	37.5	38.1	874	3448 (453)
Maternal Age					
< 25	575	38.1	29.1	531	3360 (446)
25-29	625	31.9	32.2	597	3479 (470)
30-35	538	19.5	28.2	517	3567 (471)
≥ 35	205	10.6	10.6	194	3568 (466)
Maternal					
Non-Hispanic	1168	50.4	60.2	1082	3560 (459)
Non-Hispanic	605	39.8	30.4	535	3316 (460)
Hispanic	185	9.7	9.4	169	3499 (456)
Other	--[*]			68	3445 (435)
Missing	--[*]			2	
Highest education					
High school or	561	44.3	27.7	502	3366 (481)
Some college	423	20.4	21.7	398	3455 (462)
College degree	973	35.4	50.6	955	3550 (456)
Missing	1			1	
Annual household					
<30,000	610	40.0	32.0	562	3386 (450)
30,001-60,000	511	32.4	26.9	497	3506 (476)
60,001-80,000	310	14.3	16.6	303	3496 (472)
>80,000	450	13.3	24.6	428	3593 (461)
Missing	77			66	
Employed during					
Non-employed	580	33.6	29.4	552	3514 (476)
Employed	1377	66.4	70.6	1304	3466 (467)
Missing	1				
Marital status					
Married	1334	55.8	68.9	1290	3535 (461)
Not married	623	44.3	31.1	565	3354 (466)
Missing	1			1	
Pre-pregnancy BMI					
<19.8	220	17.9	11.1	214	3363 (457)
19.8-25.9	978	47.2	51.4	936	3488 (464)
26.0-29.9	317	17.0	16.6	311	3490 (456)
>29.9	398	17.9	21.0	349	3539 (494)
Missing	45			46	
Daily caffeine					
0	496	19.5	25.7	473	3514 (483)
1-150	453	20.4	23.3	431	3471 (456)
151-300	371	19.5	18.9	346	3453 (481)
>300	638	40.7	32.1	606	3475 (464)
Parity					
Nulliparous	947	59.3	47.7	892	3429 (475)
Parous	1011	40.7	52.3	964	3527 (461)

* SGA could not be assigned for 3 births with missing maternal race or 73 births to women of "other" race.
Abbreviations: SGA = small-for-gestational-age, s.d. = standard deviation, BMI = body mass index, DBP= disinfection by-product, SGA= small-for-gestational-age

Table 46. Second trimester average residential DBP concentrations across study sites among women eligible for inclusion in the analyses of exposure to drinking water DBPs and fetal growth restriction, 2000-2004 (*n*=2,039 women eligible for both SGA and term birth weight analyses)

DBP (μg/liter)*	Chlorinated DBP site (n=929)	Brominated DBP site (n=349)	Low DBP site (n=761)
Trihalomethanes			
Chloroform	46.7 (13.3)	13.7 (3.3)	0.2 (0.2)
BDCM	15.1 (4.4)	21.1 (2.9)	1 (0.2)
DBCM	4.4 (2.1)	23.1 (6.5)	1.4 (0.2)
Bromoform	0.2 (0.2)	5.7 (3.9)	0.7 (0.1)
TTHM†	66.4 (15.8)	63.6 (11.8)	3.3 (0.6)
Haloacetic Acids			
CAA	2.8 (1.1)	1.7 (0.9)	0 (0.1)
DCAA	18.7 (3.5)	7.1 (1.8)	0 (0)
TCAA	13.6 (5)	5.3 (1.8)	0 (0.1)
BCAA	4.6 (1.3)	8.9 (1.3)	0.8 (0.7)
BDCAA	4.6 (1.4)	8.2 (0.7)	0 (0)
DBCAA	1.2 (0.6)	5.6 (1.2)	0.4 (0.6)
BAA	0.1 (0.1)	0.7 (0.5)	0 (0)
DBAA	0.7 (0.5)	6.2 (2.6)	0 (0.1)
TBAA	0.2 (0.3)	2.7 (0.9)	0.2 (0.4)
HAA5‡	35.9 (8.6)	21.1 (2.5)	0.08 (0.1)
TOX	173.8 (16.3)	195.3 (16.7)	17.7 (2.0)

* Numbers in table are mean (standard deviation)
† TTHM is the sum of chloroform, BDCM, DBCM and bromoform
‡ HAA5 is the sum of CAA, DCAA, TCAA, BAA, DBAA
Abbreviations: DBP= disinfection by-product, BDCM= bromodichloromethane, DBCM = dibromochloromethane, TTHM = total trihalomethane, CAA= chloroacetic acid, DCAA=dichloroacetic acid, TCAA=trichloroacetic acid, BCAA= bromodichloroacetic acid, BDCAA= bromodichloroacetic acid, DBCAA= dibromochloroacetic acetic acid, BAA= bromoacetic acid, DBAA= dibromoacetic acid, TBAA= tribromoacetic acid, HAA5 = sum of five haloacetic acids, TOX= total organic halides.

Table 47. Associations between trimester-specific average DBP exposure and probability of SGA among women included in the analyses of exposure to drinking water DBPs and SGA*, 2000-2004.

	First trimester average			Second trimester average			Third trimester average		
	n SGA	*n* Non-SGA	RR (95% CI)†	*n* SGA	*n* Non-SGA	RR (95% CI)†	*n* SGA	*n* Non-SGA	RR (95% CI)†
Residential TTHM concentration (µg/liter)									
2.2-4.6	43	692	1	43	692	1	43	667	1
33.1-55	21	339	1.1 (0.7, 2.0)	17	290	1.0 (0.5, 1.8)	19	258	1.2 (0.7, 2.2)
55-66.3	16	256	1.2 (0.7, 2.1)	20	289	1.3 (0.7, 2.2)	15	330	0.8 (0.4, 1.5)
66.4-74.8	18	239	1.2 (0.7, 2.2)	15	289	0.8 (0.4, 1.5)	16	256	1.2 (0.7, 2.2)
74.9-108.8	15	319	0.8 (0.4, 1.5)	18	285	1.2 (0.7, 2.1)	18	274	1.3 (0.7, 2.3)
Missing	0	0		0	0		4	60	
≥ 80 vs. <80‡	9/104	202/1,643	0.6 (0.3, 1.4)	8/105	166/1,679	0.8 (0.4, 1.7)	12/97	108/1,677	2.0 (1.1, 3.6)
TTHM exposure through showering & bathing (µg absorbed /day)									
0.02-0.09	25	446	1	25	466	1	30	511	1
0.1-0.8	24	467	0.9 (0.5, 1.6)	29	460	1.1 (0.6, 1.9)	28	419	1.2 (0.7, 2.2)
0.9-1.5	26	438	1.0 (0.6, 1.8)	24	465	1.0 (0.5, 1.8)	18	444	1.0 (0.5, 1.8)
1.6-27.1	37	490	1.3 (0.7, 2.1)	34	450	1.4 (0.8, 2.3)	33	410	1.6 (1.0, 2.7)
Missing	1	4		1	4		4	61	
Residential HAA5 concentration (µg/liter)									
0-0.9	43	692	1	43	692	1	43	667	1
17.9-22	17	267	1.2 (0.7, 2.2)	28	283	1.8 (1.1, 3.0)	30	366	1.3 (0.8, 2.2)
22.1-31.5	30	338	1.5 (0.9, 2.5)	14	289	0.9 (0.5, 1.6)	12	192	1.3 (0.7, 2.4)
31.6-40.4	11	272	0.8 (0.4, 1.5)	15	291	0.9 (0.5, 1.6)	12	234	0.9 (0.5, 1.8)
40.4-52.8	12	276	0.7 (0.4, 1.4)	13	290	0.9 (0.5, 1.6)	14	326	0.9 (0.5, 1.6)
Missing	0	0		0	0		4	60	
HAA5 exposure through tap-water consumption (µg consumed /day)									
0	35	597	1	43	538	1	48	712	1
0.01-16.1	31	408	1.5 (0.9, 2.5)	22	436	0.6 (0.3, 1.0)	16	240	1.1 (0.6, 2.0)
16.2-54.4	30	446	1.5 (0.9, 2.4)	30	427	1.0 (0.6, 1.6)	26	402	1.1 (0.6, 1.8)
54.7-369.1	17	390	0.9 (0.5, 1.7)	18	440	0.6 (0.3, 1.1)	19	430	0.8 (0.5, 1.4)
Missing	0	4		0	4		4	61	
Residential TOX concentration (µg/liter)									
14.3-22.4	43	692	1	43	692	1	43	667	1
136.7-169.6	18	338	1.0 (0.5, 1.7)	13	290	0.7 (0.4, 1.4)	16	302	0.9 (0.5, 1.7)
169.6-177.7	18	315	1.1 (0.6, 1.9)	23	286	1.5 (0.9, 2.5)	16	250	1.3 (0.7, 2.3)
177.7-192.6	18	261	1.1 (0.6, 2.0)	13	293	0.8 (0.4, 1.5)	13	288	0.8 (0.4, 1.5)
192.8-235.2	16	239	1.2 (0.6, 2.0)	21	284	1.3 (0.8, 2.3)	23	278	1.5 (0.9, 2.5)
Missing	0	0		0	0		4	60	

* Seven births born before 27 weeks' gestation and 57 births that were < 27 weeks' in gestation when water sampling ended are not included in third trimester average models; five women were missing information on showering and bathing needed to assign first and second trimester average personal TTHM exposure; four were women missing information on tap water consumption necessary to assign first and second trimester average HAA5 personal exposure; and one women was missing information on showering and bathing and tap

water consumption needed to assign third trimester average personal TTHM and HAA5 exposure.
†Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake
‡ # SGA and # non-SGA are frequency of births with TTHM ≥ 80 μg/liter / frequency of births with TTHM < 80 μg/liter.
Abbreviations: DBP = disinfection by-product, SGA = small-for-gestational-age, RR = risk ratio, CI= confidence interval, TTHM = trihalomethane, HAA5 = sum of five haloacetic acids, TOX = total organic halides

Table 48. Associations between trimester-specific average DBP exposure and average birth weight among term births to women included in the analyses of exposure to drinking water DBPs and term birth weight*, 2000-2004.

	First trimester average		Second trimester average		Third trimester average	
	N	Mean difference in grams (95% CI)	N	Mean difference in grams (95% CI)	N	Mean difference in grams (95% CI)*
Residential TTHM concentration (µg/liter)						
2.2-4.6	677	0	677	0	655	0
33.1-55	334	-10.0 (-72.3, 52.3)	295	31.2 (-33.2, 95.5)	281	-7.1 (-72.3, 58.0)
55-66.3	258	34.4 (-32.7, 101.5)	288	31.2 (-33.3, 95.8)	335	52.2 (-9.7, 114.1)
66.4-74.8	253	-21.3 (-88.6, 46.0)	294	29.7 (-35.2, 94.6)	255	33.1 (-35.1, 101.3)
74.9-108.8	332	58.6 (-3.0, 120.1)	300	-22.4 (-85.7, 40.9)	275	3.8 (-62.8, 70.4)
Missing	0		0		53	
≥ 80 vs. <80‡	214/1640	36.1 (-30.4, 102.5)	175/1679	-35.6 (-107.1, 35.9)	117/1684	-55.9 (-143.7, 31.9)
TTHM exposure through showering & bathing (µg absorbed /day)						
0.02-0.09	439	0	458	0	497	0
0.1-0.8	458	-26.0 (-87.3, 35.2)	453	13.7 (-46.8, 74.2)	425	-38.8 (-99.1, 21.6)
0.9-1.5	455	-4.6 (-65.6, 56.4)	480	3.2 (-56.0, 62.5)	457	7.2 (-51.9, 66.3)
1.6-27.1	497	-7.0 (-68.8, 54.9)	458	8.1 (-54.4, 70.7)	421	4.8 (-57.0, 66.7)
Missing	5		5		54	
Residential HAA5 concentration (µg/liter)						
0-0.9	677	0	677	0	655	0
17.9-22	268	-26.9 (-96.1, 42.3)	282	-31.5 (-100.9, 37.8)	367	-36.9 (-99.5, 25.7)
22.1-31.5	345	-57.5 (-118.7, 3.6)	294	4.4 (-59.9, 68.6)	205	68.0 (-5.5, 141.5)
31.6-40.4	280	78.6 (14.0, 143.2)	300	33.4 (-30.5, 97.3)	244	12.0 (-56.5, 80.5)
40.4-52.8	284	72.3 (8.0, 136.5)	301	48.4 (-14.7, 111.6)	330	59.0 (-2.9, 120.9)
Missing	0		0		53	
HAA5 exposure through tap-water consumption (µg consumed /day)						
0	594	0	539	0	701	0
0.01-16.1	402	-25.7 (-84.5, 33.1)	422	-31.7 (-90.7, 27.4)	243	-34.9 (-103.2, 33.4)
16.2-54.4	454	-7.6 (-65.0, 49.9)	437	10.2 (-48.7, 69.1)	417	10.1 (-46.2, 66.5)
54.7-369.1	400	57.3 (-2.4, 117.0)	452	52.9 (-5.9, 111.8)	439	61.9 (5.5, 118.4)
Missing	4		4		54	
Residential TOX concentration (µg/liter)						
14.3-22.4	677	0	677	0	655	0
136.7-169.6	340	18.8 (-42.2, 79.7)	300	69.8 (6.5, 133.1)	322	62.1 (-0.1, 124.4)
169.6-177.7	315	34.9 (-27.6, 97.5)	300	-11.9 (-75.5, 51.8)	259	-19.9 (-87.1, 47.3)
177.7-192.6	278	-14.0 (-79.7, 51.7)	295	17.3 (-47.0, 81.7)	292	64.1 (-0.1, 128.4)
192.8-235.2	244	25.6 (-44.3, 95.4)	282	-15.2 (-82.2, 51.9)	273	-39.9 (-108.6, 28.9)
Missing	0		0		53	

* 53 births that were < 27 weeks' in gestation when water sampling ended are not included in third trimester average models; five women were missing information on showering and bathing needed to assign first and second trimester average personal TTHM exposure; four women were missing information on tap water consumption necessary to assign first and second trimester average HAA5 personal exposure; and one women was missing information on showering and bathing and tap water consumption needed to assign third trimester average personal TTHM and HAA5 exposure.

† Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake

‡ # preterm and # term are frequency of births with TTHM ≥ 80 μg/liter / frequency of births with TTHM < 80 μg/liter.

Abbreviations: DBP = disinfection by-product, TTHM = trihalomethane, HAA5 = sum of five haloacetic acids, TOX = total organic halides

Table 49. Estimated effects of third trimester average concentrations of individual THMs and HAAs on fetal growth measures among women included in the analysis of exposure to drinking water DBPs and fetal growth restriction from the chlorinated DBP site, 2000-2004

			SGA*		Term birth weight (in grams)†	
	n SGA	*n* Non-SGA	MLE model OR (95% CI)‡	Bayesian Model OR (95% PI)§	MLE model Mean Δ (95% CI)‡	Bayesian Model Mean Δ (95% PI)§
Chloroform						
19.9-44.2	14	267	1	1	0	0
44.3-49	14	274	1.4 (0.6, 3.1)	2.0 (0.5, 8.2)	41.6 (-40.3, 123.6)	11.8 (-29.5, 96.0)
49.1-94.0	12	275	1.1 (0.5, 2.6)	1.8 (0.4, 8.2)	27.3 (-57.1, 111.6)	4.5 (-44.5, 75.0)
BDCM						
8.2-11.8	14	274	1	1	0	0
11.9-14.1	10	273	0.9 (0.4,2.2)	1.5 (0.7,3.0)	26.0 (-56.3,108.3)	2.4 (-39.0,56.0)
14.2-28.5	16	269	1.5 (0.7,3.5)	1.3 (0.6,2.7)	-43.6 (-126.7,39.4)	-3.3 (-72.7,40.0)
DBCM						
1.1-3.2	11	281	1	1	0	0
3.3-4.4	11	269	0.8 (0.3,2.1)	1.5 (0.6,2.7)	4.1 (-77.7,85.9)	3.9 (-30.8,65.0)
4.5-9.1	18	266	2.0 (0.9,4.4)	1.6 (0.8,3.7)	-51.5 (-135.7,32.8)	-1.2 (-54.0,53.0)
Bromoform						
0.0-0	8	278	1	1	0	0
0.1-0.2	13	275	1.5 (0.6,3.9)	1.5 (0.8,3.0)	41.7 (-40.4,123.8)	5.7 (-26.0,67.0)
0.3-0.9	19	263	2.9 (1.2,7.0)	1.8 (0.9,4.1)	-32.4 (-116.9,52.1)	-2.4 (-62.3,46.0)
CAA						
0.0-2.2	13	273	1	1	0	0
2.3-3.2	11	273	1.1 (0.5,2.7)	0.9 (0.5,2.0)	11.3 (-70.8,93.3)	0.1 (-42.1,42.0)
3.3-5.6	16	270	1.6 (0.7,3.7)	0.9 (0.4,1.8)	-18.3 (-103.3,66.7)	-0.8 (-43.7,39.0)
DCAA						
10.2-17.3	15	269	1	1	0	0
17.4-20.8	14	267	1.2 (0.5,2.7)	0.9 (0.5,2.0)	1.9 (-81.6,85.4)	-0.7 (-40.3,37.0)
20.9-26.9	11	280	0.9 (0.4,2.2)	0.9 (0.5,2.2)	23.2 (-59.8,106.2)	-0.6 (-45.7,46.0)
TCAA						
5.3-11	16	268	1	1	0	0
11-17.2	14	272	0.9 (0.4,1.9)	0.7 (0.3,1.3)	4.0 (-80.7,88.7)	1.5 (-33.4,54.0)
17.3-24.1	10	276	0.6 (0.3,1.5)	0.9 (0.4,1.8)	1.9 (-81.2,84.9)	-2.3 (-53.9,35.0)
BCAA						
0.4-3.7	16	274	1	1	0	0
3.8-4.5	8	274	0.5 (0.2,1.2)	0.7 (0.3,1.5)	49.1 (-33.2,131.5)	8.9 (-25.7,75.0)
4.6-11.7	16	268	1.2 (0.5,2.5)	0.9 (0.4,1.8)	-27.8 (-110.8,55.2)	-4.3 (-62.3,42.0)
BDCAA						
1.6-3.7	13	270	1	1	0	0
3.8-5	13	275	1.4 (0.6,3.3)	1.0 (0.5,2.2)	53.2 (-30.3,136.6)	10.3 (-20.2,76.0)
5.1-7.5	14	271	1.3 (0.6,3.1)	0.9 (0.4,1.8)	-33.5 (-116.2,49.2)	-8.5 (-67.9,27.0)
DBCAA						
0.0-0.8	11	270	1	1	0	0
0.9-1.6	15	272	1.5 (0.6,3.5)	1.0 (0.5,2.2)	10.4 (-72.5,93.3)	0.4 (-42.9,50.0)
1.7-2.4	14	274	1.6 (0.7,3.9)	1.2 (0.6,3.0)	33.9 (-49.9,117.8)	3.0 (-35.0,62.0)
BAA						
0	25	621	1	1	0	0
0.0-0.5	15	195	1.9 (0.9,3.9)	1.2 (0.6,2.7)	-73.9 (-152.8,4.9)	-5.3 (-59.8,33.0)
DBAA						
0.0-0.3	16	274	1	1	0	0
0.4-0.9	7	272	0.5 (0.2,1.2)	0.7 (0.3,1.5)	19.5 (-63.6,102.7)	4.4 (-35.1,61.0)
1-2.1	17	270	1.1 (0.5,2.3)	0.9 (0.4,1.8)	-37.0 (-121.3,47.3)	-4.2 (-55.5,42.0)
TBAA						
0	19	365	1	1	0	0
0.0-1.8	21	451	1.0 (0.5,2.0)	0.8 (0.4,1.5)	25.8 (-42.6,94.3)	4.0 (-33.4,59.0)

* N = 856 for SGA analysis; two births born before 27 weeks' gestation and 25 births that were < 27 weeks' in gestation when water sampling ended (27 births total) are not included in third trimester average SGA models

† N = 849 for term birth weight analysis; 23 births that were < 27 weeks' in gestation when water sampling ended are not included in third trimester average term birth weight models

‡ Maximum likelihood estimation models were constructed separately for each individual THM and HAA; all models were adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity

and caffeine intake

§ Fully-Bayesian models specified $\beta_j \sim N(\mu_k, \varphi^2)$ where k is an indictor for DBP class and bromination (non-brominated THM, non-brominated HAA, brominated THM, brominated HAA); models adjusted for other DBPs listed in the table and maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.

Abbreviations: SGA= small-for-gestational-age, MLE = maximum likelihood estimation, OR= odds ratios, CI = confidence interval, PI= posterior interval, DBP= disinfection by-product, BDCM= bromodichloromethane, DBCM = dibromochloromethane, CAA= chloroacetic acid, DCAA=dichloroacetic acid, TCAA=trichloroacetic acid, BCAA= bromochloroacetic acid, BDCAA= bromodichloroacetic acid, DBCAA= dibromochloroacetic acetic acid, BAA= bromoacetic acid, DBAA= dibromoacetic acid, TBAA= tribromoacetic acid

Table 50. Estimated effects of third trimester average concentrations of individual THMs and HAAs on fetal growth measures among women included in the analysis of exposure to drinking water DBPs and fetal growth restriction from the brominated DBP site, 2000-2004

			SGA*		Term birth weight (in grams)†	
	n SGA	*n* Non-SGA	MLE model OR (95% CI)‡	Bayesian Model OR (95% PI)§	MLE model Mean Δ (95% CI)‡	Bayesian Model Mean Δ (95% PI)§
Chloroform						
6.4-11.5	4	104	1	1	0	0
11.6-15.6	15	96	4.9 (1.5,15.8)	3.9 (0.6,24.8)	-87.4 (-215.8,41.1)	-9.9 (-115.0,61.0)
15.7-22.1	9	102	2.4 (0.7,8.4)	3.5 (0.6,23.8)	59.3 (-70.8,189.3)	11.7 (-64.0,129.0)
BDCM						
15.8-20.1	8	101	1	1	0	0
20.2-22.9	8	103	1.0 (0.3,2.7)	0.8 (0.3,2.1)	55.1 (-74.3,184.4)	8.4 (-62.0,108.0)
23-29.2	12	98	1.6 (0.6,4.1)	0.9 (0.4,2.5)	49.1 (-81.0,179.1)	-2.3 (-95.0,73.0)
DBCM						
15.2-19.3	14	95	1	1	0	0
19.4-26	8	103	0.5 (0.2,1.2)	0.7 (0.3,1.6)	170.9 (42.5,299.4)	32.6 (-28.0,169.0)
26.1-38.7	6	104	0.3 (0.1,0.9)	0.7 (0.3,1.8)	142.8 (14.3,271.2)	7.3 (-62.0,118.0)
Bromoform						
0.8-2.4	12	98	1	1	0	0
2.5-11.5	7	102	0.6 (0.2,1.6)	0.8 (0.3,2.0)	145.9 (16.4,275.3)	18.5 (-45.0,137.0)
11.6-15.1	9	102	0.7 (0.3,1.7)	0.9 (0.3,2.4)	76.1 (-53.0,205.2)	-1.0 (-94.0,83.0)
CAA						
0.4-0.8	7	102	1	1	0	0
0.9-1.8	9	101	1.3 (0.5,3.7)	1.1 (0.4,2.4)	-134.0 (-265.2,-2.8)	-15.4 (-124.0,41.0)
1.9-4.0	12	99	1.9 (0.7,5.3)	1.3 (0.5,3.6)	-105.9 (-234.6,22.8)	1.2 (-74.0,84.0)
DCAA						
2.7-6.5	6	103	1	1	0	0
6.6-7.8	14	98	3.0 (1.1,8.3)	1.4 (0.6,3.2)	-56.7 (-184.5,71.2)	-5.6 (-101.0,64.0)
7.9-10.3	8	101	1.5 (0.5,4.6)	1.1 (0.4,2.6)	49.7 (-82.6,182.0)	13.5 (-46.0,130.0)
TCAA						
1.8-4	6	103	1	1	0	0
4.1-5.7	10	101	1.8 (0.6,5.4)	1.2 (0.5,2.7)	-39.7 (-170.1,90.7)	-2.4 (-92.0,82.0)
5.8-9.1	12	98	2.6 (0.9,7.4)	1.3 (0.5,3.5)	-43.0 (-173.1,87.0)	-3.6 (-99.0,67.0)
BCAA						
7.0-7.8	6	103	1	1	0	0
7.9-8.4	11	99	2.2 (0.8,6.3)	1.4 (0.7,3.4)	-94.4 (-224.5,35.8)	-4.3 (-77.0,44.0)
8.5-9.9	11	100	2.0 (0.7,5.6)	1.4 (0.6,3.6)	-67.2 (-198.3,63.9)	-1.1 (-76.0,58.0)
BDCAA						
6.1-7.8	7	102	1	1	0	0
7.9-9.4	10	101	1.5 (0.5,4.1)	1.1 (0.4,2.5)	20.4 (-108.2,148.9)	8.8 (-34.0,99.0)
9.5-11.5	11	99	1.7 (0.6,4.7)	1.4 (0.6,3.9)	34.5 (-97.3,166.3)	-4.5 (-78.0,48.0)
DBCAA						
2.5-4.3	10	99	1	1	0	0
4.4-5.8	12	99	1.4 (0.5,3.4)	1.2 (0.5,2.9)	21.0 (-108.3,150.3)	0.4 (-64.0,69.0)
5.9-8.2	6	104	0.5 (0.2,1.6)	1.2 (0.5,3.1)	71.6 (-58.0,201.2)	-0.3 (-61.0,71.0)
BAA						
0.0-0.4	12	99	1	1	0	0
0.5-1.2	7	102	0.5 (0.2,1.4)	0.9 (0.4,1.8)	-39.1 (-169.2,91.1)	-3.8 (-77.0,50.0)
1.3-2.1	9	101	0.7 (0.3,1.7)	1.7 (0.8,5.1)	-12.5 (-143.6,118.6)	0.5 (-70.0,70.0)
DBAA						
2.3-4.4	13	98	1	1	0	0
4.5-7.2	10	100	0.8 (0.3,1.9)	1.3 (0.6,3.4)	12.3 (-117.7,142.4)	0.2 (-56.0,69.0)
7.3-11.4	5	104	0.3 (0.1,0.9)	1.1 (0.4,2.6)	62.3 (-69.0,193.6)	2.2 (-57.0,73.0)
TBAA						
1.5-2.6	8	102	1	1	0	0
2.7-3	14	97	1.9 (0.7,4.8)	1.7 (0.6,4.8)	-57.4 (-186.4,71.6)	-8.8 (-86.0,36.0)
3.1-5.2	6	103	0.7 (0.2,2.0)	1.3 (0.5,3.4)	-14.3 (-145.0,116.4)	-3.4 (-95.0,51.0)

* N = 330 for SGA analysis; two births born before 27 weeks' gestation and 8 births that were < 27 weeks' in gestation when water sampling ended (10 births total) are not included in third trimester average SGA models

† N = 297 for term birth weight analysis; eight births that were < 27 weeks' in gestation when water sampling ended are not included in third trimester average term birth weight models

‡ Maximum likelihood estimation models were constructed separately for each individual THM and HAA; all models were adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake

§ Fully-Bayesian models specified $\beta_j \sim N(\mu_k, \varphi^2)$ where k is an indictor for DBP class and bromination (non-brominated THM, non-brominated HAA, brominated THM, brominated HAA); models adjusted for other DBPs listed in the table and maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.

Abbreviations: SGA= small-for-gestational-age, MLE = maximum likelihood estimation, OR= odds ratios, CI = confidence interval, PI = posterior interval, DBP= disinfection by-product, BDCM= bromodichloromethane, DBCM = dibromochloromethane, CAA= chloroacetic acid, DCAA=dichloroacetic acid, TCAA=trichloroacetic acid, BCAA= bromochloroacetic acid, BDCAA= bromodichloroacetic acid, DBCAA= dibromochloroacetic acetic acid, BAA= bromoacetic acid, DBAA= dibromoacetic acid, TBAA= tribromoacetic acid

5.2 Manuscript 2: Drinking water disinfection by-product exposure and duration of gestation.

Abstract

Purpose: Recent studies suggest elevated exposure to drinking water disinfection by-products (DBPs) may be associated with decreased risk of preterm birth. We examined this association for exposure to total trihalomethane (TTHM), five haloacetic acids (HAA5) and total organic halides (TOX). **Methods:** Analysis included 2,039 women in a prospective pregnancy study conducted from 2000-2004 in three study sites. Water samples were prospectively collected and analyzed for DBPs. Participant data were collected through interviews, an early ultrasound and birth records. The association between DBP and preterm birth (< 37 weeks' gestation) was assessed using log-binomial regression. Discrete-time hazard analysis was used to model the conditional odds of delivery each week in relation to DBP exposure. **Results:** Average second trimester DBP levels were inversely associated with preterm birth. Adjusted risk ratios (95% confidence interval) for TTHM levels of 33.1-55.0, 55.1-66.3, 66.4-74.8 and 74.9-108.8 versus 2.2-4.6 micrograms/liter were 0.8 (0.5,1.3), 0.9 (0.6,1.4), 0.7 (0.4,1.1) and 0.5 (0.3,0.9). Risk ratios for HAA5 levels of 17.9-22.0, 22.1-31.5, 31.6-40.4 and 40.4-52.8 versus 0-0.9 micrograms/liter were 1.1 (0.8, 1.7), 0.8 (0.5, 1.2), 0.5 (0.3, 0.8), and 0.7 (0.4, 1.1). The conditional odds of delivery each week were decreased for the highest TTHM and HAA5 exposure groups versus the low exposure group for gestational weeks' 33-40. **Conclusions:** Results clearly indicate that the probability of preterm birth is not increased with high DBP exposure, and suggest that high exposure may be associated with delayed birth through the term gestational period.

5.2.1 Introduction

Disinfection of water to control waterborne infectious diseases is clearly an important public health measure. However, the discovery of chloroform and other trihalomethanes (THMs) in chlorinated drinking water in the 1970s has prompted concern over the potential adverse impacts of exposure to water disinfection by-products (DBPs)[1]. While initial interest in DBP exposure focused on a possible association with cancer [2-4], more recent research has focused on adverse pregnancy outcomes [5,7,8]. Most studies suggest no association with preterm birth [92,93,96-98], although more recent studies have provided limited evidence that high residential concentrations of total trihalomethane (TTHM) may in fact be associated with decreased risk of preterm birth[89,90,100].

Null findings of previous studies may be due to errors in outcome and exposure assessment, leading to attenuation of estimated effects. Multiple factors influence the distribution of DBP concentrations within a water distribution system, including source water characteristics (*e.g.,* surface versus ground water, temperature and pH), the presence of other halides in source water (*e.g.,* bromine), and the type of disinfectant method used (*e.g.,* chloramination versus chlorination)[9]. Capturing spatial and temporal variability in DBP concentrations within a distribution system is essential to accurately assign residential DBP concentrations during relevant time windows for exposure[119,120]. Furthermore, DBP exposure occurs through ingestion of contaminated water as well as inhalation and dermal absorption of DBPs during activities such as showering, bathing and swimming[12]. Failure to take individual variation in water use into account also may result in substantial exposure assessment error [18,24,121].

The purpose of this analysis was to examine the association between DBP exposure and duration of gestation as assessed through the proportion of infants born preterm (< 37 weeks' gestation) and the conditional odds of delivery each week using improved exposure data that allow account inter-individual variability to be estimated more accurately than in previous studies. This study involved the most extensive exposure assessment of any DBP study to date, including prospective collection of weekly or bi-weekly DBP measurements and incorporation of self-reported water use behaviors to estimate personal exposure.

5.2.2 Materials and methods

Study design and population

Data for this analysis come from a community-based prospective cohort study conducted from 2000-2004 to examine the effect of drinking water disinfection byproduct (DBP) exposure on pregnancy health. Details of the study design and recruitment have been published elsewhere [26,124,125]. Briefly, women were recruited early in pregnancy (≤ 12 weeks' gestation) or while planning a pregnancy from three study sites within the US. One site had moderate levels of chlorinated DBPs (hereafter referred to as "chlorinated DBP site"), one had moderate levels of brominated DBPs ("brominated DBP site"), and one had low levels of all DBPs ("low DBP site"). In addition, the chlorinated and brominated DBP sites used chloramination rather than free chlorine for terminal disinfection, which minimized spatial variability in DBP concentrations within sites. Participant data were collected through interviews conducted at screening, baseline (completed by 16 weeks' gestation) and follow-up (completed between 20 and 25 weeks' gestation), a first trimester ultrasound, and birth records.

A total of 2,766 pregnancies (68% of those screened) were enrolled from all three sites. This analysis includes 2,039 singleton live births with a complete baseline interview. We excluded 259 (9.4%) pregnancies with no or incomplete baseline interview, 347 (12.5%) pregnancies that ended in a loss, 90 (3.3%) pregnancies lost to follow-up, seven (0.2%) pregnancies without information on date of birth or birth weight, eight (0.3%) multi-gestational pregnancies, and 16 (0.6%) repeat live births to a study participant. Women retained for analysis were slightly more likely to be White and to have completed ≥ 16 years of education than all enrolled participants were, but distributions for maternal age, estimated gestational age at enrollment, and parity were similar (data not shown).

Measurement of DBP concentrations

Weekly water samples were collected from the study sites with moderate DBP levels and biweekly in the low exposure site at a single, representative location in the water distribution system. Details of sampling and verification of low spatial variability are provided elsewhere[26]. When the chlorinated and brominated sites converted to free chlorine for system flushing (during one month each year), samples were collected at additional locations to capture resultant spatial variability in DBP levels within the system and combined to estimate a system-wide weekly average. Water samples were returned overnight to the University of North Carolina and refrigerated at 4^{o}C until analyzed for all four individual THMs, all nine haloacetic acids (HAAs), and total organic halide (TOX). THM levels were analyzed using a modified version of US Environmental Protection Agency (US EPA) Method 551.1 [104] and HAAs were analyzed using a method developed by Brophy

et al.[105] based on standard methods[106,107]. Additional information on sample collection, shipment and analysis is provided in detail elsewhere[26].

Characterization of DBP exposure

This analysis focuses on exposure to aggregate DBP measures, including total trihalomethanes (TTHM), the sum of five haloacetic acids (HAA5), and total organic halides (TOX). TTHM and HAA5 are currently regulated by the US EPA[14] and TOX provides an estimate of the overall organic halide level in water. Two exposure metrics were examined: residential DBP concentrations, estimated by TTHM, HAA5 and TOX concentration in the water distribution system serving a woman's residence, and personal DBP exposure, estimated as uptake through showering and bathing for TTHM and by intake through tap water consumption for HAA. THMs are highly volatile, and a much greater proportion of the uptake of THM parent compounds occurs through inhalation and absorption rather than tap water consumption[126]. Thus, showering and bathing were considered for personal TTHM exposure but not tap water consumption. Conversely, only tap water consumption was considered for personal HAA exposure because HAAs are non-volatile and minimal exposure occurs from other water use activities[12].

Personal exposure was estimated using algorithms described in previous publications[26,125]. Briefly, women were asked about their tap water consumption, showering and bathing habits in detail during baseline and follow-up interviews. Personal TTHM exposure was estimated by integrating residential THM concentrations and self-reported information on average duration and frequency of showering and bathing into an absorbed dose (μg/day) using uptake factors derived from toxicokinetic studies[126,127]. Personal HAA

exposure was estimated in two steps. Residential HAA concentrations were first adjusted for boiling and filtering using correction factors[26,109] and then combined with self-reported information on the number and size of glasses of cold/hot filtered/unfiltered tap water drinks typically consumed per day to calculate average daily intake of HAAs (µg/day). Self-reported changes in water use habits (*e.g.,* between baseline and follow-up interviews) were accounted for by calculating time-weighted averages over periods with change.

Estimation of gestational age at birth

Self-reported last menstrual period (LMP) and an early ultrasound, both obtained during the first trimester, were combined with infant date of birth to estimate gestational age at birth. Gestational age derived from LMP was used for the majority of subjects (81.4%) unless the LMP date differed by more than +/- 7 days from the ultrasound-based estimate of gestational age (17.7%) or self-reported LMP was incomplete (0.9%), in which case the ultrasound estimate was used. Infant date of birth was obtained from medical records for 43.0% of live births, vital records for 56.5%, and participant self-report for only 0.5%.

Statistical Analysis

The association between DBP exposure and preterm birth (defined as delivery before 37 weeks' gestation) was examined using log binomial regression. Given no strong biological evidence to determine a critical time window for exposure, second trimester average DBP exposure was used in all models, as this period was identified as the relevant window for preterm birth in a previous study of TTHM[100]. Residential DBP concentrations were examined initially using restricted quadratic splines to model the dose-response in

probability of preterm birth. Linear models were constructed following visual inspection of dose-response curves to confirm the assumption of linearity was not violated.

To produce more easily interpretable risk ratios (RR) and facilitate comparison with previous studies, preterm birth models were also run using categories of residential DBP concentrations divided into quartiles of second trimester average concentrations among women from the moderate exposure sites, using the low exposure site as the referent, and dichotomizing residential TTHM levels at the current US EPA regulatory standard (≥ 80 micrograms/liter). Concentrations of HAA5 above the US EPA standard (≥ 60 micrograms/liter) were too rare for meaningful analysis. Personal DBP exposure estimates were examined using categorical coding only, as the authors believe this exposure metric is most useful for roughly separating women into "high", "moderate" and "low" exposure groups when considering the amount of error potentially introduced through use of self-reported data on water use and consumption.

Dichotomization of births as preterm versus non-preterm masks variability in the severity of prematurity among infants classified as preterm while over-emphasizing differences between deliveries occurring shortly before and after 37 weeks' gestation. Furthermore, inferences about the effect of exposure on timing of delivery throughout gestation cannot be made. Therefore, partially constrained continuation odds ratio models were constructed to model the effect of DBP exposure on the odds of delivery each week conditional on a woman not having delivered in a prior week[116], with time interactions between DBP exposure and pregnancy intervals of 20-32, 32-36, 37-40, and ≥ 41 weeks' gestation. Time-to-birth (in weeks) was defined as the time from 20 weeks' completed

gestation until gestational age at birth. This model is analogous to discrete hazard regression using a logit link and time-varying coefficients.

Time interaction intervals listed above were selected because they approximately represent very preterm, moderately preterm, term and post-term periods, respectively, and a sufficient number of births occurred during each interval to support statistical analyses. Continuation log odds models also can incorporate exposures with time-varying values. Therefore, in addition to second-trimester average exposure, two coding schemes allowing DBP exposure values to change over pregnancy were considered in separate models: a 6-week sliding average (*i.e.,* average over the index week plus the five proceeding weeks) and a 1-week "current" exposure estimate.

For both sets of analyses, confounders (listed in table 1) were identified from the literature as risk factors for preterm birth that may be independently associated with DBP exposure but not on the causal pathway between exposure and disease according to directed acyclic graph analysis [115]. Effect measure modification by maternal age (< 25, 25-29, 30-35, ≥ 35 years of age), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic and other) and swimming during pregnancy (yes/no) was assessed by constructing DBP-covariate interaction terms and were retained in the model if the *p*- value was < 0.10.

5.2.3 Results

Of the 2,039 births included in this analysis, 185 (9.1%) were born preterm. The proportion of preterm births varied considerably by site (6.1% at the chlorinated DBP site, 12.6% at the brominated DBP site, and 11.0% at the low DBP site). Women from the brominated DBP site were more likely to be Hispanic and parous, less likely to be employed

during pregnancy or married, and tended to be younger, less educated, and have a lower income than women from the chlorinated and low DBP sites (table 51). Although women from the chlorinated and low DBP sites were much more similar, women from the chlorinated site were still slightly older, more educated, had higher income and were more likely to be non-Hispanic White than those from the low DBP site.

As expected, the low DBP site had much lower concentrations of TTHM, HAA5 and TOX than the chlorinated and brominated DBP sites (table 52). TTHM concentrations were similar between the chlorinated and brominated DBP sites, but HAA5 was slightly higher and TOX lower at the chlorinated DBP site compared to the brominated DBP site. A higher relative concentration of brominated compounds at the brominated DBP site compared to the chlorinated site was also confirmed (results not shown)[26].

Preterm birth

Dose-response modeling of the association between preterm birth and DBPs suggested an overall trend of decreasing probability of preterm birth with increasing levels of residential TTHM and HAA5 concentrations, particularly at levels ≥ 60 micrograms/liter TTHM and ≥ 18 micrograms/liter HAA5 (figure 18). Estimated risk ratios (RRs) for preterm birth comparing women in the higher quantile categories of exposure to the lowest exposure group also indicated an inverse relationship for both residential and personal exposure metrics (table 53). Similar results were found in site-specific analyses, although when restricted to the brominated DBP site alone, the dose-response pattern for HAA5 was less consistent and RRs for all DBPs were less precise (results not shown). Effect measure

modification by maternal age, maternal race/ethnicity or swimming during pregnancy was not found (results not shown).

Time to birth

The odds of delivery each week, conditional on not having delivered in a previous week, were decreased for women in the higher categories of average second trimester residential TTHM and HAA5 concentrations compared to women in the lowest group for gestational weeks 33-40 (figure 19). Odds ratios (ORs) over this period ranged from 0.5-0.9 for residential TTHM concentrations and 0.4 to 1.3 for residential HAA5 concentrations. ORs for 20-32 weeks and 41-44 weeks were imprecise, as evidenced by wide confidence intervals, due to the small number of infants born during these periods. Results suggest that the conditional probability of birth each week was increased with higher DBP exposure over the 41-44 weeks period (ORs ranged from 2.1-7.3); however, these findings should be interpreted with caution. In addition to poor precision, the majority of births during the 41-44 weeks' period occurred at 41 or 42 weeks' (98%) and later births (at 43 or 44 weeks') are likely due to errors in gestational age estimation.

Conditional ORs estimates for personal TTHM and HAA5 exposure showed a pattern of association similar to residential concentrations for 37-40 weeks and 41-44 weeks but were inconsistent for 33-36 weeks (figure 19). Estimated ORs from models examining 6-week sliding average exposure and weekly exposure did not differ substantially from those shown in figure 19 (results not shown). Effect measure modification by maternal age, maternal race/ethnicity or swimming during pregnancy was not indicated (results not shown).

5.2.4 Discussion

Results of our study clearly suggest that the risk of preterm birth does not increase with exposure to high levels of TTHM or HAA5. Our study provides additional support to

recent findings suggesting that high levels of TTHM exposure during pregnancy may in fact be related to decreased risk of preterm birth. We also found that the delay in timing of birth associated with high DBP exposure continues through the term period of gestation (37-40 weeks').

Previous studies examining the association between TTHM and preterm birth have generally indicated no association, with estimated relative risks for preterm birth ranging between 0.7-1.2 and no notable dose-response trends [90,92,93,96-98]. However, a small inverse relationship between TTHM and preterm birth was reported in recent studies by Wright et al. (2004)[89] and Lewis et al. (2007)[100]. The former study examined third trimester average residential DBP exposure among births to women residing in Massachusetts from 1995 to 1998 and estimated ORs of 0.95 (0.91, 0.99) and 0.88 (0.81,0.94) comparing TTHM levels of 33-74 and 74-163 versus 0-33 micrograms/liter but did not find an association with HAA5. Lewis et al. reported hazard ratios for preterm birth of 0.87 (0.77, 0.99) and 0.82 (0.71, 0.94) comparing second trimester average residential TTHM levels 40-60 and ≥ 60 versus < 40 micrograms/liter, respectively, among births between 1999-2001 to women residing in 27 communities served by a single water utility.

Exposure assessment in all previous studies was done by linking maternal residence at the time of birth with municipal water DBP measurements and only one prior study estimated personal water use. Most investigations only had quarterly measurements of DBP concentrations from a limited number of locations within the water distribution systems. As a result, temporal and spatial variability in DBP concentrations may not have been adequately captured, resulting in exposure assessment error and attenuation of estimated effects. However, much like our study, the Lewis et al. (2007) study obtained weekly

monitoring data on TTHM measurements from a utility company that employed water treatment regimens to minimize spatial variability in TTHM concentrations[100]. In general, our study found slightly stronger inverse effects than reported by previous studies.

Another potentially important finding from our study is that high DBP exposure may be associated with delayed birth through the "term" gestational period. One previous study reported increased mean gestational length associated with higher second trimester average TTHM exposure[90]. Because labor is routinely induced at 42 weeks' gestation, such a delay could increase the portion of women requiring labor induction. However, we did not collect information on labor induction and there were too few births born postterm (at ≥ 42 weeks' gestation) to assess this association. A study of the magnitude necessary to accurately study this association is probably not warranted.

The strong relationship between residential location (*i.e.,* study site) and residential DBP concentrations in our study is both a strength and a limitation. By design, we have a range of reliable DBP measures (high/literow, chlorinated/brominated) that has never before been assembled for a study of DBPs and reproductive health, but there are also substantial differences in the population characteristics of the study sites. Women who participated from each site have different demographic profiles and show an overall difference in the proportion of births born preterm. To control for potential confounding between study sites, we adjusted for the major risk factors for preterm birth that varied in distribution between sites and performed site specific analysis to confirm that the pattern of results between DBPs and time of birth were similar across study sites. The point estimates for these analyses were similar to the main results but less stable due to small numbers. For example, RRs (95% confidence interval) for the US EPA TTHM regulatory standard (≥ 80 micrograms/liter

versus < 80 micrograms/liter) were 0.6 (0.3, 1.2) excluding the low DBP site, 0.5 (0.2, 1.4) restricting to the chlorinated DBP site alone, and 0.9 (0.3, 2.5) restricting to the brominated DBP site alone, suggesting that the preterm risk associated with DBP exposure was not substantially influenced by underlying population differences related to site. However, there may still be other unmeasured factors that influence timing of birth and vary by study site (*e.g.,* unknown environmental exposures or social influences) that biased results down and away from the null.

The proportion of preterm births may be higher during late summer and fall compared to spring[65,66] and DBP concentrations are generally higher during warm seasons compared to colder seasons[12], which could lead to confounding by season. We examined whether season of birth predicted the proportion of infants born preterm among our study population and found no association. Therefore, we did not control for season to preserve maximum temporal variability in DBP levels. Furthermore, the expected direction of bias due to seasonal confounding would be upwards, away from the null, which is counter to the inverse association found in this study.

A major strength of this study is the availability of individual-level information on water consumption, bathing and showering to estimate participants' personal DBP exposure. One other study examining preterm birth has incorporated information on individual water use to estimate personal DBP exposure, combining residential DBP concentrations with self-reported consumption of water to estimate "THM dose"[92]. However, no previous study of preterm birth has had access to such extensive data on individual water use. At the same time, it is important to acknowledge that information on water consumption and use was collected by interview and is subject to the usual concerns about the accuracy of self-reported

information on exposure in a prospective study. Ultimately, we found similar patterns of association with duration of gestation for residential and personal DBP measures.

A major strength of our study is the prospective design with individual follow-up of pregnancies to determine pregnancy outcomes. Previous studies have relied on information provided in vital records to estimate gestational age, which is prone to substantial error[102]. In our study, self-reported LMP was collected from participants during the first trimester of pregnancy (when recall is more accurate) and, first trimester ultrasounds were conducted and available to adjust LMP dates that were more than seven days discrepant with the ultrasound estimate. Therefore, estimation of gestational age at birth and classification of births as preterm is very accurate in our study.

In conclusion, our study is the most extensive study of DBP exposure and preterm birth conducted to date. Our results clearly demonstrate that high DBP exposure is not associated with increased risk of preterm birth. While concerns persist for other reproductive health risks (*e.g.,* fetal growth restriction) [5,7,8], the association between DBP exposure and preterm birth risk does not merit further investigation. Our findings also provide evidence that DBP exposure may in fact be associated with a decreased risk of preterm birth. The delay in birth was evident throughout most of gestation. While this may have implications for the proportion of births requiring labor induction, a study of the scale necessary to address this concern is probably not warranted.

5.2.5 References

Table 51. Characteristics of women included in the analysis of exposure to drinking water DBPs and duration of gestation, 2000-2004.

	All women in the analysis (n=2,039)			Chlorinated DBP site (n=929)	Brominated DBP site (n=349)	Low DBP site (n=761)
Covariate	N	Col. %	% preterm*	Col. %	Col. %	Col. %
Maternal Age (years)						
< 25	599	29.4	10.9	21.0	47.7	31.1
25-29	657	32.2	8.2	31.6	33.0	32.7
30-35	564	27.7	7.3	34.6	13.6	25.6
≥ 35	219	10.7	11.4	12.8	5.8	10.6
Maternal Race/ethnicity						
Non-Hispanic White	1169	57.4	7.4	67.1	35.9	55.5
Non-Hispanic Black	609	29.9	12.5	25.2	22.4	39.1
Hispanic	185	9.1	8.7	3.1	39.7	2.4
Other	73	3.6	6.8	4.6	2.0	3.0
Missing	3					
Highest education level obtained						
High school or less	573	28.1	12.7	16.9	53.3	30.3
Some college	440	21.6	9.5	18.5	27.2	22.8
College degree or more	1025	50.3	6.8	64.6	19.5	47.0
Missing	1					
Annual household income ($)						
<30,000	637	32.5	11.9	22.3	60.2	32.5
30,001-60,000	535	27.3	7.1	29.4	22.0	27.3
60,001-80,000	321	16.4	5.6	18.1	9.3	17.5
>80,000	465	23.8	8.0	30.2	8.4	22.7
Missing	81					
Employed during pregnancy						
Non-employed	608	29.8	9.4	28.2	37.5	28.3
Employed	1430	70.2	8.9	71.8	62.5	71.7
Missing	1					
Marital status						
Married	1390	68.2	7.2	74.9	53.2	66.9
Not married	648	31.8	13.1	25.1	46.8	33.1
Missing	1					
Pre-pregnancy BMI (kg/m^2)						
<19.8	232	11.7	7.8	13.4	8.3	11.1
19.8-25.9	1016	51.1	8.1	54.7	46.3	48.8
26.0-29.9	333	16.7	6.6	15.2	18.1	18.1
>29.9	407	20.5	14.3	16.7	27.3	22.1
Missing	51					
Daily caffeine intake (mg/day)						
0	519	25.4	9.1	27.6	23.2	23.9
1-150	468	23.0	8.1	21.3	22.6	25.1
151-300	387	19.0	10.6	16.6	21.8	20.6
>300	665	32.6	8.9	34.5	32.4	30.4
Parity						
Nulliparous	991	48.6	10.2	53.1	42.4	46.0
Parous	1048	51.4	8.0	46.9	57.6	54.0

* Percent of births within the covariate born preterm among all births in the study
Abbreviations: BMI = body mass index, DBP= disinfection by-product

Table 52. Second trimester average residential DBP concentrations*across study sites among women included in the analysis of exposure to drinking water DBPs and duration of gestation, 2000-2004.

DBP (μg/liter)	All sites (n=2,039)	Chlorinated DBP site (n=929)	Brominated DBP site (n=349)	Low DBP site (n=761)
TTHM	42.4 (32.4)	66.4 (15.8)	63.6 (11.8)	3.3 (0.6)
HAA5	20.0 (17.3)	35.9 (8.6)	21.1 (2.5)	0.08 (0.1)
TOX	119.2 (79.8)	173.8 (16.3)	195.3 (16.7)	17.7 (2.0)

* Mean (standard deviation)

Abbreviations: DBP= disinfection by-product, TTHM = total Trihalomethane, HAA5 = sum of five haloacetic acids, TOX= total organic halides.

Table 53. Association between average second-trimester DBP exposure and probability of preterm birth among included in the analysis of exposure to drinking water DBPs and duration of gestation, 2000-2004.

	n preterm	*n* term	Unadjusted RR (95% CI)*	Adjusted RR (95% CI)†
Residential TTHM Concentration (µg/liter)				
2.2-4.6	84	677	1.	1.
33.1-55	27	295	0.8 (0.5,1.1)	0.8 (0.5, 1.3)
55-66.3	30	288	0.9 (0.6,1.3)	0.9 (0.6, 1.4)
66.4-74.8	24	294	0.7 (0.4,1.1)	0.7 (0.4, 1.1)
74.9-108.8	20	300	0.6 (0.4,0.9)	0.5 (0.3, 0.9)
per 10 µg/liter			0.94 (0.90, 0.98)	0.95 (0.91, 1.00)
p for linear trend test‡			0.008	0.03
≥ 80 vs. <80**	9/176	175/1,679	0.5 (0.3,1.0)	0.5 (0.3,1.1)
TTHM exposure through showering & bathing (µg absorbed /day)				
0.02-0.09	50	458	1.	1.
0.1-0.8	56	453	1.1 (0.8,1.6)	0.9 (0.6, 1.4)
0.9-1.5	29	480	0.6 (0.4,0.9)	0.7 (0.4, 1.0)
1.6-27.1	50	458	1.0 (0.7,1.4)	0.8 (0.5, 1.2)
Residential HAA5 Concentration (µg/liter)				
0-0.9	84	677	1.	1.
17.9-22	39	282	1.1 (0.8,1.6)	1.1 (0.8, 1.7)
22.1-31.5	24	294	0.7 (0.4,1.1)	0.8 (0.5, 1.2)
31.6-40.4	18	300	0.5 (0.3,0.8)	0.5 (0.3, 0.8)
40.4-52.8	20	301	0.6 (0.4,0.9)	0.7 (0.4, 1.1)
per 10 µg/liter			0.87 (0.80, 0.94)	0.89 (0.81, .0.97)
p for trend test‡			0.001	0.01
HAA5 exposure through tap-water consumption (µg consumed /day)				
0	63	539	1.	1.
0.01-16.1	56	422	1.1 (0.8,1.6)	0.9 (0.6, 1.4)
16.2-54.4	40	437	0.8 (0.5,1.2)	0.9 (0.6, 1.4)
54.7-369.1	26	452	0.5 (0.3,0.8)	0.6 (0.4, 0.9)
Residential TOX Concentration (µg/liter)				
14.3-22.4	84	677	1.	1.
136.7-169.6	19	300	0.5 (0.3,0.8)	0.7 (0.4, 1.1)
169.6-177.7	21	300	0.6 (0.4,0.9)	0.6 (0.4, 1.0)
177.7-192.6	24	295	0.7 (0.4,1.1)	0.7 (0.4, 1.1)
192.8-235.2	37	282	1.1 (0.7,1.5)	1.1 (0.8, 1.7)
per 10 µg/liter			0.98 (0.97, 1.00)	0.99 (0.97, 1.00)
p for trend test‡			0.05	0.2

* Unadjusted model

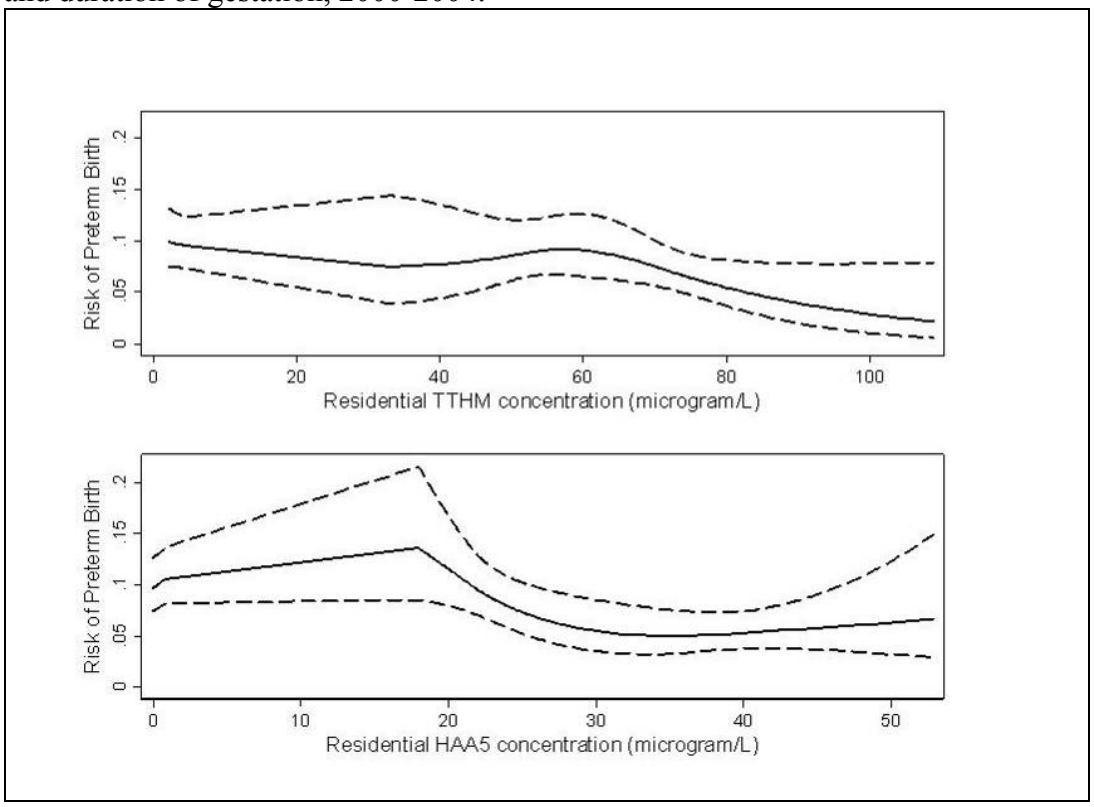
† Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake

‡ Chi-square test (H_0: $\beta_{DBP} = 0$) for a single, continuous residential DBP concentration term (*i.e.,* linear term)

** # preterm and # term are frequency of births with TTHM ≥ 80 µg/liter / frequency of births with TTHM < 80 µg/liter.

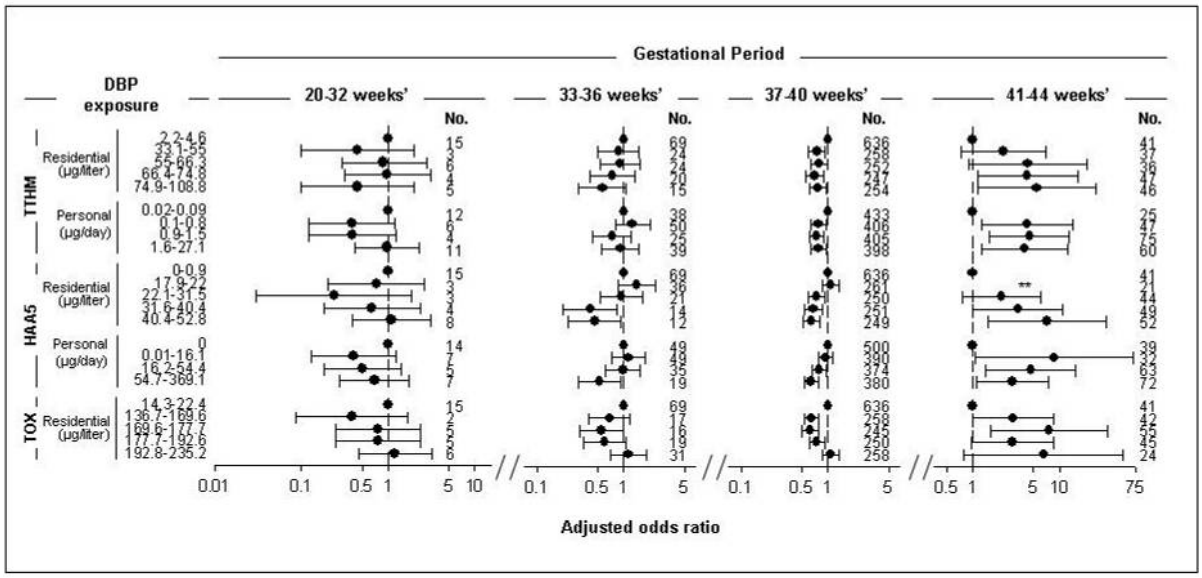
Abbreviations: RR = risk ratio, CI= confidence interval

Figure 18. Predicted risk of preterm birth by second trimester average residential concentrations of total Trihalomethane (TTHM) and five haloacetic acids (HAA5) among women included in the analysis of drinking water disinfection by-product (DBP) exposure and duration of gestation, 2000-2004.



Model adjusted for maternal age, race/ethnicity, education level, annual household income, employment status during pregnancy, marital status, pre-pregnancy BMI (kg/m^2), daily caffeine intake (mg/day) and parity. Solid line is the predicted probability of preterm birth and dashed lines are lower and upper pointwise 95% confidence interval.

Figure 19. Association between second trimester average drinking water disinfection by-products (DBP) exposure and the conditional odds of delivery each week (gestational weeks' 20-44) stratified by gestational period among women included in the analysis of exposure to drinking water DBPs and duration of gestation, 2000-2004.



Residential concentrations of total trihalomethane (TTHM), the sum of five haloacetic acids (HAA5) and total organic halides presented in µg/liter; personal exposure to TTHM through showering and bathing presented in µg absorbed/day and to HAA5 through tap water consumption as µg consumed/day; models adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake; ** = non-estimable because all infants in exposure category delivered at 41 weeks' gestation.

5.3 Manuscript 3: Comparison of gestational age at birth based on last menstrual period and ultrasound during the first trimester

Abstract

Reported last menstrual period (LMP) is commonly used to estimate gestational age (GA) but may be unreliable. Ultrasound in the first trimester is generally considered a highly accurate method of pregnancy dating. The authors compared first trimester report of LMP and first trimester ultrasound for estimating GA at birth and examined whether disagreement between estimates varied by maternal and infant characteristics. Analyses included 1,867 singleton live births to women enrolled in a prospective pregnancy cohort. Authors computed the difference between LMP and ultrasound GA estimates (GA difference) and examined the proportion of births within categories of GA difference stratified by maternal and infant characteristics. The proportion of births classified as preterm, term and postterm by pregnancy dating methods also was examined. LMP-based estimates were 0.8 days (standard deviation=8.0, median=0) longer on average than ultrasound estimates. LMP classified more births as postterm than ultrasound (4.0% versus 0.7%) but the proportions classified as preterm were similar (10.0% versus 8.9%). GA difference was greater among young women, non-Hispanic Black and Hispanic women, less educated women, women of non-optimal body weight and mothers of low birth weight infants. Results indicate first trimester report of LMP is a reliable estimate of GA.

5.3.1 Introduction

Self-report of last menstrual period is often used to estimate gestational age in clinical care and epidemiologic research. However, reported LMP may be unreliable [128]. Women

may not recall the date of LMP accurately [129,130] or misinterpret early pregnancy bleeding as normal menses [131]. In addition, the convention of assigning a 14-day interval between menstruation and ovulation, implicit in calculations of gestational age, will be inaccurate for women with irregular menstrual cycles or delayed ovulation [132,133]. This presents the dilemma of whether reported LMP has acceptable precision for research on pregnancy outcomes.

Ultrasonography before 20 weeks' gestation is generally viewed as a more accurate method of estimating gestational age than menstrual dating [134,135], with ultrasound assessment between 5 to 8 weeks' having the greatest accuracy. In general, ultrasound assessment is limited by the implicit assumption that all fetal size variability is due to gestational age [136], which can lead to systematic underestimation of gestational age among pregnancies exhibiting early growth restriction [137]. This is less of a concern for very early ultrasound scans given that variation in fetal size is minimal during the first trimester of pregnancy [138]. In practice, early ultrasounds may only be available for a select group of individuals (*i.e.,* those for whom an early ultrasound is medically indicated) [139], and generally have not been obtained in large-scale studies.

Previous studies comparing second trimester ultrasound with LMP found that ultrasound, on average, resulted in lower (younger) gestational age estimates than those derived from LMP [62,63,134,140] and that the discrepancy between estimates was increased with young maternal age, lower education, single marital status, cigarette smoking, nulliparity, non-optimal pre-pregnancy weight, and pre-pregnancy or gestational diabetes [62,63]. Ultrasound also resulted in a higher proportion of preterm births and a lower proportion of postterm births relative to LMP dating. Systematic inaccuracy of gestational age dating could

distort estimated associations between maternal characteristics and adverse pregnancy outcomes derived using gestational age (*e.g.,* preterm birth) and result in outcome misclassification.

We compared estimates of gestational age at birth based on first trimester report of LMP and very early ultrasound to determine whether LMP collected early in pregnancy could accurately date pregnancies and identify predictors of increased discrepancy between gestational age estimates.

5.3.2 Materials and Methods

Study design and population

Right from the Start (RFTS) is an ongoing, community-based prospective cohort study. Women in this analysis were participants in RFTS Phase I, conducted from 2000-2004. Details of site selection and recruitment are described elsewhere [124]. The Institutional Review Boards at the University of North Carolina, University of Tennessee, and the University of Texas approved study protocols; participants gave informed consent.

We recruited women who were early in pregnancy (≤ 12 weeks' gestation) or planning to become pregnant. Pregnant women were enrolled after providing an LMP date and date of their first positive pregnancy test (n=2,514). Women trying to become pregnant were "pre-enrolled" and followed for up to six months with free pregnancy test kits provided; those who conceived were formally enrolled (n=252). In all, 2,766 pregnancies (68 percent of those screened) were enrolled and available for assessment. This analysis includes 1,867 singleton live births with complete baseline interview, LMP (month and day of month) and ultrasound data. We excluded 347 (12.5 percent) pregnancies that ended in a loss, 90 (3.3

percent) pregnancies lost to follow-up, eight (0.3 percent) multi-gestational pregnancies, and 16 (0.6 percent) repeat live births to a RFTS participant. Additional exclusions were made for pregnancies with no or incomplete baseline interview (n=259; 9.4 percent), incomplete LMP date (*n*=18; 0.6 percent), no ultrasound data (*n*=158; 5.7 percent) and missing infant birth date (*n*=3; 0.07 percent). Women retained for analysis were similar to all enrolled participants with respect to maternal age, estimated gestational age at enrollment, and parity, but were slightly more likely to be White and to have completed ≥ 16 years of education.

Data Collection

Self-reported LMP. Information about LMP was obtained during screening and intake telephone interviews, typically at eight weeks' gestation for women pregnant at initial screening and five weeks' gestation for "pre-enrolled" women. Women were informed they might need a calendar to answer certain questions and invited to obtain a calendar for the interview. Women were asked "What was the first day of your last menstrual period?" If necessary, women were prompted to think of an event that happened around the same time as their last period (*e.g.,* a holiday, vacation, or weekend) to facilitate recall. Additional maternal characteristics also were collected by telephone interview.

Early ultrasound. First trimester endovaginal ultrasounds were conducted by clinical sonographers required to have ARDMS® certification, use state-of-the-art equipment as assessed by a study investigator (KH), conduct and document manufacturer recommended machine calibration, and have three or more years experience in pelvic and obstetric diagnostic sonography. In addition, sonographers participated in study-specific training. Measurements of the gestational sac, yolk sac, fetal pole, and fetal heart rate were fully

comparable with those required for clinical pregnancy dating. A still image was reviewed by trained staff prior to entry of ultrasound data, and a 20% quality sample was reviewed by a clinician skilled in first trimester sonography (KH). All ultrasounds were performed at or before 13 weeks' completed gestation (mean= 9, median = 8 weeks).

Birth outcomes. Multiple data sources were used to obtain and confirm live birth outcomes: birth and fetal death records, hospital discharge summaries and prenatal care records and participant self-report. For this analysis, pregnancy outcome information was documented using medical records for 42.9 percent of live births, vital records for 56.8 percent and participant self-report for only 0.4 percent.

Statistical analysis

We compared the distributions of gestational age at birth (in days) from LMP (date of birth – date of LMP) and ultrasound (date of birth – [date of ultrasound – clinical age by ultrasound at assessment]). Difference in days between LMP and ultrasound estimates was calculated (LMP estimate - ultrasound estimate, hereafter referred to as "gestational age difference") and categorized into five groups (<-14, -14 to -8, -7 to +7, +8 to +14 and >+14 days). Positive values indicate that the LMP-based estimate is "older" than the ultrasound-based estimate, and negative values indicate that the LMP-based estimate is "younger" than the ultrasound-based estimate. Mean and standard deviation values for gestational age difference and the proportion of births within categories of gestational age difference were calculated within and compared across strata of maternal and infant characteristics. Women were also stratified by self-reported certainty in LMP date ("very sure", "pretty sure", "somewhat uncertain", or "very uncertain") and pregnancy status ("trying to conceive" and

"already pregnant") at initial screening. The "already pregnant" women were further subdivided into three groups: women who had not used contraceptives in the past year or stopped using contraceptives to become pregnant, women who became pregnant during a gap or break in contraceptive use, and women who got pregnant while using contraception.

Kappa statistics and associated 95 percent confidence intervals were calculated to assess agreement between dating methods for preterm, term and postterm classification. We also calculated the proportion of births discordantly classified as preterm, term or postterm by LMP and ultrasound. Analyses were performed using Stata version 9 (College Station, TX).

5.3.3 Results

The median estimated gestational age at birth was 276 days (39 weeks' gestation) for both dating methods. Compared to LMP, ultrasound-derived gestational age was slightly shorter (mean of 273 versus 274 days), less variable (standard deviation of 14 versus 16 days), and had a narrower range (214 to 307 days versus 207 to 315 days). A slightly higher proportion of births were classified as preterm (<37 weeks' gestation) by LMP than by ultrasound (10.0 versus 8.9 percent). The proportion of births classified as postterm (>41 week's gestation) was notably higher by LMP dating (4.0 versus 0.7 percent).

Gestational age difference was within +/- 7 days for 80.8 percent of women and +/- 30 days for 98.5 percent (Figure 20). The mean difference was 0.8 days (standard deviation = 8.0, median = 0 days) and ranged from -70 to 38 days. LMP-based estimates were somewhat more likely to be higher than ultrasound-based estimates when discrepant (gestational age

difference was zero for 10.5 percent of women, positive for 47.8 percent and negative for 41.7 percent).

Women < 20 years old were more likely to have a discrepancy of > +14 days or between -14 to -8 days than other age groups (Table 54). Low education level (completed high school or less), single marital status, and non-optimal body mass index (BMI) (<18.9 or >29.0 kg/m^2) were also associated with overall increased discrepancy. Non-Hispanic Black women were more likely to have a negative discrepancy (< -8 days) compared to non-Hispanic White women. Conversely, women of Hispanic and other ethnicity were more likely to have a positive discrepancy (≥ +8 days) compared to non-Hispanic White women.

An overall increase in discrepancy was found as self-reported "certainty" in LMP date decreased, particularly for a positive discrepancy > +14 days among women who were only "somewhat sure" or "very uncertain" (Table 54). Women who were planning a pregnancy at initial screening were more likely to have a positive discrepancy and much less likely to have a negative discrepancy than women already pregnant. Among those already pregnant, women who became pregnant during a gap in contraceptive use or due to contraceptive failure had increased discrepancy in both directions.

Low birth weight (LBW) infants (<2500 grams at birth) were more likely to have a positive discrepancy of +8 to +14 days than larger infants (Table 1). The degree of discrepancy between estimates did not vary by maternal smoking, parity, or infant gender. Exclusion of women with a gestational age difference > -30 or < 30 days did not affect the pattern of associations found (results not shown).

Maternal and infant characteristics examined in this analysis are correlated. Therefore, we constructed multi-variable logistic regression models for the log odds of a

gestational age difference ≥ 8 days versus +/- 7 days and a gestational age difference ≤ -8 days versus +/- 7 days to determine whether associations remained after adjustment for other variables. Results of the regression analyses agree with those presented above with the exception of marital status, which was no longer associated with gestational age difference after adjustment (results not shown).

Classification of births as preterm, term, and postterm was concordant for 91.2% of all births (Figure 21). The Kappa coefficient for classification into these three categories was 0.59 (95% Confidence Interval [CI]: 0.54, 0.65), indicating moderate agreement [141]. Agreement for classifying live births as preterm (<37 versus ≥ 37 weeks') was higher (Kappa coefficient = 0.75, 95% CI: 0.70, 0.80). Agreement for classifying live births as postterm (≤ 41 versus > 41 weeks') was very low (Kappa coefficient = 0.05, CI:-0.02, 0.13).

5.3.4 Discussion

Findings from this study suggest that early report of LMP results in accurate dating for the majority of participants. However, LMP tended to slightly overestimate gestational age based upon ultrasound when discrepant (by approximately 1 day, on average) and resulted in a higher proportion of births classified as postterm. Proportions for preterm birth were comparable. Over ninety percent of women were concordantly classified as preterm, term or postterm by LMP and ultrasound.

The degree of difference between LMP and ultrasound-based estimates was greater among young women, non-Hispanic Black and Hispanic women, less educated women, women of non-optimal body weight and low birth weight infants. Difference also increased as maternal certainty in LMP decreased and was greater among women pregnant at initial

screening who became pregnant during a gap in contraceptive use or due to contraceptive failure. Gestational age difference did not vary by maternal smoking, parity or infant gender.

Gestational age misdating can arise from uncertainty in participant recall of LMP, as evidenced by less discrepancy in gestational age estimates among women who indicated they were "very sure" of their LMP compared to women who were less sure. We also found that gestational age difference was lower among women who were planning a pregnancy and presumably tracking their menstrual cycles closely, a finding demonstrated previously [62]. Increased gestational age difference also was found among women of young maternal age, lower education, single marital status and non-optimal body weight, consistent with previous studies [62,63,142]. Women with these characteristics may have greater difficulty recalling LMP in general [142], which would contribute to random error in menstrual dating and account for increases in both positive and negative discrepancies.

Gestational age misdating also results from systematic error. Reported LMP underestimated ultrasound-based gestational age by 8+ days for a greater proportion of young women (< 20 years) compared to other age groups. Early vaginal bleeding, often confused with menses, is more prevalent among young mothers [143]. This biological phenomenon could cause young women to systematically misrepresent their LMP and explain the apparent mismatch between the two dating methods. Furthermore, delayed ovulation, which is more common than early ovulation [144] and believed to be more prevalent among young women and those of non-optimal body weight [145], could explain the systematic overestimation of gestational age based on LMP among these women.

Hispanic women, predominately Mexican American in our study population, were more likely to have a positive gestational age difference compared to Non-Hispanic White

women, suggesting that menstrual dating could result in underestimation of the proportion of Hispanic infants born preterm. In contrast, results of a study examining birth-weight distributions within strata of gestational age by LMP suggested that term Mexican American infants may be misclassified as preterm more often than non-Hispanic Whites, which could, in part, explain the LBW paradox among Mexican American infants [146]. The proportion of Mexican American infants classified as preterm by LMP and ultrasound was similar in our study (11.4 versus 10.8), with moderately high agreement for preterm classification (kappa = 0.74, 95% CI: 0.58, 0.90), but our findings are based on a very small, non-random sample of Mexican American infants (n=176). Additional research is needed to address LMP misdating as a potential source of bias.

Among non-Hispanic Black women, LMP-based gestational age was generally younger than the gestational age resulting from early ultrasound. Given the persistent racial disparity in all adverse birth outcomes between White and Black non-Hispanic women, this could be an important finding from our study. If, on average, Black women's LMP reports' systematically underestimates their infants' actual "developmental" age, some portion of the racial disparity in birth outcomes may result from misdating. Verification in a representative sample is needed.

We found increased gestational age difference among LBW infants, predominately in a positive direction. This is consistent with previous studies based on second trimester ultrasound [63,147,148], and may be due to systematic underestimation of gestational age among growth restricted fetuses who are later LBW. However, growth restriction at 8 to 9 weeks' gestation, when ultrasounds predominately were conducted for this study, has not been

previously reported. Further research is needed to address whether first trimester growth restriction is a potential source of bias in very early ultrasound assessment of gestational age.

Maternal smoking and infant sex were not associated with increased positive gestational age difference, unlike previous studies predominantly based on second trimester ultrasounds [62,63,136]. However, differences in crown-rump length measurements have not been found by infant gender at ultrasound assessments conducted during the first trimester of pregnancy [149,150]. This may explain why we did not find evidence for systematic underestimation of gestational age at birth by ultrasound among female fetuses in our study, and similarly, among smokers.

In our study, LMP was collected early in pregnancy (by 12 weeks) and may not accurately reflect errors in menstrual dating that occur when LMP is recalled over a longer period. Therefore, our results may not be generalizable to studies collecting LMP later in pregnancy. Furthermore, participants' care providers were given a copy of the first trimester ultrasound report, which provided them with an earlier (and hence, more accurate) estimate of gestational age according to ultrasound than what is usually available. Clinicians may have been more willing to believe these ultrasounds and let women "misclassified" as postterm by LMP only (*i.e.,* not postterm by ultrasound) continue on in pregnancy. As a result, our study may overstate the excess of births classified as postterm by LMP compared to a more general setting.

Participants in the RFTS study represent a group of women who knew they were pregnant in the first trimester and volunteered to participate in a prospective pregnancy study, and thus, may not be comparable to other study samples or the general population. In a previous report, we compared maternal characteristics of pregnancies enrolled in the RFTS

study to all births identified from vital records in the same geographic location over the same time period [26]. RFTS participants were similar to the general population with respect to age but where more likely to be highly educated (≥ 16 years of education), non-Hispanic White, and nulliparous when compared to the general population.

Gestational age remains an important measurement in reproductive and perinatal research. Findings from our study suggest that menstrual dating, based upon LMP collected early in pregnancy, is a reasonably accurate method for estimating gestational age at birth in studies when first trimester ultrasound is not available. However, LMP tends to overestimate gestational age, on average, and result in a higher proportion of postterm births. Thus, LMP should not be used to date pregnancies in studies directed at examining factors associated with postterm birth. The degree of difference between LMP and ultrasound-based estimates also varies by important maternal and infant characteristics (*e.g.,* maternal race/ethnicity), which should be taken into consideration when designing and interpreting results from a study examining the association between these characteristics and pregnancy outcomes derived using gestational age.

5.3.5 References

Table 54. Difference in LMP and ultrasound-based estimates of gestational age at birth by selected maternal and infant characteristics, live births (n=1,867) to participants in the RFTS study from 2000-2004.

			GA difference (in days): LMP – US estimate					
	N	Mean (SD)	<-14	-14 to -8	± 7	+8 to +14	>+14	*p*-value*
All participants	1,867	0.8 (8.0)	2.0	4.5	80.8	8.6	4.1	
Maternal age								
<20	107	1.7 (12.2)	2.8	10.3	65.4	12.2	9.4	
20-24	426	0.5 (9.8)	2.8	5.6	75.6	11.3	4.7	
25-29	610	1.5 (7.4)	1.5	3.8	81.2	8.7	4.9	<0.001
30-34	528	0.6 (6.4)	2.3	2.8	85.8	6.6	2.5	
≥ 35	196	-0.6 (6)	1.0	5.6	85.7	6.1	1.5	
Race/ethnicity								
Non-Hispanic White	1,109	1.2 (6.5)	1.3	3.4	84.1	8.3	2.9	
Non-Hispanic Black	520	-0.5 (9.7)	3.3	7.7	76.5	7.7	4.8	0.02†
Hispanic	176	1.3 (9.3)	3.4	3.4	75.0	11.9	6.3	
Other	59	2.5 (10.1)	1.7	0	72.9	13.6	11.9	
Missing	3							
Education level								
High school or less	496	0.8 (10.8)	3.2	5.7	73.2	11.9	6.1	
Some college	417	0.6 (7.1)	1.9	4.8	80.6	9.8	2.9	<0.001
4+ years of college	954	0.9 (6.5)	1.5	3.8	84.8	6.4	3.6	
Marital status								
Married	1,298	1.1 (6.9)	1.6	3.4	83.4	8.0	3.5	<0.001
Not married	568	0.1 (10.1)	3.0	7.0	74.8	9.9	5.3	
Missing	1							
Pre-pregnancy BMI (kg/m^2)								
<19.8	192	1.5 (7.6)	0.5	6.8	77.1	9.4	6.3	
19.8-25.9	956	0.8 (7.5)	1.4	4.0	84.0	7.2	3.5	0.03
26.0-29.0	253	0.2 (8.0)	3.6	4.0	80.6	8.3	3.6	
> 29.0	418	0.8 (9.0)	2.9	5.0	76.6	10.8	4.8	
Missing	48							
Certainty of LMP date								
Very sure	1,275	0.5 (7.2)	1.7	3.7	84.2	7.8	2.6	
Pretty sure	367	0.6 (8.7)	2.7	6.8	76.6	9.3	4.6	
Somewhat sure	137	3.1 (11)	2.9	5.1	66.4	13.1	12.4	0.01†
Very uncertain	48	2.1 (12.9)	4.2	8.3	56.3	14.6	16.7	
missing	40							
Pregnancy status at screening								
Trying to conceive	153	3 (6.8)	0	0.7	83.7	9.8	5.9	
Pregnant‡	1,714	0.6 (8.1)	2.2	4.8	80.5	8.5	3.9	
No birth control use	1,236	-0.3 (8.3)	1.7	3.4	82.6	9.3	3	<0.001
Gap/Break in birth control use	323	1.4 (11.4)	4.0	9.3	74.9	6.2	5.6	
Birth control failure	147	0.6 (8.2)	2.0	6.8	76.2	7.5	7.5	
Missing	8							
Infant birth weight (grams)								

<2500	104	0.9 (10.0)	4.8	2.9	74.0	12.5	5.8	0.02
2500-3499	959	1.0 (8.4)	2.2	5.4	77.9	9.9	4.6	
3500-3999	557	0.6 (7.2)	1.4	4.3	84.2	6.6	3.4	
≥ 4000	245	0.2 (7.2)	1.6	2.0	86.9	6.5	2.9	
Missing	2							

* *p* value corresponds to two-sided Pearson Chi-square test for independence of maternal/infant characteristics and categories of gestational age (GA) difference unless otherwise specified.
† *p* value corresponds to two-sided Fisher's Exact test for independence of maternal/infant characteristics and categories of GA difference.
‡ Participants that were pregnant at enrollment were further subdivided into three categories: those who reported they had not used contraceptives in the past year or had stopped using contraceptives to become pregnant, those who reported they became pregnant during a gap or break in contraceptive use, and those who reported they became pregnant due to contraceptive failure.
Abbreviations: BMI = body mass index, GA= gestational age, LMP= last menstrual period, RFTS= Right from the Start, SD= standard deviation, US= ultrasound

Figure 20. Distribution of the number of days difference between estimated gestational age at birth derived from last menstrual period (LMP) and ultrasound (US) among live births (n=1,867) to participants in the *Right From the Start* study from 2000-2004.

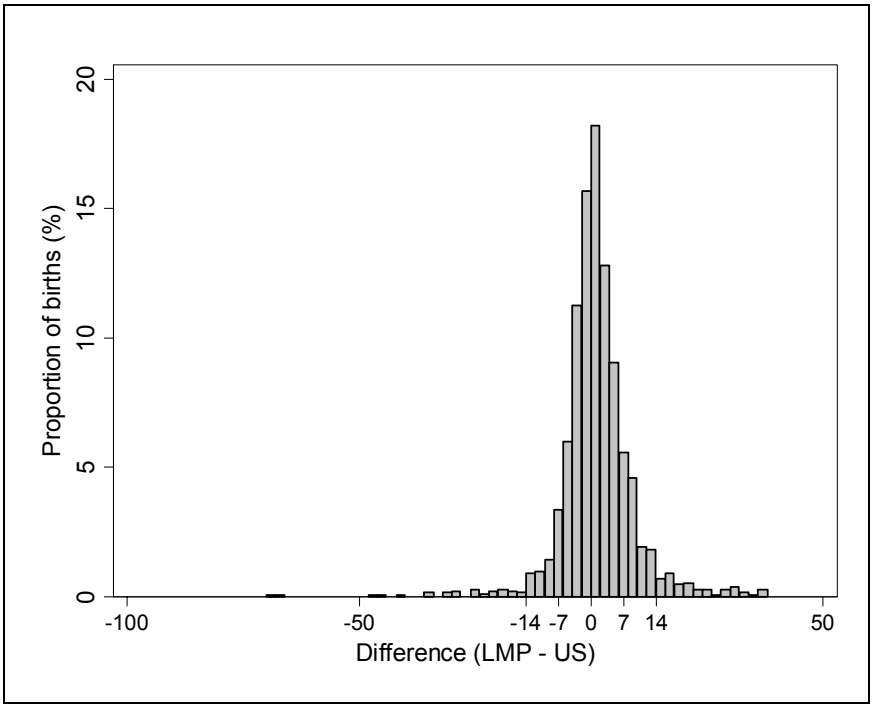
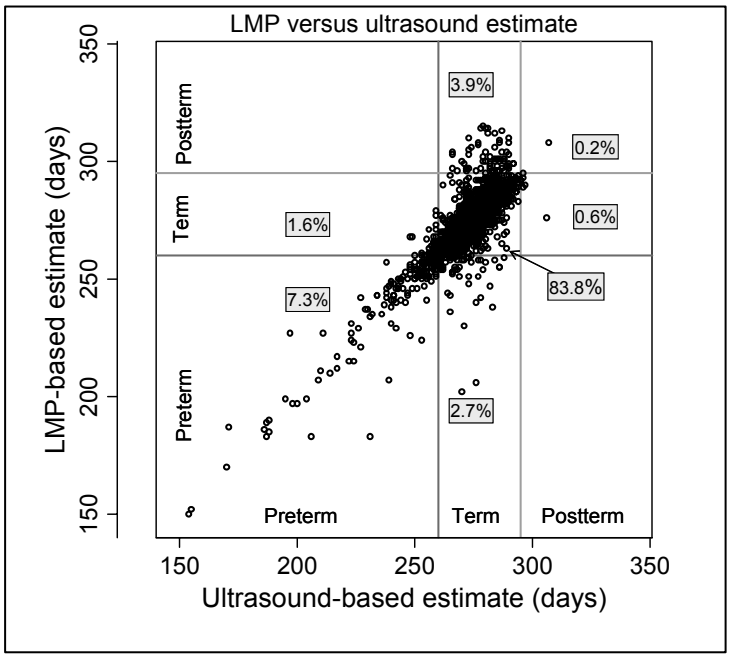


Figure 21. Scatter plot of estimated gestational age at birth derived from last menstrual period (LMP) by estimated gestational age at birth derived from ultrasound among live births (n=1,867) to participants in the *Right From the Start* study from 2000-2004. *Black line*, preterm cut-point (259 days); *striped bars*, postterm cut-point (294 days).



CHAPTER 6: DISCUSSION

6.1 Summary of findings

Findings of this study do not suggest an adverse effect of total trihalomethane (TTHM) or the sum of five haloacetic acids (HAA5) on fetal growth at residential concentrations below the current regulatory standards. In addition, no association was found with estimated personal exposure to TTHM and HAA5 or with TOX exposure. An increased probability of delivering an SGA infant was found when comparing women with average third trimester TTHM residential concentrations ≥ 80 micrograms/liter to women with average levels < 80 micrograms/liter, but few women experienced average TTHM levels that high. Findings were similar for site-specific analyses of aggregate DBP measures and fetal growth.

Findings for site-specific analyses of individual trihalomethanes (THMs) and haloacetic acids (HAAs) were unclear. Results from maximum likelihood estimation (MLE) analyses restricted to the chlorinated DBP site suggest that brominated TTHMs may be associated with increased risk of delivering an SGA infant. Conversely, MLE results from the brominated DBP site suggest that chlorinated HAAs may be associated with both increased risk of SGA and decreased mean birth weight among term births. However, results of the Bayesian analyses indicated that a null or protective effect for each of the individual DBPs on fetal growth restriction is still probable given our prior assumptions and the data at hand, as all 95% credible limits included the null value. Therefore, study results do not

provide strong support that any particular DBP (or set of DBPs) is associated with fetal growth restriction.

Finally, results of our study clearly suggest that the risk of preterm birth is not increased with exposure to high levels of TTHM or HAA5. Our study provides additional support to recent findings suggesting that high levels of TTHM exposure during pregnancy may in fact be related to decreased risk of preterm birth. We also found that the delay in timing of birth associated with high DBP exposure continues through the "moderately preterm" and "term" period of gestation (33-40 weeks' gestation).

6.2 Strengths and limitations

6.2.1 Prospective collection of DBP measurements

The greatest strength of this study is the marked improvement in exposure assessment compared to previous studies. The *Right from the start* (RFTS) study collected information on weekly (or biweekly) residential concentrations of a wide variety of individual THMs and HAAs, including four HAAs that are not regulated by the US Environmental Protection Agency (EPA). Furthermore, measurements were validated to represent DBP concentrations in tap water reaching participants' home. No other study to date has had access to such detailed and comprehensive information on residential DBP exposure information as that provided by the RFTS study. None-the-less, measured residential DBP concentrations are only applicable to locations within study sites. A small portion of RFTS participants (approximately 8%) worked outside of their respective study sight, in which case DBP measurements are not available to directly estimate exposure from water consumed at work, which could have resulted in exposure misclassification. Furthermore, despite the relatively

high frequency of water sampling in RFTS, there is still the potential for unmeasured variability in DBP concentrations within a water system over a week period, which could also contribute to exposure misclassification.

6.2.2 Selection of study sites

The inclusion of three different study sites with different exposure profiles is both a strength and a limitation of this study. By design, a range of reliable DBP measures (high/low, chlorinated/brominated) was available that has never before been assembled for a study of DBPs and reproductive health. However, there are also substantial differences in the underlying population characteristics of the study sites. Women who participated from each site have different demographic profiles and show overall differences in the proportion of births born small-for-gestational-age (SGA), the proportion of infants born preterm, and mean birth weight. To control for potential confounding between study sites, major risk factors for adverse birth outcomes that varied in distribution between sites were adjusted for and site-specific analysis were performed to confirm that the pattern of results between DBPs and adverse birth outcomes were similar across study sites. However, residual confounding by unmeasured risk factors (*e.g.,* unknown environmental exposures or social influences) cannot be dismissed.

6.2.3 Estimation of personal DBP exposure

A major strength of this study is the combination of data on residential DBP concentrations with individual-level information on water consumption, bathing and showering to estimate participants' personal DBP exposure. No other study of fetal growth

or duration of gestation to date has had access to such extensive data on individual water use and exposure. At the same time, it is important to acknowledge that information on water consumption and use was collected by interview and is subject to the usual concerns about the accuracy of self-reported information on exposure in a prospective study. The potential for pregnancy health-related distortion of personal exposure measurement (*e.g.,* whether factors related to pregnancy-health, such as nausea, might influence how much tap water a woman consumes during the first trimester) must also be considered [151].

An additional concern is that the method for estimation of personal DBP exposure used in this study does not account for exposure that occurs through swimming, washing dishes and clothes, bathing children and other activities such as washing hands and flushing the toilet, nor does it account for differences in inhalation exposure influenced by home ventilation or differential metabolism of DBPs. Incorporating all of these factors into exposure assessment would be extremely difficult, as exposure pathways are very complex, and toxicokinetic and toxicodynamic studies of DBP exposure are limited. Nonetheless, failure to incorporate these factors into exposure estimation may result in exposure misclassification. Ultimately, findings for personal DBP metrics were similar to the findings for residential DBP concentrations in this study. This is likely because the drastic contrast in residential DBP concentrations between study sites contributed more to personal exposure variability than differences in individual water use habits.

6.2.4 Prospective follow-up of participants

A major strength of this study is the prospective design with individual follow-up of pregnancies to determine pregnancy outcomes. Previous studies have relied on information

provided in vital records to estimate gestational age and classify infants as SGA. In this study, information on maternal age, race/ethnicity and parity and self-reported last menstrual period (LMP) was collected directly from participants early in pregnancy (when recall is likely more accurate). Furthermore, first trimester ultrasounds were conducted and available to adjust LMP estimates of gestational age that were more than seven days different from the ultrasound estimate. As a result, estimation of gestational age at delivery and information on maternal characteristics for SGA classification should be very accurate in this study.

The benefits of prospective follow-up did come with some costs. Unlike previous studies which used vital records, and thus are population-based, this study population represents a group of women who knew they were pregnant in the first trimester and volunteered to participate in a prospective pregnancy study. Maternal characteristics of pregnancies enrolled in the RFTS study were compared to all births identified from vital records in the same geographic location over the same time period in a previous report. RFTS participants were similar to the general population with respect to age but where more likely to be highly educated (≥ 16 years of education), non-Hispanic White, and nulliparous when compared to the general population[26]. In addition, the sample size of our study was considerably lower than most previous studies, which ultimately resulted in low precision, particularly when stratifying by study site. Similarly, low power for detecting effect estimates of a magnitude within the range found in previous studies was expected given the results of preliminary power calculations. Low power may have contributed to the predominately-null findings from analyses of aggregate DBP measures and fetal growth outcomes.

6.2.5 Assessment of fetal growth restriction

A limitation of this study was the inability to directly identify infants that were growth restricted. Fetal growth restriction describes a decrease in fetal growth rate that prevents an infant from reaching his/her growth potential at a given age. We used SGA as a surrogate for fetal growth restriction because it is used conventionally to identify more severe growth restriction in epidemiological research and has been examined in previous DBP studies. However, not all infants that are "small" at birth are growth restricted and vice versa. Heterogeneity among births identified as SGA could lead to attenuation of estimated effects, so researchers often restrict SGA analyses to term infants to obtain a "cleaner" group of infants to assess fetal growth restriction. We found similar results when we restricted analyses to infants born at ≥ 37 weeks' completed gestation.

6.2.6 Use of Bayesian analytical methods

A final strength of this study is the use of Bayesian analytical techniques to examine individual DBP exposures simultaneously. The mechanism by which DBP exposure may lead to reduced fetal growth is not well understood [7]. While previous epidemiological studies have linked TTHM exposure with adverse pregnancy outcomes, it is unclear whether a specific constituent of TTHM (*e.g.,* bromodichloromethane) is biologically active, or alternatively, TTHM is simply serving as a marker for another drinking water contaminant (*e.g.,* bromoacetic acid). Because individual THM and HAA levels are highly correlated, modeling each exposure in a separate risk model could lead to spurious associations due to confounding by other correlated DBPs, but adjustment for multiple DBP exposures in a single model using standard maximum likelihood estimation (MLE) may fail to provide

plausible results. By using Bayesian analytic techniques, the highly correlated DBP exposures could be modeled simultaneously in a single model, minimizing concern over confounding by other DBPs. In addition, prior distributions were specified to allow "borrowing" of information across sets of DBPs of the same class and bromination status. Use of this method increases confidence that no strong associations with fetal growth exist in this study.

6.3 Public health implications

In 1974, the Safe Drinking Water Act (SDWA) was passed authorizing the USEPA to set and enforce safe drinking water standards. Chloroform was first discovered in chlorinated drinking water that same year. In 1996, amendments were made to the SDWA requiring EPA to develop rules to balance the risks between microbial pathogens and DBPs. Clearly, disinfection of drinking water is necessary to control transmission of harmful waterborne diseases and plays a vital role in maintaining a healthy population. However, disinfection of drinking water is not without consequence, as evidenced by the established association between THMs and bladder cancer as well as toxicological and epidemiological data that suggests DBPs may be associated with adverse reproductive outcomes.

Maximum contaminant level (MCL) values for those DBPs currently regulated by the USEPA are derived based upon cancer risk assessments and do not take into account potential adverse reproductive outcomes associated with DBP exposure. There is some concern that current regulations may not fully protect against adverse pregnancy outcomes. Given the long-term consequences of adverse birth outcomes such as spontaneous abortion, birth defects, fetal growth restriction and preterm birth, and the fact that most pregnant

women are exposed to some amount of DBPs during pregnancy, even a small effect of exposure could have a substantial impact on a population level. To that extent, findings of this study suggest that residential concentrations of TTHM and HAA5 below the current regulatory standards are not associated with increases in fetal growth restriction or preterm birth. While increased risk of fetal growth restriction was suggested for average TTHM residential concentrations above 80 micrograms/liter (the US EPA MCL for annual running average TTHM concentrations), very few women experienced TTHM exposure this high.

6.4 Conclusions

This study is the most extensive study conducted to date examining the effects of drinking water DBP exposure during pregnancy on fetal growth and duration of gestation. The exposure and outcome assessment methods herein greatly improve upon those used in previous research in many ways. Given these improvements and the ability to better control for known confounders, I expected to find stronger estimated effects for TTHM exposure than those reported in previous studies given the assumption that TTHM is in fact associated with increased risk of fetal growth restriction or preterm birth. Findings of this study largely do not support such associations.

Taking results from previous studies into consideration, several conclusions about the effects of DBP exposure on pregnancy health can be drawn from this study. The most definitive conclusion is that DBP exposure is not associated with increased risk of preterm birth. As such, additional studies of this particular pregnancy outcome are not warranted. A more tentative conclusion is that the current MCLs for TTHM and HAA5 need not be lowered to insure that regulatory standards are sufficient to protect against fetal growth

restriction and preterm birth, albeit associations with other adverse reproductive outcomes (*e.g.,* birth defects) remain unclear [5,7,8]. Finally, with respect to individual THMs and HAAs, no particular DBPs have been consistently linked to increased risk of fetal growth restriction in this study or prior studies. Therefore, there is little epidemiological evidence to support the hypothesis that HAAs and brominated compounds as a whole are more toxic than THMs or non-brominated compounds when considering effects on fetal growth.

In this study, elevated concentrations of the "uncommon" DBPs at each study site were associated with increased risk of fetal growth restriction. What this particular finding implies is unclear. It is possible that "uncommon" DBPs serve as a marker for other unknown DBPs that were not measured. This highlights perhaps the biggest limitation of this study: over 500 DBP subspecies have been reported in the literature [13] but this study was only able to examine exposure to the chlorinated and brominated THM and HAA compounds. Future studies of drinking water DBPs should make an effort to collect data on newly emerging DBPs (*e.g.,* iodated DBPs, haloacetamides, halonitromethanes), which may be considerably more toxic than the DBPs currently regulated. Along those same lines, TOX was not associated with fetal growth restriction or preterm birth, suggesting that this aggregate DBP measure does not provide additional information about water quality beyond the aggregate DBP measures currently regulated (TTHM and HAA5). Finally, although the ability to estimate personal DBP exposure was a major strength of this study, residential concentrations were the predominate determinant in ranking women into those with "high", "moderate", and "low" personal exposure given the wide range in DBP concentrations across study sites. Future studies should consider the range of residential DBP concentrations their proposed study is expected to cover when determining how much effort to put into collecting

individual information on water use and consumption versus recruiting a larger, more representative group of women and/or conducting a more detailed assessment of water quality (*e.g.,* collect data on newly emerging DBP).

APPENDIX 1: WATER SAMPLING AND ANALYTIC METHODOLOGY

The following text was abstracted from the AWWARF technical report entitled "Drinking Water Disinfection By-Products and Pregnancy loss" prepared by Savitz et al. (2005) (Chapter 2, pp. 20-22). Specific sections abstracted include "Water Sampling Methodology" (pp. 20-22) and "Analytic Methodology" (pp. 22-23) and "Quality Assurance and Control" (pp. 23-24).

"WATER SAMPLING METHODOLOGY

Weekly samples were collected at the representative locations for THM, HAA, and TOX analysis. Residual chlorine concentrations and temperature were also measured at the time of DBP sample collection. Periodically samples were collected at several points in the distribution system to verify that the sampling locations had THM, HAA, and TOX concentrations that were representative of the system on that day. Additionally, an intensive short-term sampling program was carried out at the sampling location on several occasions to characterize temporal variability in DBP levels. Samples were collected every 6 hours for 5 consecutive days and analyzed for THM, HAAs, and TOX.

For one month each year (March), the Site 1 utility switched from combined chlorine to free chlorine to control potential microbial regrowth and biofilm problems. During the one-month conversion, samples for DBP analysis were collected weekly at up to 10 locations in the distribution system to account for the anticipated spatial variation in DBP levels. The Site 3 utility also converted to free chlorine for a period of several weeks during October 2003. Again, to account for the anticipated spatial variation in DBP levels, samples were collected weekly at a number of locations in the distribution system including the representative sample location.

Sample collection was performed by field personnel in accordance with a specified protocol. Sample collection vials were washed and labeled, and preservatives appropriate for the target analyte groups added prior to shipment to each of the three sites. Forty-milliliter clear glass VOA screw cap sample vials were used for all THM and HAA sampling events, while 250 mL amber glass screw cap bottles were used to collect samples for TOX analysis. Specific reagents were added to the clean vials and bottles prior to shipment to the sample collection sites. Approximately 20 mg of granular ammonium sulfate (Mallinckrodt, Paris, Ky.) was added as a chlorine-quenching agent for both the THM and HAA analyses. Approximately 0.7 g of phosphate buffer was also added to the THM vials to standardize the pH of all samples to be between 4.8 and 5.5. 50 μL of an 80 mg/liter aqueous solution of sodium azide (Aldrich, Milwaukee, Wis.) was added to HAA sample vials to inhibit microbial growth. One hundred sixty microliers (160 μL) of a 40 mg/mL aqueous solution of

sodium sulfite (Mallinckrodt Baker, Phillipsburg, N.J.) was added to each TOX sample bottle as a dechlorinating agent.

Identification labels were placed on all sample bottles. The labels were marked with the sampling location, target analyte, and reagents added. Spaces were provided on each label for the sampler to provide the date, time, and their initials. The vials were packed in ESS FoamPac and bubble wrap packing material and placed in the coolers with ice packs. Chain of Custody documentation and return overnight shipping labels were also included in each cooler. At the University of North Carolina (UNC), records were kept in a status spreadsheet which included cells for sampling date, target analyte, outgoing shipment date, date received back at UNC, extraction date, instrument analysis date, quantification date, and quality control review status.

The weekly THM and HAA samples were collected in quadruplicate in order to provide duplicate samples for analysis and duplicate samples to be used for matrix spike analyses. Additionally, one THM and one HAA field blank was supplied for each weekly sampling event at Sites 1 and 3; these vials were prepared with quenching agents and preservatives in the same manner as the sample vials. For Site 2, one travel blank was prepared for each sampling event to monitor possible contamination of the samples as they traveled from the laboratory to the field and back. Single TOX samples were collected because of time limitations associated with this analysis and the need to have all samples analyzed within a 14-day holding time limit.

Samples were collected near mid-day on Thursday at Site 1, Tuesday at Site 2, and Wednesday at Site 3, from a cold water tap that had been run for at least five minutes prior to sample collection. The vials were filled completely to eliminate headspace. The date and time were recorded on each vial and on the separate chain of custody document which was also used to record temperature and free and total chlorine residuals which were measured with a Hach (Loveland, Colo.) chlorine test kit pocket colorimeter. Sample bottles were re-packed in the cooler with the same packaging in which they arrived. The samples were returned by overnight delivery to the Drinking Water Research Center laboratories of UNC where they were inspected and stored in a refrigerator at 4°C."

"ANALYTICAL METHODOLOGY

THM and TOX samples were analyzed within a 14-day holding time of the sample collection date. HAA samples were analyzed within a 21-day holding time. HAA and THM extracts were analyzed using a 5890 series II gas chromatograph (Agilent Technologies, Palo Alto, Calif.) equipped with an electron capture detector (ECD). For both analyses, ultra high purity helium was used as a carrier gas (1.0–1.5 mL/min) and ultra high purity nitrogen (50 mL/min) was employed as a make-up gas.

THM Analysis

A modified version of Environmental Protection Agency (EPA) Method 551.1 (U.S. EPA 1995a) was utilized to extract each of the THM4 species from the aqueous samples. The process employed a liquid-liquid extraction of salted-out and pH-adjusted 20 mL aqueous samples with 4 mL of methyl *tert*-butyl ether (MtBE) containing internal standard (1, 2-

dibromopropane). Two microliters (2.0 μL) of the THM4 extract were injected into the gas chromatograph (GC). The injection port was maintained at 150°C and the detector at 300°C. The initial column oven temperature (35°C) was held 10 minutes and then raised from 35 to 150°C at 10°C/min. The temperature was again ramped from 150°C to 250°C at 25°C/min and held for 11 minutes. The total THM run-time was 36.5 minutes. Linear calibration for each THM species was in the range 1.0–150 μg/liter. The acceptable relative percent difference (RPD) for THM analysis duplicates was < 10% and the matrix spike recovery had to be in the range 80–120%. Any samples not meeting these criteria were flagged and examined further for analytical or instrumentation errors.

HAA Analysis

The method used for extraction of all nine HAA species was developed by Brophy et al. (2000) and based upon EPA method 552 (US EPA 1995b) and Standard Method 6251B (APHA 1998). This method requires acidification to pH < 2 of 20 mL aqueous samples to which a surrogate recovery standard (2,3-dibromopropionic acid) was previously added. This is followed by liquid-liquid extraction of the protonated acids using MtBE. The HAAs partition from the ionized aqueous environment into the organic solvent which, after separation, is removed, placed into 2 mL volumetric flasks, and subsequently methylated by previously generated diazomethane. After reacting for 15 minutes at 4°C, silicic acid n-hydrate powder is added to quench the residual diazomethane. The resulting methyl esters are transferred in the organic solvent to glass GC autosampler vials and then analyzed by GC-ECD. One microliter (1.0 μL) of the HAA extract was injected into the GC. The injection port was maintained at 180°C and the detector at 300°C. The initial oven temperature (37°C) was held 21 minutes and then raised from 37°C to 136°C at 5°C/min and held 3 minutes. The temperature was again ramped from 136°C to 250°C at 20°/min and held for 3 minutes. The total HAA run-time was 52.5 minutes.

The coefficient of variation (%CV) was calculated for the surrogate area counts of all analytical samples. The practical quantitation limit for all nine HAAs was 2.0 μg/liter, and the maximum calibration standard utilized was 150 μg/liter. Analysis and quantification of the calibration standards and aqueous samples was based on replicate precision of duplicate samples having a relative percent difference of less than 25%.

TOX Analysis

TOX analysis was performed using a model AD-2000 Adsorption Module and TOX Analyzer (Tekmar Dohrmann, Cincinnati, Ohio). Samples of 250 mL were acidified to pH < 2 with 2 mL of concentrated sulfuric acid (H_2SO_4). Samples were then loaded into an adsorption module and dispensed through two granular activated carbon columns (top and bottom) and subsequently rinsed with 2 mL of potassium nitrate (500 g/liter in laboratory grade water) to remove retained inorganic chloride. The carbon was then combusted at 850°C to volatilize organic halogens which were then analyzed by micro-coulometric detection. Preceding and following each batch of samples, a “nitrate blank” was also analyzed to determine the contribution of background organic halogen from the reagents, carbon, and carrier gases. Each blank was a single, clean column that was rinsed with 2 mL of potassium nitrate.

TOX results and breakthrough percentages are calculated for the combustion of top and bottom columns of samples based on sample results and nitrate blank values reported by the instrument data output using the following formulae (Equations 1 and 2):

$$\text{TOX } (\mu g\ Cl/liter) = \frac{(OX\ top\ column + OX\ bottom\ column) - 2*OX\ blank}{Volume\ (ml)\ of\ sample\ absorbed} \quad (1)$$

$$\text{Breakthrough } (\%) = \frac{(OX\ bottom - OX\ blank)*100}{[(OX\ top + OX\ bottom) - 2*OX\ blank]} \quad (2)$$

OX = organic halogen in μg Cl
OX blank = average of analysis of two columns

If breakthrough exceeded 10% the samples were re-analyzed within their 14-day holding time. The organic halide analyzer was checked for recovery (cell check) and the combustion performance (combustion check) prior to analysis of each sample batch ($\leq$ 6 samples). If the sodium chloride (200 ng/μL) cell check (5 μL) and the 2,4,6-trichlorophenol (500 ng/liter) combustion check (5 μL) recoveries obtained ranged between 90–110% the system was considered to be effective in the determination of the TOX content of the samples. To further evaluate the system performance, a check standard or duplicate sample was analyzed as one of the six samples in each batch.

Residual Disinfectants

Free and total chlorine levels in the water were measured using a colorimetric test kit (Hach Chemical, Loveland, Colo.). Before each sample, the colorimeter was zeroed using laboratory grade water, and the sample cell rinsed with the sample. The colorimeter reads in concentration units (mg/liter). Water with residual chlorine above the range of the colorimeter was diluted with laboratory grade water (LGW) and concentrations corrected accordingly."

"QUALITY ASSURANCE AND CONTROL

Calibration standards were prepared in LGW. Seven THM and six HAA working dilutions of standard stock solutions were utilized to cover the expected range of concentrations in samples. The calibration standards were extracted and analyzed along with the samples, using the same batch of MtBE and internal standard. The target THM and HAA analyte concentrations were measured as peak area responses on chromatograms relative to that of the internal standard. The relative areas from duplicate standards were then plotted against the prepared standard concentrations to prepare a calibration which was used to calculate sample concentrations (μg/liter) as a function of relative areas. Samples below the practical quantitation limits of 2.0 μg/liter for HAA9 and 0.1 μg/liter for THM4 are considered below the limit of quantitation and are not reported. Two or three calibration points were extracted in triplicate so that the third sample served as an analytical check

during GC analysis. The standards were run periodically throughout each analytical batch to monitor possible instrument drift or change in sensitivity that might affect calculations.

The internal standard and two stock calibration standards were checked for contamination and degradation prior to each THM4 extraction. An aliquot of extracting solvent, MtBE with internal standard, as well as two calibration point check standards were prepared, analyzed, and compared to the original check standard concentrations (made each time a stock solution was prepared). The stock solutions were re-made prior to extraction if any of the analyte concentrations deviated by more than 20% from the original detector responses obtained when the standards had been freshly prepared.

Matrix spike samples were used in THM and HAA analyses to document any method bias in a given sample matrix. Matrix spikes were created by spiking samples, in duplicate, with a known concentration of the target analytes prior to extraction.

Travel blanks or field blanks accompanied all samples throughout the sampling process in order to monitor possible contamination of the samples as they traveled from the laboratory to the sample site and back. Travel blanks were filled, prior to shipping, with LGW according to the water collection procedure described above. Field blanks were opened at the sample collection site and filled, under the same guidelines, with LGW provided in an amber bottle. Travel blanks were left unopened in the cooler.

An excel macro was created and utilized for most of the HAA9 and THM4 analyses described in this report. The chromatograms were collectively re-processed using revision A.06 HP ChemStation (Hewlett-Packard, Palo Alto, Calif.) software and then the retention time, area, and height of each analyte's peak exported into Excel files. Sample concentrations were calculated based on Excel-automated linear regression of the calibration curve and interpreted under standard operating procedure guidelines. Any duplicate sample relative areas that differed by greater than 20% or were not consistent with other observations were flagged or eliminated.

After the THM, HAA, and TOX concentrations had been measured and interpreted in accordance with standard operating procedures, they were submitted to the project supervisor for quality assurance and quality control review. This process involved further examination of the concentrations detected for feasibility in light of previously detected concentrations at each site. Also, at this point, any shifts in speciation were noted for review, as well as any inconsistencies among THM and HAA measurements for a given sampling event. The flagged results were re-addressed by the analysts for possible errors in the extraction, integration, or quantification processes. Unreasonable inconsistencies that could not be resolved resulted in the elimination of that particular sampling event from the results reported, but this occurred very infrequently in this study. For statistical interpretation of data, analytes that were below the quantifiable limit of detection were treated as zero values even though on occasion chromatographic peaks were observed for these analytes."

APPENDIX 2: CONVERSION FACTORS TO ADJUST RESIDENTIAL DBP CONCENTRATIONS FOR HEATING AND FILTRATION

	Thermal treatment (boiling)[a]		Filtration[b]	
	Chloraminated water	Chlorinated water	POU filter	Pitcher
Trihalomethanes (μg/liter)				
chloroform	0.25	0.66	0.00	0.60
BDCM	0.25	0.19	0.00	0.60
DBCM	0.30	0.18	0.00	0.60
Bromoform	0.40	0.24	0.00	0.60
Haloacetic acids (μg/liter)				
CAA	0.91[c]	1.15	0.92	0.87
BCAA	1.4	1.51	0.41	0.67
DCAA	0.91	1.59	0.55	0.70
BAA	0.93[c]	1.72[c]	0.58	0.67
TCAA	0.91	100.0	0.36	0.65
DBAA	0.93	1.72	0.33	0.66
BDCAA	0.47	0.43	0.19	0.47
DBCAA	0.00	0.00	0.16	0.42
TBAA	0.68	100.0[c]	0.09	0.35

[a]Thermal treatment conversion factors were obtained from Krasner & Wright (2005) (107) unless otherwise noted
[b]Filtration conversion factors were obtained from Savitz et al. (2005) (25)
[c]Thermal treatment conversion factor were not available from Krasner and Wright (2005) (107), so the conversion factor of the most closely related chemical structure was substituted
Abbreviations: TTHM=total trihalomethanes, BDCM=bromodichloromethane, DBCM= dibromochloromethane, THM-Br = sum of all brominated trihalomethanes, HAA5= sum of five regulated haloacetic acids, HAA9= sum of all haloacetic acids, CAA= chloroacetic acid, BCAA= bromochloroacetic acid, DCAA= dichloroacetic acid, TCAA= trichloroacetic acid, BAA= bromoacetic acid, DBAA= dibromoacetic acid, BDCAA= bromodichloroacetic acid, DBCAA= dibromochloroacetic acid, POU=point-of-use

APPENDIX 3: RIGHT FROM THE START BASELINE QUESTIONNAIRE

The attached questionnaire sequence ("Section D Water Exposure", pp. 24-35) was abstracted from the "Baseline Questionnaire" prepared by David Savitz and colleagues for the Right from the Start (RFTS) study funded by AWWARF (CATI Version 2, October 25, 2001- text updated to match CATI on December 16, 2002).

Section D Water exposure

The next set of questions is about your use of water for drinking, cooking, showering and cleaning. Water use in pregnancy and its affect on pregnancy has not yet been studied thoroughly. This is, therefore, an area that we would like to explore in some detail. To do this, I'm first going to ask about the places you have lived in the past four months.

D1a. Do you currently live at *[address from screening interview]***?**
yes→ *skip to D2.* no don't know/refused

D1b. Please tell me the street address, city and state [where you currently live/of your next most recent residence]. *[If she doesn't give us her address, we will not be able to mail her check to her.]*
Don't know

D1c. Would you tell me the city you currently live in?

D2. Have you lived at this residence for more than 4 months?
yes → *to D4 if D1a. is no*
yes → *to D6 if D1a is yes*
no

D3. When did you move to this address?
month/day/year

D4. [Is/was] the source of your tap water at _____ *[street address]***, that is the water that comes out of your faucets, from a private well or from the public water supplier [your town or city]?**
If D2=yes, → *D6.*

D5. How many addresses other than your current address have you lived at since [date 4 months ago]? *[only her primary residences ie. where she spends*

most of her time. No vacation spots unless she spends a part of the year at this residence at which time it is her primary residence.]
_____ # addresses

Ask D1b., D3, and D4 for each additional address where the woman has lived in the last 4 months.

	Residence #1	**Residence #2**	**Residence #3**
D1a.	yes →skip to D2. no		
D1b. Address	Street: Apt. or lot#. City State Zip code	Street: Apt. or lot#. City State Zip code	Street: Apt. or lot#. City State Zip code
D2.	Yes → D4.if D1a. = no Yes → D6. if D1a = yes No	yes no	yes no
D3.	_ _ /_ _/_ _ mm/dy/yr	_ _ /_ _/_ _ mm/dy/yr	_ _ /_ _/_ _ mm/dy/yr
D4.	private well city/town	private well city/town	private well city/town

D6. For the following questions about water use, please think about what you drank over the past week when answering what you typically drink in a day. Was this past week a typical week for you, meaning that you weren't on vacation or there wasn't anything unusual that would affect your water use? *[auto fill from Ca., if no just remind respondent to think of a typical week and if yes skip this question]*

Yes → For the following questions about water use, please think about what you drank over the past week when answering what you typically drink in a day.
No → A quick reminder, since last week was not typical for you, for all the following questions please think about a *different* week that you would consider a *more* typical week for you.

Total cold tap water use[home and work]

Now, I'm going to ask you questions about how much cold tap water you typically drink each day. For these questions, include both filtered and unfiltered water, from your home and work place *[if she works]*. Also include all cold drinks made from that tap water such as powdered drinks. Do not include bottled or canned drinks.
[interviewer notes: include water from the tap, refrigerator spigot or refrigerated water fountain. Cold drinks include instant iced tea but not brewed, and drinks from concentrate. No bottled water, no sodas, no canned or bottled juices. Hot water from the tap or from a hot shot should be included in the 'cold water' drinks.]

D7a.	**How many glasses of tap water, including cold drinks made with tap water, do you usually drink per day?**	__ # of glasses per day → *if 0 skip to D7c.* ____<1 per day → *D7c.* Don't know/refused → *to D7c*
D7b.	**Are those glasses usually small like a juice glass, about 4-10oz; medium like a water glass, about 12-20; or large like a giant size drink at the movies/Fast food, about 22-34oz?**	Sm Med Lg Other: _____ Don't know/refused
D7c.	**Over the past four months, have you changed the amount of tap water that you drink by more than two glasses a day?**	Yes No → *skip to D8a.* DK/refused → to D8a.
D7d.	**Before you changed, how many glasses of tap water did you usually drink per day?**	_____ # of glasses per day
D7e.	**When did you change the amount of tap water you drink?**	month: ____ day: _____ *[if doesn't remember day ask D7f.]* year: _____ ❑ doesn't remember/ refused
D7f.	**Do you remember what week in [month] that was, the first, second, third, fourth or fifth?**	_____1st ____2nd ____ 3rd _____4th _____5th ❑ doesn't remember/ refused

Total hot tap water use[home and work]

Next, I'm going to ask you questions about how many hot drinks made with tap water you typically drink each day. For these questions, include drinks made with tap water from your home and your work [if she works]. *[Hot water means that she boiled the water on the stove or in a microwave to get it hot. Hot water from the tap or from a hot shot should be included in the 'cold water' drinks.]*

D8a.	**How many cups of hot drinks made from tap water, such as coffee, tea including brewed iced tea, hot chocolate or cup-a-soups, do you usually drink per day?**	___ # of cups per day →*if 0 skip to D8c.* __<1 per day → *D8c.* DK/refused → *to D8c.*
D8b.	**Are those cups usually small like a tea cup, about 4-10 oz; medium like a coffee mug, about 12-14oz; or large like an travel mug or oversized coffee mug, about 16-24oz?**	Sm Med Lg Other: specify _____ don't know/refused
D8c.	**Over the past four months, have you changed the amount of hot drinks made with tap water that you drink by more than two cups a day?**	Yes No → *skip to D14a.* Don't know/refused → *to D14a.*

D8d. Before you changed, how many cups of hot drinks made with tap water did you usually drink per day?	____ # of cups per day
D8e. When did you change the amount of hot drinks you drink?	month: ____ day: _____ *[if doesn't remember day ask D8f.]* year: _____ ❑ doesn't remember/ refused
D8f. Do you remember what week in [month] that was, the first, second, third, fourth or fifth?	_____1st ____2nd ____ 3rd _____ 4th _____ 5th ❑ doesn't remember/ refused

→ → *after these questions skip to D14a.* →

[If all her current jobs are located in Raleigh (B4b.), do not ask D9-D13. You should ask D6-D8.]

D9. For the following questions about water use, please think about what you drank over the past week when answering what you typically drink in a day. Was this past week a typical week for you, meaning that you weren't on vacation or there wasn't anything unusual that would affect your water use? *[auto fill from Ca., if no just remind respondent to think of a typical week and if yes skip this question]*

Yes → For the following questions about water use, please think about what you drank over the past week when answering what you typically drink in a day.
No → A quick reminder, since last week was not typical for you, for all the following questions please think about a week that you would consider a typical week for you.

Cold tap water use at work

Now, I'm going to ask you questions about how much cold tap water you typically drink each day at work. For these questions, include both filtered and unfiltered water, from work place. Also include all cold drinks made from that tap water such as powdered drinks. Do not include bottled or canned drinks.
[interviewer notes: include water from the tap, refrigerator spigot or refrigerated water fountain. Cold drinks include instant iced tea but not brewed, and drinks from concentrate. No bottled water, no sodas, no canned or bottled juices. Hot water from the tap or from a hot shot should be included in the 'cold water' drinks.]

D10a. How many glasses of water from your office tap do you usually drink per day?	__ # of glasses per day → *if 0 skip to D10c.* __<1 per day → *D10c.* DK/refused → *to D10c.*
D10b. Are those glasses usually small like a juice glass, about 4-10oz; medium like a water glass, about 12-	Sm Med

20; or large like a giant size drink at the movies/Fast food, about 22-34oz?	Lg Other: specify _____ Don't know/refused
D10c. Over the past four months, have you changed the amount of office tap water that you drink per day by more than two glasses?	Yes No → *skip to D11a* DK/refused → *to D11a.*
D10d. Before you changed, how many glasses of office tap water did you usually drink per day?	_____ # of glasses per day
D10e. When did you change the amount of office tap water you drink?	month: ____ day: _____ *[if doesn't remember day ask D10f.]* year: _____ ❑ doesn't remember/ refused
D10f. Do you remember what week in [month] that was, the first, second, third, fourth or fifth?	_____1st ____2nd ____ 3rd _____ 4th _____ 5th ❑ doesn't remember/ refused

Hot tap water use at work

Next I'm going to ask you questions about how many hot drinks made with tap water from work you typically drink each day. *[Hot water means that she boiled the water on the stove or in a microwave to get it hot. Hot water from the tap or from a hot shot should be included in the 'cold water' drinks.]*

D11a. How many cups of hot drinks made from office tap water, such as coffee, tea including brewed iced tea, hot chocolate or cup-a-soups, do you usually drink each day?	___ # of cups per day → *if 0 skip to D11c.* __<1 per day → *D11c.* DK/refused → *to D11c.*
D11b. Are those cups usually small like a tea cup, about 4-10 oz; medium like a coffee mug, about 12-14oz; or large like an travel mug or oversized coffee mug, about 16-24oz?	Sm Med Lg Other: specify _____ don't know/refused
D11c. Over the past four months, have you changed the amount of hot drinks made with office tap water that you drink by more than two cups a day?	Yes No → *skip to D12a.* DK/refused → *To D12a.*
D11d. Before you changed, how many cups of hot drinks made with tap water did you usually drink each day?	____ # of cups per day
D11e. When did you change the amount of hot drinks you drink?	month: ____ day: _____ *[if doesn't remember day ask D11f.]* year: _____

	❑ doesn't remember/ refused
D11f. Do you remember what week in [month] that was, the first, second, third, fourth or fifth?	_____1st ____2nd ____ 3rd _____ 4th _____ 5th ❑ doesn't remember/ refused

Cold tap water use at home

Now, I'm going to ask you questions about how much cold tap water you typically drink each day at home. For these questions, include both filtered and unfiltered water. Also include all cold drinks made from that tap water such as powdered drinks. If you bring tap water from home to work, or other places, also include that water. Do not include bottled or canned drinks.

[interviewer notes: include water from the tap, refrigerator spigot or refrigerated water fountain. Cold drinks include instant iced tea but not brewed, and drinks from concentrate. No bottled water, no sodas, no canned or bottled juices. Hot water from the tap or from a hot shot should be included in the 'cold water' drinks.]

D12a. How many glasses of water from your home tap do you usually drink per day?	__ # of glasses per day → *if 0 skip to D12c.* __<1 per day→ *D12c.* DK/refused → *to D12c.*
D12b. Are those glasses usually small like a juice glass, about 4-10oz; medium like a water glass, about 12-20; or large like a giant size drink at the movies/Fast food, about 22-34oz?	Sm Med Lg Other: specify _____ Don't know/refused
D12c. Over the past four months, have you changed the amount of home tap water that you drink per day by more than two glasses?	Yes No → *skip to D13a* DK/refused → *to D13a.*
D12d. Before you changed, how many glasses of home tap water did you usually drink per day?	_____ # of glasses per day
D12e. When did you change the amount of home tap water you drink?	month: ____ day: _____ *[if doesn't remember day ask D12f.]* year: _____ ❑ doesn't remember/ refused
D12f. Do you remember what week in [month] that was, the first, second, third, fourth or fifth?	_____1st ____2nd ____ 3rd _____ 4th _____ 5th ❑ doesn't remember/ refused

Hot tap water use at home

The next questions I'm going to ask are about hot drinks made with home tap water. *[Hot water means that she boiled the water on the stove or in a microwave to get it hot. Hot water from the tap or from a hot shot should be included in the 'cold water' drinks.]*

D13a. How many cups of hot drinks made from home tap water, such as coffee, tea including brewed iced tea, hot chocolate or cup-a-soups, do you usually drink each day?	___ # of cups per day →if *0 skip to D13c* __<1 per day→ *D13c* DK/ refused → *to D13c.*
D13b. Are those cups usually small like a tea cup, about 4-10 oz; medium like a coffee mug, about 12-14oz; or large like an travel mug or oversized coffee mug, about 16-24oz?	Sm Med Lg Other: specify _____ don't know/refused
D13c. Over the past four months, have you changed the amount of hot drinks made with home tap water that you drink by more than two cups a day?	Yes No → *skip to D14a* DK/refused → *to D14a.*
D13d. Before you changed, how many cups of hot drinks made with tap water did you usually drink each day?	____ # of cups per day
D13e. When did you change the amount of hot drinks you drink?	month: ____ day: _____ *[if doesn't remember day ask D13f.]* year: _____ DK/ refused
D13f. Do you remember what week in [month] that was, the first, second, third, fourth or fifth?	_____1st ____2nd ____ 3rd _____ 4th _____ 5th ❑ doesn't remember/ refused

Bottled water

Now I'm going to ask you some questions about your bottled water use. Try to answer the following questions as closely to what you usually or typically drink in a day. Bottled water includes water that you purchase in bottles or plastic jugs and that you get from any water cooler, but not from a water fountain. Bottled water can include spring water, mineral water, distilled water, or sparkling water such as Quibell, Poland Spring, Perrier, Calistoga, some is flavored. Do not include tonic water, club soda, soda water, seltzer or caffeinated water about which we already asked you earlier.

[She should include Vitamin water and Fruit flavored water (distilled water with citric acid, flavors and electrolytes). Seltzer is different from sparkling water. Sparkling water is usually made with spring water whereas seltzer is usually made with tap water]

D14a. In the past four months, how much of all the water you drink is bottled water, including water used for hot and cold drinks? Is it all or nearly all, most, some, very little or none of the water?

All or nearly all
Most
Some → *skip to D15.*
Very little→ *skip to D15.*
none→ *skip to D15.*
don't know/refused → *skip to D15.*

[if woman says she drinks bottles of water rather than glasses, in Q14b. ask her the number of bottles and in Q14c. ask her the size of the bottle]

D14b. How many glasses/bottles of bottled water do you usually drink per day?	____ # of glasses per day → *if 0 skip to D15.* ____<1 per day → *skip to D15.* Don't know/refused
D14c. Are those glasses usually small like a juice glass, about 4-10oz; medium like a water glass, about 12-20; or large like a giant size drink at the movies/Fast food, about 22-34oz? **OR for Bottles:** **Are those bottles usually small, about 8-12 ounces; medium, about 14-24 ounces; or large, about 26-34 ounces?**	Sm Med Lg Other: specify _____ or small bottle [8-12] medium [14-24] large bottle [26-34] Other: specify _____
D14d. What is the primary brand of bottled water that you usually drink? *[note brand name]*	❑ Brand name _____ ❑ Name of store ____ *[if filling bottle at store]* ❑ No specific brand ❑ don't know/refused

Filtering

[Ask D15-D20a. for each residence in which she has lived during the past 4 months, one residence at a time]

D15. In the past four months, have you, in any way, filtered any of your tap water at _____ *[street address]*?

yes no → *skip to D21a.* don't know/refused

D16. Is the water filtering system at _____ *[street address]*, for the entire house or at specific locations such as a faucet, showerhead, or a pitcher?

entire house
Specific locations → *skip to D18a.*

D17. What is the brand name of the filter you use/used for the entire house?
_____ brand name → *skip to D21a.*

D18a. Do/did you have a filter on your showerhead?
yes no →*skip to D19a.* don't know/refused →*skip to D19a*

D18b. What is/was the brand name of the filter on the showerhead?
_____

D18c. How often do/did you replace the filter?
____# times per month / year

D19a. In the past four months, how much of the tap water you drink/drank at _____ [street address] has been filtered, including water used for hot and cold drinks? Was it _____ *[read choices]?*
All or nearly all
Most
Some → *skip to D20a.*
Very little→ *skip to D20a.*
none→ skip to D20a.
don't know/refused → *skip to D20a.*

D19b. Is the filter you use/used for the water you drink/drank at home, at the faucet, part of the refrigerator, or a filtering pitcher such as Brita or PUR? *[mark all that apply]*
- ❑ Faucet
- ❑ Refrigerator
- ❑ Pitcher
- ❑ Other, Specify

D19c. What brand is/was the filter on the _____? *[check spelling of brand name]*

D19d. How often do you replace the filter in the _____? *[if never code 0]*

	brand name	replacement
❑ faucet ❑ refrigerator ❑ pitcher ❑ other ❑ don't know /refused	_____ brand name _____ brand name _____ brand name _____ brand name	____# times per month / year ____# times per month / year ____# times per month / year ____# times per month / year

D20a. In the past four months, how much of the tap water you use/used for cooking at _____ *[street address]* **has been filtered? Was it _____** *[read choices]?*
All or nearly all
Most
Some
Very little
none
don't know/refused

[Ask D15-D20a. for each of the residences before continuing with D21a.]

D21a. In the past four months, how much of the tap water you drink outside your home has been filtered, including water used for hot and cold drinks? Was it ___ *[read choices]? [interviewer note: 'outside home' would include any place where she drinks a significant amount of her water such as at work, restaurants, friend's home.]*

- ❑ All or nearly all
- ❑ Most
- ❑ Some→ *skip to D22. if D15 is yes; if D15 is no skip to D23a.*
- ❑ Very little→ *skip to D22. if D15 is yes; if D15 is no skip to D23a.*
- ❑ None→ *skip to D22. if D15 is yes; if D15 is no skip to D23a.*
- ❑ don't know/refused → *skip to D22. if D15 is yes; if D15 is no skip to D23a.*

D21b. Is the filter you use for the tap water you drink outside your home, at the faucet, part of a refrigerator, or a filtering pitcher such as Brita or PUR? *[mark all that apply]*

- ❑ Faucet
- ❑ Refrigerator
- ❑ Pitcher
- ❑ Other, Specify

D21c. What brand is the filter in the _____? *[only ask for pitcher or other]*

D21d. How often do you replace the filter in the _____? *[only ask for pitcher or other]*

	brand name	replacement
❑ faucet ❑ refrigerator ❑ pitcher ❑ other ❑ don't know /refused	_____ brand name _____ brand name	____# times per month / year ____# times per month / year

D22. Thinking about the filters you use both at home and outside your home, when replacing any of these filters, how do you decide when to replace it? Is it _____ *[read choices, mark all that apply]***?**

- ❑ based on manufacturer recommendations
- ❑ when the water begins to taste bad
- ❑ when you remember
- ❑ other [specify] _____

Now I'm going to ask you about other uses of water in your home such as for showering, bathing, bathing children, and washing dishes and clothes. Again, think about what you currently do in a typical week.

Showering

D23a. How often do you shower at home?

___ times per day/week/month *[If < 2x per week, skip to D24a.]*
___ < 1x month → *skip to D24a.*

D23b. How many minutes do you usually spend actually in the shower?

_____ # minutes

D23c. How many minutes do you usually spend in the bathroom with the door closed while the shower is running before getting in?

_____ #minutes

D23d. How many minutes do you usually spend in the bathroom with the door closed after you've showered?

_____ # minutes

Bathing

D24a. How often do you take a bath at home, not including showers?

[interviewer note: include if she takes a bath with her children]
___ times per day/week/month *[if < 2x per week, skip to D25a.]*
___ < 1x month→ skip to D25a.

D24b. When you take a bath, how full is the tub: ¼, ½, ¾, or completely full?

[refers to how submerged she is]
¼ ½ ¾ full

D24c. How many minutes do you usually spend in the tub?

_____ # minutes

D24d. How many minutes do you usually spend in the bathroom with the door closed while the bathtub is filling up <u>before</u> getting in?
_____ #minutes

D24e. How many minutes do you usually spend in the bathroom with the door closed <u>after</u> you've bathed?
_____ #minutes

Children

D25a. At home, how often do you bathe infants or small children, those too young to leave alone in the bath tub? *[do not include times when she takes a bath with her children, this should be included in D24a]*
_____ # times per day / per week / per month *[if < 2 bath per week skip to D26a.]*
___ < 1x month *[if < 2 bath per week skip to D26a.]*

D25b. How many minutes per bath do you usually spend bathing children?
____ minutes per bath

D25c. How many minutes do you usually spend in the bathroom with the door closed while the bath is filling <u>before</u> you bathe children?
_____ #minutes

D25d. How many minutes do you usually spend in the bathroom with the door closed <u>after</u> you've bathed children?
_____ # minutes

Dishes

D26a. How often do you typically rinse or wash dishes by hand?
_____ # times per day / week / month *[if less than twice per week → Skip to D27a.]*
___ < 1x month *[if less than twice per week → Skip to D27a.]*

D26b. How much time do you usually spend on each occasion rinsing or washing dishes by hand?
_____ #minutes / hours per occasion

D26c. How often do you use gloves when washing the dishes, all of the time, most of the time, some of the time, or very rarely?
- ❑ All the time
- ❑ Most of the time
- ❑ Some of the time
- ❑ Rarely or never
- ❑ Refused/Don't know

Clothes

D27a. How often do you wash clothing by hand instead of machine?

____ # times per week / month /never *[if < 2x per week → skip to Section E]*
___ < 1x month *[if < 2x per week → skip to Section E]*

D27b. How much time do you usually spend each time you wash clothes by hand?

____ #minutes / hours per occasion

D27c. How often do you use gloves when washing clothing by hand, all of the time, most of the time, some of the time, or very rarely?

- ❑ All the time
- ❑ Most of the time
- ❑ Some of the time
- ❑ Rarely or never
- ❑ Don't know/refused

APPENDIX 4: RIGHT FROM THE START FOLLOW-UP QUESTIONNAIRE

The attached questionnaire sequence ("Section D Water Exposure", pp. 13-19) was abstracted from the "Still pregnant Follow-up Questionnaire" prepared by David Savitz and colleagues for the Right from the Start (RFTS) study funded by AWWARF (CATI Version 2, October 25, 2001- text updated to match CATI on December 16, 2002).

Section D Water exposure

The next questions are about your use of water for drinking, cooking, showering and cleaning. I'm first going to ask about the places you have lived since your first interview on _____ [date].

D1a. **Do you currently live at** _____ *[address(es) from D1. or D2. in first interview]***?**
yes→ skip to D2. no don't know/refused

D1b. **Please tell me the street address, city and state [where you currently live/of your next most recent residence].** *[If she doesn't give us her address, we will not be able to mail her check to her.]*
Don't know

D1c. *[if she doesn't answer D1b.]* **Would you tell me the city you currently live in?**

D2. **Have you lived at this residence since your first interview?**
yes → *if D1a is yes, skip to D6. if B4b is only Raleigh or to D9. if B4b. is* ***not*** *only Raleigh*
if D1a is not yes, continue with D4. When asking additional addresses that we're listed in the baseline, ask D3-D4.
no

D3. **When did you move to this address?**
month/day/year

D4. **[Is/was] the source of your tap water at** _____ *[street address]***, that is the water that comes out of your faucets, from a private well or from the public water supplier [your town or city]?**

D5. **How many addresses other than your current address have you lived at since** _____ *[date of the first interview]***?** *[only her primary residences ie. where she spends most of her time. No vacation spots unless she spends a part of the year at this residence at which time it is her primary residence.]*

_____ # addresses → if 1 or more continue with D1b.

Ask D1b., D3, and D4 for each additional address where the woman has lived in since the first interview.

	Residence #1	Residence #2	Residence #3
D1a.	yes →skip to D2. no		
D1b. Address	Street: Apt. or lot#. City, State, Zip code	Street: Apt. or lot#. City, State, Zip code	Street: Apt. or lot#. City, State, Zip code
D2.	Yes → No	yes no	yes no
D3.	_ _ /_ _/_ _ mm/dy/yr	_ _ /_ _/_ _ mm/dy/yr	_ _ /_ _/_ _ mm/dy/yr
D4.	private well city/town	private well city/town	private well city/town

D6. *[auto fill from Ca., if no just remind respondent to think of a typical week and if yes skip this question]* **Was this past week a typical week for you, meaning that you weren't on vacation or there wasn't anything unusual that would affect your water use?**

Yes → For the following questions about water use, please think about what you drank over the past week when answering what you typically drink in a day.

No → A quick reminder, since last week was not typical for you, for all the following questions please think about a week that you would consider a typical week for you.

Total cold tap water use[home and work]

Now, I'm going to ask you questions about how much cold tap water you typically drink each day. For these questions, include both filtered and unfiltered water, from your home and work place *[if she works]*. Also include all cold drinks made from that tap water such as powdered drinks. However, do not include bottled or canned drinks.

[interviewer notes: include water from the tap, refrigerator spigot or refrigerated water fountain. Cold drinks include instant iced tea but not brewed, and drinks from concentrate. No bottled water, no sodas, no canned or bottled juices. Hot water from the tap or from a hot shot should be included in the 'cold water' drinks.]

D7a.	**How many glasses of tap water, including cold drinks made with tap water, do you usually drink per day?**	__ # of glasses per day → if 0 skip to D8a. <1 per day → skip to D8a. DK/refused → to D8a.
D7b.	**Are those glasses usually small like a juice glass, about 4-10oz; medium like a water glass, about 12-20; or large like a giant size drink at the movies/Fast food, about 22-34oz?**	Sm Med Lg Other: _____ Don't know/refused

Total hot tap water use[home and work]

Next, I'm going to ask you questions about how many hot drinks made with tap water you typically drink each day. For these questions, include drinks made with tap water from your home and your work [if she works]. *[Hot water means that she boiled the water on the stove or in a microwave to get it hot. Hot water from the tap or from a hot shot should be included in the 'cold water' drinks. Water can be filtered and unfiltered.]*

D8a. How many cups of hot drinks made from tap water, such as coffee, tea including brewed iced tea, hot chocolate or cup-a-soups, do you usually drink per day?	___ # of cups per day →if 0 skip to D14a. <1 per day→skip to D14a. DK/refused → to D14a.
D8b. Are those cups usually small like a tea cup, about 4-10 oz; medium like a coffee mug, about 12-14oz; or large like an travel mug or oversized coffee mug, about 16-24oz?	Sm Med Lg Other: specify _____ don't know/refused

D9. *[auto fill from Ca., if no just remind respondent to think of a typical week and if yes skip this question]* **Was this past week a typical week for you, meaning that you weren't on vacation or there wasn't anything unusual that would affect your water use?**

Yes → For the following questions about water use, please think about what you drank over the past week when answering what you typically drink in a day.

No → A quick reminder, since last week was not typical for you, for all the following questions please think about a week that you would consider a typical week for you.

Cold tap water use at work

Now, I'm going to ask you questions about how much cold tap water you typically drink each day at work. For these questions, include both filtered and unfiltered water, from your work place. Also include all cold drinks made from that tap water such as powdered drinks. Do not include bottled or canned drinks.

[interviewer notes: include water from the tap, refrigerator spigot or refrigerated water fountain. Cold drinks include instant iced tea but not brewed, and drinks from concentrate. No bottled water, no sodas, no canned or bottled juices. Hot water from the tap or from a hot shot should be included in the 'cold water' drinks.]

D10a. How many glasses of water from your office tap, including cold drinks made with tap water, do you usually drink per day?	__ # of glasses per day → if 0 skip to D10c. __<1 per day → D10c. DK/refused → to D10c.
D10b. Are those glasses usually small like a juice glass, about 4-10oz; medium like a water glass, about 12-20; or large like a giant size drink at the movies/Fast food, about 22-34oz?	Sm Med Lg Other: specify _____

	Don't know/refused

Hot tap water use at work

Next I'm going to ask you questions about how many hot drinks made with tap water from work you typically drink each day. *[Hot water means that she boiled the water on the stove or in a microwave to get it hot. Hot water from the tap or from a hot shot should be included in the 'cold water' drinks.]*

D11a. How many cups of hot drinks made from office tap water, such as coffee, tea including brewed iced tea, hot chocolate or cup-a-soups, do you usually drink each day?	___ # of cups per day → if 0 skip to D11c. __<1 per day → D11c. DK/refused → to D11c.
D11b. Are those cups usually small like a tea cup, about 4-10 oz; medium like a coffee mug, about 12-14oz; or large like an travel mug or oversized coffee mug, about 16-24oz?	Sm Med Lg Other: specify _____ don't know/refused

Cold tap water use at home

Now, I'm going to ask you questions about how much cold tap water you typically drink each day at home. For these questions, include both filtered and unfiltered water. Also include all cold drinks made from that tap water such as powdered drinks. If you bring tap water from home to work, or other places, also include that water. Do not include bottled or canned drinks.

[interviewer notes: include water from the tap, refrigerator spigot or refrigerated water fountain. Cold drinks include instant iced tea but not brewed, and drinks from concentrate. No bottled water, no sodas, no canned or bottled juices. Hot water from the tap or from a hot shot should be included in the 'cold water' drinks.]

D12a. How many glasses of water from your home tap, including cold drinks made with tap water, do you usually drink per day?	__ # of glasses per day → if 0 skip to D12c. __<1 per day→ D12c. DK/refused → to D12c.
D12b. Are those glasses usually small like a juice glass, about 4-10oz; medium like a water glass, about 12-20; or large like a giant size drink at the movies/Fast food, about 22-34oz?	Sm Med Lg Other: specify _____ Don't know/refused

Hot tap water use at home

The next questions I'm going to ask are about hot drinks made with home tap water. *[Hot water means that she boiled the water on the stove or in a microwave to get it hot. Hot water from the tap or from a hot shot should be included in the 'cold water' drinks.]*

D13a. How many cups of hot drinks made from home tap water, such as coffee, tea including brewed iced tea, hot chocolate or cup-a-soups, do you usually drink each day?	___ # of cups per day →if 0 skip to D13c __<1 per day→ D13c DK/ refused → to D13c.
D13b. Are those cups usually small like a tea cup, about 4-10 oz; medium like a coffee mug, about 12-14oz; or large like an travel mug or oversized coffee mug, about 16-24oz?	Sm Med Lg Other: specify _____ don't know/refused

Bottled water

Now I'm going to ask you some questions about your bottled water use. Try to answer the following questions as closely to what you usually or typically drink in a day. Bottled water includes water that you purchase in bottles or plastic jugs and that you get from any water cooler, but not from a water fountain. Bottled water can include spring water, mineral water, distilled water, or sparkling water such as Quibell, Poland Spring, Perrier, Calistoga, some is flavored. Do not include tonic water, club soda, soda water, seltzer or caffeinated water.

[She should include Vitamin water and Fruit flavored water (distilled water with citric acid, flavors and electrolytes). Seltzer is different from sparkling water. Sparkling water is usually made with spring water whereas seltzer is usually made with tap water]

D14a. Currently, how much of all the water you drink is bottled water, including water used for hot and cold drinks? Is it all or nearly all, most, some, very little or none of the water?

All or nearly all
Most
Some → skip to D23a.
Very little→ skip to D23a.
None→ skip to D23a.
don't know/refused → skip to D23a.

[if woman says she drinks bottles of water rather than glasses, in Q14b. ask her the number of bottles and in Q14c. ask her the size of the bottle]

D14b. How many glasses/bottles of bottled water do you usually drink per day?	____ # of glasses per day → if 0 skip to D23a. <1 per day → skip to D23a. Don't know/refused

D14c. Are those glasses usually small like a juice glass, about 4-10oz; medium like a water glass, about 12-20; or large like a giant size drink at the movies/Fast food, about 22-34oz? *[OR for Bottles:]* **Are those bottles usually small, about 8-12 ounces; medium, about 14-24 ounces; or large, about 26-34 ounces?**	Sm Med Lg Other: specify _____ or small bottle [8-12] medium [14-24] large bottle [26-34] Other: specify _____
D14d. What is the primary brand of bottled water that you usually drink? *[note brand name]*	❑ Brand name _____ ❑ Name of store ____ *[if fills bottle at store]* ❑ No specific brand ❑ don't know/refused

Now I'm going to ask you about other uses of water in your home such as for showering, bathing, bathing children, and washing dishes and clothes. Again, think about what you currently do in a typical week.

Showering

D23a. How often do you shower at home?

___ times per day/week/month *[If < 2x per week, skip to D24a.]*
___ < 1x month → skip to D24a.

D23b. How many minutes do you usually spend actually in the shower?

_____ # minutes

D23c. How many minutes do you usually spend in the bathroom with the door closed while the shower is running before getting in?

_____ #minutes

D23d. How many minutes do you usually spend in the bathroom with the door closed after you've showered?

_____ # minutes

Bathing

D24a. How often do you take a bath at home, not including showers?

[interviewer note: include if she takes a bath with her children]
___ times per day/week/month [if < 2x per week, skip to D25a.]
___ < 1x month→ skip to D25a.

D24b. When you take a bath, how full is the tub: ¼, ½, ¾, or completely full?

[refers to how submerged she is]
¼ ½ ¾ full

D24c. How many minutes do you usually spend in the tub?
_____ # minutes

D24d. How many minutes do you usually spend in the bathroom with the door <u>closed</u> while the bathtub is filling up <u>before</u> getting in?
_____ #minutes

D24e. How many minutes do you usually spend in the bathroom with the door <u>closed</u> <u>after</u> you've bathed?
_____ #minutes

Children

D25a. At home, how often do you bathe infants or small children, those too young to leave alone in the bath tub? *[do not include times when she takes a bath with her children, this should be included in D24a]*
_____ # times per day / per week / per month *[if < 2 bath per week skip to D26a.]*
___ < 1x month *[if < 2 bath per week skip to D26a.]*

D25b. How many minutes per bath do you usually spend bathing children?
____ minutes per bath

D25c. How many minutes do you usually spend in the bathroom with the door <u>closed</u> while the bath is filling <u>before</u> you bathe children?
_____ #minutes

D25d. How many minutes do you usually spend in the bathroom with the door <u>closed</u> <u>after</u> you've bathed children?
_____ # minutes

Dishes

D26a. How often do you typically rinse or wash dishes by hand?
_____ # times per day / week / month *[if less than twice per week → Skip to D27a.]*
___ < 1x month *[if less than twice per week → Skip to D27a.]*

D26b. How much time do you usually spend on each occasion rinsing or washing dishes by hand?
_____ #minutes / hours per occasion

D26c. How often do you use gloves when washing the dishes, all of the time, most of the time, some of the time, or very rarely?
- ❑ All the time
- ❑ Most of the time
- ❑ Some of the time
- ❑ Rarely or never
- ❑ Refused/Don't know

Clothes

D27a. How often do you wash clothing by hand instead of machine?

____ # times per week / month /never *[if < 2x per week → skip to Section E]*

___ < 1x month *[if < 2x per week → skip to Section E]*

D27b. How much time do you usually spend each time you wash clothes by hand?

____ #minutes / hours per occasion

D27c. How often do you use gloves when washing clothing by hand, all of the time, most of the time, some of the time, or very rarely?

- ❑ All the time
- ❑ Most of the time
- ❑ Some of the time
- ❑ Rarely or never
- ❑ Don't know/refused

APPENDIX 5.1: ASSOCIATION BETWEEN DBP EXPOSURE AND PRETERM BIRTH AMONG WOMEN INCLUDED IN DURATION OF GESTATION ANALYSES*, 2000-2004.

	# preterm	# term	Unadjusted RR (95% CI)	Adjusted RR (95% CI)†
Residential TTHM Concentration (µg/liter)				
2.2-4.6	84	677	1	1
33.1-55	27	295	0.76 (0.5,1.15)	0.83 (0.54, 1.29)
55-66.3	30	288	0.85 (0.58,1.27)	0.94 (0.61, 1.43)
66.4-74.8	24	294	0.68 (0.44,1.06)	0.71 (0.44, 1.15)
74.9-108.8	20	300	0.57 (0.35,0.91)	0.55 (0.32, 0.93)
p for trend test‡			0.008	0.03
≥ 80 vs. <80**	9/176	175/1,679	0.52 (0.27,0.99)	0.54 (0.27,1.09)
TTHM exposure through showering & bathing (µg/day)				
0.02-0.09	50	458	1	1
0.1-0.8	56	453	1.12 (0.78,1.60)	0.95 (0.64, 1.40)
0.9-1.5	29	480	0.58 (0.37,0.90)	0.66 (0.42, 1.04)
1.6-27.1	50	458	1.00 (0.69,1.45)	0.79 (0.52, 1.20)
Residential HAA5 Concentration (µg/liter)				
0-0.9	84	677	1	1
17.9-22	39	282	1.10 (0.77,1.57)	1.14 (0.76, 1.72)
22.1-31.5	24	294	0.68 (0.44,1.06)	0.78 (0.49, 1.22)
31.6-40.4	18	300	0.51 (0.31,0.84)	0.48 (0.27, 0.84)
40.4-52.8	20	301	0.56 (0.35,0.90)	0.67 (0.41, 1.09)
p for trend test‡			0.001	0.01
HAA5 exposure through tap-water consumption (µg/day)				
0	63	539	1	1
0.01-16.1	56	422	1.12 (0.80,1.57)	0.94 (0.65, 1.37)
16.2-54.4	40	437	0.80 (0.55,1.17)	0.94 (0.63, 1.39)
54.7-369.1	26	452	0.52 (0.33,0.81)	0.56 (0.36, 0.89)
Residential TOX Concentration (µg/liter)				
14.3-22.4	84	677	1	1
136.7-169.6	19	300	0.54 (0.33,0.87)	0.66 (0.40, 1.07)
169.6-177.7	21	300	0.59 (0.37,0.94)	0.62 (0.38, 1.02)
177.7-192.6	24	295	0.68 (0.44,1.05)	0.66 (0.40, 1.08)
192.8-235.2	37	282	1.05 (0.73,1.51)	1.13 (0.75, 1.69)
p for trend test‡			0.05	0.2
TOX exposure through showering and bathing (µg/day)				
0-25.8	55	454	1	1
25.9-75	55	453	1.00 (0.70,1.43)	0.86 (0.59, 1.26)
75.1-252.9	38	471	0.69 (0.47,1.03)	0.66 (0.43, 1.02)
253.6-1302.9	37	472	0.67 (0.45,1.00)	0.73 (0.48, 1.09)

* 2,039 women eligible from the chlorinated DBP site; 5 term births missing information on tap water comsunption and showering and bathing needed to assign TTHM, HAA5 and TOX exposure.

† Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake

‡ Chi-square test (H_0: $\beta_{DBP} = 0$) for a single, continuous residential DBP concentration term (*i.e.,* linear term).

** # preterm and # term are No. ≥ 80 µg/liter /No. < 80 µg/liter.

Abbreviations: RR = risk ratio, CI= confidence interval, TTHM = total trihalomethane, HAA5= sum of five haloacetic acids, TOX = total organic halides

APPENDIX 5.2: ASSOCIATION BETWEEN DBP EXPOSURE AND PRETERM BIRTH WOMEN INCLUDED IN DURATION OF GESTATION ANALYSES FROM THE CHLORINATED DBP SITE*, 2000-2004.

	# preterm	# term	Unadjusted RR (95% CI)	Adjusted RR (95% CI)†
Residential TTHM Concentration (µg/liter)				
33.1-60.3	21	289	1	1
60.4-74	17	294	0.81 (0.43,1.50)	0.77 (0.41, 1.47)
74-108.8	19	289	0.91 (0.50,1.66)	0.61 (0.30, 1.23)
p for trend test‡			0.4	0.2
≥ 80 vs. <80**	6/51	153/719	0.57 (0.25,1.30)	0.55 (0.22,1.37)
TTHM exposure through showering & bathing (µg/day)				
0.08-0.9	15	294	1	1
1-1.5	15	294	1.00 (0.50,2.01)	0.86 (0.42, 1.75)
1.6-27.1	27	283	1.79 (0.97,3.31)	1.38 (0.68, 2.81)
Residential HAA5 Concentration (µg/liter)				
18.7-32.4	20	288	1	1
32.5-40.7	17	294	0.84 (0.45,1.58)	0.56 (0.28, 1.13)
40.7-52.8	20	290	0.99 (0.55,1.81)	0.74 (0.39, 1.40)
p for trend test‡			0.8	0.4
HAA5 exposure through tap-water consumption (µg/day)				
0-35.3	23	287	1	1
35.3-69.7	17	291	0.74 (0.41,1.36)	0.99 (0.51, 1.92)
69.7-369.1	17	293	0.74 (0.4,1.36)	0.87 (0.44, 1.72)
2nd-trimester Residential TOX Concentration (µg/liter)average				
136.7-169.2	19	290	1	1
169.3-178.4	18	295	0.94 (0.50,1.75)	0.72 (0.36, 1.42)
178.4-220.6	20	287	1.06 (0.58,1.95)	0.76 (0.39, 1.45)
p for trend test‡			1.0	0.7
TOX exposure through tap-water consumption (µg/day)				
0-143.9	24	285	1	1
144.6-306.7	16	294	0.66 (0.36,1.23)	0.86 (0.43, 1.72)
307-1225.5	17	292	0.71 (0.39,1.29)	0.89 (0.46, 1.73)

* 929 women eligible from the chlorinated DBP site; 1 term birth missing information on tap water comsunption and showering and bathing needed to assign TTHM, HAA5 and TOX exposure.

† Model adjusted for maternal age, race/ethnicity, income, education, employment status, marital status, pre-pregnancy BMI, parity and caffeine intake.

‡ Chi-square test (H_0: $\beta_{DBP} = 0$) for a single, continuous residential DBP concentration term (*i.e.,* linear term).

** # preterm and # term are number ≥ 80 µg/liter /number < 80 µg/liter.

Abbreviations: RR = risk ratio, CI= confidence interval, TTHM = total trihalomethane, HAA5= sum of five haloacetic acids, TOX = total organic halides

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