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EPA

Microbial/Disinfection By-Products Research Council

# Drinking Water Disinfection By-Products and Pregnancy Outcome

Subject Area:
High-Quality Water

# Drinking Water Disinfection By-Products and Pregnancy Outcome


## About the Awwa Research Foundation

The Awwa Research Foundation (AwwaRF) is a member-supported, international, nonprofit organization that sponsors research to enable water utilities, public health agencies, and other professionals to provide safe and affordable drinking water to consumers.

The Foundation's mission is to advance the science of water to improve the quality of life. To achieve this mission, the Foundation sponsors studies on all aspects of drinking water, including supply and resources, treatment, monitoring and analysis, distribution, management, and health effects. Funding for research is provided primarily by subscription payments from approximately 1,000 utilities, consulting firms, and manufacturers in North America and abroad. Additional funding comes from collaborative partnerships with other national and international organizations, allowing for resources to be leveraged, expertise to be shared, and broad-based knowledge to be developed and disseminated. Government funding serves as a third source of research dollars.

From its headquarters in Denver, Colorado, the Foundation's staff directs and supports the efforts of more than 800 volunteers who serve on the board of trustees and various committees. These volunteers represent many facets of the water industry, and contribute their expertise to select and monitor research studies that benefit the entire drinking water community.

The results of research are disseminated through a number of channels, including reports, the Web site, conferences, and periodicals.

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# Drinking Water Disinfection By-Products and Pregnancy Outcome

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# FOREWORD

The Awwa Research Foundation is a nonprofit corporation that is dedicated to the implementation of a research effort to help utilities respond to regulatory requirements and traditional high-priority concerns of the industry. The research agenda is developed through a process of consultation with subscribers and drinking water professionals. Under the umbrella of a Strategic Research Plan, the Research Advisory Council prioritizes the suggested projects based upon current and future needs, applicability, and past work; the recommendations are forwarded to the Board of Trustees for final selection. The foundation also sponsors research projects through the unsolicited proposal process; the Collaborative Research, Research Applications, and Tailored Collaboration programs; and various joint research efforts with organization such as the U.S. Environmental Protection Agency, the U.S. Bureau of Reclamation, and the Association of California Water Agencies.

This publication is a result of one of these sponsored studies, and it is hoped that its findings will be applied in communities throughout the world. The following report serves not only as a means of communicating the results of the water industry's centralized research program but also as a tool to enlist the further support of the nonmember utilities and individuals.

Projects are managed closely from their inception to the final report by the foundation's staff and large cadre of volunteers who willingly contribute their time and expertise. The foundation serves a planning and management function and awards contracts to other institutions such as water utilities, universities, and engineering firms. The funding for this research effort comes primarily from the Subscription Program, through which water utilities subscribe to the research program and make an annual payment proportionate to the volume of water they deliver and consultants and manufacturers subscribe based on their annual billings. The program offers a cost-effective and fair method for funding research in the public interest.

A broad spectrum of water supply issues is addressed by the foundation's research agenda: resources, treatment and operations, distribution and storage, water quality and analysis, toxicology, economics, and management. The ultimate purpose of the coordinated effort is to assist water suppliers to provide the highest possible quality of water economically and reliably. The true benefits are realized when the results are implemented at the utility level. The foundations trustees are pleased to offer this publication as a contribution toward this end.

Walter Bishop
Chair, Board of Trustees
Awwa Research Foundation

James F. Manwaring, P.E.
Executive Director
Awwa Research Foundation

# PREFACE

The Microbial/Disinfection By-Product Council was established in 1995 as a vehicle for the selection and funding of research to provide scientific information in the areas of health effects, exposure assessment, risk assessment, and prevention and control of contamination by microbes and disinfection by-products in drinking water. The council is composed of representatives designated by the U.S. Environmental Protection Agency (USEPA), the Awwa Research Foundation (AwwaRF) Board of Trustees, the Association of State Drinking Water Administrators, the National Resources Defense Council, the National Environmental Health Association, or their designees. Sources of funding for this research include the USEPA and AwwaRF, along with other interested parties. The council disburses these funds for research deemed to be of the highest urgency and importance in resolving critical research issues in drinking water.

# ACKNOWLEDGMENTS

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# EXECUTIVE SUMMARY

## INTRODUCTION

The interaction between chlorine and organic material in drinking water sources produces a wide range of chemical disinfection by-products (DBPs) of potential health concern, including trihalomethanes (THMs), haloacetic acids (HAAs), and other halogenated and non-halogenated compounds. Cancer has been the greatest concern in regard to these DBPs, but over the past 15 years, reproductive health has come to be of increasing interest to the research community and to the public as well. A range of reproductive health outcomes has been studied in relation to exposure to DBPs, but the greatest attention is now focused on pregnancy loss. This possibility was raised most strongly in a study conducted in Northern California by Waller et al. (1998). That research team found that women who drank five or more glasses of cold tap water per day containing at least 75 μg/L of total THMs had an odds ratio of 1.8 (95% CI = 1.1–3.0) compared to all other women, and women who consumed five or more glasses per day of cold tap water containing at least 18 μg/L bromodichloromethane ($CHBrCl_2$) had an odds ratio of 3.0 (95% CI = 1.4–6.6) after making statistical adjustments for other THMs. That study added markedly to the plausibility of an effect of DBPs on pregnancy loss but fell far short of providing definitive support.

## RESEARCH OBJECTIVES

Our study was planned and conducted primarily to address the hypothesis that exposure to DBPs causes pregnancy loss. We made several key methodologic improvements over previous research, most critically in regard to the assessment of DBP exposure, the range of DBP exposure evaluated, and the quality of assessment of pregnancy outcome. We sought to address the following study questions:

1. Is living in an area served by water with elevated levels of DBPs associated with increased risk of pregnancy loss compared to living in areas with lower DBP levels?
2. Are elevated levels of chlorinated DBPs, brominated DBPs, or any individual DBP species among THMs or HAAs associated with increased risk of pregnancy loss?
3. Are women who receive water with elevated levels of DBPs and ingest greater amounts of that water at increased risk of pregnancy loss relative to those women who drink lesser amounts of water from the same source?
4. Do the patterns of association between DBPs and pregnancy loss differ for losses that occur less than 12 weeks after the last menstrual period (LMP) versus losses that occur later than 12 weeks after the LMP, or with different stages of development prior to loss as assessed by ultrasound?
5. Is there an association between exposure to DBPs and reduced fetal growth, as measured by small-for-gestational-age births or preterm birth?
6. What is the contribution of tap water THMs to blood THM levels?

## APPROACH

Three study sites were selected to reflect a wide range of DBP concentrations and speciation typical of those found across the US. One site had moderate levels of chlorinated DBPs (Site 1), one had very low levels of all DBPs (Site 2), and one had moderate levels of brominated DBPs and lower levels of the species containing chlorine only (Site 3). For the sites with moderate DBP levels, we sought locations that used chloramines as a terminal disinfectant. With chloramination, there is little additional DBP formation in the distribution system, resulting in minimal spatial variation within the water supply service area. In addition to variation in exposure resulting from the different water sources, patterns of water use for drinking, bathing, and showering were ascertained in detail because those behaviors affect personal exposure to DBPs.

We sought to recruit women in each of the three areas who were planning a pregnancy or who were pregnant at less than 12 weeks' gestation. The study was marketed through prenatal care providers and through multiple forms of community advertising at drug stores, doctor's offices, and other settings. We successfully recruited and completed data collection for a total of 3132 women, 252 recruited prior to conception that became pregnant and enrolled in the study, and 2514 recruited early in pregnancy. Potentially eligible women were screened by telephone and, if eligible, were contacted for a telephone interview within 2 weeks of recruitment (<16 weeks' gestation) to assess behaviors and other factors that might influence the health of their pregnancy. Participants were scheduled for an ultrasound assessment between 6 and 7 weeks' gestation and no later than 14 weeks to accurately determine the dates of their pregnancy and to determine whether it was progressing normally. Participants then had a follow-up interview at 20-25 weeks' gestation to complete data collection and assess the continuation of their pregnancy. Pregnancy losses were identified by self-report, with medical records sought for confirmation, and live birth outcomes (birth weight, duration of gestation) were identified through vital records, medical records, or self-report. Recruitment occurred in Site 1 from December 2000 through February 2004, in Site 2 from June 2002 through March 2004, and in Site 3 from September 2002 through April 2004.

Tap water was sampled at frequent intervals (weekly or every other week) at the three study sites and analyzed for the four currently regulated THMs (THM4), the nine bromine- and chlorine-containing HAAs (HAA9), and total organic halide (TOX). Based on the measurements, DBP concentrations were then assigned to each weekly interval of pregnancy. More intensive sampling programs were implemented at Sites 1 and 3 during intermittent periods in which free chlorine was used in the distribution system. Because sites were chosen that either used year-round chloramination except for those intermittent periods or had low overall DBP levels, there was little within-system variation and therefore all women in a given study area were assigned the same exposure score for any given week. Based on previous epidemiologic and toxicological studies, we focused most intensively on THM4, $CHBrCl_2$, and HAA9. Overall median THM4 levels were 60.7, 3.6, and 57.8 µg/L at sites 1, 2, and 3, respectively. Overall median HAA9 concentrations were 41.5, 3.3, and 44.7 µg/L, respectively.

We examined several indices of exposure: concentration of DBPs in tap water, ingested amount of DBPs, DBP exposure from showering and bathing alone, and integrated DBP exposure combining ingestion with showering and bathing. These exposure estimates were linked to specific time intervals in the pregnancy: 4 weeks before the LMP through 3 weeks after LMP (periconceptional), weeks 4–8 after LMP (early gestation), and weeks 9–20 after LMP

(later gestation). In the interview, women were asked about changes in water use during pregnancy, and these reported changes were taken into account in the calculation of the exposure indices.

DBP exposure was calculated directly from the measured weekly or bi-weekly concentrations by generating a mean of the measured values during the pregnancy window. Ingested amount was based on these measured concentrations but modified as a function of the reported amount of water ingested during the time window. Laboratory experiments were conducted to derive estimates of changes in individual DBP concentrations due to heating water for the preparation of hot beverages and using either tap or pitcher filters prior to cold water ingestion. These estimates were combined with self-reported information on the individual's daily ingestion of cold and hot water, as well as their ingestion of filtered and unfiltered water. Showering and bathing exposure was calculated combining information on tap water DBP concentration, reported frequency and duration of those activities, and estimated absorption of DBPs as a result of these activities. Finally, integrated exposure combined those pathways of exposure into a summary estimate of total exposure to DBPs.

In the study of pregnancy loss, we examined the various indices of DBP exposure in relation to the probability of the pregnancy surviving or being lost through the period of gestation. We adjusted statistically for other known and suspected risk factors for pregnancy loss that were found to be predictive in our data, including maternal age, race/ethnicity, education, marital status, history of prior pregnancy loss, and alcohol consumption.

## CONCLUSIONS

1. Comparing our results to the primary findings of the Northern California study, we did not find the same associations relating THM4 concentration combined with water consumption to the risk of pregnancy loss. Waller et al. (1998) found that women who drank 5 or more glasses per day of tap water with >75µg/L THMs had twice the risk of pregnancy loss compared to other women (measured statistically as an odds ratio in which he odds of pregnancy loss among women with higher DBP exposure is compared to the odds of loss among women with lower DBP exposure). In contrast, we found women who drank 5 or more glasses per day of tap water with >75µg/L THMs had the same risk (an odds ratio of 1.0) compared to all other women, indicating no association between exposure and pregnancy loss. Waller et al. (1998) also comparing the upper quartiles of $CHBrCl_2$ and DBCM ($CHBr_2Cl$) exposure to the lower three quartiles and found odds ratios of 2.0 and 1.3; in our study, the same comparisons yielded odds ratios of 1.6 and 1.7, providing some indication that these specific DBPs may be associated with an increased risk of pregnancy loss..
2. In examining THM4 using the multiple indices described above, results were generally not supportive of an association with pregnancy loss with the possible exception of an increased risk for losses at >12 weeks' gestation. The array of results for $CHBrCl_2$, HAA9, and the other groups of DBPs considered provided sporadic support for elevated risk that varied across pregnancy time window, exposure index, and agent. $CHBrCl_2$ results were marginally stronger than those for THM4, and the results for TOX had the most consistently association with pregnancy loss, both for tap water concentration and ingested amount.

3. Live birth outcomes were addressed in the form of preterm birth (<37 weeks completed gestation), small-for-gestational-age (SGA) births (<10$^{th}$ percentile of weight for gestational age), and a continuous measure of birth weight among term births. Pregnancy windows were defined by the trimester of pregnancy (weeks 0–12, 13–26, 27+). Preterm birth showed a modest but consistent tendency to be rarer among women with higher exposure (i.e., an inverse association). $CHBrCl_2$ was unrelated to risk of preterm birth and HAA9 showed a weak inverse association as did chloroform, another of the THM4 species.
4. Analysis of THM4 exposure in the third trimester and SGA births generated evidence of a positive association based on the dichotomy of 80 µg/L (OR = 2.1, 95% CI = 1.1–3.8). Restriction to sites 1 and 3 enhanced the association. BDCM was also related to increased risk of SGA births, whereas HAA9 and chloroform were not.
5. Term birth weight was largely unrelated to DBP exposures, except for somewhat lower birth weights among women who were served by water with >80 µg/L of THM4 in the second and third trimesters.
6. Blood THM levels varied in the expected direction by season in Site 1 (higher in summer than in winter), and generally showed some contrast across the three sites generally, but to a much lesser extent than would have been expected based on tap water concentrations of DBPs.

## IMPLICATIONS OF FINDINGS

Policy recommendations do not follow directly from the findings of this (or any single) epidemiologic study, but we can comment on the overall nature of how these findings may shift priorities. Relative to the earlier study in Northern California (Waller et al., 1998), we found less support for an adverse effect of DBPs on pregnancy loss, logically leading to a somewhat lower level of concern with that possibility than was present prior to the conduct of our study. The failure to provide strong evidence in support of the hypothesized associations is worth noting as well, in that the methodological refinements in our epidemiologic study should have generated more persuasive evidence of adverse effects if such effects are indeed associated with DBP exposures. Nonetheless, there were sporadic indications of increased risk of pregnancy loss and fetal growth restriction associated with higher exposure to selected DBPs that may warrant further consideration.

## FUTURE RESEARCH

The logical next steps in the evolution of research on DBPs and reproductive health outcomes are not obvious. We offer the following suggestions for consideration:

1. Our results do not provide encouragement for undertaking additional, large-scale research of a similar nature in different geographic locations. To the extent that researchers can identify settings in which exposure levels differ appreciably over season within communities, there are some clear logistical and scientific advantages, namely that the study base can be more circumscribed, saving substantial time and money required to manage multiple field sites. In addition, the demographic and recruitment differences

across communities in studies such as ours make it very difficult to isolate any direct impact of DBPs in accounting for varying health patterns across communities.

2. Exposure assessment remains a key limiting factor in our study and in all studies that have preceded it. While we constructed indices that were intended to move well beyond tap water concentrations to reflect actual exposure, in the process of doing so, the limitations in making such inferences with accuracy (or even knowing the accuracy) were quite obvious. Work to develop and validate stronger approaches to characterizing exposure in epidemiologic studies is a high priority for new studies to improve upon ours. In particular, the high prevalence of use of bottled water and point of use devices calls for more extensive research into the impact on human exposure at a population level.
3. Enrollment prior to conception is very challenging, and incurs substantial sacrifices in terms of numbers of participants and their social and demographic profile, but provides a marked increment in the quality of information on the course of their pregnancy. To the extent that the logistical challenges can be overcome, there are notable advantages to enrollment before conception as compared to enrollment in very early pregnancy.

# CHAPTER 1
# BACKGROUND TO STUDY

## OVERVIEW OF HEALTH CONCERNS WITH DISINFECTION BY-PRODUCTS (DBPs)

Chlorination of public drinking water supplies has provided substantial public health benefits through control of infectious disease. However, the interaction between chlorine and organic material in surface water produces a wide range of chemical disinfection by-products (DBPs) of health concern, including trihalomethanes (THMs), haloacetic acids (HAAs) (Rook 1974, Bellar et al. 1974, Singer 1994), and other compounds, which may well be more directly relevant to adverse health effects (Orme-Zavaleta and Hauchman 1999). Some DBPs are mutagenic, teratogenic, or carcinogenic (Bull 1985, Boorman et al. 1999).

Much of the early epidemiologic research focused on cancer, especially bladder cancer, but interest has spread to other cancer sites and to reproductive health outcomes. The primary challenge in the studies of cancer is the need to take into account decades of exposure as being potentially relevant to etiology, since the information available to reconstruct exposure over such prolonged periods is limited. In contrast, the study of reproductive health effects of drinking water DBPs is concerned with exposures over periods of weeks to several months.

The basis for concern with potential reproductive effects of DBPs on pregnancy comes from several lines of research and other considerations. Pregnancy is generally recognized as a period of enhanced vulnerability to environmental insults because of the fetus's heightened susceptibility. Agents that might not cause discernible harm to adults may still be hazardous to the reproductive process. Experimental studies of DBPs have demonstrated possible fetotoxicity (Thompson et al. 1974, Ruddick et al. 1983) and fetal resorption (Narotksy et al. 1997). Beyond any scientific basis for concerns with reproductive health effects of DBPs, there is a special public concern with health of pregnancy continuing through infancy and childhood. Combining the widespread exposure to DBPs, toxicology indicative of potential reproductive effects, and public concern with reproduction, there has been much recent interest and resulting research by epidemiologists to assess whether the potential hazard is real.

## OVERVIEW OF EPIDEMIOLOGIC STUDIES OF DBPs AND REPRODUCTIVE HEALTH OUTCOMES

A sizable body of research has accumulated addressing the potential reproductive toxicity of DBPs. In a comprehensive review of this topic, Nieuwenhuijsen et al. (2000) summarized studies addressing a wide range of outcomes, including spontaneous abortion, stillbirth, birth defects, preterm birth, and reduced birth weight. Over the intervening period since the literature for that review was assembled, a sizable number of studies have been published, extending the knowledge of those topics and broadening the outcomes to include male reproductive effects. We will not attempt to conduct a comprehensive review, but focus instead on the state of knowledge regarding spontaneous abortion, pregnancy loss prior to 20 weeks' gestation. At the time of Nieuwenhuijsen et al.'s review and continuing to the present, the most supportive evidence pertains to pregnancy loss, including stillbirth (Aschengrau et al. 1989, Swan et al. 1992, Deane et al. 1992, Wrensch et al. 1992, Savitz et al. 1995, Swan et al. 1998, Waller et al. 1998), with much more limited evidence linking DBPs to birth defects and growth restriction.

The most recent studies of pregnancy loss in the range of < 20 weeks' gestation are the most important, given their size, quality, and efforts to consider specific chemical compounds within the class of THMs. Using a cohort of 5,100 pregnancies, of which 474 ended in spontaneous abortion, Swan et al. (1998) examined amount and source of drinking water, followed by Waller et al. (1998) who considered THMs directly. Swan et al. (1998) observed a positive association between drinking six or more glasses of cold tap water per day and spontaneous abortion (OR = 2.2, 95% CI = 1.2–3.9), but only in one of the three regions studied, a region served by a mixture of surface and ground water and not in the region served solely by surface water. Waller et al. (1998) reported no association between consumption of large amounts of cold tap water or receiving tap water with high levels of THMs and spontaneous abortion. However, a personal exposure score that combined amount of cold tap water consumed with level of THMs present in the water yielded a more substantial association. Women who consumed five or more glasses of cold tap water per day containing at least 75 μg/L THM4 had an odds ratio of 1.8 (95% CI = 1.1–3.0) compared to all other women, and women who consumed five or more glasses per day of cold tap water containing at least 18 μg/L bromodichloromethane had an odds ratio of 3.0 (95% CI = 1.4–6.6), with statistical adjustment for other THMs. A subsequent publication (Waller et al. 2001) considered alternate approaches to exposure assignment, including using the nearest monitoring site rather than system average (with spatial variability a concern for these chlorinated systems), and weighting to account for uncertainty in exposure assignment. Both studies were based on sparse data, both spatially and temporally, of THM levels in the distribution system. Modest differences from the original results were found, not materially changing the results or conclusions from the original report. Uncertainty in pregnancy onset dates and timing of losses, as well as questionable validity of exposure assignment to individuals are serious, recognized limitations in these studies, but the results strongly encourage continued evaluation.

Methodologic improvements are being made, but the evidence falls far short of indicating a causal relation between exposure to DBPs and spontaneous abortion. Medically treated spontaneous abortions, considered by Aschengrau et al. (1989) and Savitz et al. (1995) are known to be an incomplete subset of all pregnancy losses (Savitz et al. 1994). Although, the Northern California studies (Swan et al. 1998, Waller et al. 1998) improved ascertainment by enrolling women prior to the first prenatal care visit, none of the studies have effectively addressed the incompleteness and inaccuracy associated with dating of pregnancy and early spontaneous abortions and DBP exposure assessment. A critical analytic strategy to minimize bias is to incorporate the gestational age at the time of enrollment in a life table analysis, which was applied to some (Hertz-Picciotto et al. 1989) but not all (Swan et al. 1998, Waller et al. 1998) previous studies.

Studies have begun to incorporate behavioral determinants of exposure, but the scope of inquiry could be broadened to include sources of DBP exposure such as water consumption at work and showering and bathing (Shimokura et al. 1998). The accurate assessment of the levels of DBPs in the tap water at the subject's home remains a substantial challenge as well, with the quarterly or annual average for the water utility sometimes generating a poor estimate for an individual home at a specific point in time, in light of substantial day-to-day and system-wide variability, especially in chlorinated systems (Brett et al. 1979, Chen and Weisel 1998, Singer 2001, Pereira et al. 2004). Furthermore, although total THMs are a convenient marker, they may well not be the agent of most relevance. Additional effort is needed to consider individual THM species, as well as other by-products such as HAAs to the extent possible in observational studies. Through improvements in DBP exposure assessment and the accurate, early identification of spontaneous abortion, our study offers a substantial advancement in exposure

assessment based on the selection of sites, systematic monitoring of tap water DBP levels and incorporation of detailed water use behaviors.

## STUDY AIMS

Despite a growing body of research addressing the question of whether exposure to elevated levels of DBPs is associated with adverse pregnancy outcome, the essential question remains unresolved. We designed a study that had a very different structure from those that had been done previously and extended the approach to exposure assessment considerably. The research questions guiding the design and conduct of the study were as follows:

1. Is living in an area served by water with elevated levels of DBPs associated with increased risk of pregnancy loss compared to living in areas with lower DBP levels?
2. Is living in an area served by water with elevated levels of chlorinated DBPs, brominated DBPs, or individual DBP species associated with increased risk of pregnancy loss?
3. Are women who receive water with elevated levels of DBPs and ingest greater amounts of that water at increased risk of pregnancy loss relative to those women who drink lesser amounts of water from the same source?
4. Do the patterns of association between DBPs and pregnancy loss differ for losses that occur less than 12 weeks after the last menstrual period versus later than 12 weeks after the LMP, with different stages of development prior to loss as assessed by ultrasound?
5. Is there an association between exposure to DBPs and reduced fetal growth, as measured by small-for-gestational-age births or preterm birth?
6. What is the contribution of tap water THMs to blood THM levels?

# CHAPTER 2
# STUDY METHODOLOGY

## SITE SELECTION AND CHARACTERIZATION

Three water utilities with different DBP attributes were chosen for this study. One of the sites (Site 1) had moderate levels of trihalomethanes (THMs) and haloacetic acids (HAAs) in their finished water. Because of the low bromide concentration in the source water, the THMs and HAAs comprised primarily chlorine-containing species [i.e., chloroform ($CHCl_3$), dichloracetic acid ($Cl_2AA$), and trichloracetic acid ($Cl_3AA$)]. A second site (Site 3) had similar total THM and HAA concentrations but, because of the relatively high concentrations of bromide in the source water, speciation was dominated by bromine-containing by-products, e.g., bromodichloromethane ($CHBrCl_2$), dibromochloromethane ($CHBr_2Cl$), bromochloroacetic acid (BrClAA), bromodichloroacetic acid ($BrCl_2AA$), dibromochloroacetic acid ($Br_2ClAA$). The third utility (Site 2) had relatively low overall DBP concentrations in their finished water because they drew their water from deep wells with low organic carbon concentration.

It has been widely documented that water utilities using free chlorine as a residual (terminal) disinfectant in their distribution system experience significant temporal and spatial variations in DBP levels in their systems (e.g., Krasher et al. 1989, Singer 1994, Singer 2001). Such variation is difficult to characterize without extensive monitoring of the distribution system, which was impractical for this study. Therefore, to facilitate characterization of THM, HAA, and total organic halide (TOX) exposure and minimize spatial variation in DBP concentrations, the two systems with moderate DBP concentrations were chosen for this study because they used combined chlorine as a terminal disinfectant. Such practices tend to minimize spatial variation in THM and HAA concentrations throughout a given distribution system on any given sampling date because THM and HAA formation in the absence of free chlorine is minimal. The low DBP site used free chlorine as a terminal disinfectant, but spatial variation was not a concern because of the low overall DBP concentrations.

Each of the three utilities was visited by a member of the project team 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. After reviewing the DBP results from the initial sampling trip and verifying that THM, HAA, and TOX levels exhibited little spatial variation, a representative sampling location was chosen for each utility for the remainder of the study, based on logistics. Because Site 3 had several booster chlorination stations that served a large portion of its population, two sampling locations were chosen, one at the treatment plant (the point of entry to the distribution system) and another on the downstream side of the booster station. The amount of chlorine applied at the booster station was relatively minor (0.3 to 0.5 mg/L) so it was expected that residual free ammonia in the water would convert the additional free chlorine to combined chlorine, with little additional formation of DBPs.

## STUDY POPULATION

Approximately 3,000 women from the three study sites participated in this prospective, community-based study of early pregnancy health. Women were recruited from private and public prenatal care venues, and directly from the community at large. The cohort of study

participants consisted of pregnant women recruited at ≤ 12 weeks' gestation and women trying to conceive. Eligibility criteria were as follows:

- maternal age of 18 years or older, if pregnant, or between the ages of 18 and 45 (inclusive), if trying to conceive.
- residence in the geographic study area served by city water.
- no assisted reproductive technology used to conceive.
- having a positive pregnancy test.
- intention to carry pregnancy to term.
- no intention to move out of the area prior to delivery.
- ability to speak, read, and write English or Spanish, in one of the three sites.
- if trying to conceive, cannot have been trying for more than 6 months. These women were pre-enrolled and followed for a maximum of 6 months and enrolled if they reported a positive pregnancy test.

As described in Table 2.1, enrollment and water sampling began much earlier in Site 1 than in Sites 2 and 3, for a number of reasons. First, we needed the time to fully develop a functional protocol at one location before attempting to scale up to multiple sites. Second, even when we were ready to implement the protocol in other locations, there were major delays incurred in the process of setting up subcontracts and in obtaining the needed Institutional Review Board approvals. Third, around the time that we had hoped to begin recruitment in Site 3, the water utility was expanding their plant to increase the geographic area to which they could deliver water. We waited until they had completed the expansion and had achieved a consistent degree of operation before we initiated our preliminary sampling program. While we were able to successfully complete the desired volume of recruitment in Site 2 despite the delayed start, in Site 3, the smaller population precluded attaining the originally desired number of participants, despite extending the study in time for the maximum duration possible.

**Table 2.1**
**Enrollment and water sampling time frames**

| Site | Enrollment period | Water sampling period |
|---|---|---|
| 1 | 12/2000–2/29/2004 | 10/10/2000–2/29/2004 |
| 2 | 6/2002–3/31/2004 | 7/30/2001–8/1/2004 |
| 3 | 9/2002–4/30/2004 | 6/3/2002–9/5/2004 |

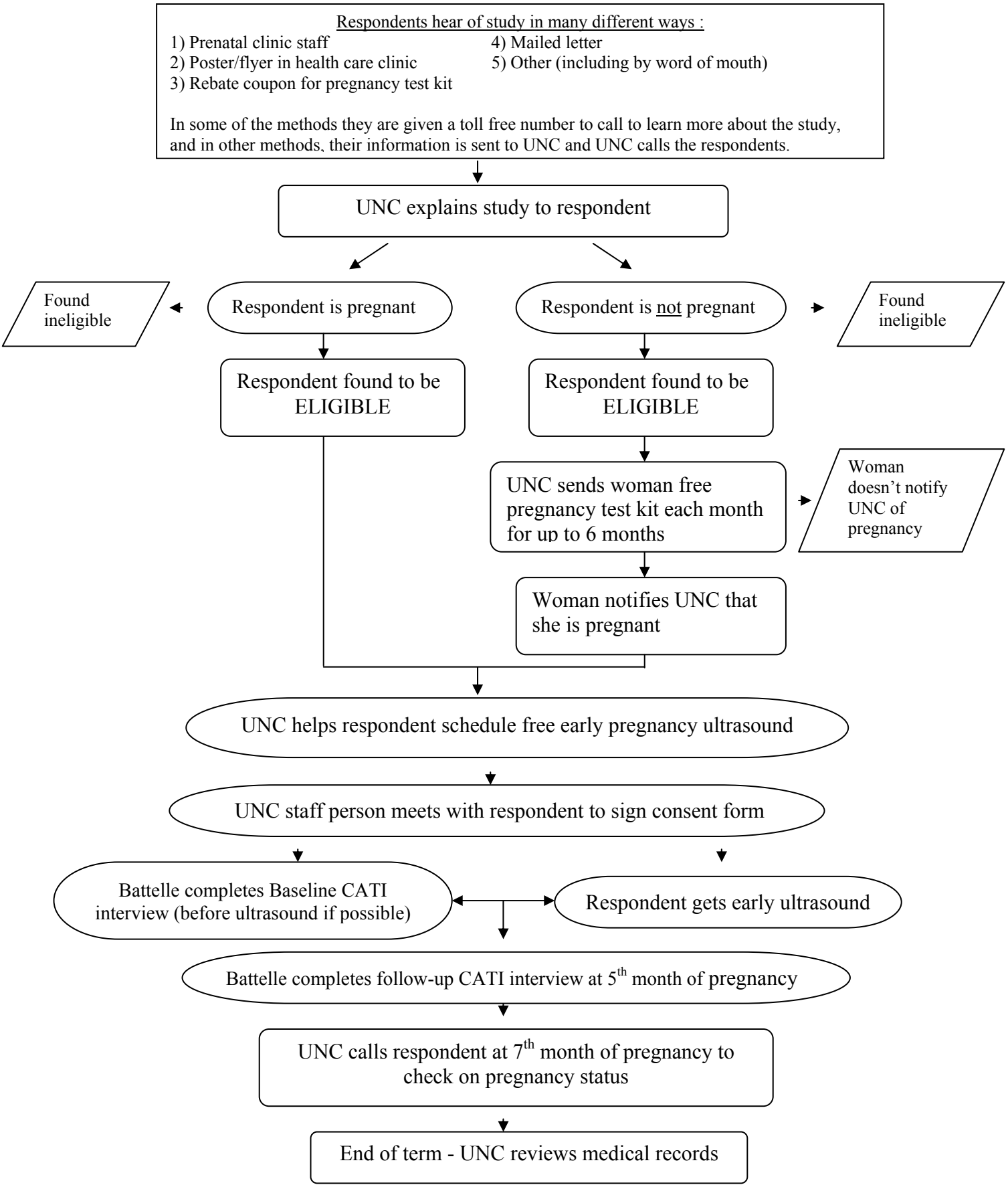



**Figure 2.1 Overview of recruitment and data collection**

## SCREENING

The overall process by which women were recruited and the subsequent data collection are summarized in Figure 2.1. A 5-minute telephone screening interview was completed with interested women to determine eligibility. Once eligibility was determined and the woman enrolled, study staff completed an additional 5 to 10-minute interview to collect personal information and schedule study activities. Interview data were entered directly into the Access database by the interviewer to track data and determine eligibility. A five-digit study ID number was assigned to each individual who was eligible and agreed to participate in the study. A participant who was enrolled in the study for a previous pregnancy was required to complete all aspects of the study for each pregnancy for which she was enrolled.

In clinics where Right from the Start (RFTS) staff recruited women on site, staff completed a preliminary screening interview with interested women. At the same time, staff obtained a signed consent from those women who were eligible and interested.

## PROMOTIONAL MATERIALS

Study materials were designed with a unique logo representing RFTS which helped with name recognition across the recruitment areas. Materials briefly described the study focus, eligibility criteria, what participants were asked to do, and provided a toll-free number and a web site address (which had a direct email link) for women to reach study staff. The format of promotional materials included a brochure, wallet sized card, rebate coupon and a variety of flyers.

## SUBJECT IDENTIFICATION AND RECRUITMENT STRATEGIES

Women were recruited from private and public prenatal care venues and from the community at large and through more direct methods of recruitment such as targeted mailings (Figure 2.2).

### Private and Public Obstetric Practices

Collaboration with local obstetricians, medical practices, and university medical centers enabled identification of women contacting a health care provider for preconception counseling, pregnancy testing, or prenatal care. Over 50 private OB/GYN clinics, including nearly all of the larger practices in each recruitment area, and all public prenatal care sites including county health department clinics and university medical centers were involved in recruitment. Because clinic flow and patient populations are different for each practice, study coordinators worked with each medical practice individually to develop a plan for recruitment and collaboration.

In addition to displaying study posters and brochures in waiting and exam rooms, many clinics also discussed the study with their patients, collected contact information for interested women to be faxed to the study office, or included a study brochure in their prenatal care packets or mailings, often prior to the first office visit. Some offices forwarded their patient calls directly to the study office if women were interested in learning about the study.

Study investigators helped initiate contact with some medical practices and clinics. Investigators or a study staff nurse familiar with the obstetric community in the study sites brought legitimacy to the study. We used a variety of strategies for gaining entry into private practices including sending a letter from an investigator, presentations at professional meetings,

making a telephone call or setting-up an in-person meeting with the office manager, nurse manager or lead physician. At times a brief presentation at a staff meeting was an efficient and successful way to introduce the study. Once the initial contact has been made, the study coordinator was very effective at establishing and maintaining the collaborative relationships including leading a planning meeting, responding to questions or concerns, and maintaining ongoing communications with the office or nurse manager. Ensuring that all staff in a practice were aware of the study resulted in better recruitment and data collection efforts. The study coordinator maintained close and ongoing relationships with each practice as the study progressed to assure the highest level of recruitment possible.

**Community-Based Strategies and Targeted Mailings**

Multiple approaches to community recruitment were implemented throughout the study areas. Informational posters and brochures were posted in drug stores, bookstores, childcare facilities, coffee shops, fitness centers, retail stores, grocery stores, libraries, beauty salons, worksites, and churches. Venues were visited as needed to keep study materials stocked. Flyers with tear-off tabs that included the study toll-free number were posted on public bulletin boards. Brochures and information cards were also displayed in pediatric and family practice waiting rooms and exam rooms. Materials were distributed at some health fairs and other community events that gave study coordinators an opportunity to promote the study in person. Pregnancy test rebate coupons were made available in drug stores and eligible women contacting RFTS redeemed the coupon to receive $5.

Advertisements were placed in community, worksite, and church publications. One local utility participating in the study ran an advertisement on their hold message for customers who called their office and were put on hold. Some employers ran a message briefly describing the study on their daily bulletin. Advertisements about RFTS were included in local employee or professional association newsletters. Some local employers agreed to send informational emails about the study to their employees, and a mass email was sent through a commercial service to the study's target population.

Letters describing the study along with a pregnancy test rebate were mailed to targeted groups: new home owners and women who delivered a child within the past three years. When women phoned RFTS, study staff explained the study purpose and procedures and invited women to complete a screening interview to determine eligibility. Displaying brochures, informational cards, posters and pregnancy test rebate coupons in the community at large was a recruitment strategy that focused particularly on recruiting women who were trying to conceive.

Access to chain retail stores usually required a formal agreement with the corporate office. Once an official agreement was reached, the study coordinator was able to contact the stores to drop of materials. A brief meeting with the store manager or pharmacist to provide a brief overview of the study and describe the drug store's role in recruitment efforts usually helped with maintenance of promotional material displays in the store. Ideally, the corporate office had contacted store managers prior to the coordinators efforts to contact the store.

Participants were provided with small gifts donated by local merchants for referring an eligible friend. Participants who miscarried were encouraged to contact RFTS if they again tried to become pregnant. Women who became pregnant after an unsuccessful pre-enrollment period were also encouraged to enroll.

## Incentives for Participants and Collaborators

The RFTS first trimester ultrasound provided a significant incentive for both participants and medical practices. This ultrasound was performed free of charge for participants. Other participant benefits included a small gift donated by an area business given at enrollment, $10 for each completed interview, an additional $10 for completing all parts of the study, and a newsletter. Women trying to conceive were given up to six free pregnancy test kits and women who referred their friends or family members received a small gift.

Obstetrics practices whose sonographers and equipment met study criteria were reimbursed $100 for each ultrasound, which included providing documentation as indicated in the study protocol. To express gratitude for collaborator effort and to help maintain long-term enthusiasm for the study, RFTS frequently provided thank you gifts, such as gift baskets, RFTS mugs and t-shirts, donations from local businesses and gift certificates, to all participating prenatal care providers, drug stores, pediatric and family practice offices, and occasionally practice staff and sonographers. A quarterly newsletter with recruitment tips and information on study progress was also sent to these collaborators to keep them informed and involved.

## Recruitment Results

Private and public obstetric practices offered the most successful source for enrolling newly pregnant participants (Figure 2.2), particularly when a collaborative approach and positive relationship were developed with the practice. Drugstores, mailed letters to homeowners, re-enrollment and referral by friends and family provided the study with the greatest number of women who were trying to conceive. Recruitment results differed by site (Figures 2.3–2.5).

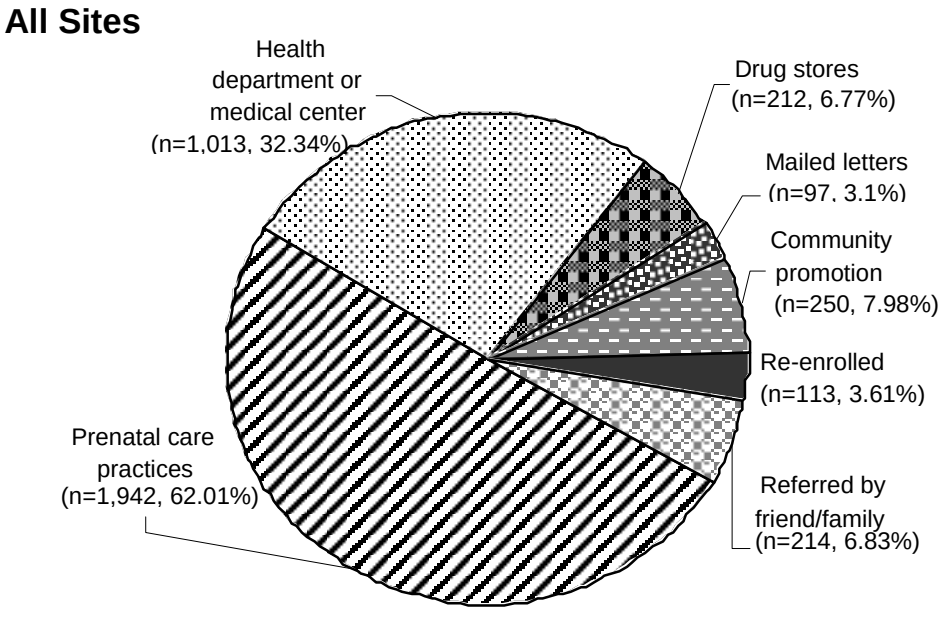



**Figure 2.2 Recruitment sources (all sites, n = 3,132)**

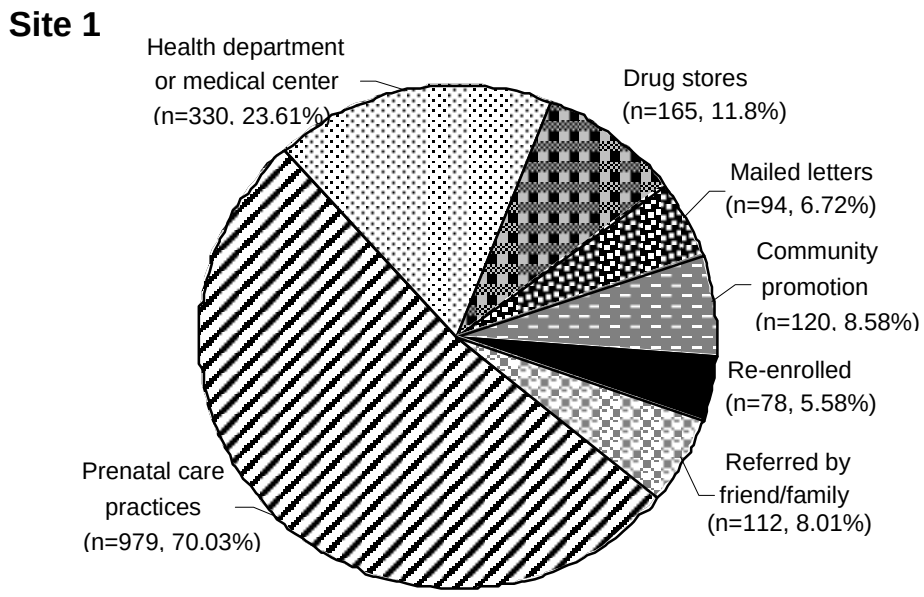



**Figure 2.3 Recruitment sources for site 1 (n = 1,398)**

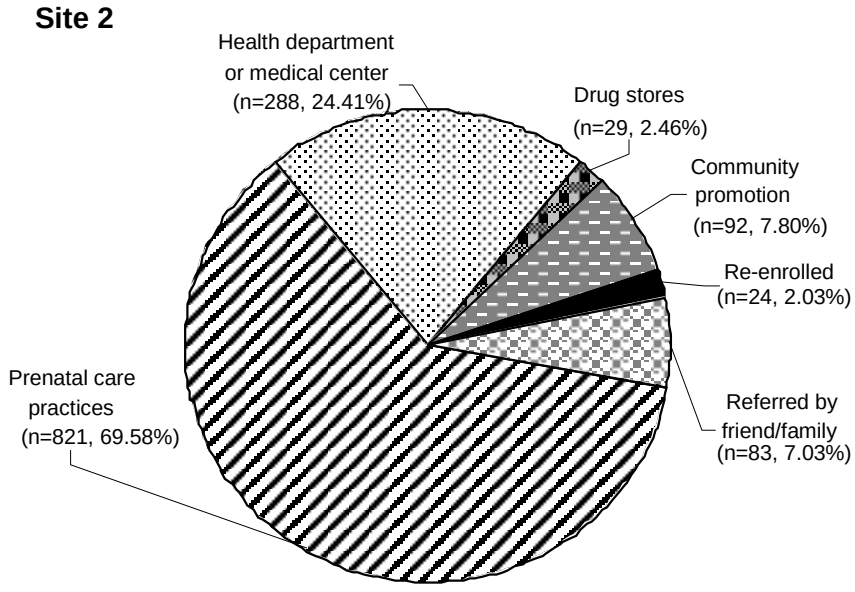



**Figure 2.4 Recruitment sources for site 2 (n = 1,180)**

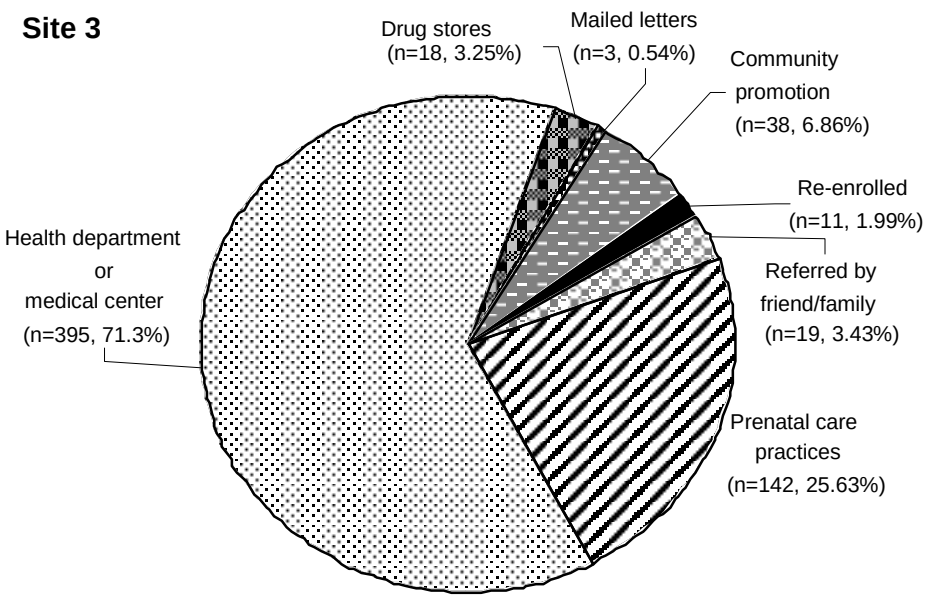



**Figure 2.5 Recruitment sources for site 3 (n = 554)**

## ENROLLMENT SUMMARY

Figure 2.6 indicates the reasons for attrition, starting with the number of women who contacted the study office to be screened. Exclusions were women who failed to meet the criteria to be enrolled in the study: trying to get pregnant for over 6 months, estimated gestational age at enrollment based on the ultrasound greater than 12 weeks; unable to reach by telephone for >7 weeks; or moved out of the study area. Some otherwise eligible participants withdrew from the study by their own choice 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 to be asked in the interview were too personal. The total number of participants who were excluded or withdrawn by site and overall is listed in Table 2.2.

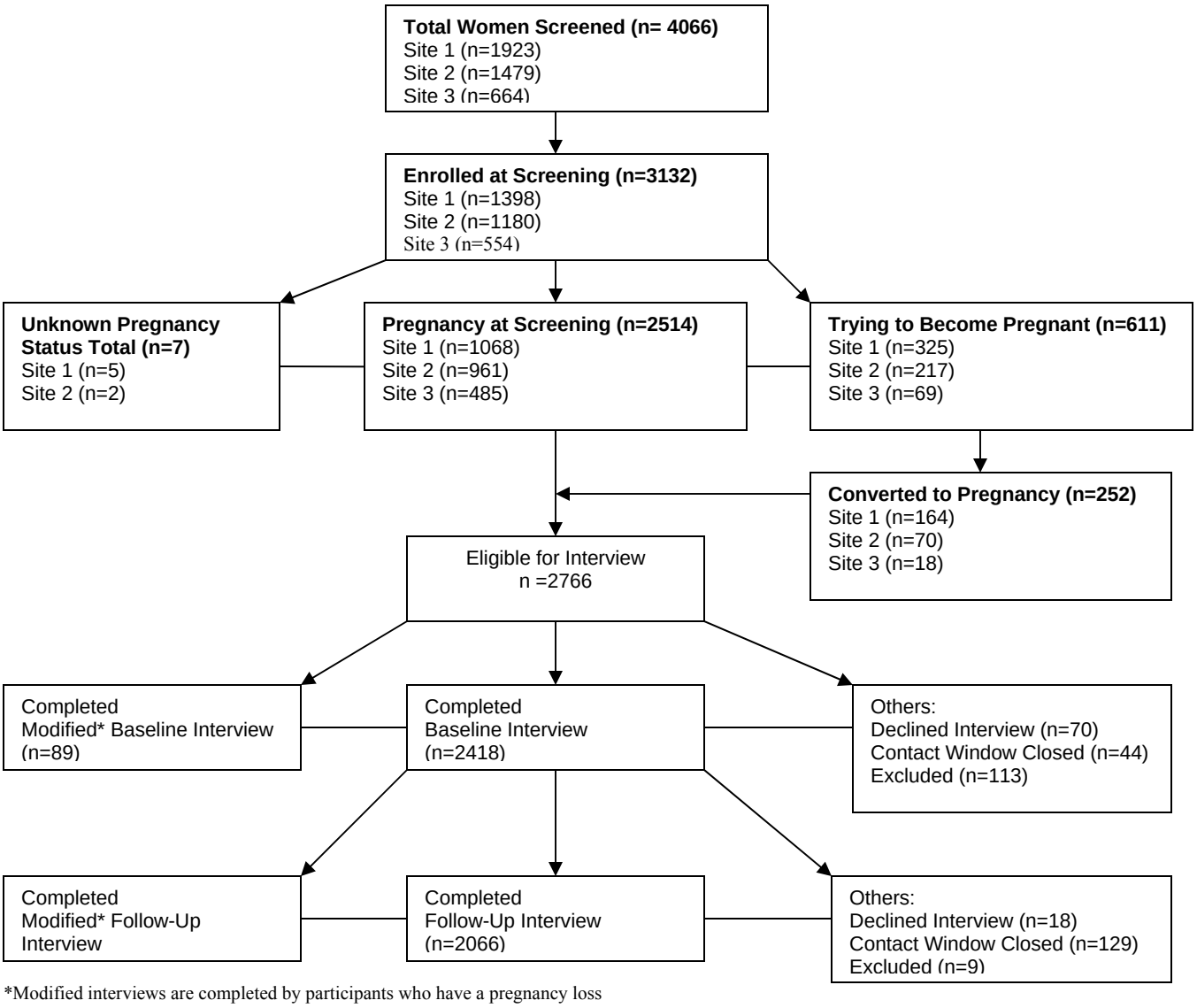



**Figure 2.6 Summary of enrollment process and completion of study activities**

**Table 2.2**
**Withdrawals and exclusions by study site**

| | All sites | Site 1 | Site 2 | Site 3 |
|---|---|---|---|---|
| Withdrew | 85 | 38 | 35 | 12 |
| Excluded | 499 | 204 | 209 | 86 |

In preparing the data for the analyses included in this report, some additional criteria were imposed for inclusion. As indicated in Figure 2.7, those in the analysis had to have a valid date assigned for their last menstrual period, they needed to have had the pregnancy in a time period in which water measurements were being conducted, and only one pregnancy per woman was included to avoid violating assumptions of independence of events. These additional

exclusions resulted in 2,413 pregnancies in the final analysis. Some additional losses were incurred for selected analyses due to pregnancy losses prior to the time window of interest or missing data on key covariates.

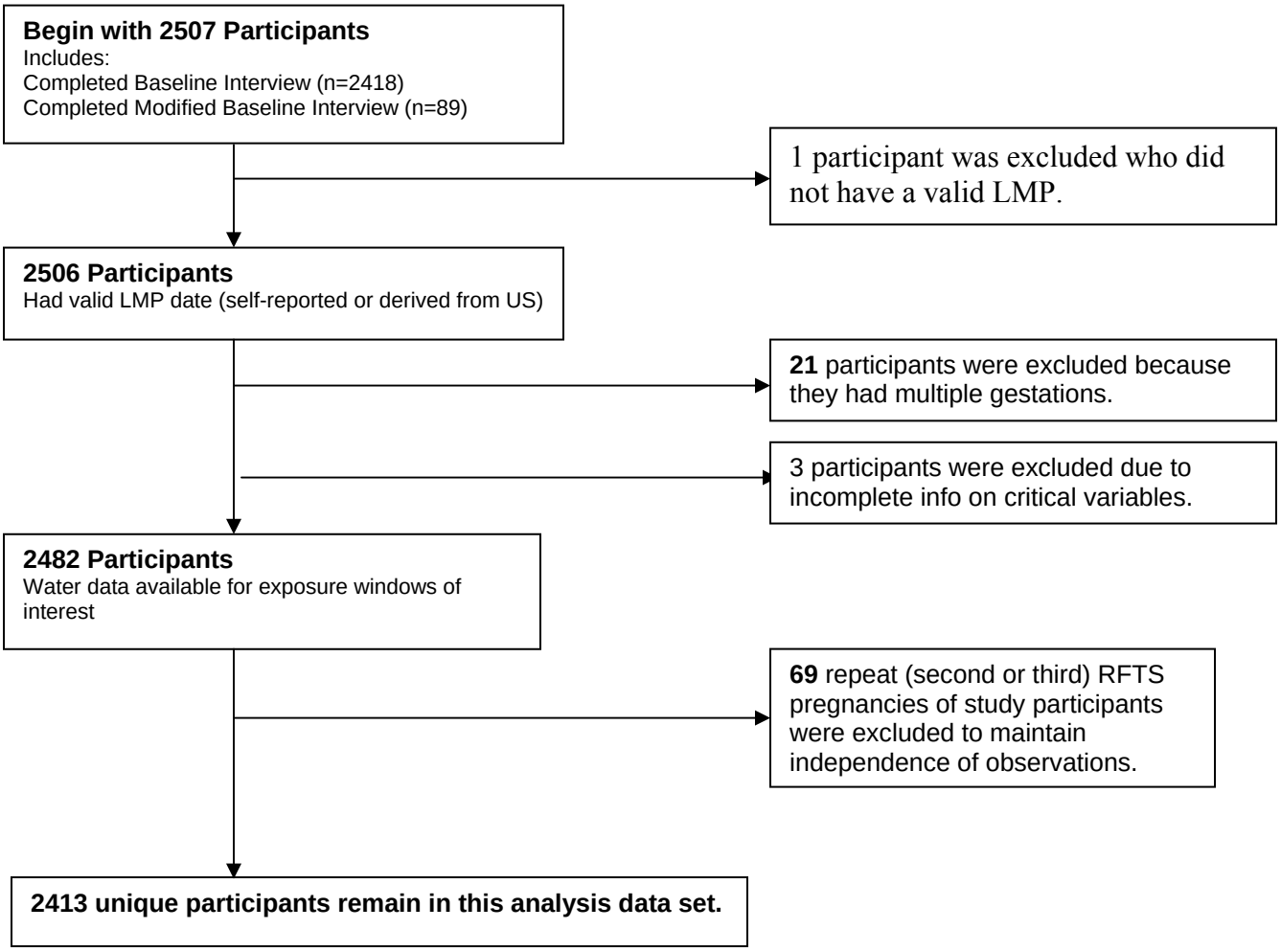



**Figure 2.7 Inclusion criteria for analysis completed in this report: arriving at n = 2,413**

## COMPARISON OF WOMEN WHO GAVE BIRTH IN THE STUDY AREAS AND WOMEN IN THE ANALYSIS

Although we attempted to recruit a cross-section of women from the participating geographic areas, we recognize that the population that agreed to join the study is far from random and may well not be representative. In order to assess the degree to which participating women differ from their counterparts who live in the area and gave birth over the same time period as the study, we obtained and analyzed vital records from the relevant state health departments (Table 2.3). In Site 1, the participants were similar to the total population with respect to age, but much more highly educated, less likely to be Hispanic and more likely to be non-Hispanic White, and more likely to be nulliparous. In Site 2, participants were again similar by age, but more likely to be White, non-Hispanic than Black or Hispanic, more likely to be nulliparous, and again more highly educated than the total population of the area. Site 3 yielded a study group that was more likely to be Hispanic and less likely to be non-Hispanic White or Black than the total population, more likely to be nulliparous, and similar with respect to education and age.

**Table 2.3**
**Comparison of Mother's Demographic Characteristics of Total Population and Population in the Analysis**

| **Mother's Demographic Characteristics** | **Site 1: percent (n)** | | **Site 2: percent (n)** | | **Site 3: percent (n)** | |
|---|---|---|---|---|---|---|
| | *Total population* | *Study population* | *Total population* | *Study population* | *Total population* | *Study population* |
| Age at pregnancy start | | | | | | |
| 18 – 19 years | 6.2 (354) | 4.77 (52) | 11.5 (1474) | 6.34 (57) | 10.9 (366) | 9.46 (40) |
| 20 – 34 years | 80.5 (4623) | 81.58 (890) | 79.3 (10204) | 82.65 (743) | 79.3 (2663) | 82.51 (349) |
| ≥ 35 years | 13.3 (764) | 13.66 (149) | 9.2 (1187) | 11.01 (99) | 9.8 (329) | 8.04 (34) |
| Race/ethnicity | | | | | | |
| White, non-Hispanic | 46.6 (2669) | 65.81 (718) | 34.3 (4412) | 53.12 (477) | 52.7 (1760) | 36.26 (153) |
| Black, non-Hispanic | 29.0 (1658) | 26.58 (290) | 55.6 (7144) | 41.76 (375) | 18.2 (607) | 23.70 (100) |
| Other, non-Hispanic | 5.0 (287) | 4.86 (53) | 3.2 (410) | 2.78 (25) | 3.7 (123) | 2.61 (11) |
| Hispanic | 19.4 (1113) | 2.75 (30) | 6.9 (890) | 2.34 (21) | 25.4 (848) | 37.44 (158) |
| Parity | | | | | | |
| Nulliparous | 41.6 (2388) | 53.71 (586) | 34.5 (4432) | 47.05 (423) | 34.3 (1129) | 43.50 (184) |
| Parous | 58.4 (3348) | 46.29 (505) | 65.5 (8411) | 52.95 (476) | 65.7 (2160) | 56.5 (239) |
| Education | | | | | | |
| ≤ 12 years | 37.1 (2128) | 18.42 (201) | 50.5 (6276) | 31.4 (282) | 54.8 (1834) | 54.85 (232) |
| 13 – 15 years | 18.3 (1049) | 18.33 (200) | 23.0 (2855) | 23.5 (211) | 21.0 (704) | 25.3 (107) |
| ≥ 16 years | 44.7 (2564) | 63.24 (690) | 26.5 (3287) | 45.1 (405) | 24.2 (811) | 19.86 (84) |

## DEMOGRAPHICS OF ENROLLED WOMEN AND WOMEN IN THE ANALYSIS

Table 2.4 indicates that study participants were ethnically diverse, with a sizable proportion African-American and Hispanic. They were highly educated, on average. Those who enrolled after conception were of 8 weeks' gestation, on average, and those who we were able to enroll prior to conception came under observation approximately 2.5 weeks earlier. The characteristics of those who enrolled and those in the analysis were quite similar overall, providing some evidence that the exclusions were not likely to introduce selection bias.

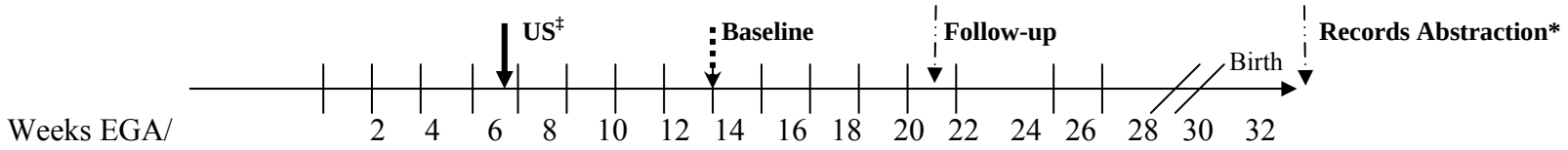
**Table 2.4**
**Demographics of enrolled women (n = 3,132) and of women included in data analysis (n = 2,413 )**

| | Enrolled women | Women in analysis |
|---|---|---|
| Race/ethnicity | | |
| African-American | 1,102 (35.19%) | 769 (31.87%) |
| White | 1,732 (55.30%) | 1,411 (58.47%) |
| Hispanic origin | 276 (8.81%) | 209 (8.67%) |
| Asian/Pacific Islander | 58 (1.85%) | 47 (1.95%) |
| Other | 228 (7.28%) | 176 (7.29%) |
| | | |
| Education | | |
| ≤12 years | 1014 (32.38%) | 715 (29.64%) |
| >12-<16 years | 679 (21.68%) | 518 (21.48%) |
| 16 + years | 1439 (45.95%) | 1179 (48.88%) |
| | | |
| Mean age at enrollment | 28.34 | 28.42 |
| Mean EGA at enrollment (pregnant) | 56.26 | 56.72 |
| Mean EGA at enrollment (converted) | 39.70 | 39.58 |
| Months trying to Conceive while pre-enrolled | 2.37 | 2.35 |
| | | |
| Parity | | |
| 0 | 45.51% | 46.07% |
| 1 | 34.07% | 33.78% |
| 2+ | 20.42% | 20.16% |

## OBTAINING INFORMED CONSENT

All study participants were required to review and sign the *Consent to Participate in a Research Study* form. Whenever possible, study staff met in-person with each enrolled study participant. This meeting was scheduled shortly after the screening interview was completed and eligibility is confirmed. On the rare occasion that meeting in person was not possible, consent forms were sent by mail or faxed and reviewed by telephone. Participants were asked to mail consent forms back to RFTS. Participants who did not sign a consent form did not receive a study ultrasound or have their medical records reviewed. The interviews were conducted with participants regardless of whether signed consent was obtained prior to the interview because, as is customarily accepted, verbal consent was obtained when the participant agreed to complete the interview.

Study staff explained the information on the consent form and answered any questions that the participant had. If RFTS staff recruited in person, if appropriate, they obtained the signed consent once eligibility was determined. Staff were responsible for ensuring that the participant had a clear understanding of what she was being asked to do in the study. The participant should have been made aware of the number and length of telephone interviews, the need to complete an early ultrasound as close to 7–8 weeks gestation as possible, the limited nature of the study ultrasound, that her medical charts would be reviewed at the end of pregnancy, and that she might be asked to participate in other parts of the study in the future.




**‡ ideal window**

*** completed for participants who had a loss of pregnancy and for some women who gave birth**

IDEAL TIME FRAMES AND DEADLINES FOR ULTRASOUNDS AND CATI

All Participants

First Trimester US ideal time: 6 2/7 – 7 5/7 weeks*; no later than 14 0/7 weeks

Baseline CATI: preferably within 2 weeks of enrolling and no later than 16 0/7 weeks

Follow-up CATI: 20 0/7 – 25 0/7 weeks

*Note that in order to avoid ambiguity about duration of pregnancy in partial or completed weeks, the intervals are noted in weeks and fractions of a week (# of days out of 7).

**Figure 2.8 Flow diagram of study activities**

## DATA COLLECTION

Figure 2.8 summarizes the elements and their timing over the sequence of data collection. Note that in order to avoid ambiguity about duration of pregnancy in partial or completed weeks, the intervals are noted in weeks and fractions of a week (# of days out of 7). Key elements are as follows.

### First Trimester Ultrasound

First trimester ultrasounds were conducted on all women enrolled in the study who agreed to do so. The first trimester ultrasound was sought between weeks 6 2/7 and 7 5/7 of pregnancy. Ultrasounds were done no later than 14 0/7 weeks' gestation. In most cases, ultrasounds were scheduled with the participating ultrasound technicians by study staff. In some cases, women already had an appointment with a participating provider. In cases where women already had an appointment with a non-participating provider, they were required to complete an additional ultrasound for the study. Study staff provided assurance that ultrasound results would be sent to the health care provider designated by them for medical care and follow-up. Right from the Start did not provide medical advice or medical care. A participant who had a pregnancy loss prior to getting her study ultrasound did not have an ultrasound.

### Baseline Telephone Interview

The baseline telephone interview was completed 1 to 2 weeks after enrollment and no later than 16 completed weeks' gestation. Battelle, a research and evaluation company with a survey research office in Durham, N.C., 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: 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, and social, household, and income information.

If a participant had a pregnancy loss prior to completing the baseline interview, she only completed a modified version of the baseline interview. The language in the interview was amended to take into consideration the pregnancy loss and sections that were unique to the follow-up interview, such as maternal health and pregnancy history, were added to the modified baseline questionnaire. If a participant did not complete the baseline interview by 16 completed weeks' gestation, regardless of whether or not she had her ultrasound, she did not complete the follow-up interview.

### Follow-Up Telephone Interview

The follow-up interview was completed with participants starting at 20 weeks' gestation. Every attempt was made to complete the follow-up interview during Week 20 and all follow-up interviews were completed no later than 25 weeks' gestation. Battelle conducted the follow-up interview which lasted on average 30 minutes. This interview ascertained changes in water use habits, health behaviors, pregnancy-related symptoms, pregnancy history, medical history, father's characteristics and information regarding prenatal care and delivery choices.

If a participant had a pregnancy loss by the time she was called to complete the follow-up interview, she completed the modified version in which the language had been amended.

Interviewers provided contact information for a counseling or support service for women who had a pregnancy loss.

### Medical Record Abstraction

Medical records could be reviewed for all participants who signed a consent form and who did not withdraw from the study. For women with a pregnancy loss, study staff reviewed and abstracted information from medical records of each participant (Table 2.5). For women who had a live birth in 2001–2003, vital records were used to access key information on pregnancy outcome, namely the date of delivery and the birth weight. For those women who gave birth in 2004 and for whom vital records were not available at the time of data analysis, we abstracted hospital discharge summaries and prenatal care records to obtain this information.

**Table 2.5**
**Information obtained from medical records for women who had a pregnancy loss**

| Categories of data for all prenatal medical records |
|---|
| a) Maternal medical history |
| b) Summary of reproductive history |
| c) Laboratory test results |
| d) Clinical ultrasound and genetic testing |
| e) Blood pressure changes |
| f) Adequacy of care |

| Categories of data for problem visits |
|---|
| a) Symptoms and exam |
| b) Ultrasound findings |
| c) Laboratory results |
| d) Pathology report |
| e) Treatment decision |
| f) Planned clinical follow-up |

**Information obtained from medical records for pregnancies that ended in a live birth**

| Categories of data for all prenatal medical records |
|---|
| a) Pregnancy and birth |
| b) Infant characteristics (weight, apgar, sex, anomalies |
| c) Delivery method |
| d) Preterm type |

## 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/L 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/L. 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/L, and the maximum calibration standard utilized was 150 μg/L. 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/L 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 2.1 and 2.2):

$$\text{TOX } (\mu g\ Cl/L) = \frac{(\text{OX top column} + \text{OX bottom column}) - 2*\text{OX blank}}{\text{Volume (ml) of sample absorbed}} \quad (2.1)$$

$$\text{Breakthrough } (\%) = \frac{(\text{OX bottom} - \text{OX blank})*100}{[(\text{OX top} + \text{OX bottom}) - 2*\text{OX blank}]} \quad (2.2)$$

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/L) 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/L). 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/L) as a function of relative areas. Samples below the practical quantitation limits of 2.0 μg/L for HAA9 and 0.1 μg/L 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.

# CHAPTER 3
# METHODS FOR ASSIGNMENT OF EXPOSURE

## DBP MEASUREMENT RESULTS

### Verification of Study Design

As noted in the site selection portion of the Methodology Section, Sites 1 and 3 were selected for this study because both utilities employ combined chlorine as the terminal disinfectant, and they have different bromide concentrations in their source water leading to different speciation patterns among the halogenated DBPs formed. Because THMs and HAAs are not produced to any significant degree by combined chlorine (Singer 1994, Speitel 1999) it was expected that there would be little spatial variation in DBP concentrations throughout the distribution system of each utility on any given day. Figures 3.1 and 3.2 confirm this for THM concentrations at Sites 1 and 3, respectively. Figure 3.1 shows that, apart from the sample at the point of entry (POE) to the distribution system, indicated by the hydraulic retention time (HRT) of 0 hours, THM4 concentrations at the other six sampling locations at Site 1, with water ages up to 52 hours, were approximately the same, ranging from 51 to 57 µg/L, with essentially the same concentrations for each of the THM species. The POE value is lower than the others because the sample was taken before the ammonia was fully mixed into the finished water. For Site 3, THM4 concentrations were also approximately the same, ranging from 89 to 99 µg/L at the seven sampling locations, including location A which is the POE, and illustrated consistent THM4 speciation. Similar results showing the uniformity in THM4 concentrations were found on the two other system wide sampling occasions for Site 1 and on the one other system wide sampling occasion for Site 3. Likewise, the concentrations of HAA9 and TOX were found to be approximately the same on the two occasions examined for Site 1 and on the one occasion examined for Site 3. Accordingly one of the distribution system sampling stations shown in Figure 3.1 was selected as being an accessible sampling point for Site 1 from which collected samples contained DBP concentrations which would be representative of those concentrations across the entire distribution system. The POE location was selected for a similar purpose at Site 3, with one modification for locations downstream of the booster chlorination stations (see below).

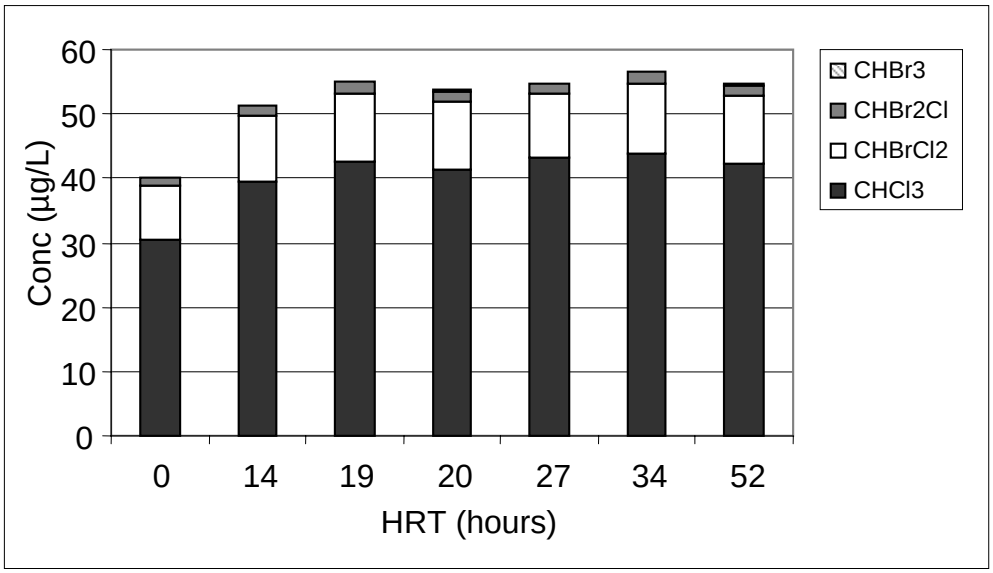



**Figure 3.1 Spatial variability of THM species at Site 1 for different hydraulic residence times (HRTs), February 2003**

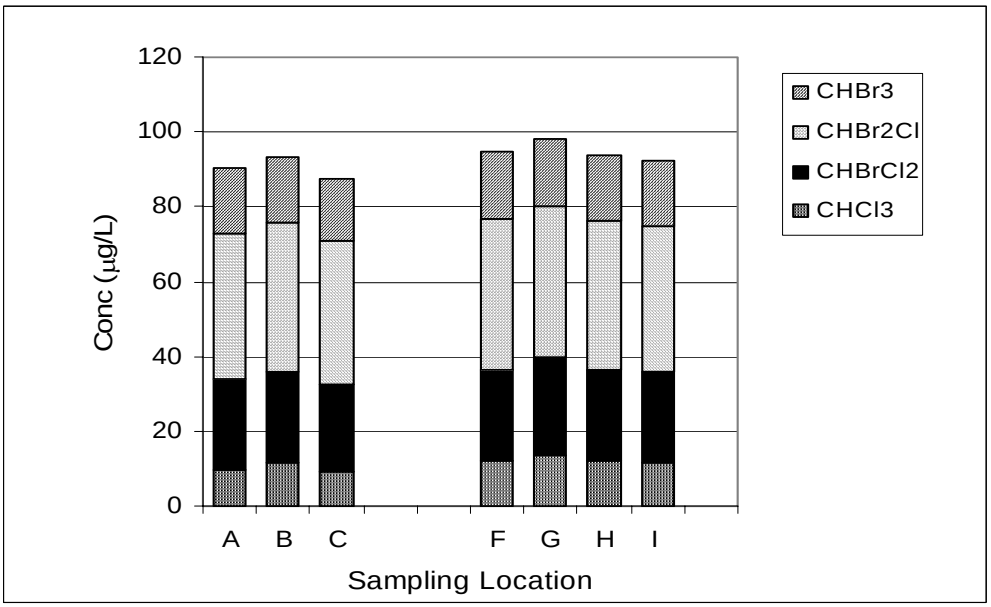



**Figure 3.2 Spatial variability of THM species at Site 3, June 2003**

Figures 3.3 and 3.4 demonstrate the diurnal variation in THM concentrations over several consecutive days at the representative sampling locations selected for Sites 1 and 3, respectively. Samples were collected every 4-6 hours at Site 1 and every 6 hours at Site 3. For Site 1, Figure 3.3 shows that THM4 concentrations were relatively consistent, ranging from 77 to 69 µg/L over

the 4-day sampling period, with an average of 72.5 µg/L and a coefficient of variation of 3%. At Site 3, with the exception of one sampling point, THM4 concentrations were relatively uniform, ranging from 29 to 40 µg/L over the 5-day sampling period, with an average of 34.7 µg/L and a coefficient of variation of 13% (see Figure 3.4). Similar results were found on the three other occasions examined at Site 1 and on the two other occasions examined at Site 3. Accordingly, one sample was analyzed each week at the selected sampling location for that Site and the measured DBP values were assumed to be representative of the weekly DBP concentrations for that site.

THM concentrations at Site 3 were found to increase slightly as a result of booster chlorination, as illustrated in Figure 3.5. The mean increases in $CHCl_3$, $CHBrCl_2$, $CHBr_2Cl$, and $CHBr_3$ concentrations were 1.5, 1.6, 1.4, and 0.8 µg/L, respectively. Accordingly, all subjects receiving water after booster chlorination were assigned the weekly measured THM concentrations at the POE plus the mean increase for each species. No systematic difference was observed for HAA9 and TOX concentrations between the POE location and the location after booster chlorination (see Figures 3.6 and 3.7). Hence, the weekly POE measurements for HAAs and TOX were used for all subjects in the Site 3 system.

In March of each year, Site 1 switches from combined chlorine to free chlorine as its terminal disinfectant in order to control microbial regrowth in their distribution system. Accordingly, weekly samples were taken on the same day at several locations during each week in March and analyzed for THMs, HAAs, and TOX. An illustration of these results for one week is given in Figure 3.8. Noticeable variations in THM concentrations were observed, although there is no consistent pattern of increasing THM levels with increasing water age as expected. Site 3 switched from combined chlorine to free chlorine on one occasion; the switch lasted for three weeks. During this time, weekly DBP samples were collected on the same day at eleven locations. Figure 3.9 shows the illustrative variations in THM levels encountered at Site 3. Because it was impractical to sample at each subject's residence when the utility was using free chlorine, and we had no rational means of assigning DBP concentrations to each residence, it was decided to use the mean of the measured DBP concentrations at each of the sampling locations as the exposure metric for that week. This was done for 12 of the 176 weeks of the study at Site 1 and three of the 106 weeks of the study for Site 3.

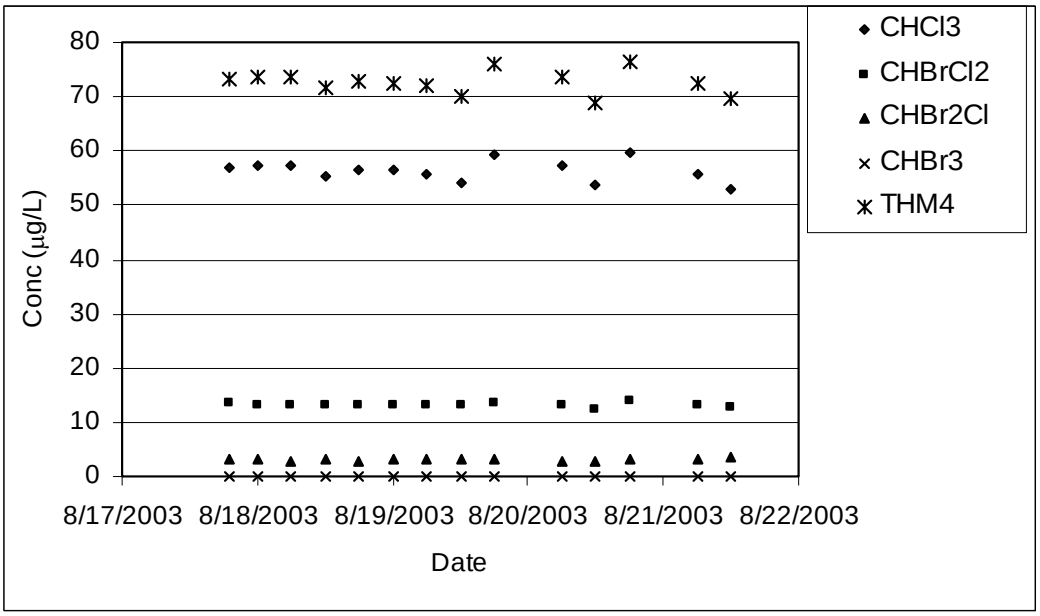



**Figure 3.3 Diurnal variation in THM concentrations at representative distribution system sampling point for Site 1**

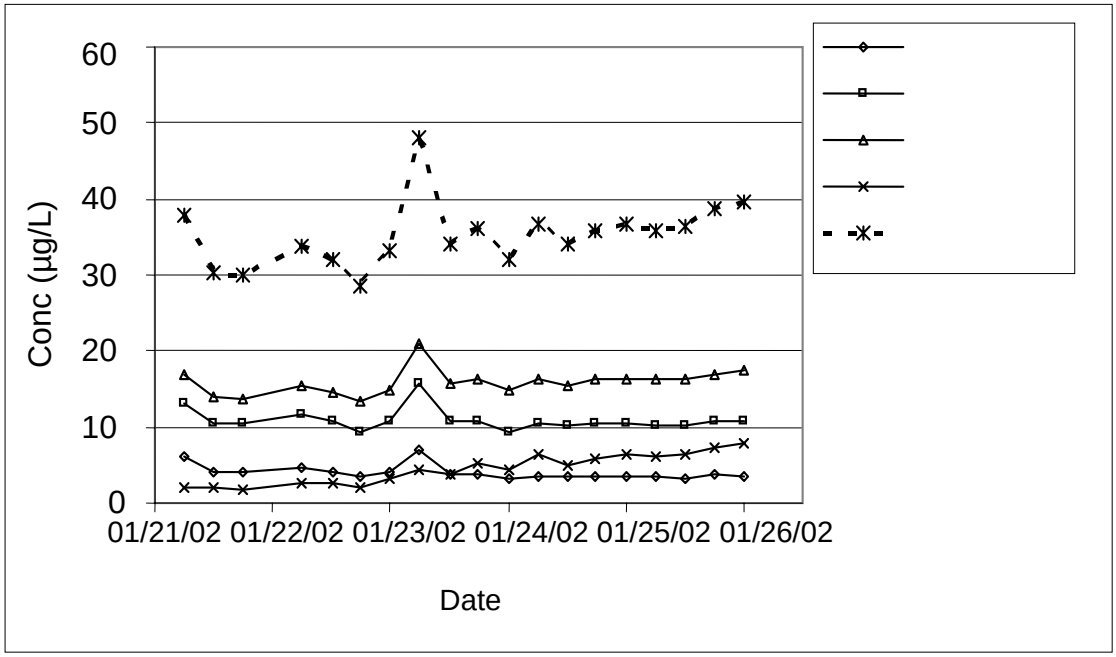



**Figure 3.4 Diurnal variation in THM concentrations at representative distribution system sampling point for Site 3**

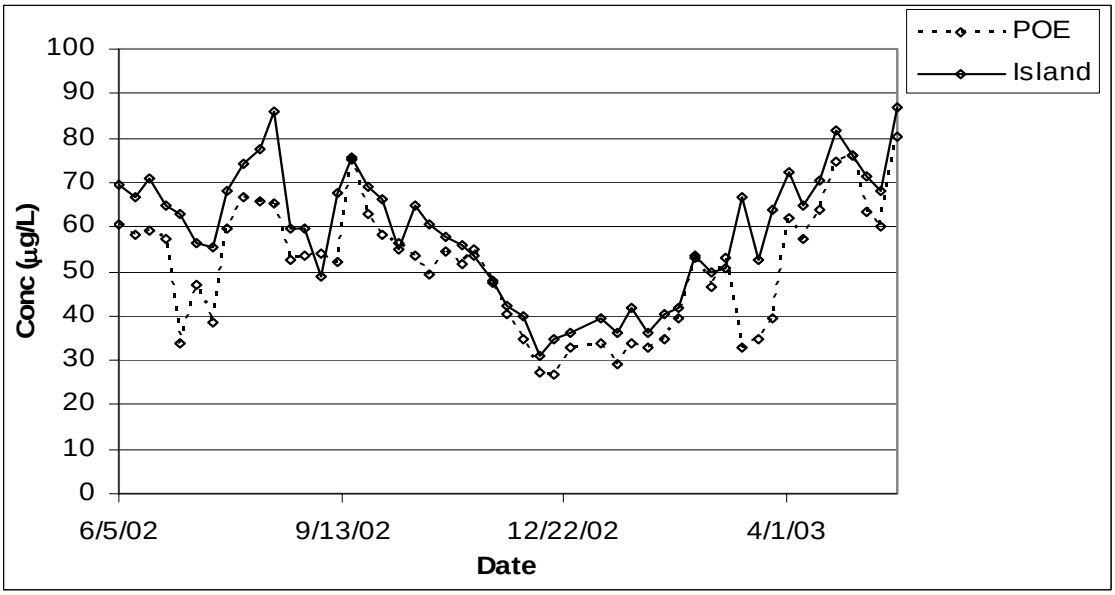



**Figure 3.5 THM4 concentrations at the POE and after the booster chlorination station at Site 3**

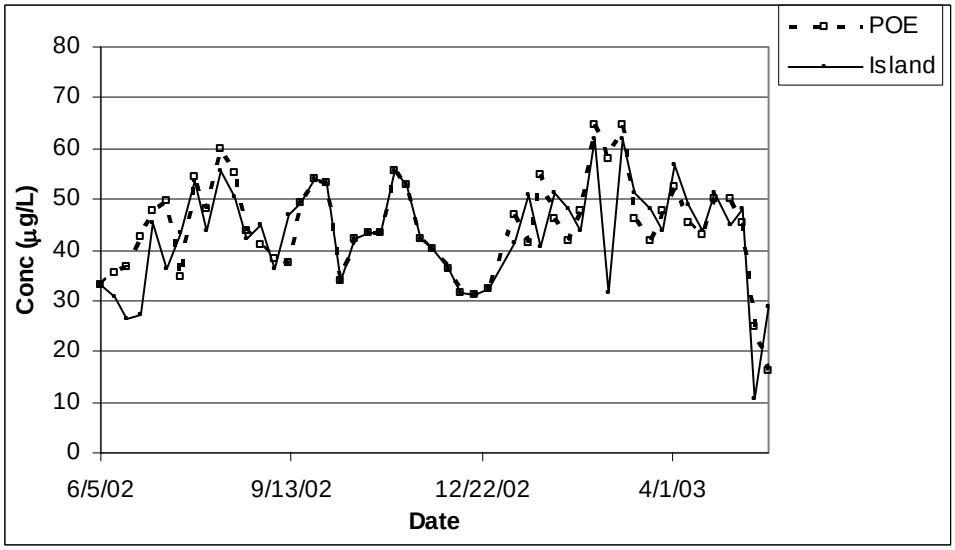



**Figure 3.6 HAA9 concentrations at the POE and after the booster chlorination station at Site 3**

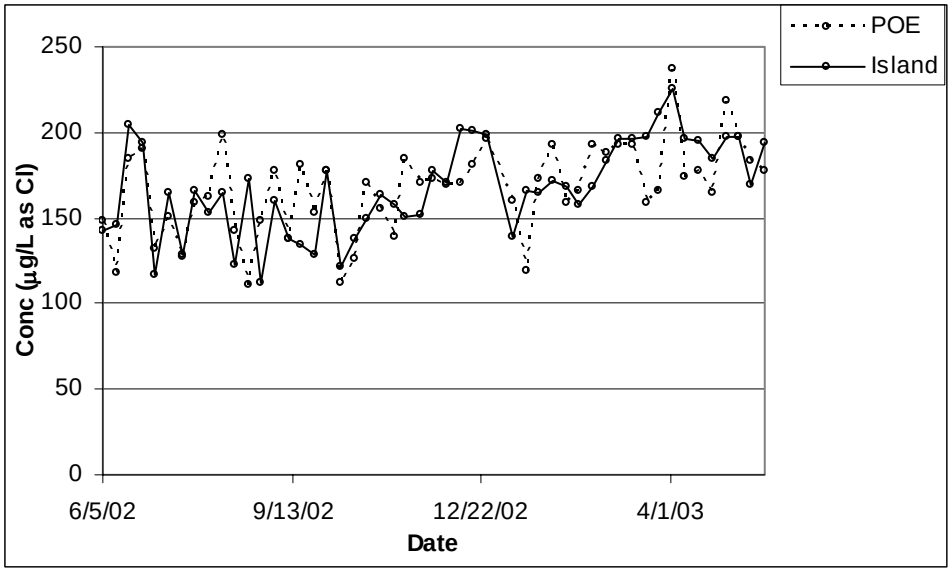



**Figure 3.7 TOX concentrations at the POE and after the booster chlorination station at Site 3**

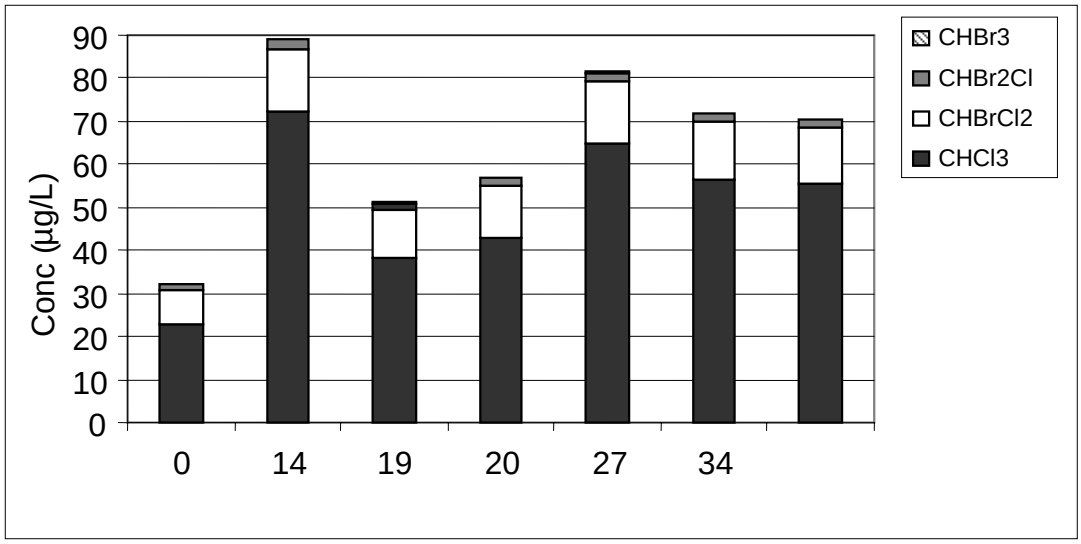



**Figure 3.8 Spatial variability in THM concentrations at Site 1 when utility used free chlorine in the distribution system, March 12, 2003**

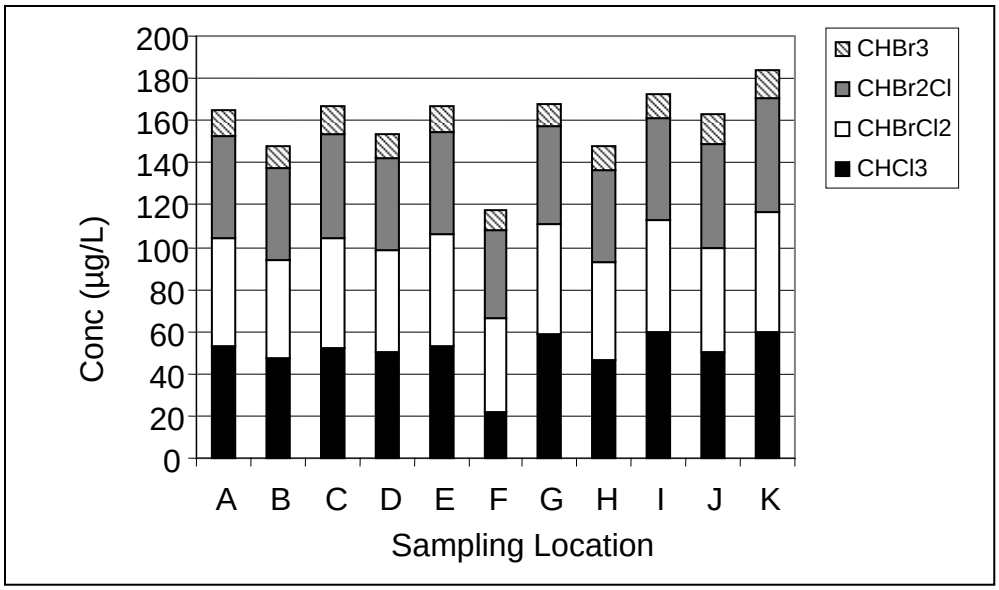



**Figure 3.9 Spatial variability in THM concentrations at Site 3 when utility used free chlorine in the distribution system, October 15, 2003**

**Record of Weekly THM4, HAA9, and TOX Concentrations at Sites 1, 2, and 3**

Figures 3.10–3.19 illustrates the weekly THM4, HAA9, and TOX concentrations at the three study sites. At Site 1, the fully chlorinated DBP species were the dominant species found, as expected for this utility with low concentrations of bromide in its raw water source. Figure 3.10 shows that chloroform is the dominant THM species for Site 1, with tap water concentrations ranging from about 20 to 120 µg/L over the 40-month monitoring period. Overall THM4 concentrations ranged from about 30 to 150 µg/L. A pronounced seasonal pattern was observed, with peak concentrations occurring in the summer months, and lower concentrations in the winter months A second peak in THM levels is seen in March 2001 when the utility switched from combined chlorine to free chlorine to control microbial regrowth.

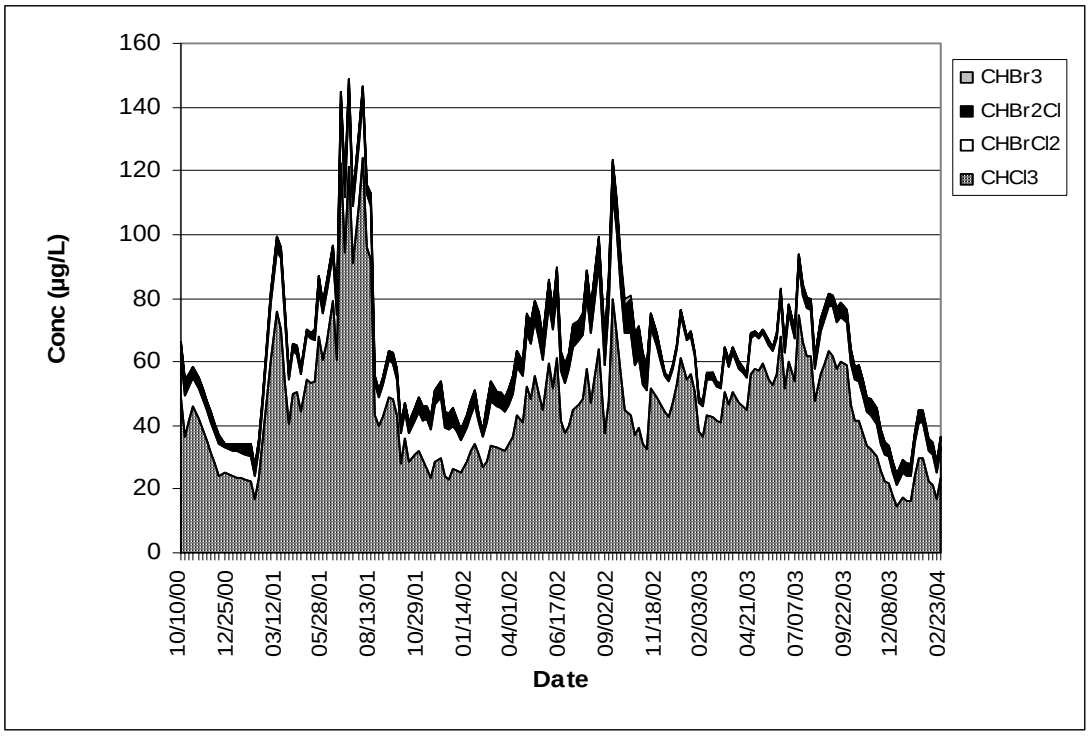



**Figure 3.10 Weekly measured THM concentrations at Site 1**

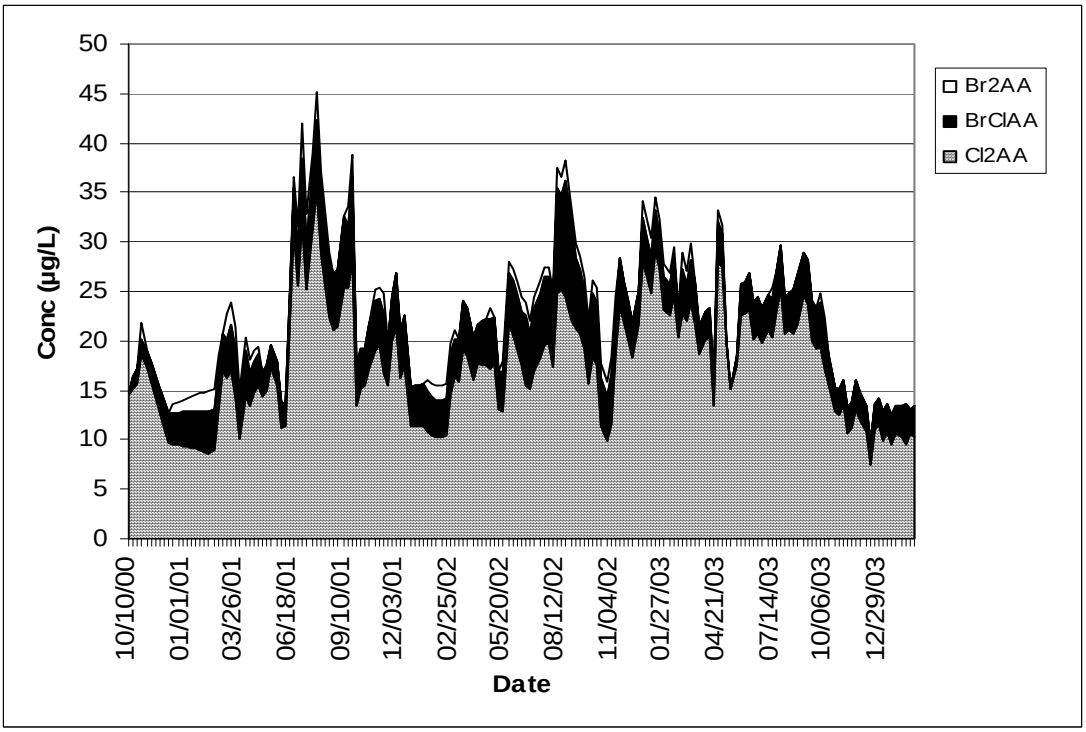



**Figure 3.11 Weekly measured dihalogenated acetic acid concentrations at Site 1**

Dichloroacetic acid ($Cl_2AA$) was the dominant dihalogenated HAA species (see Figure 3.11) and trichloroacetic acid ($Cl_3AA$) was the dominant trihalogenated HAA species (see Figure 3.12) at Site 1. Total HAA9 concentrations ranged from 15 to 79 µg/L at Site 1 over the 41-month monitoring period. TOX concentrations ranged from 120 to 270 µg/L as Cl at Site 1 (see Figure 3.13).

Figures 3.14 and 3.15 show the weekly average THM and TOX concentrations, respectively, for Site 2, the control site selected because of its low levels of DBPs. THM4 concentrations ranged from 2 to 16 µg/L, and TOX concentrations ranged from about 10 to 27 µg/L. Both ranges are far below the levels observed for Site 1. HAA9 plots are not shown because each of the HAA species had concentrations near or below the detection limits for the HAAs (2 µg/L).

The DBP species at Site 3 were dominated by the bromine-containing species, as expected. Figure 3.16 shows that chloroform constituted less than 25% of the overall THM4 concentration and was the second lowest abundant species. Dibromochloromethane ($CHBr_2Cl$) was the THM species found at the highest concentration; bromodichloromethane ($CHBrCl_2$) was the second most abundant THM species at Site 3. Overall THM4 concentrations ranged from about 30 to165 µg/L over the 24-month monitoring period, with a pronounced peak occurring in October 2003 when the utility switched from combined chlorine to free chlorine. Discounting the October 2003 peak, THM4 concentrations ranged from about 30 to 80 µg/L. Seasonal variations in THM levels were less apparent than at Site 1.

HAA concentrations at Site 3 were dominated by the bromine-containing species as shown in Figures 3.17 and 3.18 for the di- and trihalogenated HAAs, respectively. Overall HAA9 concentrations ranged from 30 to 99 µg/L over the 24-month monitoring period. The October 2003 peak was more pronounced for the dihalogenated HAAs than for the trihalogenated HAAs. TOX concentrations ranged from 120 to 280 µg/L as Cl (see Figure 3.19). Total organic bromine (TOBr) was not measured, but it is likely that the majority of the TOX consisted of brominated organic compounds.

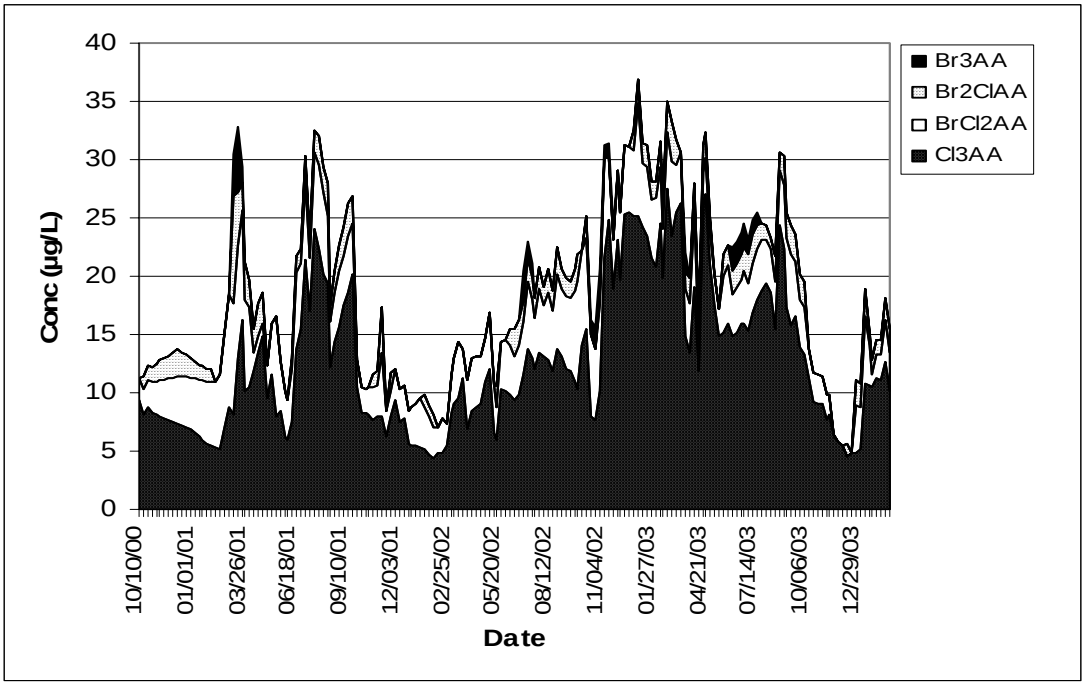



**Figure 3.12 Weekly measured trihalogenated acetic acid concentrations at Site 1**

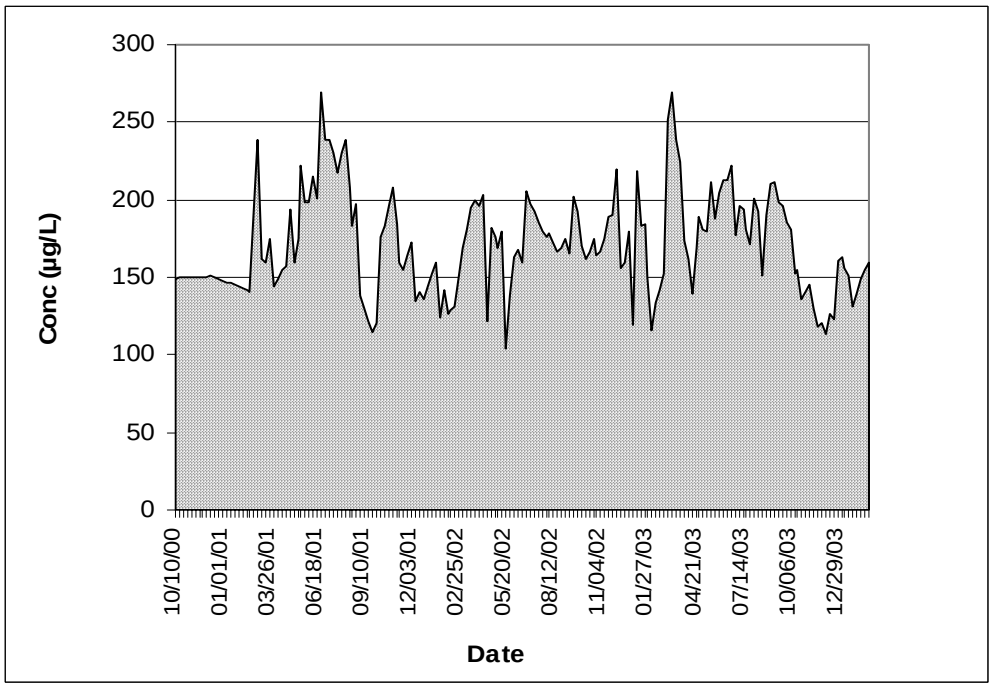



**Figure 3.13 Weekly measured TOX concentration at Site 1**

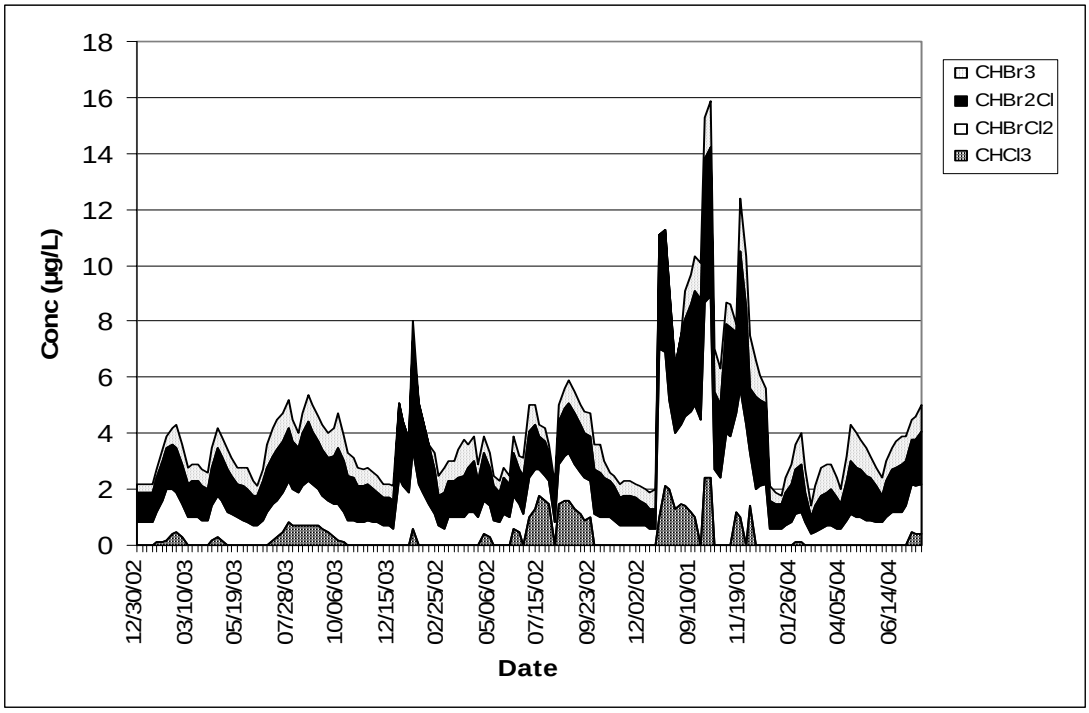



**Figure 3.14 Weekly measured THM concentrations at Site 2**

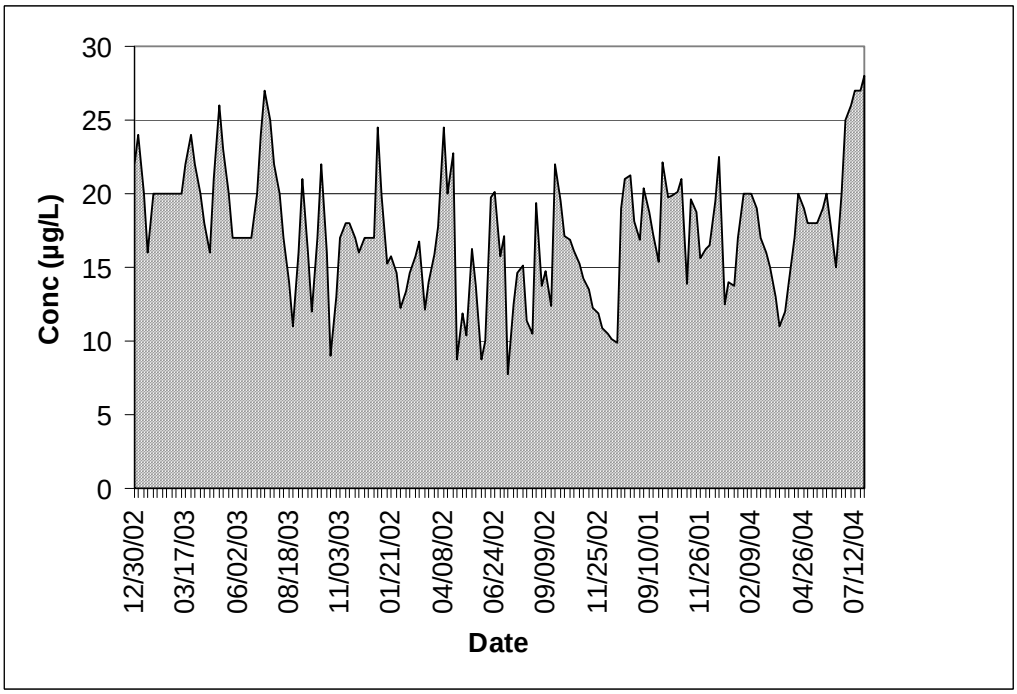



**Figure 3.15 Weekly measured TOX concentration at Site 2**

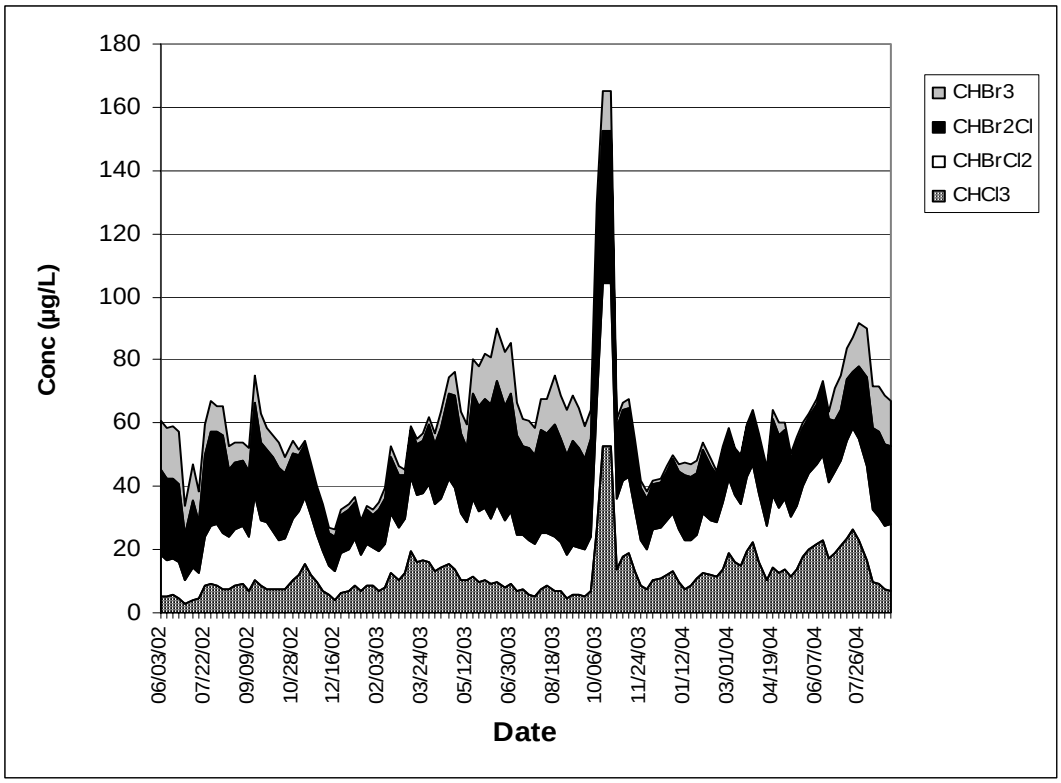



**Figure 3.16 Weekly measured THM concentrations at Site 3**

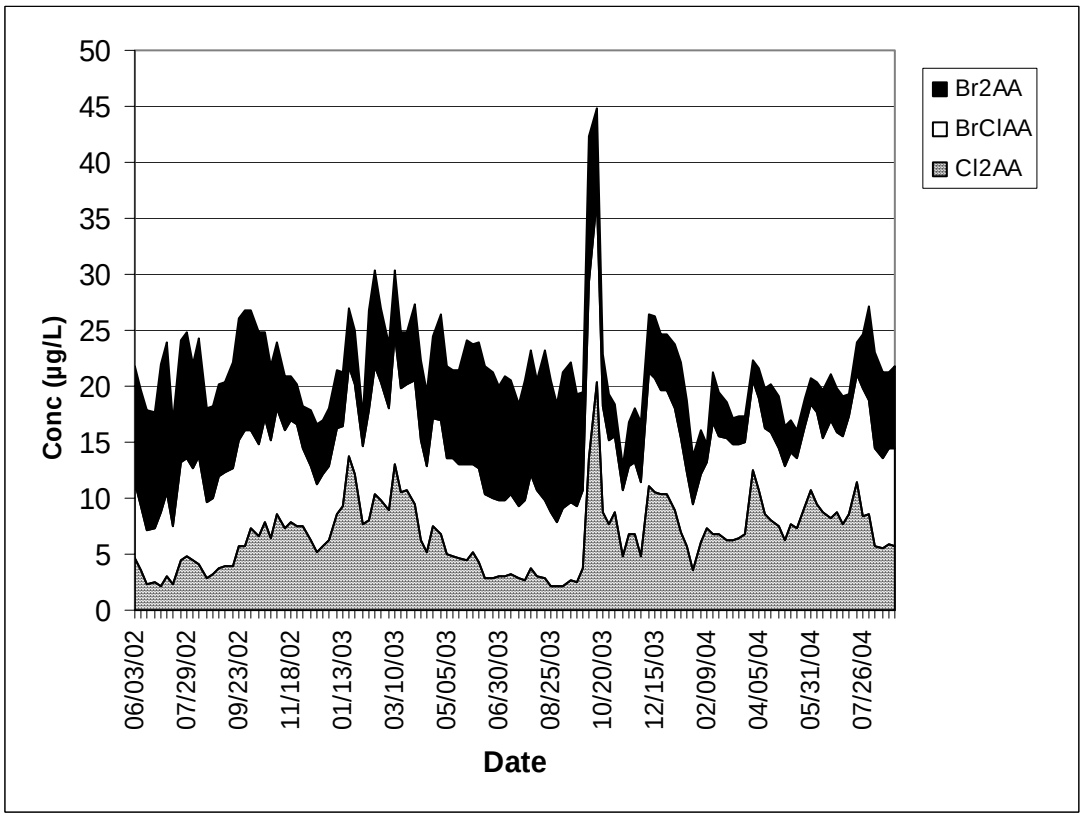



**Figure 3.17 Weekly measured dihalogenated acetic acid concentrations at Site 3**

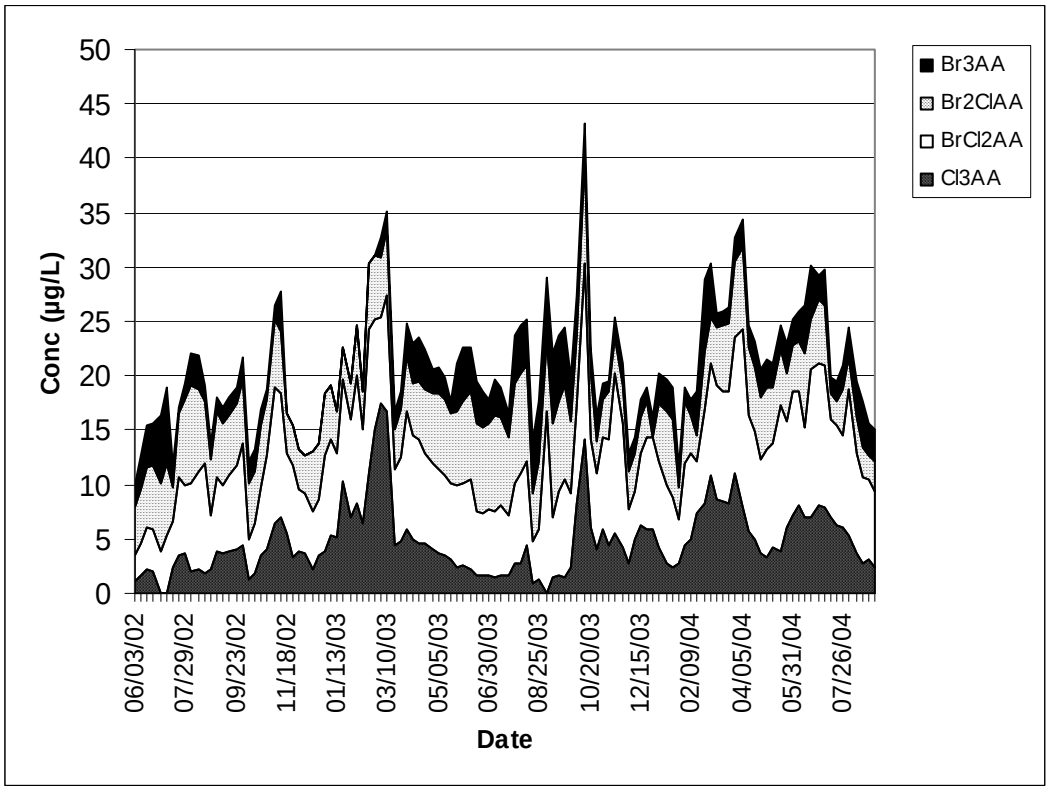



**Figure 3.18 Weekly measured trihalogenated acetic acid concentration at Site 3**

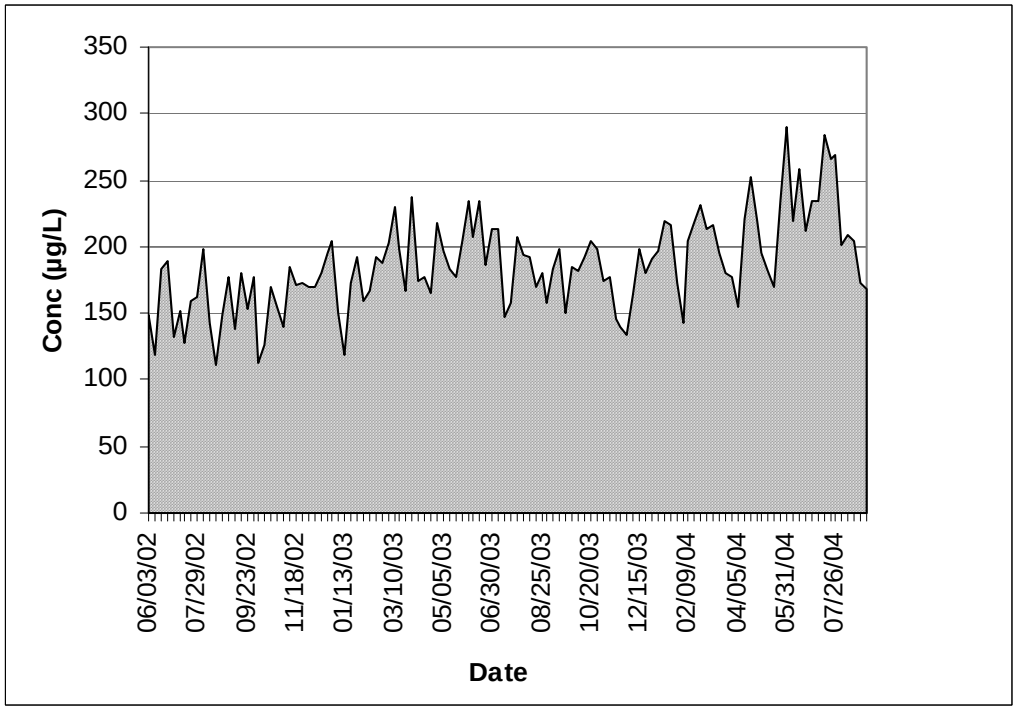



**Figure 3.19 Weekly measured TOX concentration at Site 3**

**Comparative Distribution of DBP Species at the Three Study Sites**

Figures 3.20–3.22 are cumulative frequency distribution curves showing the distribution of THM4, HAA9, and TOX, respectively, for all of the monitoring data collected at Sites 1, 2, and 3. The median THM4 concentrations are 60.7 µg/L at Site 1, 57.8 µg/L at Site 3, and 3.6 µg/L at Site 2 (see Figure 3.20). The median HAA9 concentrations are 41.5 µg/L at Site 1 and 44.7 µg/L at Site 3 (see Figure 3.21). The median HAA9 concentration at Site 2 was 3.3 µg/L (not shown). For TOX, the median concentrations were 171 µg/L at Site 1, 180 µg/L at Site 3, and 15.9 µg/L at Site 2 (see Figure 3.22). The cumulative frequency distributions of each of the THM and HAA species at all three sites are given in the Appendix.

Despite the difference in THM and HAA speciation for Sites 1 and 3, the distributions of all three DBP measures for Sites 1 and 3 were similar, and were quite different from the distribution at Site 2, the control site.

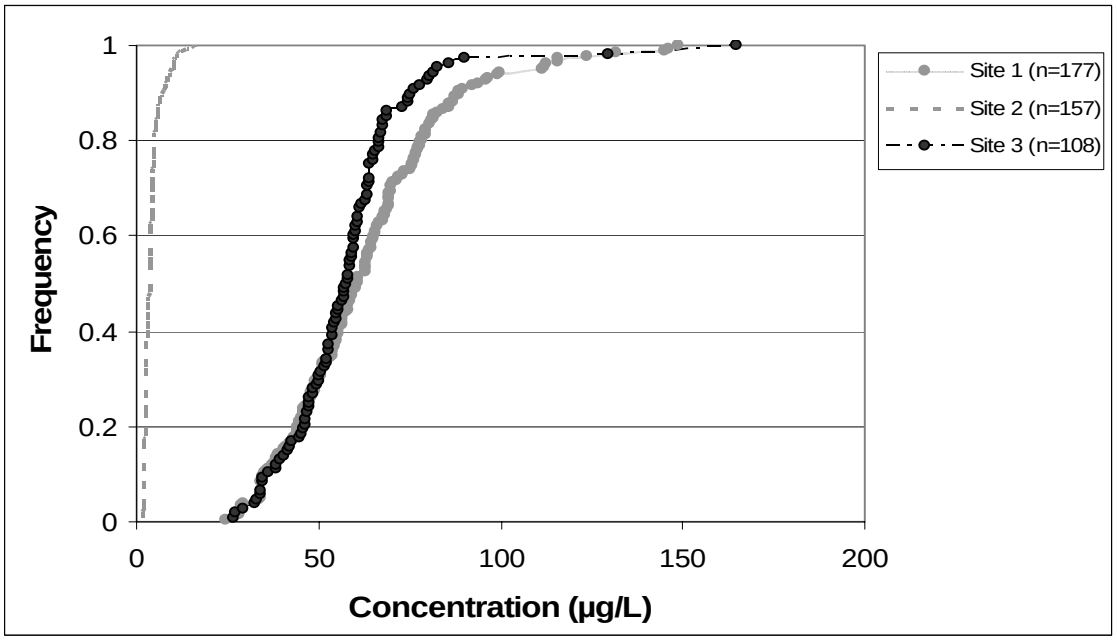



**Figure 3.20 Cumulative frequency distribution of THM4 concentration at Sites 1, 2, and 3**

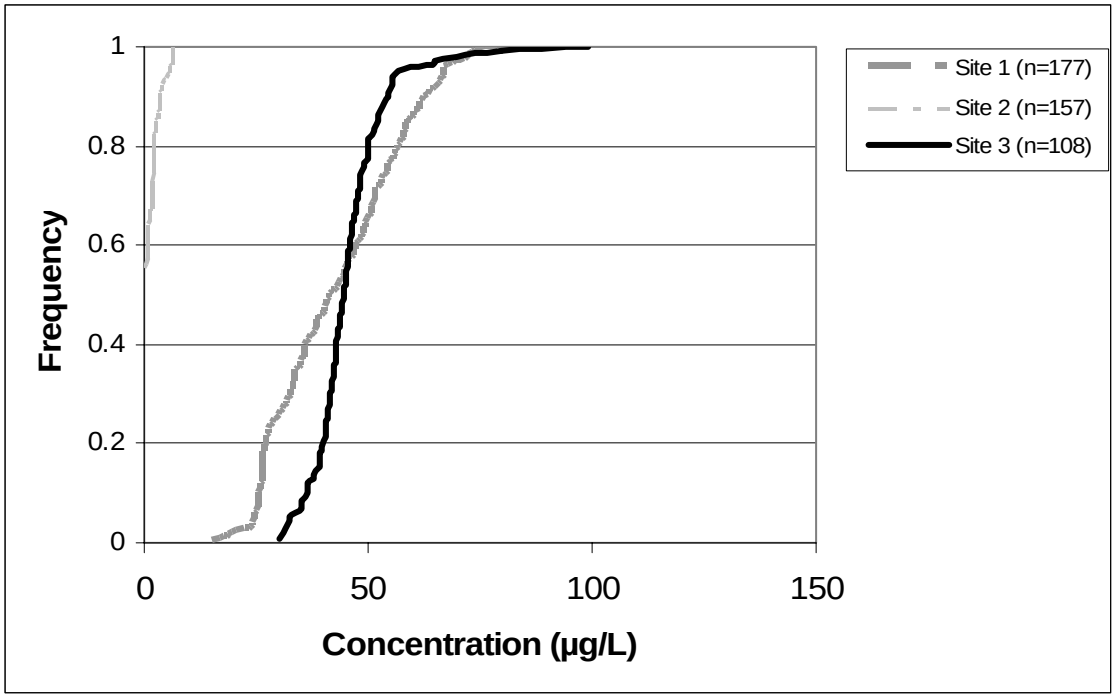



**Figure 3.21 Cumulative frequency distribution of HAA9 concentration at Sites 1, 2, and 3**

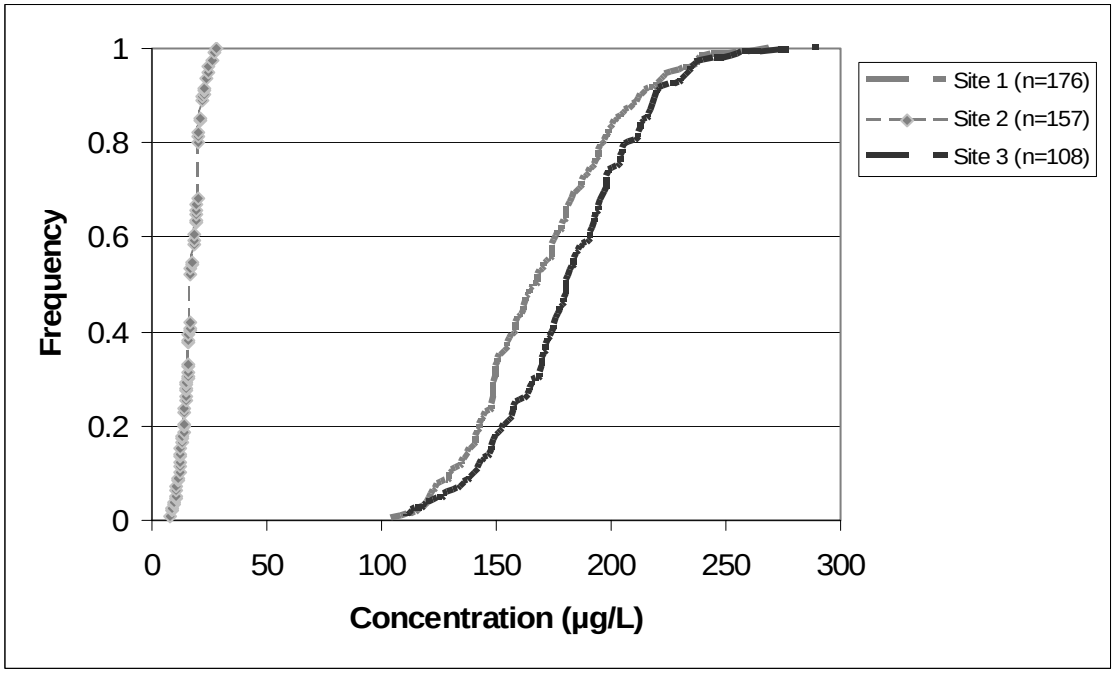
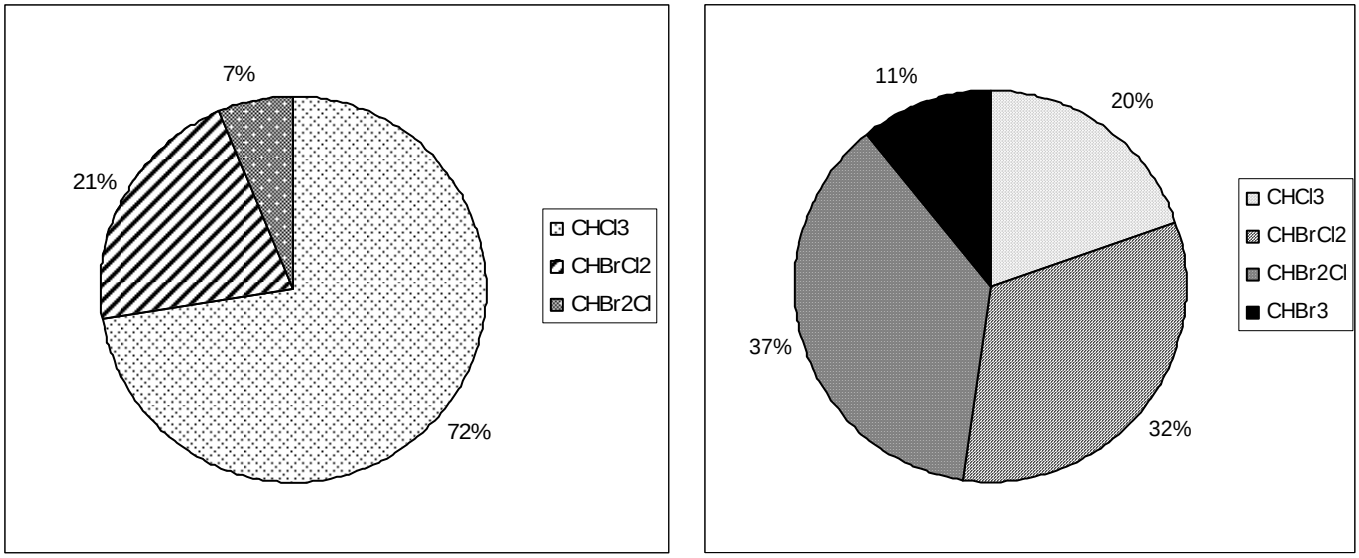
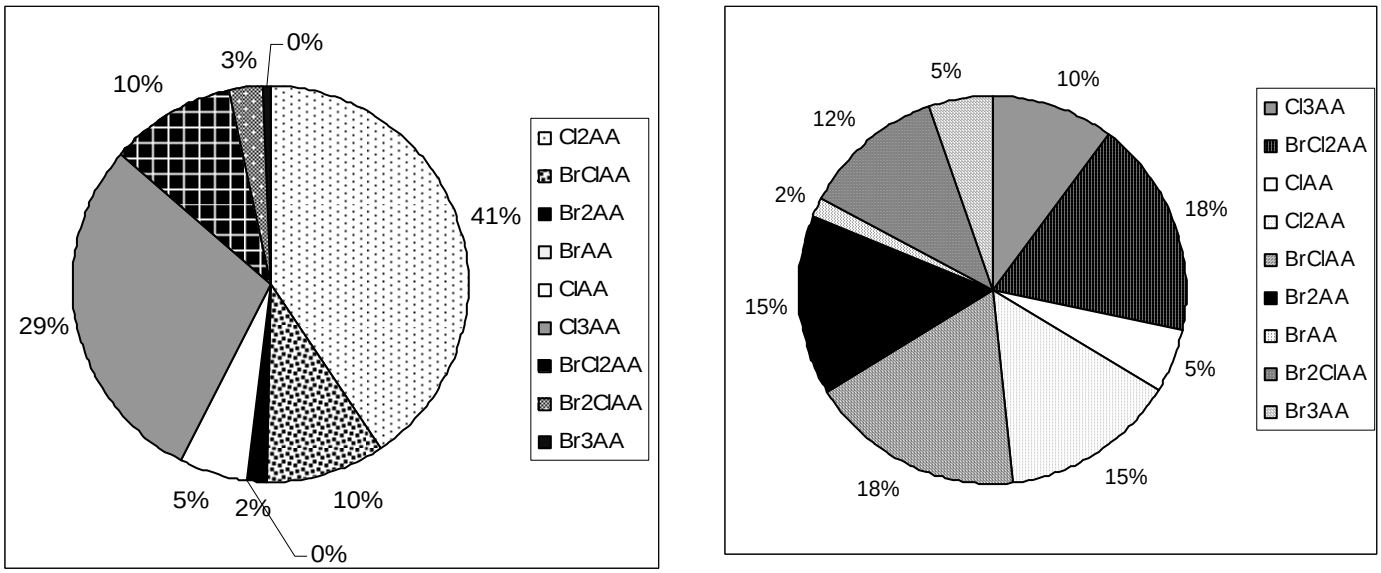



**Figure 3.22 Cumulative frequency distribution of TOX concentration at Sites 1, 2, and 3**

The mean THM4 and HAA9 concentrations at Sites 1 and 3 and the corresponding distribution of THM and HAA species are shown in Figures 3.23 and 3.24, respectively. The mean THM4 and HAA9 concentrations are similar, but the distributions among the fully chlorinated and bromine-containing species are distinctly different.




Site 1: Mean THM4 = 63.3 ± 17.2 µg/L; Site 3: Mean THM4 = 60.5 ± 13.4 µg/L
**Figure 3.23 Mean THM speciation for Sites 1 and 3**




Site 1: Mean HAA9 = 43.2 ± 12.4 µg/L; Site 3: Mean HAA9 = 45.7 ± 6.0 µg/L
**Figure 3.24 Mean HAA speciation for Sites 1 and 3**

**Exposure Assessment Metrics**

The basis for selecting specific DBPs for analysis was guided by several considerations. First, the contribution of individual and groups of chemicals to the total amount of DBPs was considered, favoring those present in larger amounts all other considerations equal. Second, evidence from toxicology regarding potential reproductive toxicity was considered, encouraging evaluation of the agents most likely to be directly responsible for adverse reproductive effects, should any be found. Third, previous epidemiologic studies were considered, following leads that they suggested and more generally addressing a number of the same agents as others had studied. Fourth, the availability of monitoring data and the status of regulation was considered.

The following parameters were selected as exposure assessment metrics for the epidemiological analyses that follow in subsequent sections of this report:

- THM4
- $CHCl_3$
- $CHBrCl_2$
- HAA5
- HAA9
- TOX
- THM-Br
- HAA-Br

THM4 is included because it represents the sum of the concentrations of all four chlorine- and bromine-containing THM species and is a regulated parameter. Chloroform ($CHCl_3$) is included because of the major body of literature on this particular THM species. Bromodichloromethane ($CHBrCl_2$) is included because it has been singled out in a number of epidemiological and toxicological studies as the THM species most closely associated with adverse reproductive and developmental outcomes, including spontaneous abortion (e.g. Waller et al. 1998). HAA5 represents the sum of the concentrations of monochloroacetic acid (ClAA), monobromoacetic acid (BrAA). dichloroacetic acid ($Cl_2AA$), dibromoacetic acid ($Br_2AA$), and trichloroacetic acid ($Cl_3AA$) and is a regulated measure of HAA occurrence. HAA9 is included because it represents the sum of the concentrations of all nine chlorine- and bromine-containing HAA species (HAA5 plus bromochloroacetic acid (BrClAA), bromodichloroacetic acid ($BrCl_2AA$), dibromochloroacetic acid ($Br_2ClAA$), and tribromoacetic acid ($Br_3AA$), and is a more complete measure of total HAA occurrence. TOX is included because it represents the presence of all organo-halogenated DBPs in the water, although it does not distinguish between chlorinated and brominated organic compounds. THM-Br and HAA-Br represent the sum of all of the bromine-containing THMs and HAAs, respectively, and are included as exposure metrics because of the body of literature suggesting that bromine-containing DBPs are of greater health concern than their fully chlorinated counterparts.

Table 3.1 is a summary of these eight exposure metrics for all three Sites in terms of their mean, median, maximum, and minimum concentrations. Starting with this list of agents of interest, we examined correlations among them. If two or more agents were very highly correlated with one another (correlation coefficient of 0.8 or greater), it would make it difficult if not impossible to distinguish potential effects of one from another. While correlations of some magnitude were observed, they were not so large as to preclude attempts to examine individual agents, so that this was not a major consideration in the final decisions. However, we did use this to decide which of the chosen indices to highlight in the results. Integrating all the considerations

above, we chose to focus on three primary indices: THM4 (the sum of the four chlorine and bromine containing THMs), bromodichloromethane, and HAA9 (the sum of the 9 HAA levels). Total THMs are the most widely studied class of agents in prior epidemiologic studies, bromodichloromethane is the single agent most directly implicated for reproductive toxicity in those studies, and HAA9 reflects the set of chemicals which is more likely to include directly toxic agents and ones that are of increasing potential regulatory interest. Analyses based on these agents are presented and discussed in some detail in the body of the report, with the others considered but in less detail.

**Table 3.1**
**Summary of DBP exposure assessment variables at the three study sites**

| Location | Mean concentration (µg/L) | Median concentration (µg/L) | Maximum concentration (µg/L) | Minimum concentration (µg/L) |
|---|---|---|---|---|
| **Site 1** | | | | |
| THM4 | 63.3 | 60.7 | 149 | 24.7 |
| $CHCl_3$ | 45.6 | 43.5 | 124 | 14.7 |
| $CHBrCl_2$ | 13.8 | 12.5 | 33.3 | 6.8 |
| THM-Br | 17.8 | 16.2 | 43.5 | 9.0 |
| HAA5 | 33.2 | 31.9 | 62.2 | 12.1 |
| HAA9 | 43.2 | 41.5 | 78.9 | 15.4 |
| HAA-Br | 10.8 | 10.2 | 28.7 | 1.9 |
| TOX | 172 | 171 | 269 | 104 |
| **Site 2** | | | | |
| THM4 | 4.2 | 3.6 | 15.9 | 1.4 |
| $CHCl_3$ | BMRL | BMRL | 2.4 | BMRL |
| $CHBrCl_2$ | 1.5 | 1.1 | 6.5 | BMRL |
| THM-Br | 3.9 | 3.4 | 13.5 | 1.4 |
| HAA5 | BMRL | BMRL | 3.1 | BMRL |
| HAA9 | 3.5 | 3.3 | 6.5 | BMRL |
| HAA-Br | BRML | BMRL | 6.4 | BMRL |
| TOX | 16.5 | 15.9 | 28.0 | 7.7 |
| **Site 3** | | | | |
| THM4 | 60.5 | 58.9 | 165.0 | 26.6 |
| $CHCl_3$ | 11.9 | 10.1 | 52.7 | 3.0 |
| $CHBrCl_2$ | 19.6 | 18.8 | 51.7 | 7.1 |
| THM-Br | 48.5 | 46.2 | 112.3 | 21.4 |
| HAA5 | 21.5 | 20.0 | 53.1 | 13.2 |
| HAA9 | 45.7 | 44.7 | 98.9 | 30.4 |
| HAA-Br | 32.0 | 31.4 | 55.7 | 20.4 |
| TOX | 186 | 183 | 290 | 111 |

BMRL: Below minimum reporting level. In calculating the concentrations for group parameters, the concentrations of individual species that were below the minimum reporting level (MRL) were assigned a value of zero. Assignment of BRML values to a group parameter indicates that the concentrations of the individual species constituting the group parameter was below the minimum reporting level.

## DETERMINATION OF EXPOSURE ADJUSTMENT FACTORS

### Objectives

Because DBP levels in tap water may be altered if the consumer employs a point of use treatment device or boils water prior to ingestion, it was necessary to adjust the tap water concentrations to take these factors into account. While a number of studies have been published exploring such changes, the different outcomes of these previously published investigations, makes it a difficult task to make adjustments to tap water levels of DBPs based on home-based pretreatment prior to consumption. Thus, in support of this epidemiological study, the effect of various handling and pretreatments on tap water collected from Site 1 was studied. This included an evaluation of point-of-use (POU) filtration systems, tap water boiled via microwave and kettle, frozen tap water (ice) added to beverages, and commonly consumed bottled water brands. Four POU devices were studied in homes within the Site 1 distribution systems and two POU devices were further examined in a controlled laboratory experiment simulating a tap water closer in DBP concentrations to that of Site 3. The effect of boiling and freezing on DBP levels in tap water were also examined in the laboratory under conditions similar to those employed in the study participants' homes.

### Approaches and Results

#### *POU Study*

Four POU filtration devices identified from questionnaires as among those most commonly used by study participants were purchased from retail stores in the same region as the Site 1 cohort (see Table 3.2). All tested residential filters contain activated carbon for organics removal, and pitcher models additionally have an ion exchange resin for total dissolved solids reduction. Table 1 displays specifications on the four filtration units examined. The model, lot number of the cartridges examined, cost of the units, and filter types are listed. The manufacturer's inserts also list ideal operating conditions for each unit and provide information about contaminant removal. Chlorine and THM4 removal claims (shown in Table 3.2) are calculated based on NSF International (an independent party) testing and certification (ANSI/NSF Standard 53).

Each filtration unit was installed and used according to the manufacturers' packaged directions in representative Site 1 homes. Duplicate samples for THM4 and HAA9 analysis, but only a single TOX sample, were collected weekly from the tap (influent) and the filter effluent. POU samples were analyzed in the same analytical batch as routine weekly Site 1 samples and therefore additional samples for matrix spikes were not collected from the homes as these were already included in the quality control for the routine analyses. All home-POU sampling was carried out from April–July 2003 while Site 1 was utilizing chloramination for disinfection. Tap water (influent) was collected either directly before or after the water was used in the filtration devices to create the sampled filter effluent. A journal was kept for each POU to determine the approximate volume of water filtered between collections. When not in use, the pitchers were stored on the countertop with water in contact with the filter. Pitcher filter effluent samples were collected directly after filtrate accumulated by pouring water from a full pitcher of filtered water into the collection vials. This enabled measurement of DBPs directly after filtration, without sitting time during which DBPs might volatilize. Samples were collected, approximately every eight gallons (16 pitchers), from both pitchers until the capacity (40 gal) was exceeded.

The faucet-mounted models, studied at one of the locations in the Site 1 service area, remained screwed onto the kitchen tap faucet throughout the sampling period. The faucet-mounted filters were run in the filtering position for approximately 5 seconds prior to effluent collection (as recommended by the manufacturer).

**Table 3.2**
**Point-of-use devices**

| | PUR Advantage Pitcher | BRITA Classic Pitcher | BRITA On-Tap Faucet Filter | PUR Ultimate Faucet Filter |
|---|---|---|---|---|
| Testing site | Site 1M | Site 1M, lab | Site 1D | Site 1D, 1M, lab |
| Style | Pitcher | Pitcher | Faucet-mounted | Faucet-mounted |
| Model nos. system/cartridge | CR-1500R/CRF-1550 | OB01/OB03 | FF-100 / FR-200 | FM-4700-L |
| Lot # | 22834223 | B14024 226 | 19529.100XP1 | 1-M, 36242230(1) lab, 3353422301 |
| Cost (unit/replacement cartridge) | $18/$10 | $20/$6 | $30/$15 | $40/$20 |
| Filter type | Activated carbon ion exchange resin | Activated carbon ion exchange resin | Activated carbon | Activated carbon |
| Capacity | 40 gal (151 L) | 40 gal (151 L) | 100 gal (378 L) | 100 gal (378 L) |
| (Rated) Service flow rate: | 2 gal/day | N/A | 0.67 gpm (2.54 L/min) | 0.66 gal/min @ 60 psi |
| Working pressure (minimum/maximum) | N/A | N/A | 20/100 psig | 20/100 psi |
| Filtered water temp (minimum/maximum) | 34/82°F | 32/85°F | 34/100°F | 34/100°F |
| Chlorine removal[1] *(average/minimum influent conc.)* | 97.3%/88% *(1.9/2.1 mg/L)* | 98/95% *(2.0 mg/L)* | 99.9%/99.9% *(2.0 mg/L)* | 98%/97% *(1.9/2.0 mg/L)* |
| THM4 reduction[1] *(average/minimum influent conc)* | 98%/95% (0.415/0.43 mg/L) | Not reported | Not reported | 98.5/96.9 (0.4/0.46 mg/L) |

[1]Testing carried out by NSF International and published in manufacturer's performance data sheet inserts

Two of the POUs evaluated in the home study were examined more thoroughly in the laboratory using a simulated tap water prepared from laboratory tap water spiked with a cocktail of THM4 (131 to 259 μg/L) and HAA9 (110 to 203 μg/L). Effluent water was collected from the first filtered pitcher, and every 16th pitcher, or 8 gal, thereafter until 80 gall total had been filtered (11 collections). A 12-gal influent reservoir tank was refilled when it reached the 1-gal marker. Samples for HAA9 and THM4 analysis were collected in duplicate while only a single TOX sample was collected from both the pitcher effluent and the influent. An additional duplicate was collected from the pitcher effluent every third collection to serve to prepare a matrix spike for THM4 and HAA9 analysis. The total and free chlorine residuals in the influent and effluent were measured during every collection.

A similar study was carried out in a faucet-mounted PUR Ultimate POU filter. Effluent water was collected from the first liter of filtered water and every 20 gal thereafter until the filter monitor on the faucet mount housing indicated that the filtration cartridge was expired (110 gal, 110% capacity). At this time there was also sufficient back pressure to dramatically drop the rate of effluent flow. Spiked tap water was pumped through the filter and the filtrate was collected in a 5-gal collection tank. Once the collection tank was full of filtrate it was emptied and this was repeated so that 10 gal were filtered daily. In order to collect samples for DBP and chlorine residual analysis, at the end of every 20 gal, a 1-L Erlenmeyer flask was used in place of the 5-gal tank to collect 1 L of filter effluent. Collection of filter influent for analysis was achieved by switching the system to the off (bypass filter) position and a 1-L Erlenmeyer flask was placed below the POU to receive the filter influent that had cycled through the pump, but bypassed the POU. This water was used for influent sample collection and chlorine residual measurement. Duplicate HAA9 and THM4 and single TOX analyses were performed for each sample collected. An additional duplicate was collected from the filter effluent every third collection to serve for a matrix spike. The influent reservoir tank was refilled with 10 gal of the spiked tap water after every 10 gal that passed through the pump and filter.

All POU devices removed greater than 80% of THM4 in the tap water during use of up to 20% of faucet-mounted POU capacity, and 100% of pitcher POU capacity. The filtration devices removed greater than 60% of HAA9 and TOX initially, but removal was varied and declined about 20% over the 40-gal pitcher POU capacity. The faucet-mounted POU devices were not examined over their entire 100-gal capacity. THM4 and HAA9 constitute approximately half of the TOX in the influent but only about a quarter of the TOX in the POU-filtrate. This suggests that THM4 and HAA9 are preferentially removed by the POUs compared to the unidentified components of the TOX.

Two POU devices were studied in the laboratory with DBP-spiked, chlorinated tap water in order to monitor the POU devices' effect on removal of elevated levels of both brominated and chlorinated DBPs, simulating the tap water of Site 3. All 4 THM species were completely removed by the faucet-mounted model, while the pitcher POU removed only 41% of THM4 on average. The pitcher POU studied in the laboratory was utilized every day until the capacity was spent and was subjected to higher levels of THM4, HAA9, and their bromine-containing constituents over the course of the cartridge capacity. There was negligible difference in the removal efficiency between individual THM species in the laboratory study although there was a clear difference in the filters' ability to remove HAA species from tap water. HAA removal efficiency increases as the degree of bromination and halogenation increases. The pitcher POU removed 30% of HAA5 and 41% of HAA9 on average, while the faucet-mounted POU removed 48% of HAA5 and 63% of HAA9 on average.

The pitcher and faucet-mounted POU devices removed 46% and 74% of the TOX, respectively. This is slightly higher average removal than the 41% demonstrated in the same

pitcher POU over 100% capacity during the home study. TOX studies indicate that, like in the home study, THMs and HAAs are removed more effectively than the portion of TOX that is not accounted for by these two classes, again suggesting that THM4 and HAA9 are preferentially removed by POU filtration.

***Bottled Water***

Three bottled water brands consumed frequently among study participants were purchased at a retail store that sold products from the same local distributor that supplied the Site 1 cohort. According to manufacturer's websites, Dasani is purified municipal drinking water treated with reverse osmosis and Aquafina is municipal water that is treated with filtration, reverse osmosis, and ozonation. Deerpark, according to the manufacturer's label, is spring water disinfected utilizing ozonation and filtration. These bottles were stored in the laboratory at room temperature until the date they were extracted. The bottles were opened (seal broken) and transferred to collection vials directly prior to extraction. A new bottle, with unbroken seal, was used each time an extraction was performed. All three brands were tested for HAA9 and THM4, but none were found.

***Ice Addition to Cold Water***

An experiment was conducted to test the significance of DBP contributions from ice that is added to beverages. Ice prepared from tap water may be added to beverages that otherwise have negligible levels of DBPs. Consumers often use tap water from their home to fill up their ice cube trays or have icemakers in their refrigerators that may not be linked to refrigerator filters. It is unclear whether DBPs present in the water used to make ice will contribute to exposure once it is consumed as it melts in beverages. Chloraminated tap water from a local utility was spiked with THM and HAA analytes such that individual DBP species' concentrations ranged from approximately 15–50 μg/L and 5–30 μg/L for THM4 and HAA9, respectively. Aliquots of the resulting mixtures were analyzed for THM4 and HAA9 before the water was frozen.

Five hundred milliliters (500 mL) of the spiked tap water was transferred from the volumetric flask to a 600 mL beaker to ease filling of the ice cube trays. The water was poured slowly down the side of the beaker to minimize aeration and volatilization. The beaker was used to fill Rubbermaid ice cube trays, holding 16 cubes, purchased from a local retailer. Two trays were filled with 500 mL each of the spiked tap water and two additional trays were filled with unspiked LGW to serve as a control. The uncovered trays were immediately placed into a freezer (–15°C) where they sat until the studies were performed (between 1 day and 3 weeks). The controls were utilized to examine any possible background contamination that might have occurred from the freezer environment that also contained a small volume of closed inorganic chemicals which remained in the freezer during the process.

Eight ice cubes of spiked tap water or LGW were added, using sterile nitrile gloves, to 300 mL of (unspiked) LGW in a 600 mL Pyrex beaker. The beakers, containing LGW and ice, were left in the laboratory hood at room temperature for 30 minutes. After the allotted time, before samples were collected, each beaker was swirled and then poured into a graduated cylinder to record the total liquid volume. Duplicate sample vials for HAA9 and THM4 analysis were filled from the graduated cylinder. The ice remaining in the beaker, after the water was poured off into the cylinders, was allowed to finish melting, as it might after a beverage is

consumed. One vial for THM4 analysis and one vial for HAA9 analysis were collected from the melted leftover ice.

The ice appeared to contribute minimal amounts of DBPs to water after melting for fewer than 30 minutes. THMs are prone to volatilization in the freezing and thawing process and thus melted ice contains about one third of its original (pre-freeze) concentration. However, although that melted ice may contain twice the concentration of HAAs found in the tap water before ice formation, subsequent dilution with the beverage appears to lower the concentration of the individual HAA species to below detection.

***Thermal Treatment***

Experiments were undertaken to monitor changes in DBP concentrations of waters heated by microwave oven (in a mug) or boiled in a kettle for hot beverage preparation, i.e. tea, instant coffee, etc. Chlorinated and chloraminated tap waters from a local utility were spiked with each of the THM4 (20–60 μg/L) and HAA9 (10–30 μg/L) species in order to simulate a tap water matrix having a chlorine or combined chlorine residual exhibiting high levels of all bromine- and chlorine-containing DBPs. LGW was also spiked with THM4 and HAA9 to observe the behavior of DBPs in water containing neither a chlorine (free or combined) residual nor NOM. Aliquots of the resulting mixtures were collected for disinfectant residual measurements, THM4 and HAA9 analysis, before the water was subjected to thermal treatment. After boiling, water was held in mugs, each at a different holding time, between three and seven minutes before transfer to a sample vial for subsequent analysis.

While THMs are completely volatilized from chloraminated water that is boiled in a kettle, their concentrations barely change when the same water is subjected to microwave heating. DBPs are not readily formed from precursors and chloramine residual, and increased volatilization likely occurs at boiling temperatures in a kettle, whereas the microwave-heated water only reaches ~72°C after 3 minutes. Overall HAA9 concentration remains relatively constant in chloraminated water under both heating conditions because HAAs are non-volatile and thermally stabile. Only the brominated, tri-halogenated HAAs are consistently lost by thermal treatment because they are more thermally labile than the other HAAs. Chlorinated tap water heated in a microwave or kettle is much more prone to the continued formation of chloroform and chlorinated HAAs.

***Summary***

Table 3.3 lists what the concentrations of THM4 and HAA9 might be at Sites 1 and 3 if the tap water undergoes the treatments that were examined. This assumes that species within the waters at Sites 1 and 3 would behave identically to the spiked tap waters that were examined. While this is not ideal, it provides the best estimate of the DBP concentrations in Site 1 and 3 tap waters after various treatments prior to ingestion. Percent changes (usually reductions) from the simulated water studies were used to modify tap water concentrations prior to ingestion as shown in Equation 3.1:

Species concentration after treatment (μg/L) =
tap water species concentration (μg/L)*Percent change/100 (3.1)

THM4 and HAA9 were not detected in bottled water, thus exposure due to ingestion of bottled water is assumed to be zero and is not included in Table 3.3. The listing for “melted ice” is

strictly the concentration which would come from the ice, if it is prepared with the tap water at Site 1 or 3. The listed concentration does not account for the dilution by the beverage to which it is added. Since the distribution systems at Sites 1 and 3 employ chloramines for disinfection 11 months of the year, only the thermal treatments from chloramination (not chlorination) are summarized in Table 3.3.

**Table 3.3**
**Average DBP concentrations in source and treated tap water at sites 1 and 3**

| | Tap | | PUR faucet-filtered | | BRITA pitcher-filtered | | Thermally Treated (kettle, chloramine) | | Thermally treated (microwave, chloramine) | | Melted ice | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Site | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 | 1 | 3 |
| Trihalomethanes (µg/L) | | | | | | | | | | | | |
| $CHCl_3$ | 47.9 | 11.7 | 0.0 | 0.0 | 28.3 | 6.9 | 0.0 | 0.0 | 39.3 | 9.6 | 16.3 | 4.0 |
| $CHBrCl_2$ | 11.7 | 19.7 | 0.0 | 0.0 | 6.8 | 11.4 | 0.0 | 0.0 | 9.0 | 15.2 | 3.4 | 5.7 |
| $CHBr_2Cl$ | 2.8 | 25.3 | 0.0 | 0.0 | 1.7 | 14.9 | 0.0 | 0.0 | 2.4 | 21.3 | 0.8 | 7.3 |
| $CHBr_3$ | 0.0 | 7.2 | 0.0 | 0.0 | 0.0 | 4.4 | 0.0 | 0.0 | 0.0 | 7.5 | 0.0 | 3.5 |
| THM4 | 62.4 | 63.9 | 0.0 | 0.0 | 36.7 | 37.6 | 0.0 | 0.0 | 50.6 | 53.5 | 20.5 | 20.5 |
| Haloacetic acids (µg/L) | | | | | | | | | | | | |
| ClAA | 4.0 | 2.0 | 3.7 | 1.8 | 3.3 | 1.7 | 3.6 | 1.8 | 4.2 | 2.1 | 0.0 | 0.0 |
| BrAA | 0.0 | 1.0 | 0.0 | 0.6 | 0.0 | 0.7 | 0.0 | 1.0 | 0.0 | 1.0 | 0.0 | 0.0 |
| $Cl_2AA$ | 19.7 | 6.7 | 10.8 | 3.7 | 13.8 | 4.7 | 26.2 | 8.9 | 20.5 | 7.0 | 0.0 | 0.0 |
| BrClAA | 3.3 | 8.4 | 1.4 | 3.4 | 2.2 | 5.6 | 3.5 | 8.8 | 3.4 | 8.7 | 0.0 | 0.0 |
| $Cl_3AA$ | 16.8 | 4.9 | 6.0 | 1.8 | 10.9 | 3.2 | 11.6 | 3.4 | 16.8 | 4.9 | 0.0 | 0.0 |
| $Br_2AA$ | 0.0 | 8.0 | 0.0 | 2.6 | 0.0 | 5.3 | 0.0 | 8.1 | 0.0 | 7.9 | 0.0 | 0.0 |
| $BrCl_2AA$ | 4.3 | 8.5 | 0.8 | 1.6 | 2.0 | 4.0 | 1.2 | 2.4 | 4.2 | 8.3 | 3.8 | 7.5 |
| $Br_2ClAA$ | 0.0 | 5.9 | 0.0 | 0.9 | 0.0 | 2.5 | 0.0 | 1.2 | 0.0 | 4.1 | 0.0 | 0.0 |
| $Br_3AA$ | 0.0 | 2.5 | 0.0 | 0.2 | 0.0 | 0.9 | 0.0 | 0.6 | 0.0 | 0.9 | 0.0 | 2.2 |
| HAA9 | 49.0 | 47.5 | 18.1 | 17.6 | 32.3 | 28.5 | 46.1 | 36.2 | 49.1 | 44.9 | 3.8 | 9.7 |
| Total organic halide (µg Cl/L) | | | | | | | | | | | | |
| TOX | 179 | 183 | 47 | 48 | 97 | 99 | NA | NA | NA | NA | NA | NA |

NA: not available.

Assignment of DBP levels via ingestion will be calculated utilizing a series of adjustment factors and equations based on the findings reported from this study. These adjustments will be made to each of the DBP parameters as defined earlier in this report. In the following descriptions, $[DBP]_{cold}$ represents the measured weekly concentration of the DBP obtained from the representative distribution system sample.

### *Ingestion Correction Factors for Boiled Water*

Results indicated that when water was heated to boiling in a kettle, the THMs were completely lost. Therefore the concentrations of THMs and brominated THMs in hot water will be represented as shown in Equations 3.2, 3.3:

$$[THM4]_{hot} = 0 \quad (3.2)$$

$$[THM_{Br}]_{hot} = 0 \quad (3.3)$$

Little change during boiling was demonstrated in the concentration of HAA6 (HAA5 plus BrClAA), but HAA3 levels (BrCl2AA, Br2ClAA, and Br3AA) were reduced by approximately 75% when water was heated to boiling in a kettle. Equations 3.4 and 3.5 will be used to adjust the concentration of HAAs in hot water:

$$[HAA9]_{hot} = 0.25\,[HAA3]_{cold} + [HAA6]_{cold} \quad (3.4)$$

$$[HAA_{Br}]_{hot} = 0.25[HAA3]_{cold} + [BrAA]_{cold} + [BrClAA]_{cold} + [Br_2AA]_{cold} \quad (3.5)$$

The TOX adjustment factors for hot water are based on a weighted average of the volatile (THM4) losses for each site. This assumes that the volatile portion of the TOX is lost while the rest of the TOX remains unchanged as demonstrated, for example, by HAA6. The correction factors at Sites 1, 2, and 3 were calculated for each year and then averaged for a single correction factor at each Site (Equations 3.6, 3.7, 3.8) because the standard deviation on the correction factor for all years was small (standard deviations: Site 1 = 0.026, Site 2 = 0.11, and Site 3 = 0).

The correction factor for Site 1 is: $[TOX]_{hot} = 0.71[TOX]_{cold}$ (3.6)

The correction factor for Site 2 is: $[TOX]_{hot} = 0.82[TOX]_{cold}$ (3.7)

The correction factor for Site 3 is: $[TOX]_{hot} = 0.80[TOX]_{cold}$ (3.8)

Chlorine consumption has also been tracked in all three waters as a surrogate for DBP formation in the distribution system. Equation 3.9 adjusts chlorine consumption in hot water by assuming that the change in overall consumption of chlorine is correlated to the change in TOX concentrations:

$$(\text{Chlorine consumption})_{hot} = (\text{Chlorine consumption})_{cold} \times (TOX_{hot}/TOX_{cold}) \quad (3.9)$$

***Ingestion Correction Factors for Filtered Water***

THMs are completely lost during faucet POU filtration (f-filtered) and therefore the concentration in faucet-filtered water (Equation 3.10) is zero:

$$[THM4]_{f\text{-}filtered} = [THM_{Br}] = [BrCl_2CH] = 0\ \mu g/L \quad (3.10]$$

Pitcher-filtered (p-filtered) water contains 60% of the THMs that are present in the influent tap water and thus the THMs in pitcher filtered water will be adjusted according to Equations 3.11–3.13:

$$[THM4]_{p\text{-}filtered} = 0.6[THM4]_{cold} \quad (3.11)$$

$$[THM_{Br}]_{p\text{-}filtered} = 0.6[THM_{Br}]_{cold} \quad (3.12)$$

$$[BrCl_2CH]_{p\text{-}filtered} = 0.6[BrCl_2CH]_{cold} \quad (3.13)$$

The removal of HAAs in filtered water differs according to species and filter type. Thus they will be adjusted according to Equations 3.14 and 3.15:

Pitcher-filtered water: $[HAA9]_{p\text{-}filtered} = 0.87[ClAA] + 0.67[BrAA] + 0.70[Cl_2AA] + 0.67[BrClAA] + 0.65[Cl_3AA] + 0.66[Br_2AA\} + 0.47[BrCl_2AA] + 0.42[Br_2ClAA] + 0.35[Br_3AA]$ (3.14)

Faucet-filtered water : $[HAA9]_{f\text{-}filtered} = 0.92[ClAA] + 0.58[BrAA] + 0.55[Cl_2AA] + 0.41[BrClAA] + 0.36[Cl_3AA] + 0.33[Br_2AA\} + 0.19[BrCl_2AA] + 0.16[Br_2ClAA] + 0.09[Br_3AA]$ (3.15)

The TOX concentrations in filtered water will be adjusted according to Equations 3.16 and 3.17:

Pitcher -filtered water: $[TOX]_{p\text{-}filtered} = 0.59[TOX]_{cold}$ (3.16)

Faucet-filtered water: $[TOX]_{f\text{-}filtered} = 0.26[TOX]_{cold}$ (3.17)

Chlorine consumption from POU-filtered water (Equation 3.18) will be adjusted assuming that the overall change in "chlorine consumption" is correlated to the loss of TOX

$$(\text{Chlorine consumption})_{filtered} = (\text{Chlorine consumption})_{cold} \times (TOX_{filtered}/TOX_{cold}) \quad (3.18)$$

## ASSIGNMENT OF DBP CONCENTRATION, INGESTED AMOUNT, AND INTEGRATED EXPOSURE

### Background

There are several approaches to estimating individual exposure to DBPs during pregnancy, with potential gains in accuracy from incorporating more detailed behavioral information but at the price of increasing dependence on assumptions about the accuracy of the behavioral information that was provided and the ability to correctly use such information to estimate the biologically relevant exposure.

The simplest level of analysis defined exposure based solely on the weekly concentrations of DBPs in tap water in the treatment system serving the woman's home, as measured for the purposes of the study. Use of tap water concentration alone ignores all behavioral information on ingestion amounts, bathing and showering, use of filters, etc. At the same time, on average, there is good reason to be confident that tap water concentration is highly correlated with other measures of exposure, despite variation in the behavioral determinants among individuals in the study. Given the vulnerability of the more sophisticated indices to error in the self-reports or inferences based on those reports, a simple measure of this sort has merit as a means of distinguishing among women who are very likely to have differing exposures based solely on the tap water coming into their home. This index corresponds most closely to the measures that have been used in previous epidemiologic studies and is most directly applicable to policies regulating DBP concentrations.

The next level of exposure assignment incorporates information on ingestion of tap water and the major influences on DBP concentrations in ingested tap water, namely use of filters and heating. As described below, this is a good deal more complex to derive and relies on self-reported data on habitual tap water ingestion, changes in water consumption in the period of early pregnancy, and details of filter use and heating of water, both at home and at work. The nature of the data collection required further assumptions and extrapolations to derive estimates. To the extent that water use information is provided with accuracy and our assumptions about how to use the information to derive ingested amounts are accurate, the exposure measure will be more accurate in distinguishing individuals than the tap water concentration.

Finally, we added information on showering and bathing to the information on ingestion to more completely estimate exposure to THMs, which are volatilized and inhaled as well as being absorbed dermally. The duration of showering and bathing, combined with knowledge of

the DBP concentrations in the tap water, was used to estimate absorbed and inhaled amounts based on previous literature and integrated with the information on ingested amounts to derive a more complete indication of dose. We considered but ultimately chose not to try to extend the model by incorporating information on swimming or use of Jacuzzis, even though such sources may account for substantial exposure. Lacking any information on DBP levels in swimming pools or Jacuzzis precluded quantitative estimates other than by making a global assumption about the concentrations with no empirical support. We did consider the association between such exposures at the simple level of frequency of use but were not able to integrate a quantitative exposure contribution into a summary index.

**Assignment of DBP Concentrations in Tap Water**

Assignment of DBP concentrations for each woman required information on the timing of her pregnancy, specification of time windows of interest in relation to the pregnancy, and the array of week-specific DBP measurements. We used self-reported information on the date of the last menstrual period (LMP) prior to pregnancy to anchor the onset of pregnancy, recognizing that conception occurs on average around 14 days after the LMP. Keeping with the tradition of obstetrical dating of pregnancy, we refer to pregnancy time windows in relation to the LMP.

For consideration of exposure, we chose to consider three different windows, given that there are multiple potential mechanisms for affecting pregnancy loss. To address periconceptional exposures, the first window was set to be 4 weeks before the LMP through 3 weeks after the LMP (–4 to +3 weeks). The second window addresses potential influences on the supportiveness of the uterine environment for fetal survival, in the range of 4-8 weeks following the LMP. The third window, 9–20 weeks post-LMP, is primarily concerned with direct fetal toxicity. Given the gradual shifts in concentrations from week to week, results would not differ substantially in response to small shifts in the window boundaries. The number of pregnancies and pregnancy losses available for analysis by time window is provided in Table 3.4.

For each woman, we examined the measured DBP concentrations over the duration of the interval. Because a pregnancy loss truncates the interval, in the analysis we compared the mean exposure up to the time of loss for a woman who had a loss in a given window to the exposures of other women over the same period. If, for example, a loss occurred in week 6 post-LMP, her exposure in the first time window (–4 to +3) would be complete, but her exposure for the second time window would be the average of weeks 4, 5, and 6, and compared to other women's week 4-6 exposure whose pregnancies continued, ignoring their exposure thereafter. She would not enter into the third time window at all, given a loss prior to the onset of that window.

**Table 3.4**
**Number of pregnancies entering and losses in time windows of gestation used in the analysis of DBPs and pregnancy loss**

| | Site 1 | | | Site 2 | | | Site 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | #Preg | #Loss | #Other | #Preg | #Loss | #Other | #Preg | #Loss | #Other |
| Window 1: –4 to +3 wks | 1091 | 0 | 0 | 899 | 0 | 0 | 423 | 0 | 0 |
| Window 2: 4 to 8 wks | 1048 | 38 | 5 | 836 | 31 | 32 | 396 | 12 | 15 |
| Window 3: 9 to 20 wks | 958 | 83 | 7 | 767 | 61 | 8 | 354 | 36 | 6 |

*Other category includes other losses than spontaneous abortion (induced abortion, ectopic, tubal, molar) and unknown outcome due to loss of contact with participants.

The tap water concentrations, when averaged over the entire window, were highly correlated across windows (Table 3.5), not surprising given the temporal proximity of the windows to one another. Despite these high correlations, we did observe some differences in association with pregnancy loss as reported later. The average, minimum, and maximum levels across sites and across pregnancy windows for the DBPs of interest is provided in Table 3.6. The levels of all DBPs are quite low in Site 2 and elevated in Sites 1 and 3, with brominated species especially notable in Site 3. These patterns correspond as expected to the tap water measurements presented earlier.

**Table 3.5**
**Correlation of DBP concentrations in tap water across pregnancy windows**

| DBP | Correlation between Window 1 and 2 | Correlation between Window 1 and 3 | Correlation between Window 2 and 3 |
|---|---|---|---|
| THM4 | 0.89 | 0.82 | 0.89 |
| Chloroform | 0.89 | 0.80 | 0.89 |
| BDCM | 0.89 | 0.85 | 0.89 |
| THMBr | 0.91 | 0.86 | 0.92 |
| HAA9 | 0.94 | 0.90 | 0.94 |
| HAA5 | 0.94 | 0.89 | 0.94 |
| HAABr | 0.95 | 0.92 | 0.95 |
| TOX | 0.95 | 0.92 | 0.95 |

**Table 3.6**
**Average and range of DBP concentrations in pregnancy window 1 (–4 to +3 wks) by study site**

| | Site 1 | | | Site 2 | | | Site 3 | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ave | Min | Max | Ave | Min | Max | Ave | Min | Max | Ave | Min | Max |
| THM4 | 67.11 | 32.31 | 128.45 | 3.29 | 2.14 | 5.01 | 63.03 | 31.79 | 102.85 | 42.62 | 2.14 | 128.45 |
| Chloroform | 47.90 | 20.34 | 106.24 | 0.24 | 0.00 | 1.36 | 12.44 | 6.38 | 26.97 | 23.93 | 0.00 | 106.24 |
| $CHBrCl_2$ | 14.97 | 7.90 | 27.41 | 1.04 | 0.66 | 1.46 | 20.31 | 12.16 | 32.82 | 10.72 | 0.66 | 32.82 |
| THM-Br | 19.40 | 10.24 | 37.34 | 3.04 | 2.10 | 4.11 | 50.58 | 24.98 | 81.29 | 18.77 | 2.10 | 81.29 |
| HAA9 | 45.24 | 21.46 | 66.54 | 1.78 | 0.00 | 5.86 | 45.87 | 36.43 | 57.49 | 29.16 | 0.00 | 66.54 |
| HAA5 | 34.62 | 16.61 | 54.94 | 0.17 | 0.00 | 1.28 | 21.60 | 17.79 | 30.89 | 19.50 | 0.00 | 54.94 |
| HAA-Br | 11.50 | 4.26 | 18.52 | 1.69 | 0.00 | 5.86 | 32.28 | 23.17 | 43.38 | 11.49 | 0.00 | 43.38 |
| TOX | 173.72 | 130.14 | 238.75 | 17.49 | 11.65 | 21.50 | 182.33 | 149.89 | 208.90 | 117.02 | 11.65 | 233.75 |

## Assignment of Ingested Amounts of DBPs

Conceptually, the goal in constructing indices of ingested amounts of DBPs is straightforward—to estimate the cumulative amount of specific DBPs in the water that women actually consume through drinking tap water, expressed in µg per day. The concentration of DBPs in the tap water provided to their household is one determinant of that quantity, but there are a number of other major influences that have to be considered that influence exposure through ingestion. First, we considered the amount of tap water ingested by each woman over the course of the time windows defined in relation to her pregnancy (from 4 weeks before to 20 weeks after the LMP). We queried the number of cups or glasses per day of hot and cold tap water, and asked about the typical cup size. To help anchor the description of cup sizes, we provided quantitative measures in ounces. For cold drinks, small was 4–10 ounces, medium was 12–20, and large was 22–34. For hot drinks, small was 4–10 ounces, medium was 12–14, and large was 16–24. We assigned the midpoint of the range provided for each cup or glass size to generate the total ounces per day of hot and cold tap water ingested.

In reporting the amount of water ingested, women first reported the amount they currently ingested (at the time of the interview) and were then asked if they had changed that amount since 4 weeks before the onset of pregnancy. If they did report having changed their water ingestion, we asked what the amounts were previously and when that change occurred (in calendar time). With this information, we were able to calculate ingested amounts in ounces per day prior to the time of change. To characterize the daily ingestion over the entire pregnancy window of interest, we calculated a time-weighted average when a change was reported to have occurred at some time during the window. If there was no change during the window, this value was simply the reported average daily amount. Thus, for each woman for each of the three pregnancy time windows, we generated average daily consumption of hot and cold tap water, taking into account potential changes in ingestion or water treatments.

As shown in Table 3.7, changes were quite common and tended to reflect increased amount ingested over the course of pregnancy much more often than decreased amounts (Table 3.8). Perhaps the recommendation to drink adequate amounts of water or some physiologic changes associated with the pregnancy result in greater consumption. It would appear that there are not large numbers of women curtailing tap water intake as a perceived health-protective behavior.

**Table 3.7**
**Number of women who changed tap water consumption by timing of change in pregnancy windows**

| | Before pregnancy Window 1 (<-28) | Pregnancy Window 1 | Pregnancy Window 2 | Pregnancy Window 3 | After pregnancy Window 3 | Total |
|---|---|---|---|---|---|---|
| Site 1 | 17 | 138 | 236 | 7 | 1 | 399 |
| Site 2 | 16 | 97 | 185 | 8 | 0 | 306 |
| Site 3 | 4 | 31 | 53 | 4 | 1 | 93 |
| Total | 37 | 266 | 474 | 19 | 2 | 798 |

**Table 3.8**
**Number of women who increased and decreased tap water consumption in any of pregnancy windows**

| | Cold tap water | | Hot tap water | | Total | |
|---|---|---|---|---|---|---|
| | Increased | Decreased | Increased | Decreased | Increased | Decreased |
| Site 1 | 343 | 59 | 278 | 124 | 334 | 46 |
| Site 2 | 263 | 39 | 234 | 68 | 256 | 35 |
| Site 3 | 80 | 17 | 68 | 29 | 72 | 17 |
| Total | 686 | 115 | 580 | 221 | 662 | 98 |

Point of use filters, principally on the tap or pitcher filters, were used quite commonly by women in the study Table 3.9) and have great influence on the levels of DBPs that are ingested, with differing efficacy of the two major filter types (see equations 3.10–3.18). Therefore, it was necessary to derive estimates of how much of the total hot and cold tap water ingested was filtered using a tap filter and a filtered pitcher. Because filter use could differ for home versus work, we distinguished those between two sources, which required us to estimate the following 8 water consumption quantities: 1) Home—cold—filtered; 2) Home—cold—unfiltered; 3) Home—hot—filtered; 4) Home—hot—unfiltered; 5) Work—cold—filtered; 6) Work—cold—unfiltered; 7) Work—hot—filtered; 8) Work—hot—unfiltered. Once derived, we combined home and work since the ingested DBPs were not expected to differ within categories of filtering and heating.

**Table 3.9**
**Frequency of filter use by type, location, and site**

| | Site 1 | | Site 2 | | Site 3 | | Total | |
|---|---|---|---|---|---|---|---|---|
| | # | % | # | % | # | % | # | % |
| Home | | | | | | | | |
| Tap filter (faucet) | 101 | 9.26 | 39 | 4.34 | 24 | 5.67 | 164 | 6.8 |
| Pitcher filter | 163 | 14.94 | 45 | 5.01 | 24 | 5.67 | 232 | 9.61 |
| Filter, unknown type | 63 | 5.77 | 44 | 4.89 | 8 | 1.89 | 115 | 4.77 |
| Work | | | | | | | | |
| Tap filter (faucet) | 43 | 3.94 | 10 | 1.11 | 15 | 3.55 | 68 | 2.82 |
| Pitcher filter | 43 | 3.94 | 8 | 0.89 | 16 | 3.78 | 67 | 2.78 |
| Filter, unknown type | 265 | 24.29 | 192 | 21.36 | 54 | 12.77 | 511 | 21.18 |

Only those women who worked outside the water service area in which they lived were questioned in a way that distinguished location of water consumption (N = 197), whereas those women who lived and worked in the same service area (N = 1,287) or were not employed (N = 906) were only asked about total consumption. Querying the two sources separately resulted in greater total amounts of reported consumption by those commuting outside the area, 77.1 and 65.3 ounces per day for commuters versus non-commuters for cold tap water, and 7.7 and 6.3 ounces per day for commuters versus non-commuters for hot tap water. Assuming that this is an artifact of the way the questions were asked, and not a reflection of truly greater consumption among such women, we reduced the levels for women working outside the area proportionately

so their means were equal. This required reducing the reported consumption among out-of-area commuters by 15.3% for cold tap water and 18.2% for hot tap water. Average consumption for the first pregnancy window by site is provided in Table 3.10, dividing cold and hot tap water consumption.

**Table 3.10**
**Average cold and hot tap water consumption in ounces by work status and location in –4 to +3 week window of pregnancy**

| | Site 1 | | | Site 2 | | | Site 3 | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | # | Cold | Hot | # | Cold | Hot | # | Cold | Hot | # | Cold | Hot |
| Total | 1089 | 48.00 | 4.83 | 898 | 50.77 | 5.85 | 423 | 31.98 | 4.90 | 2410 | 46.22 | 5.22 |
| Not employed | 384 | 50.56 | 5.29 | 334 | 52.03 | 6.19 | 193 | 33.72 | 4.90 | 912 | 47.53 | 5.54 |
| Employed in water service area | 571 | 46.88 | 4.82 | 529 | 50.02 | 5.32 | 199 | 31.16 | 5.54 | 1299 | 45.75 | 5.13 |
| Employed outside of water service area | 134 | 45.43 | 3.57 | 35 | 50.03 | 10.77 | 31 | 26.42 | 0.72 | 200 | 36.08 | 3.66 |

In order to assign the total reported water consumption into home versus work for the women who reported only the aggregate amounts (those who worked in the same service area as they resided), we used information from the subset of women who provided such a breakdown with the assumption that the proportions would be similar (Table 3.11). Thus, among those who separated the sources into home and work, 62% of cold tap water was consumed at home and 38% at work, and 53% of hot tap water was consumed at home and 37% at work. These proportions were applied to women who had not been asked to distinguish home and work in order to generate estimates of the volume of hot and cold tap water at home and work for all women in the study, which were required so that adjustments for filter use at home and work could be made.

**Table 3.11**
**Distribution of cold and hot tap water consumption at home and work for women who provided separate estimates**

| | Site 1 | Site 2 | Site 3 | Total |
|---|---|---|---|---|
| # Women | 134 | 35 | 31 | 200 |
| Home tap water consumption | | | | |
| Cold tap water average | 36.60 | 41.04 | 27.42 | 35.95 |
| Cold tap water 25$^{th}$ percentile | 13.44 | 23.52 | 0.0 | 11.76 |
| Cold tap water 50$^{th}$ percentile | 26.88 | 40.32 | 11.76 | 26.88 |
| Cold tap water 75$^{th}$ percentile | 53.76 | 53.76 | 52.92 | 53.76 |
| Hot tap water average | 2.77 | 4.47 | 1.04 | 2.80 |
| Hot tap water 25$^{th}$ percentile | 0.0 | 0.0 | 0.0 | 0.0 |
| Hot tap water 50$^{th}$ percentile | 0.0 | 0.0 | 0.0 | 0.0 |
| Hot tap water 75$^{th}$ percentile | 0.0 | 5.53 | 0.0 | 0.0 |
| Work tap water consumption | | | | |
| Cold tap water average | 20.66 | 27.22 | 17.97 | 21.38 |
| Cold tap water 25$^{th}$ percentile | 0.0 | 0.0 | 0.0 | 0.0 |
| Cold tap water 50$^{th}$ percentile | 5.88 | 13.44 | 0.0 | 5.88 |
| Cold tap water 75$^{th}$ percentile | 40.32 | 47.04 | 26.88 | 40.32 |
| Hot tap water average | 1.67 | 7.30 | 1.22 | 2.56 |
| Hot tap water 25$^{th}$ percentile | 0.0 | 0.0 | 0.0 | 0.0 |
| Hot tap water 50$^{th}$ percentile | 0.0 | 0.0 | 0.0 | 0.0 |
| Hot tap water 75$^{th}$ percentile | 0.0 | 0.0 | 0.0 | 0.0 |

In reporting use of filters, women were asked to indicate the filter type (tap or pitcher) for hot and cold tap water, as used at home and at work. They described the amount of water filtered as "all," "most," "some," "little," and "none." We adopted the estimated quantities of 100%, 75%, 40%, 20%, and 0% to correspond to those adjectives and applied those proportions to derive quantitative estimates of the filtered amounts (Table 3.12).

**Table 3.12**
**Average daily volume (ounces) of cold and hot, unfiltered and filtered tap water and bottled water by study site for pregnancy window 1 (–4 to + 3 wks)**

| | Site 1 | Site 2 | Site 3 | Total |
|---|---|---|---|---|
| Cold total | 48.00 | 50.77 | 31.98 | 46.22 |
| Unfiltered cold total | 28.36 | 42.08 | 24.52 | 32.80 |
| Filtered cold total | 19.62 | 8.69 | 7.46 | 13.41 |
| Hot total | 4.83 | 5.85 | 4.90 | 5.22 |
| Unfiltered hot total | 3.12 | 4.96 | 4.30 | 4.01 |
| Filtered hot total | 1.72 | 0.89 | 0.59 | 1.21 |
| Bottled water | 18.29 | 11.92 | 36.72 | 19.13 |

Because the efficacy of the two filter types differed, and a sizable proportion of women did not know the filter type at home (N = 115) and at work (N = 511), we needed to derive some estimate for those women as well. Those who did not know if their water was filtered at work (N = 114) were assumed not to have used a filter, but those who knew it was filtered with type unknown were assigned a filter efficacy that was the weighted average of the two types with weight corresponding to the proportion of use in our population. That is, we created a synthetic filter "unknown type" that had an efficacy that was the weighted average of the known filter types.

Finally, changes in reported ingestion required calculation of these amounts before and after the ingestion change and weighting for the pregnancy window by the proportion of the window in which each amount was used. The end product of this series of calculations was the estimated amount in ounces per day in 8 cells:

1. Cold, tap filter
2. Cold, pitcher filter
3. Cold, filter unknown type
4. Cold, no filter
5. Hot, tap filter
6. Hot, pitcher filter
7. Hot, filter unknown type
8. Hot, no filter

For the time windows, with the corresponding concentration data, and correction factors for filters and heating, we were able to sum across these units (Table 3.13) and derive daily ingested amounts of each DBP or group of DBPs of interest, in units of "µg/day" (Table 3.14).

**Table 3.13**
**Average daily volume (ounces) of cold and hot, unfiltered and filtered tap water and bottled water by pregnancy window**

| | Window 1, –4 to +3 wks | Window 2, 4 to 8 wks | Window 3, 9 to 20 wks |
|---|---|---|---|
| Cold total | 46.22 | 54.76 | 57.38 |
| Unfiltered cold total | 32.80 | 38.93 | 40.97 |
| Filtered cold total | 13.41 | 15.82 | 16.41 |
| Hot total | 5.22 | 5.46 | 5.56 |
| Unfiltered hot total | 4.01 | 4.17 | 4.25 |
| Filtered hot total | 1.21 | 1.29 | 1.31 |
| Bottled water* | 19.13 | 19.13 | 19.13 |

*Changes in bottled water consumption were not obtained.

**Table 3.14**
**Average and range of ingested amounts of DBP (µg/day) in pregnancy window 1 (–4 to +3 wks) by study site**

| DBP | Site 1 | | | Site 2 | | | Site 3 | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ave | Min | Max | Ave | Min | Max | Ave | Min | Max | Ave | Min | Max |
| THM4 | 73.12 | 0.0 | 582.21 | 4.70 | 0.0 | 32.04 | 56.42 | 0.0 | 474.67 | 44.69 | 0.0 | 583.21 |
| Chloroform | 52.51 | 0.0 | 477.85 | 0.35 | 0.0 | 7.74 | 10.98 | 0.0 | 99.74 | 25.77 | 0.0 | 477.85 |
| $CHBrCl_2$ | 16.11 | 0.0 | 127.75 | 1.49 | 0.0 | 12.33 | 18.02 | 0.0 | 134.88 | 11.00 | 0.0 | 134.88 |
| THM-Br | 20.82 | 0.0 | 171.60 | 4.35 | 0.0 | 29.98 | 45.43 | 0.0 | 410.67 | 19.01 | 0.0 | 410.67 |
| HAA9 | 63.87 | 0.0 | 406.56 | 2.72 | 0.0 | 27.80 | 47.82 | 0.0 | 351.12 | 38.27 | 0.0 | 406.56 |
| HAA5 | 50.50 | 0.0 | 330.09 | 0.29 | 0.0 | 9.73 | 23.83 | 0.0 | 200.70 | 27.10 | 0.0 | 330.09 |
| HAA-Br | 14.58 | 0.0 | 97.79 | 2.56 | 0.0 | 27.80 | 32.91 | 0.0 | 212.49 | 13.33 | 0.0 | 212.49 |
| TOX | 222.25 | 0.0 | 1248.08 | 28.58 | 0.0 | 197.49 | 189.13 | 0.0 | 1246.26 | 144.27 | 0.0 | 1248.08 |

**Calculation of Exposure from Showering and Bathing**

In order to quantify the expected absorption and inhalation from showering and bathing, we needed to integrate data on the THM levels present in the tap water, the average duration and frequency of showers and baths, and estimates of an uptake factor that links the duration and water concentration into an absorbed dose. The weekly water concentrations of THMs were those used for addressing ingestion. The showers and baths was ascertained in the questionnaire and converted to average minutes per day engaged in each. Uptake factors were available from previous studies that measured blood THMs in relation to known duration of showering in water of known THM concentration, with sufficient differences between chloroform and other THMs as to warrant separate calculations. Although there are a modest number of such studies, they do generate reasonably consistent and credible estimates.

The calculations were as follows:

Showering exposure index (chloroform) = chemical water Concentration * duration (min/day) * update rate (0.001536261)

Showering exposure index (for all other THM species) = chemical water Concentration * duration (min/day) * update rate (0.001352065)

Bathing exposure index (chloroform) = chemical water Concentration * duration (min/day) * update rate (0.001320755)

Bathing exposure index (for all other THM species) = chemical water Concentration * duration (min/day) * update rate (0.00129571)

**Calculation of Integrated Exposure to Trihalomethanes**

Exposure to THMs is a function not only of the amount that is ingested through drinking tap water but also influenced by respiratory and dermal absorption in showering, bathing, and other water use activities. A comprehensive list would consider swimming, washing dishes, clothing, or small children, ambient levels and ventilation in the home and other indoor environments, and incidental use of water such as hand washing. Obviously, it would be extremely difficult to capture these many sources comprehensively and accurately, and difficult to incorporate them into a total exposure estimate. However, with bathing and showering, estimates of DBP levels are available (the same tap water concentrations used for ingestion) and studies have been done to allow translation of the minutes spent in showering or in bathing into estimated exposures through inhalation and dermal absorption. This allows for calculation of an integrated dose, combining the estimated dose from ingestion with the estimated amount of inhaled and dermally absorbed dose from showering and bathing, taking into account the THM levels in the water and the duration of the showering or bathing activity, expressed in units of "µg per day." Each of the individual THMs has its own uptake factor translating concentration in the water and duration of activity into dose, so that the exposures through bathing and showering must be derived for each individual THM and then summed to derive the total for all four THMs.

As indicated above, we derived estimated uptake from bathing and showering. Previously, the algorithm for ingestion exposure was presented. In order to convert the exposure through ingestion, expressed in µg per day, to uptake of the same nature as that derived for showering and bathing, calculated from previous studies relating ingestion to blood chloroform as THMs as 0.00490 and for other THMs as 0.00112. This value was applied to each of the individual and aggregated THMs. Thus, we were able to sum the contributions from showering, bathing, and ingestion into a single index presumably related to resulting blood THM levels for each of the three pregnancy time windows (since both ingested amounts and tap water concentrations changed over time). Because ingested THMs are rapidly metabolized by the liver, in contrast to inhaled or dermally absorbed THMs, which are not, we also calculated indices solely based on bathing and showering under the assumption that the unmetabolized THMs are the critical exposure potentially affecting reproductive health outcomes.

# CHAPTER 4
# PREGNANCY AND PREGNANCY OUTCOME ASSESSMENT

All women interested in participating were asked the date of their first positive pregnancy test at the time of enrollment. If they had not had a pregnancy test or could not provide a date, we asked them to complete a home pregnancy test kit or see a care provider for a test and to contact us with the result. If necessary or desired, a pregnancy test kit was mailed to the potential participant. Commercially available home pregnancy test kits are now fully comparable to urine pregnancy test kits used in clinical care settings. Such kits are both highly sensitive and specific for detecting pregnancy as early as the day of the missed menses.

## RATIONALE FOR USING ULTRASOUND

Early obstetric ultrasound has excellent precision for dating pregnancy (± 3 days) and for evaluating fetal anatomy. As early as the fourth week of gestation, ultrasound can be used to document fetal development. We incorporated ultrasound into the study to evaluate accuracy of self-reported pregnancy dating and to assess development and fetal viability earlier than usually possible in prenatal care.

Ultrasound also allows us to relate timing of clinical losses to probable stage of fetal development prior to the loss. Clinical reports of loss, or onset of symptoms that herald loss, may reflect any level of fetal development. A women who correctly reports her last menstrual period as eleven weeks prior to a miscarriage may have had a normally developing eleven week fetus with a heart rate in the uterus the day prior to the loss, an empty gestational sac without any fetal development, or any stage in between. Since viable trophoblastic tissue (placental elements) can persist for weeks to months without fetal development and even after the death of the fetal components of the conceptus, calendar date of the pregnancy loss is not fully informative. We also hypothesized that specific exposures such as water disinfection by-products are likely to have windows of time during development when they are more (or less) likely to pose a risk to the conceptus. Thus, our specific goals for incorporation of ultrasound for all participants were to:

1. precisely assign gestational age to normally developing pregnancies (learning indirectly about the presumed accuracy of those who had losses)
2. ascertain viability early in pregnancy,
3. estimate the stage of development achieved among those who had losses.

## OPERATIONAL DEFINITIONS OF LOSS

Spontaneous abortion is the loss or miscarriage of a pregnancy before the twentieth week of gestation. For the purposes of this analysis, we have classified losses as spontaneous abortions if the end of the pregnancy occurred on or before 140 days gestation calculated from the self-reported LMP. We have four primary sources of information to use to assign outcomes:

1. Pro-active self-report: a participant calls or otherwise notifies the study office of her loss.
2. Self-report at the time of the baseline interview or the follow-up interview.

3. Abstracted medical records from prenatal care provider offices, emergency room, and other care settings.
4. Linkage to vital records or brief abstract of birth records to document a live birth or fetal death after 20 weeks' gestation.

Our gold standard for classification of pregnancy outcome as a loss is a self-reported pregnancy loss (either a proactive call to the study office or in response to interview) with confirmation of the loss by medical record abstraction and lack of corresponding live birth in vital records. The date of the loss used for data analysis was the date reported by the participant at the earliest point of contact. For instance if a participant called the study office on the day of an emergency room visit and report she had had a miscarriage, the date of loss recorded in that contact was used in preference to the date she subsequently reported in a telephone interview two weeks later. Self-report either in the form of calling the study office, reporting loss during an interview, or in follow-up contact from study staff, was used in preference to medical record dates. Abstracted medical records were used to assign a date only when contact with the participant was lost and interview data were not available. Medical records were used to clarify discordance in the few instances in which a woman had a live birth within the time that could have represented the index pregnancy or in which they reported a loss and were not able to report a date. In those instances review of the abstracted data by an obstetrician was used to assign a date. The date used corresponded to the date of the clinical care visit or other contact with the patient at which the uterus was known to be empty and no risk of ectopic gestation was suspected.

## RFTS PREGNANCIES EVALUATED BY ULTRASOUND

At the time of the study enrollment phone call, study staff scheduled ultrasounds appointments for the sixth to seventh week of gestation based on LMP. For women who enrolled later in pregnancy, the ultrasound was arranged as promptly as possible. Among the women included in the analysis for this report, 2,285 had an ultrasound. Their mean gestational age at ultrasound based on LMP was nine weeks with a median just below eight weeks. Accuracy of reported LMP was very high as assessed by comparison with ultrasound measures. The mean difference in number of days between ultrasound estimate and LMP estimate of gestational age was $-0.9 \pm 5.5$ days (mean $\pm$ s.d.) with a median discrepancy of zero days. The proportion of women who reported they were "very sure" of their LMP was similar among women who went onto have normal pregnancies (68% very sure) and those who had losses (73% very sure). More than 87% of both groups report they were very sure, or pretty sure of their LMP.

As noted, we can use the accuracy observed among those who had ongoing pregnancies to estimate the accuracy of LMP for the entire cohort including both those who had losses before their scheduled ultrasound, those that had losses with abnormal development documented by ultrasound, and those few individuals with normal gestations who declined or missed their ultrasound appointments. Eighty-one percent of participants with normal pregnancies had an ultrasound estimated gestation age within one week of the estimate based on LMP. When discrepancies of more than a one-week were noted, 14% were in the direction of the pregnancy being one week "younger," i.e., earlier in pregnancy, by ultrasound than estimated from LMP. Thus, 95% of ultrasounds of normal pregnancies placed the participant at no more than one week further along than her self-reported dates. Therefore the expected maximal gestational age for abnormal gestations is not substantially greater than one week beyond that predicted by LMP.

This level of accuracy facilitates grouping of developmental stages for outcome analysis as well as supporting the overall accuracy of assignment of exposure windows.

## PREDICTORS OF PREGNANCY LOSS

To identify potential confounders, we began with a review of previous literature on known and suspected influences on pregnancy loss. Although there are many speculative candidates for risk factors, established influences are quite limited—maternal age, prior loss, and tobacco use, with prior loss a marker rather than a cause per se. We had to make some judgment about which among the next level of candidates, those with more limited or inconsistent support should be screened and arrived at the list presented in Table 4.1.

Those potential confounders that were considered and were not found to be influential on the outcome based on a p-value of < 0.20 and did not change effect estimates for the exposure of interest by 10% or greater were excluded. Candidate confounders of interest included maternal age (< 25, 25–30, 30–35, or >=35), black race, Hispanic ethnicity, education (high school, some college, college or greater), marital status (married or not), income (< 40,000/year, 40,000–80,000/year, > 80,000/year), smoking (dichotomized at 10 cigarettes per day), alcohol use (any/none), caffeine consumption (categorized using the groupings developed by Fenster et al. (1997), which are 0 mg/day, 1–150 mg/day, 151–300 mg/day, and > 300 mg/day), BMI (underweight, normal, overweight, obese), age at menarche (<= 11, 12–13, >= 14), employment (yes/no), diabetes (none, gestational, chronic), pregnancy history (no prior pregnancy, prior pregnancy with no prior pregnancy loss, prior pregnancy loss), induced abortion history (yes/no), and vitamin use (yes/no). Crude and adjusted odds ratios relating these potential confounders to pregnancy loss are presented in Table 4.1.

Maternal age is strongly predictive of loss, as expected. A modestly increased risk was found for Black women and a markedly decreased risk found for Hispanic women. Married women were at lower risk, women who consumed alcohol had a markedly elevated odds ratio. An increased risk was found for diabetes, and after adjustment, little increased risk for women with a history of prior pregnancy loss. Candidate confounders retained in the final models using the above criteria were maternal age, black race, Hispanic ethnicity, education, marital status, and alcohol use, but we also considered pregnancy history despite not meeting the above criteria because of the well-established association between prior and subsequent pregnancy loss. We investigated whether there was any evidence of effect modification of water exposure and pregnancy loss by prior pregnancy loss and found none ($p > 0.70$ for interaction) so we did not examine this further.

**Table 4.1**
**Association between potential confounders and pregnancy loss in RFTS**

| Potential Confounder | Crude OR | Adjusted* OR |
|---|---|---|
| Maternal age | | |
| <25 | 1.0 | 1.0 |
| [25,30) | 0.79 (0.52, 1.20) | 1.09 (0.67, 1.76) |
| [30,35) | 1.00 (0.67, 1.50) | 1.39 (0.81, 2.37) |
| >=35 | 2.53 (1.68, 3.81) | 3.24 (1.86, 5.65) |
| Race | | |
| Black | 1.68 (1.25, 2.27) | 1.34 (0.89, 2.02) |
| Non-black | 1.0 | 1.0 |
| Ethnicity | | |
| Hispanic | 0.24 (0.09, 0.64) | 0.23 (0.07, 0.76) |
| Non-Hispanic | 1.0 | 1.0 |
| Education | | |
| High school only | 1.25 (0.91, 1.72) | 1.55 (0.94, 2.55) |
| Some college | 0.64 (0.41, 0.99) | 0.74 (0.44, 1.24) |
| Completed college | 1.0 | 1.0 |
| Marital status | | |
| Unmarried | 1.0 | 1.0 |
| Married | 0.67 (0.50, 0.90) | 0.56 (0.34, 0.91) |
| Income | | |
| <= $40,000/year | 1.0 | 1.0 |
| $40,000-$80,000/year | 0.85 (0.60, 1.21) | 1.19 (0.74, 1.93) |
| >$80,000/year | 1.07 (0.74, 1.54) | 1.42 (0.80, 2.51) |
| Smoking status | | |
| <10 cigarettes/day | 1.0 | 1.0 |
| >=10 cigarettes/day | 0.94 (0.48, 1.85) | 0.72 (0.32, 1.59) |
| Alcohol use during pregnancy | | |
| None | 1.0 | 1.0 |
| Any | 4.19 (2.35, 7.46) | 4.51 (2.42, 8.40) |
| Caffeine consumption | | |
| 0 mg/day | 1.0 | 1.0 |
| 1-150 mg/day | 1.05 (0.69, 1.59) | 0.95 (0.61, 1.47) |
| 150-300 mg/day | 1.09 (0.71, 1.68) | 0.88 (0.56, 1.40) |
| >300 mg/day | 0.88 (0.59, 1.31) | 0.74 (0.48, 1.13) |
| Body mass index (BMI) | | |
| Underweight | 0.78 (0.46, 1.31) | 0.75 (0.44, 1.28) |
| Normal weight | 1.0 | 1.0 |
| Overweight | 0.90 (0.56, 1.46) | 0.89 (0.54, 1.46) |
| Obese | 1.13 (0.79, 1.60) | 0.81 (0.54, 1.22) |

(continued)

**Table 4.1 (continued)**

| Potential Confounder | Crude OR | Adjusted* OR |
|---|---|---|
| Age at menarche | | |
| <=11 | 0.84 (0.57, 1.24) | 0.73 (0.48, 1.12) |
| 12-13 | 1.0 | 1.0 |
| >=14 | 1.04 (0.73, 1.48) | 0.96 (0.67, 1.38) |
| Employment | | |
| Unemployed | 1.0 | 1.0 |
| Employed | 1.06 (0.76, 1.47) | 1.11 (0.77, 1.60) |
| Diabetes | | |
| None | 1.0 | 1.0 |
| Gestational only | 2.28 (0.72, 7.25) | 1.98 (0.58, 6.67) |
| Chronic | 1.72 (0.80, 3.68) | 1.52 (0.68, 3.39) |
| Spontaneous abortion history | | |
| No prior pregnancy | 1.0 | 1.0 |
| Prior pregnancy with no prior pregnancy loss | 1.36 (0.94, 1.97) | 1.09 (0.71, 1.66) |
| Prior pregnancy loss | 1.58 (1.04, 2.41) | 1.19 (0.74, 1.93) |
| Induced abortion history | | |
| No prior induced abortion | 1.0 | 1.0 |
| Prior induced abortion | 1.12 (0.77, 1.62) | 0.87 (0.57, 1.34) |
| Vitamin use | | |
| No | 1.0 | 1.0 |
| Yes | 0.68 (0.51, 0.92) | 0.75 (0.52, 1.09) |

*Adjusted for all other potential confounders in table.

# CHAPTER 5
# STATISTICAL METHODS

## POPULATION CONSIDERED

The population of interest for statistical modeling of the relationship between DBP exposure and pregnancy loss includes 2,409 women for analysis, among whom 258 had a pregnancy loss. For each model of interest, the total sample size may vary due to availability of confounder data, exposure window of interest (for example, when considering only late exposures, women with early losses are excluded), site exclusions (certain analyses were replicated excluding the low exposure site, Site 2), and availability of personal exposure data including water filtering practices or bathing habits.

## CHARACTERIZING EXPOSURE

We considered a number of exposure metrics of interest. The continuous exposure index was analyzed using restricted cubic splines to model the relationship between DBP exposure and pregnancy loss, though results are presented in tables for quantiles of exposure (as well as for exposures categorized at regulatory cutpoints where appropriate) for ease of interpretation. This approach provides a flexible strategy for examining the pattern of risk across the spectrum of exposures, and presenting the results in this manner allows for examination of dose-response gradients. In addition, we conducted a subset of analyses using the cutpoints and exposure definitions developed by Waller et al. (1998) in order to replicate their analysis in the RFTS data.

We considered separate models for the association between each of 8 individual DBPs or DBP groups and pregnancy loss, both adjusted and unadjusted for potential confounders. The primary agents of interest were THM4, $CHBrCl_2$, and HAA9, with a secondary interest in $CHCl_3$, THM-Br, HAA5, HAA-Br, and TOX. Due to high correlations among DBPs of interest, not all analyses are presented for all compounds. We did not adjust models for any one DBP or group of DBPs for the presence of other DBPs given the high correlations among individual DBPs and the lack of an established relationship between any DBP and pregnancy loss.

As discussed previously, we considered three exposure windows to be of interest, corresponding to periconceptional exposure, exposure relevant to development of the uterine environment, and exposure potentially causing direct fetal toxicity. In each exposure window, we considered a number of exposure indices meant to reflect differences in ingested, dermal or inhaled, and total exposure. For each trihalomethane or trihalomethane group of interest (THM4, $CHCl_3$, $CHBrCl_2$, and THM-Br), we considered the following four exposure indices:

1. Water concentration (as determined by weekly water measurements within each site)
2. Ingested amount (combining weekly water measurements with data on personal consumption, heating, and filter use provided by study subjects)
3. Shower/bath exposure (combining weekly water measurements with data on human biological uptake rates of various THMs during showering and bathing and data on personal showering and bathing habits provided by study subjects)
4. Total integrated exposure (combining weekly water measurements with appropriate uptake rates and personal ingestion, showering, and bathing data)

For haloacetic acids and total organic halides, we did not consider the dermal and inhalation exposures in (3) and (4) to be pertinent, so we only considered the first two indices above.

## OUTCOME MODEL

To model the association between DBP exposure and time of pregnancy loss, we used a discrete-time survival model (cf. Singer and Willett 2003) with a logit link. Three main features of the data make this approach particularly appropriate. First, the dependent variable (pregnancy loss) is the time until the loss of pregnancy measured in discrete time, which is accompanied by an exposure that is time-varying. Second, observations are censored by multiple processes: (1) for some subjects, the event of interest does not occur, and others are lost to follow-up before the risk period of interest has ended, or (2) all subjects are not observed during their entire time at risk for the event (i.e., subjects enroll after a positive pregnancy test, with enrollment varying over a number of weeks with different baseline probabilities of pregnancy loss) and others are unable to identify losses early in the risk period. Finally, there are explanatory variables whose effect on the time to pregnancy loss we wish to assess or control.

In this framework, we model the probability of reporting a loss at a given week $j$, given that a subject has not experienced a loss before week $j$. Given DBP exposure summary $x_{ij}$ at week $j$, we denote this conditional probability for subject $i$ at week $j$ by

$$h(t_{ij}) = \Pr(T_i = j \mid T_i >= j, x_{ij}),$$

in which $T_i$ is the pregnancy week of loss for subject $i$, $j$ indexes week of pregnancy, and $x_{ij}$ is the DBP concentration summary for subject $i$ at pregnancy week $j$.

The model for $h()$ is given explicitly by

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

in which $\beta$ describes the association between DBP exposure and pregnancy loss, $x_{ij}$ is the DBP exposure summary for subject $i$ at week $j$, and $z_{ij}'\alpha$ contains potential confounders of interest as well as week-specific intercepts to account for varying baseline loss probabilities as pregnancy progresses.

The crude probability of pregnancy loss declined after week 12, making it necessary to include time-specific intercepts to account for this secular trend. In this model, $\exp(\beta)$ represents the odds ratio for the outcome of interest given a 1-unit increase in the predictor $x$.

## PATTERN OF PREGNANCY LOSS ACROSS WEEKS OF GESTATION

The RFTS study allowed us to examine the probability of pregnancy losses that occurred *after* a positive pregnancy test result. The first time of any reported loss was 4 completed weeks of gestation, which was combined with week 5 for analysis due to small numbers of subjects who enrolled early enough for us to ascertain losses in this time period.

When fitting the hazard model, we treated the DBP exposure within each window of interest as a time-varying exposure. That is, when we modeled the probability of pregnancy loss at a given week, say week 12, of gestation, conditional on a woman's still being pregnant at the

beginning of that week, we constructed DBP summary exposures that could involve exposures in weeks before the loss week but not after the loss week. As pregnancies progressed through exposure windows of interest, each woman's exposure was re-calculated using a moving average of water quality exposures within the window.

Effect estimates of interest provided by the model are standard odds ratios. We fit a subset of models with time-varying coefficients that allowed us to investigate whether any potential DBP/pregnancy loss association differed by timing of pregnancy loss (in particular, we considered 12 weeks as a cutpoint of interest).

# CHAPTER 6
# RESULTS

## PATTERN OF PREGNANCY LOSS

The conditional loss probability (conditional on no loss in a prior gestational week) for each gestational week of interest is shown below (Figure 6.1). As expected, there is imprecision in the earliest weeks of gestation, with indications of a higher week-specific probability of loss, diminishing steadily from weeks 9 to the end of the period of interest, 20 weeks.

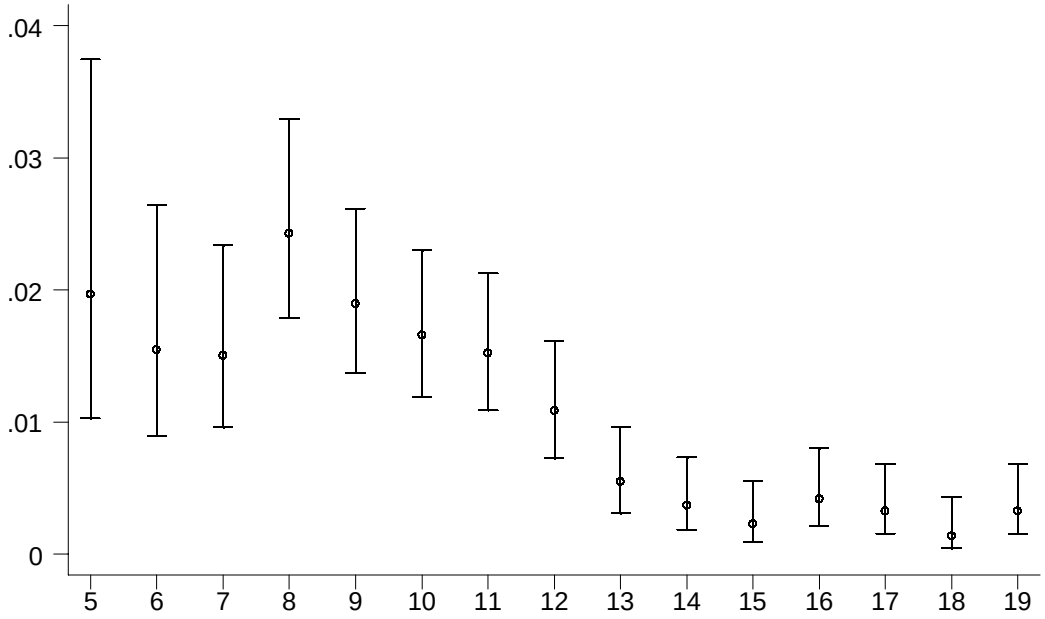



**Figure 6.1 Probability of pregnancy loss (and 95% CIs) by completed gestational week, conditional on a woman's not having a loss in a previous week**

## REPLICATION OF WALLER ET AL. (1998) FINDINGS

Before taking advantage of the more detailed exposure assessment available in RFTS, we first constructed simple exposure summaries and used logistic regression analysis to carry out an analysis to compare our results to those generated using that approach by Waller et al. (1998) in their study in northern California.

Tap water THM concentrations for this analysis were calculated by taking averages over the first trimester of pregnancy. Waller et al. used a cutpoint of 75 µg/L for defining subjects with higher exposure to THM4 (reflecting the top quartile in their data), sometimes coupled with a requirement of drinking 5 or more glasses of cold tap water per day. For individual THMs, the cutpoint of the uppermost quartile was 17 µg/L for chloroform, 16 µg/L for bromoform, 18 µg/L for bromodichloromethane, and 31 µg/L for dibromochloromethane. Models were adjusted for

the same confounders used by Waller et al. (1998), which were gestational age at interview (<= 8 or > 8 weeks), maternal age at interview (>= 35, < 35), cigarette smoking (any, none), history of pregnancy loss (>= 2, < 2 losses), race (black+Asian vs. white+Hispanic), and employment during pregnancy.

As shown in Table 6.1, using the simple cutpoint of 75 µg/L, we found no association whereas Waller et al. (1998) showed a very weak positive effect. In much sharper contrast, they found a far stronger association by combining data on THM concentration and number of glasses of tap water consumed, with an odds ratio of 2.0, and again, our results were completely null using that exposure metric (OR = 1.0, 95% CI = 0.6–1.7), with a similar contrast when dichotomized into high versus low personal exposure. In addition to the notable association they observed for high personal consumption, the other key finding was an indication that bromodichloromethane was most strongly associated with increased risk of pregnancy loss. Here, our results are similar in the relative pattern (Table 6.2), with the largest odds ratio for bromodichloromethane (OR = 1.6, 95% CI = 1.0–2.4), but the absolute strength of association Waller et al. observed for bromodichloromethane was somewhat greater (OR = 2.0, 95% CI = 1.2–3.5).

**Table 6.1**
**THM4 exposure results from RFTS compared to Waller et al. results**

| THM4 exposure | % SAB in RFTS | RFTS results Crude OR | RFTS results Adjusted* OR | Waller et al. results Crude OR | Waller et al. results Adjusted* OR |
|---|---|---|---|---|---|
| <75 µg/L | 11.1% | 1.0 | | 1.0 | 1.0 |
| >=75 µg/L | 10.7% | 0.96 (0.68, 1.35) | 0.96 (0.68, 1.35) | 1.3 (1.0, 1.6) | 1.2 (1.0, 1.5) |
| <75 µg/L and <5 glasses cold tap/day | 10.7% | 1.0 | 1.0 | 1.0 | 1.0 |
| >= 75 µg/L and < 5 glasses cold tap/day | 9.9% | 0.92 (0.58, 1.46) | 0.93 (0.58, 1.48) | 1.2 (0.9, 1.5) | 1.1 (0.9, 1.4) |
| <75 µg/L and >=5 glasses cold tap/day | 11.7% | 1.0 | 1.0 | 1.0 | 1.0 |
| >=75 µg/L and >=5 glasses cold tap/day | 11.8% | 1.01 (0.61, 1.67) | 0.99 (0.59, 1.67) | 2.0 (1.1, 3.6) | 2.0 (1.1, 3.6) |
| Low personal THM4 exposure (<75 µg/L or <5 glasses/day) | 11.0% | 1.0 | 1.0 | 1.0 | 1.0 |
| High personal THM4 exposure (>=75 µg/L and >=5 glasses/day) | 11.8% | 1.09 (0.68, 1.75) | 1.06 (0.65, 1.72) | 1.8 (1.1, 2.9) | 1.8 (1.1, 3.0) |

*Adjusted for maternal age, gestational age at interview, SAB history, race, employment, and cigarette consumption.

**Table 6.2**
**Component THM exposure results from RFTS compared to Waller et al. results**

| Trihalomethane | RFTS* | RFTS** | Waller et al. |
|---|---|---|---|
| Chloroform | 0.98 (0.71, 1.36) | 0.92 (0.60, 1.40) | 0.9 (0.5, 1.6) |
| Bromoform | None exposed | 1.22 (0.78, 1.91) | 1.0 (0.5, 2.0) |
| Bromodichloromethane | 1.59 (1.02, 2.47) | 1.58 (1.03, 2.41) | 2.0 (1.2, 3.5) |
| Chlorodibromomethane | 1.69 (0.63, 4.53) | 1.30 (0.82, 2.05) | 1.3 (0.7, 2.4) |

*Exposed=upper quartile based on Waller's data.
**Exposed=upper quartile based on RFTS data.

## RESULTS FOR TOTAL TRIHALOMETHANES AND PREGNANCY LOSS

The sequence of presentation in the tables is identical across agents. There are three tables, corresponding to the three time windows of interest in relation to the pregnancy. Within each table, we first present the results for tap water concentration, then for ingested amount, then for integrated exposure, then for showering/bathing alone. We examined ingested amount across all participants, restricted to Sites 1 and 3 only (given the extremely low levels in Site 2), restricted to Site 1 only, each with stratification into early and later pregnancy losses. Finally, where there is an applicable regulatory cutpoint applicable to water concentration, we dichotomize the exposure as above versus below that cutpoint.

Table 6.3 presents results for the first time window for THM4, with no evidence of an association between water concentration or ingested amount and pregnancy loss. For later losses, after 12 weeks, there is a suggestion of increased risk for the third and fourth quintiles, but not a clear dose-response gradient. Integrated exposure shows a slightly elevated risk in the uppermost quintile as well, particularly for later pregnancy loss (OR = 1.9, 0.9–3.8). Other indices, including the use of the cutpoint of 80 µg/L, show essentially no association.

For the second window, results are quite similar (Table 6.4), with a few different minor elevations and reductions in the odds ratios but again some tendency for elevated risks in the upper ranges for losses after 12 weeks for integrated exposure, with a slightly greater association now found for showering and bathing.

In the third pregnancy window (Table 6.5), overall results for both concentration and ingested amount are again largely null. Some greater irregularity is found for the ingested amount restricted to Sites 1 and 3, with elevations in the third and fifth quintiles, and for exposures at or above 80 µg/L or above, but there is no evidence whatsoever of a more regular monotonic relationship.

Overall, there is little support for an association between THM4 exposure and pregnancy loss in the range that was studied. There are the expected irregularities across the many indices, time windows, and subsets considered. Whether the increases observed in the upper levels for losses of > 12 weeks are of significance is not clear.

**Table 6.3**
**Association between periconceptional (4 weeks prior to LMP to 3 weeks after LMP) THM4 exposure and subsequent pregnancy loss**

| THM4 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| THM4 water concentration (µg/L) | | | |
| [0, 3.28] | 56 | 1.0 | 1.0 |
| (3.28, 42.55] | 44 | .79 (.53, 1.18) | .82 (.55, 1.23) |
| (42.55, 58.2] | 52 | .91 (.63, 1.34) | 1.07 (.72, 1.59) |
| (58.2, 72.96] | 55 | .97 (.67, 1.42) | 1.11 (.76, 1.62) |
| >72.96 | 51 | .89 (.61, 1.3) | .91 (.62, 1.35) |
| Early losses (before 12 weeks) | | | |
| [0, 3.28] | 43 | 1.0 | 1.0 |
| (3.28, 42.55] | 29 | .69 (.43, 1.11) | .74 (.46, 1.2) |
| (42.55, 58.2] | 31 | .7 (.44, 1.12) | .84 (.52, 1.36) |
| (58.2, 72.96] | 38 | .88 (.56, 1.36) | 1 (.64, 1.57) |
| >72.96 | 42 | .94 (.61, 1.44) | .97 (.63, 1.5) |
| Late losses (after 12 weeks) | | | |
| [0, 3.28] | 13 | 1.0 | 1.0 |
| (3.28, 42.55] | 15 | 1.12 (.53, 2.36) | 1.07 (.5, 2.28) |
| (42.55, 58.2] | 21 | 1.62 (.81, 3.24) | 1.79 (.89, 3.63) |
| (58.2, 72.96] | 17 | 1.3 (.63, 2.68) | 1.45 (.7, 3.01) |
| >72.96 | 9 | .7 (.3, 1.64) | .72 (.31, 1.69) |
| THM4 ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 51 | 1.0 | 1.0 |
| (0, 4.71] | 43 | .92 (.61, 1.38) | .79 (.52, 1.2) |
| (4.71, 24.61] | 52 | 1.05 (.71, 1.56) | .9 (.6, 1.33) |
| (24.61, 79.94] | 55 | 1.1 (.75, 1.62) | 1.06 (.72, 1.57) |
| >79.94 | 56 | 1.13 (.77, 1.65) | 1.02 (.69, 1.5) |
| Sites 1 only | | | |
| [0, 0] | 27 | 1.0 | 1.0 |
| (0, 33.77] | 21 | .91 (.51, 1.62) | .76 (.42, 1.37) |
| (33.77, 67.53] | 26 | 1.06 (.62, 1.83) | 1 (.57, 1.73) |
| (67.53, 123.55] | 16 | .65 (.35, 1.21) | .68 (.36, 1.28) |
| >123.55 | 29 | 1.17 (.69, 1.99) | 1.1 (.64, 1.88) |
| Sites 1 and 3 only | | | |
| [0, 0] | 38 | 1.0 | 1.0 |
| (0, 28.24] | 22 | 1.07 (.63, 1.82) | .92 (.53, 1.57) |
| (28.24, 63.04] | 39 | 1.32 (.84, 2.07) | 1.14 (.72, 1.8) |
| (63.04, 117.01] | 29 | .99 (.61, 1.61) | .93 (.56, 1.53) |
| >117.01 | 38 | 1.3 (.82, 2.04) | 1.09 (.69, 1.73) |

(continued)

**Table 6.3 (continued)**

| THM4 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Early losses (before 12 weeks) | | | |
| [0, 0] | 38 | 1.0 | 1.0 |
| (0, 4.71] | 30 | .87 (.54, 1.41) | .75 (.46, 1.23) |
| (4.71, 24.61] | 38 | 1.04 (.66, 1.63) | .87 (.55, 1.38) |
| (24.61, 79.94] | 37 | .99 (.63, 1.56) | .96 (.6, 1.52) |
| >79.94 | 40 | 1.08 (.69, 1.69) | .99 (.63, 1.56) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 13 | 1.0 | 1.0 |
| (0, 4.71] | 13 | 1.06 (.49, 2.28) | .91 (.42, 1.97) |
| (4.71, 24.61] | 14 | 1.11 (.52, 2.37) | .97 (.45, 2.07) |
| (24.61, 79.94] | 18 | 1.44 (.71, 2.95) | 1.36 (.66, 2.79) |
| >79.94 | 16 | 1.28 (.61, 2.66) | 1.1 (.52, 2.32) |
| | | | |
| THM4 total integrated exposure (µg/day) | | | |
| [0, .09] | 48 | 1.0 | 1.0 |
| (.09, .63] | 51 | 1.08 (.72, 1.6) | .9 (.59, 1.36) |
| (.63, 1.36] | 47 | .95 (.64, 1.43) | .95 (.63, 1.44) |
| (1.36, 2.19] | 48 | .99 (.66, 1.48) | 1.01 (.67, 1.52) |
| >2.19 | 62 | 1.3 (.89, 1.9) | 1.31 (.88, 1.95) |
| Early losses (before 12 weeks) | | | |
| [0, .09] | 35 | 1.0 | 1.0 |
| (.09, .63] | 36 | 1.05 (.66, 1.69) | .86 (.53, 1.39) |
| (.63, 1.36] | 32 | .88 (.54, 1.42) | .87 (.53, 1.43) |
| (1.36, 2.19] | 40 | 1.12 (.71, 1.78) | 1.13 (.71, 1.8) |
| >2.19 | 39 | 1.13 (.71, 1.79) | 1.13 (.7, 1.82) |
| Late losses (after 12 weeks) | | | |
| [0, .09] | 13 | 1.0 | 1.0 |
| (.09, .63] | 15 | 1.13 (.54, 2.39) | 1.01 (.47, 2.14) |
| (.63, 1.36] | 15 | 1.17 (.56, 2.47) | 1.17 (.55, 2.5) |
| (1.36, 2.19] | 8 | .62 (.26, 1.5) | .65 (.27, 1.58) |
| >2.19 | 23 | 1.74 (.88, 3.44) | 1.78 (.89, 3.56) |
| THM4 shower/bath (µg/day) | | | |
| [0, .08] | 46 | 1.0 | 1.0 |
| (.08, .53] | 50 | 1.1 (.73, 1.64) | .93 (.61, 1.41) |
| (.53, 1.12] | 48 | 1.02 (.68, 1.53) | .99 (.65, 1.5) |
| (1.12, 1.92] | 53 | 1.13 (.76, 1.68) | 1.17 (.78, 1.76) |
| >1.92 | 59 | 1.3 (.88, 1.92) | 1.34 (.89, 2.02) |

(continued)

**Table 6.3 (continued)**

| THM4 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Early losses (before 12 weeks) | | | |
| [0, .08] | 34 | 1.0 | 1.0 |
| (.08, .53] | 32 | .96 (.59, 1.56) | .79 (.48, 1.3) |
| (.53, 1.12] | 36 | 1.01 (.63, 1.62) | 1 (.62, 1.62) |
| (1.12, 1.92] | 43 | 1.23 (.78, 1.93) | 1.25 (.78, 1.98) |
| >1.92 | 37 | 1.12 (.7, 1.79) | 1.15 (.7, 1.88) |
| Late losses (after 12 weeks) | | | |
| [0, .08] | 12 | 1.0 | 1.0 |
| (.08, .53] | 18 | 1.47 (.71, 3.07) | 1.32 (.63, 2.78) |
| (.53, 1.12] | 12 | 1.02 (.46, 2.28) | .94 (.41, 2.15) |
| (1.12, 1.92] | 10 | .84 (.36, 1.96) | .93 (.4, 2.17) |
| >1.92 | 22 | 1.79 (.88, 3.63) | 1.86 (.91, 3.82) |
| | | | |
| THM4 regulatory cutpoint | | | |
| <80 µg/L | 231 | 1.0 | 1.0 |
| >=80 µg/L | 27 | 0.97 (0.65, 1.45) | 0.88 (0.59, 1.33) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

**Table 6.4**
**Association between THM4 exposure in window pertinent to development of uterine environment (4 weeks after LMP to 8 weeks after LMP) and subsequent pregnancy loss**

| THM4 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| THM4 water concentration (µg/L) | | | |
| [0, 3.16] | 59 | 1.0 | 1.0 |
| (3.16, 41.02] | 42 | .7 (.47, 1.05) | .68 (.45, 1.02) |
| (41.02, 57.92] | 61 | 1.01 (.7, 1.45) | 1.09 (.75, 1.58) |
| (57.92, 73.38] | 50 | .82 (.56, 1.2) | .9 (.61, 1.33) |
| >73.38 | 46 | .76 (.52, 1.12) | .8 (.54, 1.19) |
| Early losses (before 12 weeks) | | | |
| [0, 3.16] | 43 | 1.0 | 1.0 |
| (3.16, 41.02] | 27 | .62 (.38, 1.01) | .62 (.38, 1.02) |
| (41.02, 57.92] | 44 | .98 (.64, 1.51) | 1.06 (.69, 1.63) |
| (57.92, 73.38] | 35 | .78 (.49, 1.22) | .85 (.54, 1.34) |
| >73.38 | 34 | .76 (.48, 1.2) | .8 (.5, 1.26) |

(continued)

**Table 6.4 (continued)**

| THM4 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Late losses (after 12 weeks) | | | |
| [0, 3.16] | 16 | 1.0 | 1.0 |
| (3.16, 41.02] | 15 | .93 (.46, 1.89) | .84 (.4, 1.75) |
| (41.02, 57.92] | 17 | 1.08 (.54, 2.13) | 1.18 (.59, 2.34) |
| (57.92, 73.38] | 15 | .95 (.47, 1.93) | 1.04 (.51, 2.12) |
| >73.38 | 12 | .76 (.36, 1.6) | .81 (.38, 1.71) |
| THM4 ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 51 | 1.0 | 1.0 |
| (0, 5.56] | 44 | .94 (.62, 1.41) | .83 (.55, 1.26) |
| (5.56, 28.01] | 59 | 1.2 (.82, 1.75) | 1 (.68, 1.47) |
| (28.01, 93.32] | 50 | 1.01 (.68, 1.5) | .94 (.63, 1.4) |
| >93.32 | 53 | 1.07 (.72, 1.57) | .98 (.66, 1.46) |
| Sites 1 only | | | |
| [0, 0] | 27 | 1.0 | 1.0 |
| (0, 41.1] | 28 | 1.22 (.71, 2.07) | 1.11 (.64, 1.91) |
| (41.1, 84.36] | 19 | .78 (.43, 1.4) | .65 (.35, 1.21) |
| (84.36, 140.22] | 18 | .73 (.4, 1.33) | .77 (.42, 1.41) |
| >140.22 | 27 | 1.1 (.64, 1.88) | 1.01 (.59, 1.74) |
| Sites 1 and 3 only | | | |
| [0, 0] | 38 | 1.0 | 1.0 |
| (0, 32.31] | 28 | 1.36 (.83, 2.22) | 1.16 (.7, 1.91) |
| (32.31, 75.35] | 34 | 1.16 (.73, 1.84) | 1.11 (.69, 1.79) |
| (75.35, 133.49] | 27 | .92 (.56, 1.51) | .75 (.45, 1.25) |
| >133.49 | 39 | 1.33 (.85, 2.09) | 1.13 (.71, 1.78) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 38 | 1.0 | 1.0 |
| (0, 5.56] | 31 | .89 (.55, 1.44) | .81 (.5, 1.31) |
| (5.56, 28.01] | 43 | 1.17 (.75, 1.82) | .97 (.62, 1.51) |
| (28.01, 93.32] | 33 | .89 (.56, 1.43) | .84 (.52, 1.35) |
| >93.32 | 38 | 1.02 (.65, 1.61) | .96 (.6, 1.51) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 13 | 1.0 | 1.0 |
| (0, 5.56] | 13 | 1.06 (.49, 2.29) | .92 (.42, 1.99) |
| (5.56, 28.01] | 16 | 1.27 (.61, 2.65) | 1.11 (.53, 2.32) |
| (28.01, 93.32] | 17 | 1.35 (.66, 2.79) | 1.21 (.59, 2.52) |
| >93.32 | 15 | 1.2 (.57, 2.53) | 1.07 (.5, 2.28) |

(continued)

**Table 6.4 (continued)**

| THM4 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| THM4 total integrated exposure (µg/day) | | | |
| [0, .09] | 52 | 1.0 | 1.0 |
| (.09, .66] | 46 | .9 (.61, 1.35) | .75 (.49, 1.14) |
| (.66, 1.37] | 45 | .84 (.56, 1.26) | .85 (.56, 1.28) |
| (1.37, 2.22] | 53 | 1.01 (.69, 1.49) | 1.07 (.72, 1.58) |
| >2.22 | 60 | 1.17 (.8, 1.7) | 1.15 (.78, 1.71) |
| Early losses (before 12 weeks) | | | |
| [0, .09] | 37 | 1.0 | 1.0 |
| (.09, .66] | 34 | .96 (.6, 1.54) | .78 (.48, 1.27) |
| (.66, 1.37] | 31 | .8 (.5, 1.3) | .82 (.5, 1.34) |
| (1.37, 2.22] | 45 | 1.21 (.78, 1.88) | 1.26 (.81, 1.98) |
| >2.22 | 35 | .97 (.61, 1.54) | .96 (.59, 1.55) |
| Late losses (after 12 weeks) | | | |
| [0, .09] | 15 | 1.0 | 1.0 |
| (.09, .66] | 12 | .78 (.36, 1.66) | .68 (.31, 1.47) |
| (.66, 1.37] | 14 | .95 (.46, 1.97) | .92 (.44, 1.95) |
| (1.37, 2.22] | 8 | .53 (.23, 1.26) | .58 (.24, 1.37) |
| >2.22 | 25 | 1.63 (.86, 3.1) | 1.61 (.84, 3.1) |
| THM4 shower/bath (µg/day) | | | |
| [0, .08] | 51 | 1.0 | 1.0 |
| (.08, .53] | 47 | .94 (.63, 1.4) | .78 (.51, 1.18) |
| (.53, 1.14] | 50 | .96 (.65, 1.42) | .96 (.64, 1.43) |
| (1.14, 1.91] | 45 | .88 (.58, 1.31) | .94 (.62, 1.41) |
| >1.91 | 63 | 1.26 (.87, 1.82) | 1.29 (.87, 1.91) |
| Early losses (before 12 weeks) | | | |
| [0, .08] | 36 | 1.0 | 1.0 |
| (.08, .53] | 32 | .92 (.57, 1.49) | .77 (.47, 1.26) |
| (.53, 1.14] | 38 | 1.01 (.64, 1.6) | 1.01 (.63, 1.61) |
| (1.14, 1.91] | 38 | 1.05 (.66, 1.66) | 1.1 (.69, 1.76) |
| >1.91 | 38 | 1.09 (.69, 1.73) | 1.12 (.7, 1.81) |
| Late losses (after 12 weeks) | | | |
| [0, .08] | 15 | 1.0 | 1.0 |
| (.08, .53] | 15 | .98 (.48, 2) | .81 (.39, 1.69) |
| (.53, 1.14] | 12 | .82 (.38, 1.75) | .84 (.39, 1.81) |
| (1.14, 1.91] | 7 | .47 (.19, 1.15) | .52 (.21, 1.28) |
| >1.91 | 25 | 1.63 (.86, 3.09) | 1.65 (.85, 3.17) |

(continued)

**Table 6.4 (continued)**

| THM4 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| THM4 regulatory cutpoint | | | |
| <80 µg/L | 228 | 1.0 | 1.0 |
| >=80 µg/L | 30 | 0.92 (0.63, 1.36) | 0.92 (0.62, 1.36) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

**Table 6.5**
**Association between THM4 exposure pertinent to direct fetal toxicity (9 weeks after LMP to 20 weeks after LMP) and subsequent pregnancy loss. For the analysis of THM exposure in the window from 9 weeks after LMP to 20 weeks after LMP, all person-weeks of observation before the beginning of this time window were eliminated from analysis. This of course excluded women with SAB before this time period from the analysis**

| THM Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| THM4 water concentration (µg/L) | | | |
| [0, 3.22] | 33 | 1.0 | 1.0 |
| (3.22, 41.49] | 36 | 1.06 (.66, 1.71) | 1 (.62, 1.61) |
| (41.49, 58.63] | 48 | 1.41 (.9, 2.2) | 1.45 (.91, 2.29) |
| (58.63, 73.13] | 27 | .81 (.49, 1.36) | .89 (.53, 1.5) |
| >73.13 | 35 | 1.08 (.67, 1.75) | 1.2 (.74, 1.96) |
| Early losses (before 12 weeks) | | | |
| [0, 3.22] | 20 | 1.0 | 1.0 |
| (3.22, 41.49] | 17 | .81 (.42, 1.55) | .77 (.4, 1.48) |
| (41.49, 58.63] | 29 | 1.37 (.77, 2.43) | 1.46 (.81, 2.62) |
| (58.63, 73.13] | 17 | .84 (.44, 1.61) | .94 (.49, 1.81) |
| >73.13 | 22 | 1.14 (.62, 2.1) | 1.27 (.69, 2.36) |
| Late losses (after 12 weeks) | | | |
| [0, 3.22] | 13 | 1.0 | 1.0 |
| (3.22, 41.49] | 19 | 1.47 (.72, 2.98) | 1.34 (.66, 2.73) |
| (41.49, 58.63] | 19 | 1.47 (.73, 2.99) | 1.42 (.68, 2.94) |
| (58.63, 73.13] | 10 | .78 (.34, 1.78) | .82 (.36, 1.89) |
| >73.13 | 13 | 1 (.46, 2.16) | 1.1 (.51, 2.39) |
| THM4 ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 36 | 1.0 | 1.0 |
| (0, 5.39] | 23 | .68 (.4, 1.15) | .59 (.35, 1) |
| (5.39, 29.05] | 44 | 1.26 (.81, 1.96) | 1.03 (.65, 1.61) |
| (29.05, 96.98] | 37 | 1.05 (.66, 1.66) | .97 (.6, 1.54) |
| >96.98 | 39 | 1.11 (.7, 1.75) | 1.02 (.64, 1.62) |

(continued)

**Table 6.5 (continued)**

| THM Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Sites 1 only | | | |
| [0, 0] | 18 | 1.0 | 1.0 |
| (0, 42.49] | 19 | 1.16 (.61, 2.22) | 1.1 (.57, 2.12) |
| (42.49, 85.35] | 15 | .88 (.44, 1.76) | .78 (.38, 1.58) |
| (85.35, 138.61] | 8 | .48 (.21, 1.1) | .47 (.2, 1.09) |
| >138.61 | 22 | 1.3 (.69, 2.43) | 1.3 (.69, 2.45) |
| Sites 1 and 3 only | | | |
| [0, 0] | 25 | 1.0 | 1.0 |
| (0, 33.9] | 21 | 1.51 (.84, 2.7) | 1.32 (.73, 2.38) |
| (33.9, 75.84] | 24 | 1.22 (.69, 2.14) | 1.08 (.61, 1.92) |
| (75.84, 133.35] | 16 | .82 (.44, 1.54) | .71 (.38, 1.35) |
| >133.35 | 32 | 1.67 (.99, 2.83) | 1.44 (.84, 2.47) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 23 | 1.0 | 1.0 |
| (0, 5.39] | 12 | .55 (.27, 1.12) | .49 (.24, 1) |
| (5.39, 29.05] | 25 | 1.11 (.62, 1.96) | .89 (.5, 1.58) |
| (29.05, 96.98] | 22 | .96 (.53, 1.73) | .9 (.49, 1.63) |
| >96.98 | 23 | 1.02 (.57, 1.82) | .95 (.53, 1.71) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 13 | 1.0 | 1.0 |
| (0, 5.39] | 11 | .9 (.4, 2.01) | .75 (.34, 1.69) |
| (5.39, 29.05] | 19 | 1.52 (.75, 3.08) | 1.28 (.63, 2.6) |
| (29.05, 96.98] | 15 | 1.2 (.57, 2.53) | 1.08 (.51, 2.3) |
| >96.98 | 16 | 1.27 (.61, 2.65) | 1.14 (.54, 2.41) |
| THM4 total integrated exposure (µg/day) | | | |
| [0, .09] | 32 | 1.0 | 1.0 |
| (.09, .66] | 33 | 1.05 (.65, 1.72) | .79 (.48, 1.32) |
| (.66, 1.37] | 37 | 1.14 (.71, 1.84) | 1.17 (.72, 1.91) |
| (1.37, 2.26] | 35 | 1.11 (.69, 1.81) | 1.22 (.74, 1.99) |
| >2.26 | 41 | 1.29 (.81, 2.06) | 1.2 (.74, 1.95) |
| Early losses (before 12 weeks) | | | |
| [0, .09] | 18 | 1.0 | 1.0 |
| (.09, .66] | 19 | 1.11 (.58, 2.12) | .8 (.41, 1.57) |
| (.66, 1.37] | 24 | 1.31 (.71, 2.43) | 1.37 (.74, 2.56) |
| (1.37, 2.26] | 22 | 1.26 (.67, 2.37) | 1.36 (.72, 2.57) |
| >2.26 | 22 | 1.24 (.66, 2.33) | 1.15 (.6, 2.19) |

(continued)

**Table 6.5 (continued)**

| THM Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Late losses (after 12 weeks) | | | |
| [0, .09] | 14 | 1.0 | 1.0 |
| (.09, .66] | 14 | .98 (.47, 2.07) | .78 (.37, 1.67) |
| (.66, 1.37] | 13 | .93 (.44, 1.98) | .91 (.42, 1.99) |
| (1.37, 2.26] | 13 | .93 (.44, 1.98) | 1.04 (.48, 2.22) |
| >2.26 | 19 | 1.36 (.68, 2.71) | 1.27 (.62, 2.57) |
| THM4 shower/bath (µg/day) | | | |
| [0, .08] | 34 | 1.0 | 1.0 |
| (.08, .54] | 31 | .93 (.57, 1.51) | .69 (.42, 1.16) |
| (.54, 1.12] | 33 | .98 (.6, 1.58) | 1.01 (.62, 1.65) |
| (1.12, 1.97] | 41 | 1.21 (.76, 1.91) | 1.3 (.82, 2.07) |
| >1.97 | 39 | 1.17 (.74, 1.86) | 1.08 (.66, 1.75) |
| Early losses (before 12 weeks) | | | |
| [0, .08] | 19 | 1.0 | 1.0 |
| (.08, .54] | 17 | .93 (.48, 1.81) | .67 (.34, 1.33) |
| (.54, 1.12] | 20 | 1.06 (.56, 2) | 1.13 (.59, 2.14) |
| (1.12, 1.97] | 30 | 1.58 (.89, 2.83) | 1.68 (.93, 3.02) |
| >1.97 | 19 | 1.04 (.55, 1.97) | .95 (.49, 1.85) |
| Late losses (after 12 weeks) | | | |
| [0, .08] | 15 | 1.0 | 1.0 |
| (.08, .54] | 14 | .92 (.44, 1.9) | .72 (.34, 1.51) |
| (.54, 1.12] | 13 | .87 (.41, 1.83) | .86 (.4, 1.85) |
| (1.12, 1.97] | 11 | .73 (.34, 1.6) | .81 (.37, 1.78) |
| >1.97 | 20 | 1.32 (.68, 2.59) | 1.22 (.61, 2.44) |
| THM4 regulatory cutpoint | | | |
| <80 µg/L | 161 | 1.0 | 1.0 |
| >=80 µg/L | 18 | 0.84 (0.51, 1.37) | 0.92 (0.56, 1.50) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

## RESULTS FOR BROMODICHLOROMETHANE AND PREGNANCY LOSS

For bromodichloromethane, all indices of exposure in the first time window showed small increases in risk for later pregnancy losses, especially for integrated and shower/bath exposure for which the uppermost quintile had adjusted odds ratios of 1.6–1.7 (Table 6.6). The second time window (Table 6.7) yielded only sporadic, modestly elevated odds ratios, somewhat more so for early than for late pregnancy losses, but more so in the fourth than fifth quintile (Table 6.7). In the third pregnancy time window (Table 6.8), concentration and especially integrated exposure and shower/bath exposure generated elevated odds ratios for later pregnancy losses in the uppermost quintile only. Overall, the evidence for an association is somewhat stronger than for total trihalomethanes, but still modest in magnitude and showing little overall dose-response gradient.

**Table 6.6**
**Association between periconceptional (4 weeks prior to LMP to 3 weeks after LMP) $CHBrCl_2$ exposure and subsequent pregnancy loss**

| $CHBrCl_2$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| $CHBrCl_2$ water concentration (µg/L) | | | |
| [0, 1.11] | 50 | 1.0 | 1.0 |
| (1.11, 10.45] | 54 | 1.07 (.72, 1.57) | 1.01 (.68, 1.49) |
| (10.45, 13.97] | 50 | .97 (.65, 1.44) | 1.04 (.69, 1.55) |
| (13.97, 17.83] | 48 | .93 (.63, 1.39) | 1.05 (.7, 1.57) |
| >17.83 | 56 | 1.11 (.75, 1.63) | 1.21 (.82, 1.8) |
| Early losses (before 12 weeks) | | | |
| [0, 1.11] | 38 | 1.0 | 1.0 |
| (1.11, 10.45] | 37 | .96 (.61, 1.52) | .91 (.57, 1.45) |
| (10.45, 13.97] | 34 | .85 (.53, 1.35) | .91 (.57, 1.46) |
| (13.97, 17.83] | 35 | .88 (.55, 1.4) | 1.02 (.64, 1.63) |
| >17.83 | 39 | 1.01 (.64, 1.59) | 1.09 (.69, 1.73) |
| Late losses (after 12 weeks) | | | |
| [0, 1.11] | 12 | 1.0 | 1.0 |
| (1.11, 10.45] | 17 | 1.4 (.67, 2.93) | 1.31 (.62, 2.78) |
| (10.45, 13.97] | 16 | 1.36 (.64, 2.88) | 1.44 (.68, 3.07) |
| (13.97, 17.83] | 13 | 1.09 (.5, 2.39) | 1.14 (.51, 2.55) |
| >17.83 | 17 | 1.41 (.67, 2.95) | 1.6 (.76, 3.38) |
| $CHBrCl_2$ ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 51 | 1.0 | 1.0 |
| (0, 1.53] | 44 | .93 (.62, 1.4) | .79 (.52, 1.2) |
| (1.53, 5.94] | 50 | 1.02 (.69, 1.52) | .88 (.59, 1.3) |
| (5.94, 19.62] | 56 | 1.12 (.76, 1.64) | 1.07 (.73, 1.58) |
| >19.62 | 56 | 1.13 (.77, 1.66) | 1.04 (.7, 1.53) |

(continued)

**Table 6.6 (continued)**

| $CHBrCl_2$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Early losses (before 12 weeks) | | | |
| [0, 0] | 38 | 1.0 | 1.0 |
| (0, 1.53] | 31 | .89 (.55, 1.44) | .75 (.46, 1.22) |
| (1.53, 5.94] | 37 | 1.02 (.65, 1.62) | .87 (.55, 1.39) |
| (5.94, 19.62] | 40 | 1.06 (.67, 1.65) | 1.03 (.65, 1.62) |
| >19.62 | 37 | 1 (.64, 1.58) | .93 (.59, 1.48) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 13 | 1.0 | 1.0 |
| (0, 1.53] | 13 | 1.06 (.49, 2.3) | .92 (.42, 2) |
| (1.53, 5.94] | 13 | 1.03 (.48, 2.22) | .88 (.41, 1.91) |
| (5.94, 19.62] | 16 | 1.29 (.62, 2.69) | 1.21 (.58, 2.53) |
| >19.62 | 19 | 1.51 (.74, 3.06) | 1.33 (.65, 2.73) |
| $CHBrCl_2$ total integrated exposure (µg/day) | | | |
| [0, .03] | 46 | 1.0 | 1.0 |
| (.03, .14] | 48 | 1.05 (.7, 1.58) | .88 (.58, 1.34) |
| (.14, .26] | 51 | 1.08 (.72, 1.61) | 1.06 (.7, 1.59) |
| (.26, .47] | 55 | 1.17 (.79, 1.73) | 1.14 (.77, 1.71) |
| >.47 | 56 | 1.25 (.84, 1.85) | 1.37 (.9, 2.09) |
| Early losses (before 12 weeks) | | | |
| [0, .03] | 33 | 1.0 | 1.0 |
| (.03, .14] | 32 | .99 (.6, 1.61) | .8 (.49, 1.33) |
| (.14, .26] | 39 | 1.13 (.71, 1.81) | 1.11 (.69, 1.79) |
| (.26, .47] | 43 | 1.26 (.79, 1.99) | 1.21 (.76, 1.93) |
| >.47 | 35 | 1.11 (.69, 1.8) | 1.22 (.74, 2.03) |
| Late losses (after 12 weeks) | | | |
| [0, .03] | 13 | 1.0 | 1.0 |
| (.03, .14] | 16 | 1.21 (.58, 2.52) | 1.08 (.51, 2.27) |
| (.14, .26] | 12 | .94 (.43, 2.06) | .89 (.4, 2) |
| (.26, .47] | 12 | .94 (.43, 2.06) | .95 (.43, 2.1) |
| >.47 | 21 | 1.56 (.78, 3.12) | 1.72 (.84, 3.51) |
| $CHBrCl_2$ shower/bath (µg/day) | | | |
| [0, .03] | 46 | 1.0 | 1.0 |
| (.03, .12] | 46 | 1.02 (.67, 1.54) | .88 (.57, 1.34) |
| (.12, .24] | 51 | 1.08 (.72, 1.61) | 1.04 (.69, 1.57) |
| (.24, .45] | 59 | 1.26 (.86, 1.86) | 1.25 (.84, 1.86) |
| >.45 | 54 | 1.2 (.81, 1.79) | 1.32 (.86, 2.01) |

(continued)

**Table 6.6 (continued)**

| $CHBrCl_2$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Early losses (before 12 weeks) | | | |
| [0, .03] | 32 | 1.0 | 1.0 |
| (.03, .12] | 31 | 1 (.61, 1.64) | .84 (.51, 1.4) |
| (.12, .24] | 42 | 1.25 (.79, 2) | 1.22 (.76, 1.96) |
| (.24, .45] | 44 | 1.33 (.84, 2.11) | 1.31 (.82, 2.09) |
| >.45 | 33 | 1.08 (.66, 1.77) | 1.19 (.71, 1.98) |
| Late losses (after 12 weeks) | | | |
| [0, .03] | 14 | 1.0 | 1.0 |
| (.03, .12] | 15 | 1.05 (.51, 2.19) | .95 (.46, 2) |
| (.12, .24] | 9 | .66 (.28, 1.53) | .6 (.25, 1.43) |
| (.24, .45] | 15 | 1.1 (.53, 2.28) | 1.12 (.54, 2.33) |
| >.45 | 21 | 1.45 (.73, 2.85) | 1.58 (.79, 3.18) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

**Table 6.7**
**Association between $CHBrCl_2$ exposure in window pertinent to development of uterine environment (4 weeks after LMP to 8 weeks after LMP) and subsequent pregnancy loss**

| $CHBrCl_2$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| $CHBrCl_2$ water concentration (µg/L) | | | |
| [0, 1.05] | 60 | 1.0 | 1.0 |
| (1.05, 10.43] | 44 | .73 (.49, 1.08) | .67 (.45, 1) |
| (10.43, 13.63] | 46 | .75 (.51, 1.11) | .76 (.51, 1.13) |
| (13.63, 18.19] | 52 | .85 (.58, 1.23) | .95 (.65, 1.39) |
| >18.19 | 56 | .93 (.64, 1.34) | 1.02 (.7, 1.48) |
| Early losses (before 12 weeks) | | | |
| [0, 1.05] | 44 | 1.0 | 1.0 |
| (1.05, 10.43] | 31 | .7 (.44, 1.12) | .65 (.4, 1.03) |
| (10.43, 13.63] | 32 | .71 (.45, 1.13) | .72 (.45, 1.15) |
| (13.63, 18.19] | 34 | .75 (.48, 1.17) | .84 (.53, 1.32) |
| >18.19 | 42 | .95 (.62, 1.46) | 1.03 (.66, 1.59) |
| Late losses (after 12 weeks) | | | |
| [0, 1.05] | 16 | 1.0 | 1.0 |
| (1.05, 10.43] | 13 | .81 (.39, 1.69) | .74 (.35, 1.57) |
| (10.43, 13.63] | 14 | .87 (.42, 1.79) | .85 (.4, 1.77) |
| (13.63, 18.19] | 18 | 1.13 (.58, 2.23) | 1.27 (.64, 2.51) |
| >18.19 | 14 | .87 (.42, 1.79) | .99 (.48, 2.05) |

(continued)

**Table 6.7 (continued)**

| $CHBrCl_2$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| $CHBrCl_2$ ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 51 | 1.0 | 1.0 |
| (0, 1.7] | 47 | 1 (.67, 1.49) | .87 (.58, 1.3) |
| (1.7, 6.75] | 50 | 1.02 (.69, 1.51) | .86 (.58, 1.28) |
| (6.75, 22.86] | 51 | 1.03 (.69, 1.52) | .97 (.65, 1.44) |
| >22.86 | 58 | 1.17 (.8, 1.71) | 1.07 (.73, 1.58) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 38 | 1.0 | 1.0 |
| (0, 1.7] | 34 | .97 (.61, 1.55) | .85 (.53, 1.37) |
| (1.7, 6.75] | 37 | 1.02 (.65, 1.61) | .85 (.53, 1.35) |
| (6.75, 22.86] | 33 | .88 (.55, 1.41) | .85 (.53, 1.36) |
| >22.86 | 41 | 1.1 (.71, 1.72) | 1.02 (.65, 1.61) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 13 | 1.0 | 1.0 |
| (0, 1.7] | 13 | 1.07 (.49, 2.31) | .92 (.42, 2) |
| (1.7, 6.75] | 13 | 1.02 (.47, 2.21) | .9 (.41, 1.94) |
| (6.75, 22.86] | 18 | 1.44 (.7, 2.94) | 1.3 (.63, 2.67) |
| >22.86 | 17 | 1.36 (.66, 2.8) | 1.21 (.58, 2.53) |
| $CHBrCl_2$ total integrated exposure (µg/day) | | | |
| [0, .03] | 52 | 1.0 | 1.0 |
| (.03, .14] | 45 | .89 (.59, 1.32) | .74 (.49, 1.12) |
| (.14, .27] | 40 | .75 (.5, 1.14) | .74 (.49, 1.14) |
| (.27, .49] | 65 | 1.24 (.86, 1.78) | 1.26 (.87, 1.84) |
| >.49 | 54 | 1.07 (.73, 1.57) | 1.14 (.76, 1.72) |
| Early losses (before 12 weeks) | | | |
| [0, .03] | 36 | 1.0 | 1.0 |
| (.03, .14] | 33 | .96 (.6, 1.55) | .79 (.49, 1.3) |
| (.14, .27] | 29 | .78 (.47, 1.27) | .79 (.48, 1.31) |
| (.27, .49] | 51 | 1.39 (.9, 2.14) | 1.4 (.91, 2.18) |
| >.49 | 33 | .97 (.6, 1.56) | 1.04 (.63, 1.71) |
| Late losses (after 12 weeks) | | | |
| [0, .03] | 16 | 1.0 | 1.0 |
| (.03, .14] | 12 | .73 (.34, 1.54) | .62 (.29, 1.33) |
| (.14, .27] | 11 | .7 (.32, 1.51) | .63 (.29, 1.4) |
| (.27, .49] | 14 | .88 (.43, 1.81) | .94 (.46, 1.93) |
| >.49 | 21 | 1.26 (.66, 2.42) | 1.32 (.68, 2.59) |

(continued)

**Table 6.7 (continued)**

| $CHBrCl_2$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| $CHBrCl_2$ shower/bath (µg/day) | | | |
| [0, .03] | 53 | 1.0 | 1.0 |
| (.03, .12] | 42 | .81 (.54, 1.22) | .68 (.45, 1.04) |
| (.12, .24] | 41 | .75 (.5, 1.14) | .74 (.48, 1.12) |
| (.24, .47] | 67 | 1.24 (.87, 1.79) | 1.28 (.89, 1.86) |
| >.47 | 53 | 1.03 (.7, 1.51) | 1.09 (.73, 1.65) |
| Early losses (before 12 weeks) | | | |
| [0, .03] | 37 | 1.0 | 1.0 |
| (.03, .12] | 28 | .79 (.48, 1.3) | .65 (.39, 1.09) |
| (.12, .24] | 34 | .88 (.55, 1.41) | .89 (.55, 1.43) |
| (.24, .47] | 51 | 1.35 (.88, 2.07) | 1.37 (.89, 2.12) |
| >.47 | 32 | .92 (.57, 1.48) | .98 (.59, 1.61) |
| Late losses (after 12 weeks) | | | |
| [0, .03] | 16 | 1.0 | 1.0 |
| (.03, .12] | 14 | .85 (.41, 1.74) | .74 (.36, 1.52) |
| (.12, .24] | 7 | .44 (.18, 1.08) | .38 (.15, .98) |
| (.24, .47] | 16 | 1.01 (.5, 2.02) | 1.08 (.54, 2.17) |
| >.47 | 21 | 1.26 (.65, 2.41) | 1.32 (.67, 2.58) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

**Table 6.8**
**Association between $CHBrCl_2$ exposure pertinent to direct fetal toxicity (9 weeks after LMP to 20 weeks after LMP) and subsequent pregnancy loss**

| $CHBrCl_2$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| $CHBrCl_2$ water concentration (µg/L) | | | |
| [0, 1.02] | 38 | 1.0 | 1.0 |
| (1.02, 10.23] | 32 | .83 (.52, 1.33) | .79 (.49, 1.27) |
| (10.23, 13.75] | 34 | .92 (.58, 1.47) | .97 (.6, 1.57) |
| (13.75, 18.62] | 30 | .8 (.5, 1.3) | .89 (.55, 1.46) |
| >18.62 | 45 | 1.21 (.78, 1.87) | 1.44 (.92, 2.25) |
| Early losses (before 12 weeks) | | | |
| [0, 1.02] | 24 | 1.0 | 1.0 |
| (1.02, 10.23] | 16 | .64 (.34, 1.22) | .63 (.33, 1.2) |
| (10.23, 13.75] | 18 | .8 (.43, 1.49) | .9 (.48, 1.69) |
| (13.75, 18.62] | 19 | .83 (.45, 1.52) | .95 (.51, 1.75) |
| >18.62 | 28 | 1.19 (.69, 2.06) | 1.44 (.82, 2.52) |

(continued)

**Table 6.8 (continued)**

| $CHBrCl_2$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Late losses (after 12 weeks) | | | |
| [0, 1.02] | 14 | 1.0 | 1.0 |
| (1.02, 10.23] | 16 | 1.16 (.57, 2.39) | 1.05 (.51, 2.16) |
| (10.23, 13.75] | 16 | 1.11 (.54, 2.29) | 1.07 (.51, 2.24) |
| (13.75, 18.62] | 11 | .77 (.35, 1.71) | .82 (.37, 1.82) |
| >18.62 | 17 | 1.24 (.61, 2.53) | 1.43 (.69, 2.96) |
| $CHBrCl_2$ ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 36 | 1.0 | 1.0 |
| (0, 1.65] | 23 | .68 (.4, 1.16) | .58 (.34, .98) |
| (1.65, 6.99] | 41 | 1.16 (.74, 1.82) | .98 (.62, 1.54) |
| (6.99, 23.1] | 37 | 1.04 (.66, 1.66) | .92 (.58, 1.48) |
| >23.1 | 42 | 1.2 (.77, 1.88) | 1.14 (.72, 1.8) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 23 | 1.0 | 1.0 |
| (0, 1.65] | 11 | .51 (.25, 1.06) | .43 (.21, .9) |
| (1.65, 6.99] | 25 | 1.09 (.62, 1.94) | .92 (.52, 1.64) |
| (6.99, 23.1] | 21 | .91 (.5, 1.66) | .81 (.44, 1.49) |
| >23.1 | 25 | 1.11 (.63, 1.96) | 1.08 (.6, 1.92) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 13 | 1.0 | 1.0 |
| (0, 1.65] | 12 | .98 (.45, 2.15) | .83 (.37, 1.82) |
| (1.65, 6.99] | 16 | 1.27 (.61, 2.65) | 1.08 (.51, 2.25) |
| (6.99, 23.1] | 16 | 1.28 (.61, 2.67) | 1.11 (.53, 2.34) |
| >23.1 | 17 | 1.36 (.66, 2.8) | 1.25 (.6, 2.61) |
| $CHBrCl_2$ total integrated exposure (µg/day) | | 1.0 | 1.0 |
| [0, .03] | 33 | .93 (.57, 1.53) | .73 (.43, 1.21) |
| (.03, .14] | 31 | .8 (.48, 1.34) | .81 (.48, 1.36) |
| (.14, .27] | 27 | 1.26 (.8, 1.99) | 1.3 (.81, 2.07) |
| (.27, .5] | 42 | 1.39 (.89, 2.19) | 1.43 (.88, 2.33) |
| >.5 | 45 | | |
| Early losses (before 12 weeks) | | | |
| [0, .03] | 19 | 1.0 | 1.0 |
| (.03, .14] | 16 | .84 (.43, 1.64) | .63 (.32, 1.25) |
| (.14, .27] | 18 | .92 (.48, 1.77) | .94 (.49, 1.82) |
| (.27, .5] | 30 | 1.54 (.86, 2.75) | 1.61 (.9, 2.9) |
| >.5 | 22 | 1.21 (.65, 2.25) | 1.23 (.65, 2.35) |

(continued)

**Table 6.8 (continued)**

| $CHBrCl_2$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Late losses (after 12 weeks) | | | |
| [0, .03] | 14 | 1.0 | 1.0 |
| (.03, .14] | 15 | 1.06 (.51, 2.2) | .86 (.41, 1.81) |
| (.14, .27] | 9 | .64 (.28, 1.48) | .64 (.28, 1.49) |
| (.27, .5] | 12 | .87 (.4, 1.88) | .86 (.39, 1.9) |
| >.5 | 23 | 1.62 (.83, 3.16) | 1.69 (.85, 3.37) |
| $CHBrCl_2$ shower/bath (µg/day) | | | |
| [0, .02] | 33 | 1.0 | 1.0 |
| (.02, .12] | 31 | .93 (.57, 1.53) | .74 (.44, 1.23) |
| (.12, .25] | 23 | .68 (.4, 1.17) | .68 (.4, 1.17) |
| (.25, .48] | 48 | 1.43 (.92, 2.23) | 1.49 (.95, 2.35) |
| >.48 | 43 | 1.33 (.84, 2.09) | 1.36 (.83, 2.21) |
| Early losses (before 12 weeks) | | | |
| [0, .02] | 18 | 1.0 | 1.0 |
| (.02, .12] | 17 | .94 (.48, 1.84) | .72 (.36, 1.42) |
| (.12, .25] | 16 | .87 (.44, 1.71) | .88 (.44, 1.74) |
| (.25, .48] | 34 | 1.82 (1.02, 3.25) | 1.92 (1.07, 3.44) |
| >.48 | 20 | 1.15 (.61, 2.19) | 1.16 (.6, 2.27) |
| Late losses (after 12 weeks) | | | |
| [0, .02] | 15 | 1.0 | 1.0 |
| (.02, .12] | 14 | .92 (.44, 1.9) | .77 (.37, 1.61) |
| (.12, .25] | 7 | .46 (.19, 1.14) | .46 (.18, 1.13) |
| (.25, .48] | 14 | .95 (.46, 1.97) | .96 (.45, 2.03) |
| >.48 | 23 | 1.51 (.79, 2.91) | 1.58 (.8, 3.1) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

## RESULTS FOR HAA9 AND PREGNANCY LOSS

In the first time window (Table 6.9), HAA9 indices were consistently unrelated to risk of pregnancy loss. While isolated findings were below or above the null, with extreme adjusted odds ratios as low as 0.5 and as high as 1.4, in no case was there any pattern across levels of exposure. In the second time window (Table 6.10), there was some indications of a positive association but limited to concentration for the third and fourth, but not the fifth, quintile.

In the third pregnancy window, more notable associations were found for ingested amount (Table 6.11), though the patterns were not monotonic across levels. Across all sites, the third and fourth quintile showed a increased odds ratios for early and later losses, but restriction to Sites 1 and 3, eliminating the low exposure site, eliminated this pattern despite Site 2 not making a contribution to the upper categories. This may suggest that modest shifts in the cutpoints eliminated the pattern, perhaps indicating it is strongly influenced by random error.

**Table 6.9**
**Association between periconceptional (4 weeks prior to LMP to 3 weeks after LMP) HAA9 exposure and subsequent pregnancy loss**

| HAA9 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| HAA9 water concentration (µg/L) | | | |
| [0, 2.02] | 58 | 1.0 | 1.0 |
| (2.02, 27.56] | 38 | .65 (.43, .98) | .63 (.42, .96) |
| (27.56, 42.24] | 57 | .96 (.66, 1.38) | 1.08 (.74, 1.57) |
| (42.24, 50.03] | 55 | .94 (.65, 1.36) | 1.06 (.72, 1.56) |
| >50.03 | 50 | .84 (.57, 1.22) | .86 (.58, 1.26) |
| Early losses (before 12 weeks) | | | |
| [0, 2.02] | 43 | 1.0 | 1.0 |
| (2.02, 27.56] | 25 | .58 (.35, .95) | .56 (.34, .92) |
| (27.56, 42.24] | 35 | .78 (.5, 1.22) | .92 (.58, 1.45) |
| (42.24, 50.03] | 41 | .94 (.61, 1.45) | 1.05 (.67, 1.63) |
| >50.03 | 39 | .86 (.56, 1.34) | .88 (.57, 1.38) |
| Late losses (after 12 weeks) | | | |
| [0, 2.02] | 15 | 1.0 | 1.0 |
| (2.02, 27.56] | 13 | .86 (.41, 1.81) | .85 (.4, 1.79) |
| (27.56, 42.24] | 22 | 1.48 (.77, 2.86) | 1.52 (.77, 2.99) |
| (42.24, 50.03] | 14 | .93 (.45, 1.92) | 1.09 (.52, 2.28) |
| >50.03 | 11 | .75 (.34, 1.63) | .77 (.35, 1.69) |
| HAA9 ingested amount (µg/day) | | | |
| All sites | | | |
| [0, .12] | 53 | 1.0 | 1.0 |
| (.12, 4.96] | 45 | .85 (.57, 1.26) | .76 (.5, 1.14) |
| (4.96, 28.78] | 40 | .73 (.49, 1.11) | .63 (.41, .97) |
| (28.78, 72.54] | 62 | 1.14 (.79, 1.64) | 1.23 (.84, 1.81) |
| >72.54 | 57 | 1.04 (.71, 1.51) | .98 (.67, 1.45) |
| Site 1 only | | | |
| [0, 17.78] | 26 | 1.0 | 1.0 |
| (17.78, 37.37] | 15 | .58 (.31, 1.1) | .51 (.26, .99) |
| (37.37, 62.72] | 27 | 1.04 (.6, 1.79) | .99 (.56, 1.74) |
| (62.72, 103.85] | 21 | .81 (.46, 1.45) | .82 (.45, 1.51) |
| >103.85 | 30 | 1.14 (.67, 1.94) | 1.03 (.59, 1.79) |
| Sites 1 and 3 only | | | |
| [0, 11.23] | 31 | 1.0 | 1.0 |
| (11.23, 32.82] | 24 | .76 (.45, 1.3) | .58 (.33, 1.01) |
| (32.82, 58.2] | 33 | 1.04 (.63, 1.71) | .93 (.56, 1.55) |
| (58.2, 98.09] | 36 | 1.14 (.7, 1.86) | 1.06 (.64, 1.75) |
| >98.09 | 42 | 1.31 (.82, 2.09) | 1.01 (.62, 1.64) |

(continued)

**Table 6.9 (continued)**

| HAA9 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Early losses (before 12 weeks) | | | |
| [0, .12] | 38 | 1.0 | 1.0 |
| (.12, 4.96] | 32 | .84 (.52, 1.35) | .74 (.46, 1.21) |
| (4.96, 28.78] | 28 | .7 (.43, 1.15) | .6 (.36, 1) |
| (28.78, 72.54] | 44 | 1.1 (.71, 1.7) | 1.19 (.76, 1.87) |
| >72.54 | 41 | 1.01 (.65, 1.58) | .97 (.62, 1.54) |
| Late losses (after 12 weeks) | | | |
| [0, .12] | 15 | 1.0 | 1.0 |
| (.12, 4.96] | 13 | .87 (.41, 1.82) | .78 (.37, 1.66) |
| (4.96, 28.78] | 12 | .81 (.38, 1.74) | .71 (.33, 1.53) |
| (28.78, 72.54] | 18 | 1.23 (.62, 2.45) | 1.34 (.67, 2.68) |
| >72.54 | 16 | 1.1 (.54, 2.23) | 1 (.49, 2.07) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

**Table 6.10**
**Association between HAA9 exposure in window pertinent to development of uterine environment (4 weeks after LMP to 8 weeks after LMP) and subsequent pregnancy loss**

| HAA9 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| HAA9 water concentration (µg/L) | | | |
| [0, 1.87] | 49 | 1.0 | 1.0 |
| (1.87, 26.9] | 53 | 1.08 (.73, 1.6) | 1.1 (.74, 1.63) |
| (26.9, 42.68] | 61 | 1.21 (.83, 1.77) | 1.29 (.87, 1.9) |
| (42.68, 51.67] | 56 | 1.13 (.77, 1.66) | 1.35 (.91, 2.01) |
| >51.67 | 39 | .78 (.51, 1.19) | .83 (.54, 1.27) |
| Early losses (before 12 weeks) | | | |
| [0, 1.87] | 35 | 1.0 | 1.0 |
| (1.87, 26.9] | 38 | 1.1 (.69, 1.74) | 1.13 (.71, 1.8) |
| (26.9, 42.68] | 39 | 1.06 (.67, 1.68) | 1.14 (.71, 1.83) |
| (42.68, 51.67] | 41 | 1.15 (.73, 1.82) | 1.42 (.89, 2.26) |
| >51.67 | 30 | .83 (.51, 1.35) | .89 (.54, 1.46) |
| Late losses (after 12 weeks) | | | |
| [0, 1.87] | 14 | 1.0 | 1.0 |
| (1.87, 26.9] | 15 | 1.06 (.51, 2.19) | 1.04 (.5, 2.15) |
| (26.9, 42.68] | 22 | 1.6 (.82, 3.14) | 1.66 (.84, 3.29) |
| (42.68, 51.67] | 15 | 1.07 (.51, 2.21) | 1.19 (.56, 2.5) |
| >51.67 | 9 | .65 (.28, 1.49) | .67 (.29, 1.56) |

(continued)

**Table 6.10 (continued)**

| HAA9 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| HAA9 ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 53 | 1.0 | 1.0 |
| (0, 5.51] | 39 | 1.07 (.7, 1.62) | .9 (.59, 1.37) |
| (5.51, 35.55] | 65 | 1.42 (.99, 2.05) | 1.24 (.86, 1.8) |
| (35.55, 84.62] | 43 | .94 (.63, 1.41) | .95 (.63, 1.44) |
| >84.62 | 57 | 1.23 (.84, 1.79) | 1.11 (.75, 1.63) |
| Sites 1 only | | | |
| [0, 20.66] | 26 | 1.0 | 1.0 |
| (20.66, 46.35] | 23 | .9 (.51, 1.58) | .87 (.49, 1.57) |
| (46.35, 75.98] | 22 | .86 (.49, 1.52) | .79 (.44, 1.44) |
| (75.98, 115.88] | 23 | .88 (.5, 1.55) | .87 (.49, 1.56) |
| >115.88 | 25 | .97 (.56, 1.68) | .87 (.49, 1.55) |
| Sites 1 and 3 only | | | |
| [0, 10.78] | 32 | 1.0 | 1.0 |
| (10.78, 39.6] | 38 | 1.17 (.73, 1.88) | .96 (.59, 1.57) |
| (39.6, 68.93] | 27 | .83 (.5, 1.4) | .69 (.41, 1.18) |
| (68.93, 109.39] | 32 | .98 (.6, 1.61) | .87 (.52, 1.44) |
| >109.39 | 37 | 1.13 (.7, 1.81) | .86 (.52, 1.42) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 38 | 1.0 | 1.0 |
| (0, 5.51] | 28 | 1.08 (.66, 1.77) | .91 (.55, 1.49) |
| (5.51, 35.55] | 45 | 1.36 (.88, 2.1) | 1.16 (.75, 1.81) |
| (35.55, 84.62] | 32 | .97 (.6, 1.55) | .98 (.6, 1.59) |
| >84.62 | 40 | 1.18 (.75, 1.84) | 1.07 (.68, 1.69) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 15 | 1.0 | 1.0 |
| (0, 5.51] | 11 | 1.03 (.47, 2.24) | .88 (.4, 1.92) |
| (5.51, 35.55] | 20 | 1.59 (.81, 3.11) | 1.46 (.74, 2.86) |
| (35.55, 84.62] | 11 | .87 (.4, 1.9) | .88 (.4, 1.93) |
| >84.62 | 17 | 1.36 (.68, 2.74) | 1.21 (.59, 2.46) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

**Table 6.11**
**Association between HAA9 exposure pertinent to direct fetal toxicity (9 weeks after LMP to 20 weeks after LMP) and subsequent pregnancy loss**

| HAA9 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| HAA9 water concentration (µg/L) | | | |
| [0, 1.85] | 37 | 1.0 | 1.0 |
| (1.85, 26.93] | 35 | .98 (.62, 1.57) | .93 (.58, 1.48) |
| (26.93, 43.29] | 42 | 1.15 (.74, 1.79) | 1.25 (.8, 1.97) |
| (43.29, 51.7] | 40 | 1.19 (.76, 1.86) | 1.34 (.85, 2.12) |
| >51.7 | 25 | .69 (.42, 1.16) | .73 (.43, 1.23) |
| Early losses (before 12 weeks) | | | |
| [0, 1.85] | 22 | 1.0 | 1.0 |
| (1.85, 26.93] | 19 | .94 (.51, 1.74) | .85 (.45, 1.59) |
| (26.93, 43.29] | 23 | 1.06 (.59, 1.91) | 1.19 (.65, 2.15) |
| (43.29, 51.7] | 24 | 1.3 (.72, 2.33) | 1.43 (.79, 2.58) |
| >51.7 | 17 | .82 (.43, 1.56) | .88 (.46, 1.68) |
| Late losses (after 12 weeks) | | | |
| [0, 1.85] | 15 | 1.0 | 1.0 |
| (1.85, 26.93] | 16 | 1.04 (.51, 2.11) | 1.03 (.51, 2.09) |
| (26.93, 43.29] | 19 | 1.28 (.65, 2.53) | 1.35 (.67, 2.7) |
| (43.29, 51.7] | 16 | 1.05 (.52, 2.12) | 1.23 (.6, 2.5) |
| >51.7 | 8 | .52 (.22, 1.23) | .51 (.21, 1.27) |
| HAA9 ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 36 | 1.0 | 1.0 |
| (0, 5.03] | 23 | 1.12 (.66, 1.9) | .95 (.56, 1.61) |
| (5.03, 35.27] | 45 | 1.59 (1.02, 2.47) | 1.37 (.88, 2.14) |
| (35.27, 83.1] | 36 | 1.25 (.79, 1.99) | 1.3 (.81, 2.08) |
| >83.1 | 39 | 1.36 (.86, 2.15) | 1.29 (.8, 2.05) |
| Sites 1 only | | | |
| [0, 20.41] | 17 | 1.0 | 1.0 |
| (20.41, 48.45] | 19 | 1.1 (.57, 2.14) | 1.07 (.54, 2.13) |
| (48.45, 75.2] | 16 | .95 (.48, 1.9) | .95 (.47, 1.92) |
| (75.2, 113.45] | 11 | .67 (.31, 1.43) | .64 (.3, 1.4) |
| >113.45 | 19 | 1.1 (.57, 2.13) | 1.09 (.55, 2.13) |
| Sites 1 and 3 only | | | |
| [0, 11.42] | 21 | 1.0 | 1.0 |
| (11.42, 39.55] | 26 | 1.22 (.68, 2.18) | 1 (.55, 1.82) |
| (39.55, 69.47] | 22 | 1.03 (.56, 1.87) | .9 (.49, 1.67) |
| (69.47, 108.63] | 19 | .91 (.49, 1.7) | .78 (.41, 1.47) |
| >108.63 | 30 | 1.39 (.8, 2.44) | 1.13 (.63, 2.02) |

(continued)

**Table 6.11 (continued)**

| HAA9 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Early losses (before 12 weeks) | | | |
| [0, 0] | 20 | 1.0 | 1.0 |
| (0, 5.03] | 13 | 1.24 (.61, 2.5) | 1.05 (.52, 2.13) |
| (5.03, 35.27] | 26 | 1.69 (.94, 3.05) | 1.43 (.79, 2.59) |
| (35.27, 83.1] | 24 | 1.52 (.84, 2.76) | 1.59 (.87, 2.92) |
| >83.1 | 22 | 1.39 (.76, 2.56) | 1.33 (.72, 2.48) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 16 | 1.0 | 1.0 |
| (0, 5.03] | 10 | .98 (.44, 2.17) | .83 (.37, 1.83) |
| (5.03, 35.27] | 19 | 1.46 (.75, 2.84) | 1.3 (.66, 2.53) |
| (35.27, 83.1] | 12 | .93 (.44, 1.96) | .94 (.44, 2.01) |
| >83.1 | 17 | 1.32 (.67, 2.62) | 1.22 (.61, 2.47) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

## RESULTS FOR OTHER TRIHALOMETHANES AND PREGNANCY LOSS

Odds ratios for chloroform and pregnancy loss (Tables 6.12–6.14) were close to the null across all indices and time windows, with fairly consistent elevations for the third quintile for later losses, but less so for the uppermost quintile. THM-Br (Tables 6.15–6.17) provided some of the strongest evidence we observed for an increased risk in the uppermost quintile of exposure but restricted to late losses. For concentration in the first time window (Table 6.15), the adjusted odds ratio for later pregnancy losses was 2.3 (1.1–5.1), 1.6 for ingested amount, 1.5 for integrated exposure, and 1.6 for shower/bath exposure. There was not a monotonic gradient across the middle quintiles. The same general pattern was found for the second time window (Table 6.16), with more consistency for early and later losses for integrated exposure. Modestly elevated odds ratios were found in the third time window (Table 6.17), least apparent for ingested amount and often more so in the fourth than the fifth quintile.

**Table 6.12**
**Association between periconceptional (4 weeks prior to LMP to 3 weeks after LMP) $CHCl_3$ exposure and subsequent pregnancy loss**

| $CHCl_3$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| $CHCl_3$ water concentration (µg/L) | | | |
| [0, .13] | 54 | 1.0 | 1.0 |
| (.13, 8.68] | 45 | .83 (.56, 1.24) | .81 (.54, 1.21) |
| (8.68, 29.39] | 56 | 1.03 (.71, 1.51) | 1.19 (.81, 1.76) |
| (29.39, 49.34] | 54 | .96 (.66, 1.4) | 1.01 (.69, 1.5) |
| >49.34 | 49 | .87 (.59, 1.29) | .84 (.57, 1.25) |
| Early losses (before 12 weeks) | | | |
| [0, .13] | 39 | 1.0 | 1.0 |
| (.13, 8.68] | 30 | .78 (.48, 1.27) | .74 (.46, 1.21) |
| (8.68, 29.39] | 37 | .95 (.6, 1.5) | 1.11 (.69, 1.76) |
| (29.39, 49.34] | 36 | .86 (.55, 1.37) | .93 (.58, 1.48) |
| >49.34 | 41 | .99 (.63, 1.54) | .95 (.6, 1.49) |
| Late losses (after 12 weeks) | | | |
| [0, .13] | 15 | 1.0 | 1.0 |
| (.13, 8.68] | 15 | .96 (.47, 1.97) | .97 (.47, 1.99) |
| (8.68, 29.39] | 19 | 1.24 (.63, 2.45) | 1.41 (.7, 2.82) |
| (29.39, 49.34] | 18 | 1.22 (.61, 2.42) | 1.25 (.62, 2.52) |
| >49.34 | 8 | .54 (.23, 1.28) | .53 (.23, 1.27) |
| $CHCl_3$ ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 68 | 1.0 | 1.0 |
| (0, .19] | 31 | .9 (.59, 1.38) | .83 (.54, 1.28) |
| (.19, 10.46] | 54 | 1.06 (.74, 1.52) | .91 (.63, 1.32) |
| (10.46, 45.65] | 55 | 1.06 (.74, 1.52) | 1 (.69, 1.43) |
| >45.65 | 49 | .94 (.65, 1.36) | .89 (.61, 1.29) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 51 | 1.0 | 1.0 |
| (0, .19] | 22 | .85 (.51, 1.41) | .78 (.47, 1.3) |
| (.19, 10.46] | 36 | .95 (.62, 1.46) | .8 (.51, 1.24) |
| (10.46, 45.65] | 35 | .89 (.58, 1.38) | .86 (.55, 1.33) |
| >45.65 | 39 | .99 (.65, 1.51) | .93 (.6, 1.42) |

(continued)

**Table 6.12 (continued)**

| $CHCl_3$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Late losses (after 12 weeks) | | | |
| [0, 0] | 17 | 1.0 | 1.0 |
| (0, .19] | 9 | 1.05 (.47, 2.36) | .98 (.43, 2.21) |
| (.19, 10.46] | 18 | 1.39 (.71, 2.7) | 1.26 (.65, 2.45) |
| (10.46, 45.65] | 20 | 1.58 (.82, 3.02) | 1.41 (.73, 2.74) |
| >45.65 | 10 | .79 (.36, 1.72) | .75 (.34, 1.65) |
| $CHCl_3$ total integrated exposure (µg/day) | | | |
| [0, 0] | 53 | 1.0 | 1.0 |
| (0, .23] | 46 | .88 (.59, 1.32) | .8 (.53, 1.2) |
| (.23, .76] | 48 | .91 (.61, 1.35) | 1 (.67, 1.5) |
| (.76, 1.37] | 47 | .87 (.58, 1.29) | .88 (.59, 1.32) |
| >1.37 | 62 | 1.15 (.8, 1.67) | 1.14 (.78, 1.66) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 40 | 1.0 | 1.0 |
| (0, .23] | 31 | .8 (.5, 1.29) | .71 (.44, 1.15) |
| (.23, .76] | 29 | .73 (.45, 1.18) | .82 (.5, 1.34) |
| (.76, 1.37] | 34 | .82 (.52, 1.3) | .81 (.51, 1.3) |
| >1.37 | 48 | 1.18 (.77, 1.8) | 1.16 (.76, 1.79) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 13 | 1.0 | 1.0 |
| (0, .23] | 15 | 1.12 (.53, 2.37) | 1.08 (.51, 2.28) |
| (.23, .76] | 19 | 1.45 (.71, 2.94) | 1.54 (.75, 3.17) |
| (.76, 1.37] | 13 | 1.01 (.47, 2.19) | 1.09 (.5, 2.36) |
| >1.37 | 14 | 1.08 (.51, 2.31) | 1.07 (.5, 2.28) |
| $CHCl_3$ shower/bath (µg/day) | | | |
| [0, 0] | 50 | 1.0 | 1.0 |
| (0, .19] | 50 | 1.01 (.68, 1.5) | .9 (.6, 1.35) |
| (.19, .61] | 46 | .92 (.61, 1.38) | 1.01 (.67, 1.53) |
| (.61, 1.14] | 48 | .94 (.63, 1.4) | .94 (.63, 1.42) |
| >1.14 | 62 | 1.22 (.84, 1.78) | 1.24 (.84, 1.81) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 38 | 1.0 | 1.0 |
| (0, .19] | 32 | .86 (.54, 1.39) | .77 (.47, 1.25) |
| (.19, .61] | 31 | .81 (.5, 1.31) | .9 (.55, 1.46) |
| (.61, 1.14] | 35 | .89 (.56, 1.41) | .87 (.54, 1.4) |
| >1.14 | 46 | 1.18 (.77, 1.83) | 1.2 (.77, 1.87) |

(continued)

**Table 6.12 (continued)**

| $CHCl_3$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Late losses (after 12 weeks) | | | |
| [0, 0] | 12 | 1.0 | 1.0 |
| (0, .19] | 18 | 1.47 (.71, 3.05) | 1.32 (.63, 2.78) |
| (.19, .61] | 15 | 1.25 (.58, 2.67) | 1.38 (.64, 2.97) |
| (.61, 1.14] | 13 | 1.09 (.5, 2.4) | 1.17 (.53, 2.58) |
| >1.14 | 16 | 1.34 (.63, 2.85) | 1.35 (.64, 2.88) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

**Table 6.13**
**Association between $CHCl_3$ exposure in window pertinent to development of uterine environment (4 weeks after LMP to 8 weeks after LMP) and subsequent pregnancy loss**

| $CHCl_3$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| $CHCl_3$ water concentration (µg/L) | | | |
| [0, .09] | 59 | 1.0 | 1.0 |
| (.09, 8.35] | 38 | .65 (.43, .98) | .6 (.4, .92) |
| (8.35, 30.74] | 70 | 1.2 (.85, 1.7) | 1.41 (.98, 2.03) |
| (30.74, 49.58] | 43 | .7 (.47, 1.05) | .74 (.49, 1.1) |
| >49.58 | 48 | .79 (.54, 1.17) | .8 (.54, 1.18) |
| Early losses (before 12 weeks) | | | |
| [0, .09] | 44 | 1.0 | 1.0 |
| (.09, 8.35] | 25 | .59 (.36, .96) | .55 (.33, .9) |
| (8.35, 30.74] | 46 | 1.07 (.7, 1.63) | 1.26 (.82, 1.93) |
| (30.74, 49.58] | 31 | .67 (.42, 1.06) | .7 (.44, 1.12) |
| >49.58 | 37 | .82 (.52, 1.27) | .81 (.52, 1.28) |
| Late losses (after 12 weeks) | | | |
| [0, .09] | 15 | 1.0 | 1.0 |
| (.09, 8.35] | 13 | .82 (.39, 1.74) | .76 (.35, 1.63) |
| (8.35, 30.74] | 24 | 1.56 (.82, 2.99) | 1.85 (.96, 3.59) |
| (30.74, 49.58] | 12 | .81 (.38, 1.73) | .85 (.39, 1.82) |
| >49.58 | 11 | .73 (.33, 1.59) | .74 (.34, 1.63) |
| $CHCl_3$ ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 79 | 1.0 | 1.0 |
| (0, .15] | 22 | 1.01 (.63, 1.63) | .94 (.58, 1.51) |
| (.15, 11.61] | 53 | 1.07 (.75, 1.52) | .93 (.65, 1.34) |
| (11.61, 55.43] | 57 | 1.12 (.8, 1.58) | 1.1 (.77, 1.56) |
| >55.43 | 46 | .9 (.62, 1.3) | .83 (.57, 1.2) |

(continued)

**Table 6.13 (continued)**

| $CHCl_3$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Early losses (before 12 weeks) | | | |
| [0, 0] | 58 | 1.0 | 1.0 |
| (0, .15] | 18 | 1.16 (.68, 1.99) | 1.1 (.64, 1.89) |
| (.15, 11.61] | 33 | .93 (.6, 1.43) | .79 (.51, 1.23) |
| (11.61, 55.43] | 42 | 1.13 (.76, 1.69) | 1.13 (.75, 1.7) |
| >55.43 | 32 | .85 (.55, 1.32) | .79 (.51, 1.22) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 21 | 1.0 | 1.0 |
| (0, .15] | 4 | .64 (.22, 1.88) | .56 (.19, 1.65) |
| (.15, 11.61] | 20 | 1.44 (.78, 2.65) | 1.3 (.7, 2.4) |
| (11.61, 55.43] | 15 | 1.1 (.57, 2.15) | 1 (.51, 1.99) |
| >55.43 | 14 | 1.03 (.52, 2.04) | .94 (.48, 1.86) |
| $CHCl_3$ total integrated exposure (µg/day) | | | |
| [0, 0] | 56 | 1.0 | 1.0 |
| (0, .23] | 44 | .81 (.54, 1.2) | .72 (.48, 1.08) |
| (.23, .79] | 55 | .98 (.67, 1.42) | 1.08 (.74, 1.59) |
| (.79, 1.42] | 46 | .81 (.54, 1.19) | .82 (.55, 1.23) |
| >1.42 | 55 | .98 (.67, 1.43) | .98 (.67, 1.44) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 41 | 1.0 | 1.0 |
| (0, .23] | 31 | .8 (.5, 1.28) | .71 (.44, 1.15) |
| (.23, .79] | 38 | .92 (.59, 1.44) | 1 (.64, 1.59) |
| (.79, 1.42] | 35 | .83 (.53, 1.31) | .85 (.53, 1.35) |
| >1.42 | 37 | .9 (.58, 1.41) | .91 (.58, 1.43) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 15 | 1.0 | 1.0 |
| (0, .23] | 13 | .83 (.4, 1.75) | .73 (.34, 1.57) |
| (.23, .79] | 17 | 1.14 (.57, 2.28) | 1.3 (.64, 2.63) |
| (.79, 1.42] | 11 | .73 (.34, 1.6) | .76 (.34, 1.66) |
| >1.42 | 18 | 1.19 (.6, 2.36) | 1.18 (.59, 2.35) |
| $CHCl_3$ shower/bath (µg/day) | | | |
| [0, 0] | 58 | 1.0 | 1.0 |
| (0, .19] | 43 | .76 (.51, 1.13) | .68 (.45, 1.02) |
| (.19, .63] | 49 | .84 (.57, 1.24) | .94 (.63, 1.39) |
| (.63, 1.14] | 51 | .86 (.59, 1.26) | .87 (.59, 1.29) |
| >1.14 | 55 | .95 (.65, 1.37) | .98 (.67, 1.44) |

(continued)

**Table 6.13 (continued)**

| $CHCl_3$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Early losses (before 12 weeks) | | | |
| [0, 0] | 43 | 1.0 | 1.0 |
| (0, .19] | 28 | .68 (.42, 1.11) | .62 (.38, 1.01) |
| (.19, .63] | 35 | .81 (.52, 1.28) | .9 (.57, 1.42) |
| (.63, 1.14] | 38 | .86 (.55, 1.34) | .86 (.55, 1.35) |
| >1.14 | 38 | .89 (.57, 1.38) | .93 (.59, 1.45) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 15 | 1.0 | 1.0 |
| (0, .19] | 15 | .95 (.46, 1.95) | .85 (.41, 1.77) |
| (.19, .63] | 14 | .92 (.44, 1.91) | 1.04 (.5, 2.18) |
| (.63, 1.14] | 13 | .86 (.41, 1.82) | .91 (.43, 1.92) |
| >1.14 | 17 | 1.11 (.55, 2.23) | 1.13 (.56, 2.29) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

**Table 6.14**
**Association between $CHCl_3$ exposure pertinent to direct fetal toxicity (9 weeks after LMP to 20 weeks after LMP) and subsequent pregnancy loss**

| $CHCl_3$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| $CHCl_3$ water concentration (µg/L) | | | |
| [0, .06] | 37 | 1.0 | 1.0 |
| (.06, 8.6] | 31 | .89 (.55, 1.44) | .82 (.51, 1.34) |
| (8.6, 30.27] | 46 | 1.33 (.86, 2.06) | 1.66 (1.06, 2.61) |
| (30.27, 48.71] | 34 | .92 (.58, 1.48) | .89 (.55, 1.45) |
| >48.71 | 31 | .86 (.53, 1.39) | .95 (.58, 1.54) |
| Early losses (before 12 weeks) | | | |
| [0, .06] | 22 | 1.0 | 1.0 |
| (.06, 8.6] | 15 | .76 (.39, 1.47) | .7 (.36, 1.37) |
| (8.6, 30.27] | 29 | 1.47 (.84, 2.57) | 1.88 (1.06, 3.34) |
| (30.27, 48.71] | 19 | .86 (.46, 1.6) | .87 (.47, 1.63) |
| >48.71 | 20 | .95 (.52, 1.75) | 1.06 (.57, 1.97) |
| Late losses (after 12 weeks) | | | |
| [0, .06] | 15 | 1.0 | 1.0 |
| (.06, 8.6] | 16 | 1.06 (.52, 2.15) | .98 (.48, 1.99) |
| (8.6, 30.27] | 17 | 1.15 (.57, 2.3) | 1.37 (.67, 2.8) |
| (30.27, 48.71] | 15 | 1.02 (.5, 2.09) | .93 (.44, 1.94) |
| >48.71 | 11 | .73 (.33, 1.59) | .79 (.36, 1.73) |

(continued)

**Table 6.14 (continued)**

| $CHCl_3$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| $CHCl_3$ ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 61 | 1.0 | 1.0 |
| (0, .11] | 6 | .54 (.23, 1.25) | .49 (.21, 1.13) |
| (.11, 12.34] | 39 | 1.11 (.74, 1.67) | .97 (.64, 1.47) |
| (12.34, 55.02] | 41 | 1.13 (.76, 1.68) | 1.09 (.72, 1.64) |
| >55.02 | 32 | .89 (.58, 1.37) | .85 (.55, 1.31) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 38 | 1.0 | 1.0 |
| (0, .11] | 3 | .66 (.2, 2.16) | .58 (.18, 1.91) |
| (.11, 12.34] | 19 | .95 (.54, 1.65) | .82 (.47, 1.44) |
| (12.34, 55.02] | 27 | 1.25 (.76, 2.06) | 1.26 (.76, 2.09) |
| >55.02 | 18 | .85 (.48, 1.49) | .81 (.46, 1.44) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 23 | 1.0 | 1.0 |
| (0, .11] | 3 | .46 (.14, 1.53) | .42 (.12, 1.4) |
| (.11, 12.34] | 20 | 1.33 (.73, 2.43) | 1.17 (.64, 2.15) |
| (12.34, 55.02] | 14 | .95 (.49, 1.85) | .85 (.43, 1.69) |
| >55.02 | 14 | .95 (.49, 1.85) | .9 (.46, 1.76) |
| $CHCl_3$ total integrated exposure (µg/day) | | | |
| [0, 0] | 36 | 1.0 | 1.0 |
| (0, .24] | 32 | .94 (.58, 1.52) | .88 (.54, 1.42) |
| (.24, .78] | 36 | 1.04 (.66, 1.66) | 1.15 (.71, 1.86) |
| (.78, 1.4] | 35 | .99 (.62, 1.58) | 1.09 (.68, 1.76) |
| >1.4 | 39 | 1.12 (.71, 1.77) | 1.14 (.72, 1.81) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 21 | 1.0 | 1.0 |
| (0, .24] | 18 | .95 (.51, 1.8) | .88 (.46, 1.68) |
| (.24, .78] | 21 | 1.08 (.59, 1.99) | 1.2 (.64, 2.23) |
| (.78, 1.4] | 22 | 1.07 (.59, 1.96) | 1.21 (.65, 2.23) |
| >1.4 | 23 | 1.16 (.64, 2.1) | 1.2 (.66, 2.2) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 15 | 1.0 | 1.0 |
| (0, .24] | 14 | .92 (.44, 1.91) | .86 (.41, 1.8) |
| (.24, .78] | 15 | 1 (.49, 2.04) | 1.09 (.52, 2.29) |
| (.78, 1.4] | 13 | .87 (.41, 1.84) | .94 (.44, 1.99) |
| >1.4 | 16 | 1.06 (.52, 2.16) | 1.06 (.52, 2.16) |

(continued)

**Table 6.14 (continued)**

| $CHCl_3$ Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| $CHCl_3$ shower/bath (µg/day) | | | |
| [0, 0] | 37 | 1.0 | 1.0 |
| (0, .2] | 31 | .89 (.55, 1.43) | .81 (.5, 1.32) |
| (.2, .62] | 37 | 1.03 (.65, 1.63) | 1.12 (.7, 1.8) |
| (.62, 1.12] | 31 | .87 (.54, 1.4) | .98 (.6, 1.6) |
| >1.12 | 42 | 1.17 (.75, 1.82) | 1.19 (.76, 1.86) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 21 | 1.0 | 1.0 |
| (0, .2] | 17 | .9 (.47, 1.72) | .82 (.43, 1.58) |
| (.2, .62] | 22 | 1.11 (.61, 2.02) | 1.21 (.65, 2.23) |
| (.62, 1.12] | 21 | 1.06 (.58, 1.95) | 1.23 (.66, 2.28) |
| >1.12 | 24 | 1.2 (.67, 2.17) | 1.23 (.68, 2.24) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 16 | 1.0 | 1.0 |
| (0, .2] | 14 | .85 (.42, 1.76) | .79 (.38, 1.63) |
| (.2, .62] | 15 | .93 (.46, 1.89) | 1.01 (.49, 2.08) |
| (.62, 1.12] | 10 | .63 (.28, 1.38) | .68 (.31, 1.51) |
| >1.12 | 18 | 1.12 (.57, 2.2) | 1.12 (.57, 2.21) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

**Table 6.15**
**Association between periconceptional (4 weeks prior to LMP to 3 weeks after LMP) THM-Br exposure and subsequent pregnancy loss**

| THM-Br Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| THM-Br water concentration (µg/L) | | | |
| [0, 3.11] | 56 | 1.0 | 1.0 |
| (3.11, 12.51] | 42 | .75 (.5, 1.13) | .8 (.53, 1.2) |
| (12.51, 18.08] | 53 | .91 (.62, 1.33) | .98 (.66, 1.44) |
| (18.08, 29.53] | 55 | .97 (.67, 1.41) | 1.07 (.73, 1.57) |
| >29.53 | 52 | .93 (.63, 1.36) | 1.15 (.78, 1.72) |
| Early losses (before 12 weeks) | | | |
| [0, 3.11] | 46 | 1.0 | 1.0 |
| (3.11, 12.51] | 26 | .58 (.35, .94) | .62 (.38, 1.01) |
| (12.51, 18.08] | 35 | .71 (.46, 1.11) | .78 (.49, 1.22) |
| (18.08, 29.53] | 43 | .92 (.6, 1.4) | 1.01 (.66, 1.56) |
| >29.53 | 33 | .72 (.46, 1.13) | .91 (.57, 1.45) |

(continued)

**Table 6.15 (continued)**

| THM-Br Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Late losses (after 12 weeks) | | | |
| [0, 3.11] | 10 | 1.0 | 1.0 |
| (3.11, 12.51] | 16 | 1.54 (.7, 3.41) | 1.59 (.72, 3.53) |
| (12.51, 18.08] | 18 | 1.84 (.85, 3.99) | 1.88 (.86, 4.13) |
| (18.08, 29.53] | 12 | 1.2 (.52, 2.78) | 1.31 (.56, 3.04) |
| >29.53 | 19 | 1.85 (.86, 3.99) | 2.22 (1.02, 4.87) |
| THM-Br ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 51 | 1.0 | 1.0 |
| (0, 4.04] | 46 | .97 (.65, 1.46) | .84 (.56, 1.27) |
| (4.04, 9.97] | 46 | .94 (.63, 1.4) | .8 (.53, 1.2) |
| (9.97, 27.97] | 52 | 1.04 (.7, 1.53) | .98 (.66, 1.45) |
| >27.97 | 62 | 1.26 (.87, 1.84) | 1.16 (.79, 1.7) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 38 | 1.0 | 1.0 |
| (0, 4.04] | 32 | .92 (.57, 1.47) | .79 (.49, 1.28) |
| (4.04, 9.97] | 34 | .93 (.58, 1.49) | .79 (.49, 1.26) |
| (9.97, 27.97] | 39 | 1.03 (.66, 1.62) | .98 (.62, 1.55) |
| >27.97 | 40 | 1.1 (.7, 1.72) | 1.02 (.65, 1.61) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 13 | 1.0 | 1.0 |
| (0, 4.04] | 14 | 1.15 (.54, 2.45) | .99 (.46, 2.11) |
| (4.04, 9.97] | 12 | .95 (.43, 2.09) | .83 (.38, 1.82) |
| (9.97, 27.97] | 13 | 1.05 (.48, 2.26) | .96 (.44, 2.09) |
| >27.97 | 22 | 1.74 (.87, 3.46) | 1.56 (.78, 3.13) |
| THM-Br integrated metric (µg/day) | | | |
| [0, .08] | 49 | 1.0 | 1.0 |
| (.08, .21] | 44 | .89 (.59, 1.34) | .77 (.51, 1.17) |
| (.21, .37] | 52 | 1.04 (.7, 1.54) | .94 (.63, 1.4) |
| (.37, .79] | 59 | 1.18 (.81, 1.73) | 1.15 (.78, 1.7) |
| >.79 | 52 | 1.09 (.74, 1.62) | 1.22 (.8, 1.87) |
| Early losses (before 12 weeks) | | | |
| [0, .08] | 34 | 1.0 | 1.0 |
| (.08, .21] | 33 | .96 (.59, 1.55) | .82 (.5, 1.34) |
| (.21, .37] | 38 | 1.08 (.68, 1.72) | .96 (.6, 1.54) |
| (.37, .79] | 45 | 1.28 (.82, 2.01) | 1.27 (.8, 2) |
| >.79 | 32 | .99 (.61, 1.62) | 1.11 (.66, 1.85) |

(continued)

**Table 6.15 (continued)**

| THM-Br Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Late losses (after 12 weeks) | | | |
| [0, .08] | 15 | 1.0 | 1.0 |
| (.08, .21] | 11 | .74 (.34, 1.6) | .65 (.3, 1.43) |
| (.21, .37] | 14 | .95 (.46, 1.97) | .89 (.43, 1.86) |
| (.37, .79] | 14 | .95 (.46, 1.97) | .88 (.42, 1.86) |
| >.79 | 20 | 1.28 (.66, 2.51) | 1.45 (.72, 2.89) |
| THM-Br shower/bath (µg/day) | | | |
| [0, .08] | 46 | 1.0 | 1.0 |
| (.08, .19] | 48 | 1.04 (.69, 1.56) | .91 (.6, 1.38) |
| (.19, .35] | 51 | 1.09 (.73, 1.62) | .96 (.64, 1.44) |
| (.35, .76] | 56 | 1.2 (.81, 1.77) | 1.15 (.77, 1.72) |
| >.76 | 55 | 1.23 (.83, 1.83) | 1.45 (.95, 2.22) |
| Early losses (before 12 weeks) | | | |
| [0, .08] | 32 | 1.0 | 1.0 |
| (.08, .19] | 36 | 1.12 (.69, 1.8) | .98 (.6, 1.59) |
| (.19, .35] | 37 | 1.12 (.69, 1.8) | .97 (.6, 1.58) |
| (.35, .76] | 43 | 1.31 (.82, 2.08) | 1.28 (.8, 2.05) |
| >.76 | 34 | 1.13 (.69, 1.83) | 1.32 (.79, 2.21) |
| Late losses (after 12 weeks) | | | |
| [0, .08] | 14 | 1.0 | 1.0 |
| (.08, .19] | 12 | .85 (.39, 1.85) | .77 (.36, 1.68) |
| (.19, .35] | 14 | 1.01 (.48, 2.13) | .93 (.44, 1.97) |
| (.35, .76] | 13 | .94 (.44, 2) | .85 (.39, 1.85) |
| >.76 | 21 | 1.44 (.73, 2.84) | 1.71 (.85, 3.43) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

**Table 6.16**
**Association between THM-Br exposure in window pertinent to development of uterine environment (4 weeks after LMP to 8 weeks after LMP) and subsequent pregnancy loss**

| THM-Br Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| THM-Br water concentration (µg/L) | | | |
| [0, 3.05] | 60 | 1.0 | 1.0 |
| (3.05, 12.44] | 38 | .62 (.41, .94) | .59 (.39, .9) |
| (12.44, 18.04] | 53 | .86 (.59, 1.25) | .91 (.62, 1.32) |
| (18.04, 29.78] | 49 | .79 (.54, 1.15) | .87 (.59, 1.29) |
| >29.78 | 58 | .96 (.67, 1.38) | 1.13 (.78, 1.65) |
| Early losses (before 12 weeks) | | | |
| [0, 3.05] | 45 | 1.0 | 1.0 |
| (3.05, 12.44] | 25 | .55 (.33, .89) | .53 (.32, .87) |
| (12.44, 18.04] | 41 | .87 (.57, 1.33) | .92 (.59, 1.42) |
| (18.04, 29.78] | 31 | .65 (.41, 1.03) | .74 (.46, 1.18) |
| >29.78 | 41 | .91 (.59, 1.39) | 1.05 (.68, 1.63) |
| Late losses (after 12 weeks) | | | |
| [0, 3.05] | 15 | 1.0 | 1.0 |
| (3.05, 12.44] | 13 | .85 (.41, 1.8) | .78 (.37, 1.68) |
| (12.44, 18.04] | 12 | .81 (.38, 1.74) | .86 (.4, 1.85) |
| (18.04, 29.78] | 18 | 1.21 (.61, 2.42) | 1.28 (.64, 2.59) |
| >29.78 | 17 | 1.12 (.56, 2.25) | 1.36 (.67, 2.76) |
| THM-Br ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 51 | 1.0 | 1.0 |
| (0, 4.6] | 50 | 1.06 (.71, 1.57) | .94 (.63, 1.41) |
| (4.6, 11.9] | 46 | .94 (.63, 1.41) | .81 (.54, 1.22) |
| (11.9, 32.75] | 48 | .96 (.65, 1.43) | .87 (.58, 1.31) |
| >32.75 | 62 | 1.25 (.86, 1.82) | 1.14 (.78, 1.67) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 38 | 1.0 | 1.0 |
| (0, 4.6] | 36 | 1.03 (.65, 1.63) | .92 (.58, 1.47) |
| (4.6, 11.9] | 33 | .91 (.57, 1.46) | .78 (.48, 1.25) |
| (11.9, 32.75] | 33 | .88 (.55, 1.41) | .81 (.5, 1.3) |
| >32.75 | 43 | 1.17 (.75, 1.81) | 1.07 (.69, 1.67) |

(continued)

**Table 6.16 (continued)**

| THM-Br Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Late losses (after 12 weeks) | | | |
| [0, 0] | 13 | 1.0 | 1.0 |
| (0, 4.6] | 14 | 1.15 (.54, 2.45) | 1.01 (.47, 2.16) |
| (4.6, 11.9] | 13 | 1.03 (.47, 2.22) | .91 (.42, 1.96) |
| (11.9, 32.75] | 15 | 1.2 (.57, 2.53) | 1.06 (.5, 2.24) |
| >32.75 | 19 | 1.51 (.75, 3.07) | 1.34 (.65, 2.76) |
| THM-Br integrated metric (µg/day) | | | |
| [0, .08] | 50 | 1.0 | 1.0 |
| (.08, .2] | 45 | .9 (.6, 1.35) | .8 (.53, 1.22) |
| (.2, .37] | 46 | .91 (.61, 1.36) | .9 (.59, 1.35) |
| (.37, .79] | 57 | 1.13 (.77, 1.66) | 1.09 (.74, 1.61) |
| >.79 | 58 | 1.19 (.81, 1.75) | 1.41 (.94, 2.13) |
| Early losses (before 12 weeks) | | | |
| [0, .08] | 35 | 1.0 | 1.0 |
| (.08, .2] | 33 | .95 (.59, 1.53) | .84 (.51, 1.36) |
| (.2, .37] | 34 | .95 (.59, 1.53) | .93 (.57, 1.51) |
| (.37, .79] | 45 | 1.28 (.82, 2) | 1.25 (.79, 1.96) |
| >.79 | 35 | 1.05 (.66, 1.69) | 1.25 (.76, 2.06) |
| Late losses (after 12 weeks) | | | |
| [0, .08] | 15 | 1.0 | 1.0 |
| (.08, .2] | 12 | .8 (.37, 1.71) | .73 (.34, 1.58) |
| (.2, .37] | 12 | .81 (.38, 1.73) | .82 (.38, 1.77) |
| (.37, .79] | 12 | .8 (.37, 1.71) | .74 (.34, 1.61) |
| >.79 | 23 | 1.48 (.77, 2.85) | 1.75 (.89, 3.43) |
| THM-Br shower/bath (µg/day) | | | |
| [0, .07] | 51 | 1.0 | 1.0 |
| (.07, .19] | 43 | .84 (.56, 1.27) | .75 (.5, 1.14) |
| (.19, .34] | 44 | .85 (.57, 1.28) | .82 (.54, 1.23) |
| (.34, .76] | 61 | 1.19 (.82, 1.73) | 1.15 (.78, 1.68) |
| >.76 | 57 | 1.15 (.78, 1.68) | 1.34 (.89, 2.02) |
| Early losses (before 12 weeks) | | | |
| [0, .07] | 35 | 1.0 | 1.0 |
| (.07, .19] | 31 | .89 (.55, 1.45) | .78 (.48, 1.29) |
| (.19, .34] | 32 | .89 (.55, 1.45) | .86 (.53, 1.4) |
| (.34, .76] | 49 | 1.39 (.9, 2.15) | 1.35 (.86, 2.1) |
| >.76 | 35 | 1.05 (.65, 1.68) | 1.23 (.75, 2.03) |

(continued)

**Table 6.16 (continued)**

| THM-Br Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Late losses (after 12 weeks) | | | |
| [0, .07] | 16 | 1.0 | 1.0 |
| (.07, .19] | 12 | .75 (.35, 1.58) | .69 (.32, 1.46) |
| (.19, .34] | 12 | .76 (.36, 1.61) | .73 (.35, 1.56) |
| (.34, .76] | 12 | .75 (.35, 1.59) | .7 (.32, 1.52) |
| >.76 | 22 | 1.33 (.7, 2.54) | 1.55 (.8, 3.01) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

**Table 6.17**
**Association between THM-Br exposure pertinent to direct fetal toxicity (9 weeks after LMP to 20 weeks after LMP) and subsequent pregnancy loss**

| THM-Br Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| THM-Br water concentration (µg/L) | | | |
| [0, 3.13] | 35 | 1.0 | 1.0 |
| (3.13, 12.3] | 35 | .95 (.59, 1.52) | .92 (.57, 1.47) |
| (12.3, 17.83] | 30 | .94 (.57, 1.53) | .96 (.58, 1.59) |
| (17.83, 32.26] | 37 | 1 (.63, 1.6) | 1.1 (.68, 1.76) |
| >32.26 | 42 | 1.24 (.79, 1.95) | 1.54 (.96, 2.46) |
| Early losses (before 12 weeks) | | | |
| [0, 3.13] | 21 | 1.0 | 1.0 |
| (3.13, 12.3] | 20 | .85 (.46, 1.57) | .84 (.45, 1.57) |
| (12.3, 17.83] | 18 | 1.01 (.54, 1.91) | 1.09 (.57, 2.09) |
| (17.83, 32.26] | 19 | .82 (.44, 1.53) | .92 (.49, 1.74) |
| >32.26 | 27 | 1.35 (.76, 2.41) | 1.7 (.94, 3.07) |
| Late losses (after 12 weeks) | | | |
| [0, 3.13] | 14 | 1.0 | 1.0 |
| (3.13, 12.3] | 15 | 1.11 (.54, 2.32) | 1.04 (.5, 2.16) |
| (12.3, 17.83] | 12 | .85 (.39, 1.83) | .8 (.36, 1.78) |
| (17.83, 32.26] | 18 | 1.3 (.65, 2.63) | 1.35 (.67, 2.74) |
| >32.26 | 15 | 1.08 (.52, 2.24) | 1.3 (.61, 2.77) |
| THM-Br ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 36 | 1.0 | 1.0 |
| (0, 4.71] | 25 | .73 (.44, 1.22) | .63 (.37, 1.06) |
| (4.71, 11.91] | 39 | 1.13 (.71, 1.78) | .96 (.61, 1.52) |
| (11.91, 32.94] | 33 | .92 (.57, 1.49) | .8 (.49, 1.3) |
| >32.94 | 46 | 1.31 (.85, 2.04) | 1.23 (.78, 1.92) |

(continued)

**Table 6.17 (continued)**

| THM-Br Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Early losses (before 12 weeks) | | | |
| [0, 0] | 23 | 1.0 | 1.0 |
| (0, 4.71] | 12 | .55 (.27, 1.1) | .47 (.23, .95) |
| (4.71, 11.91] | 25 | 1.14 (.64, 2.02) | .98 (.55, 1.74) |
| (11.91, 32.94] | 18 | .77 (.41, 1.44) | .67 (.36, 1.26) |
| >32.94 | 27 | 1.19 (.68, 2.09) | 1.13 (.64, 1.99) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 13 | 1.0 | 1.0 |
| (0, 4.71] | 13 | 1.06 (.49, 2.3) | .91 (.42, 1.97) |
| (4.71, 11.91] | 14 | 1.11 (.52, 2.36) | .94 (.44, 2.01) |
| (11.91, 32.94] | 15 | 1.2 (.57, 2.53) | 1.03 (.49, 2.19) |
| >32.94 | 19 | 1.52 (.75, 3.08) | 1.4 (.68, 2.87) |
| THM-Br integrated metric (µg/day) | | | |
| [0, .08] | 32 | 1.0 | 1.0 |
| (.08, .2] | 29 | .91 (.55, 1.51) | .79 (.47, 1.33) |
| (.2, .38] | 31 | .98 (.6, 1.62) | .94 (.57, 1.56) |
| (.38, .82] | 44 | 1.38 (.87, 2.18) | 1.34 (.84, 2.14) |
| >.82 | 42 | 1.34 (.85, 2.14) | 1.48 (.9, 2.44) |
| Early losses (before 12 weeks) | | | |
| [0, .08] | 17 | 1.0 | 1.0 |
| (.08, .2] | 17 | 1.03 (.52, 2.02) | .86 (.43, 1.71) |
| (.2, .38] | 19 | 1.15 (.6, 2.23) | 1.12 (.57, 2.17) |
| (.38, .82] | 32 | 1.91 (1.05, 3.45) | 1.88 (1.03, 3.43) |
| >.82 | 20 | 1.24 (.65, 2.38) | 1.36 (.69, 2.67) |
| Late losses (after 12 weeks) | | | |
| [0, .08] | 15 | 1.0 | 1.0 |
| (.08, .2] | 12 | .79 (.37, 1.68) | .72 (.33, 1.54) |
| (.2, .38] | 12 | .79 (.37, 1.7) | .76 (.35, 1.63) |
| (.38, .82] | 12 | .8 (.37, 1.71) | .74 (.34, 1.63) |
| >.82 | 22 | 1.44 (.74, 2.78) | 1.59 (.8, 3.16) |
| THM-Br shower/bath (µg/day) | | | |
| [0, .08] | 34 | 1.0 | 1.0 |
| (.08, .18] | 26 | .78 (.47, 1.31) | .68 (.4, 1.14) |
| (.18, .35] | 34 | 1.01 (.62, 1.62) | .95 (.58, 1.54) |
| (.35, .78] | 42 | 1.24 (.79, 1.96) | 1.21 (.76, 1.93) |
| >.78 | 42 | 1.26 (.8, 1.99) | 1.38 (.84, 2.25) |

(continued)

**Table 6.17 (continued)**

| THM-Br Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| Early losses (before 12 weeks) | | | |
| [0, .08] | 19 | 1.0 | 1.0 |
| (.08, .18] | 15 | .83 (.42, 1.65) | .7 (.35, 1.4) |
| (.18, .35] | 22 | 1.17 (.63, 2.18) | 1.11 (.6, 2.08) |
| (.35, .78] | 30 | 1.6 (.9, 2.86) | 1.59 (.88, 2.85) |
| >.78 | 19 | 1.05 (.55, 1.99) | 1.14 (.58, 2.22) |
| Late losses (after 12 weeks) | | | |
| [0, .08] | 15 | 1.0 | 1.0 |
| (.08, .18] | 11 | .72 (.33, 1.56) | .65 (.3, 1.43) |
| (.18, .35] | 12 | .8 (.37, 1.7) | .75 (.35, 1.6) |
| (.35, .78] | 12 | .8 (.37, 1.71) | .75 (.34, 1.63) |
| >.78 | 23 | 1.51 (.78, 2.89) | 1.65 (.84, 3.26) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

## RESULTS FOR OTHER HALOACETIC ACIDS AND PREGNANCY LOSS

HAA5 was examined because of its role in regulation (Tables 6.18–6.20), but due to insufficiently high exposures to women in the study, the cutpoint of 60 µg/L could not be evaluated. Across the second and third time windows, the middle two quartiles showed modestly elevated odds ratios but the results were otherwise not indicative of an association with pregnancy loss.

HAA-Br was weakly associated with later pregnancy loss in all three pregnancy window (Tables 6.21–6.23) based on modestly elevated odds ratios in the uppermost quintile. In the third time window, the same elevations in odds ratios in the uppermost quintile were noted for early pregnancy losses as well.

**Table 6.18**
**Association between periconceptional (4 weeks prior to LMP to 3 weeks after LMP) HAA5 exposure and subsequent pregnancy loss**

| HAA5 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| HAA5 water concentration (µg/L) | | | |
| [0, .25] | 68 | 1.0 | 1.0 |
| (.25 20.7] | 54 | 0.79 (0.55, 1.13) | 0.80 (0.55, 1.15) |
| (20.7, 33.08] | 76 | 1.11 (0.79, 1.54) | 1.23 (0.88, 1.73) |
| >33.08 | 60 | 0.85 (0.60, 1.20) | 0.85 (0.59, 1.21) |
| Early losses (before 12 weeks) | | | |
| [0, .25] | 48 | 1.0 | 1.0 |
| (.25 20.7] | 38 | 0.79 (0.51, 1.21) | 0.81 (0.52, 1.25) |
| (20.7, 33.08] | 48 | 0.98 (0.66, 1.47) | 1.11 (0.74, 1.67) |
| >33.08 | 49 | 0.96 (0.64, 1.43) | 0.96 (0.63, 1.44) |
| Late losses (after 12 weeks) | | | |
| [0, .25] | 20 | 1.0 | 1.0 |
| (.25 20.7] | 16 | 0.80 (0.41, 1.54) | 0.80 (0.40, 1.53) |
| (20.7, 33.08] | 28 | 1.40 (0.79, 2.50) | 1.53 (0.85, 2.75) |
| >33.08 | 11 | 0.57 (0.27, 1.18) | 0.57 (0.27, 1.20) |
| HAA5 ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 78 | 1.0 | 1.0 |
| (0, 8.52] | 43 | 1.05 (0.72, 1.52) | 0.92 (0.63, 1.34) |
| (8.52, 41.86] | 64 | 1.05 (0.76, 1.47) | 1.07 (0.76, 1.50) |
| >41.86 | 72 | 1.17 (0.85, 1.62) | 1.13 (0.81, 1.58) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 55 | 1.0 | 1.0 |
| (0, 8.52] | 30 | 1.03 (0.66, 1.61) | 0.89 (0.57, 1.40) |
| (8.52, 41.86] | 43 | 0.99 (0.66, 1.48) | 0.99 (0.66, 1.50) |
| >41.86 | 55 | 1.24 (0.85, 1.81) | 1.22 (0.83, 1.79) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 23 | 1.0 | 1.0 |
| (0, 8.52] | 13 | 1.09 (0.55, 2.21) | 0.98 (0.49, 1.95) |
| (8.52, 41.86] | 21 | 1.22 (0.67, 2.21) | 1.25 (0.69, 2.28) |
| >41.86 | 17 | 1.00 (0.53, 1.88) | 0.92 (0.48, 1.75) |
| HAA5 regulatory cutpoint | | ** | ** |
| <60 µg/L | | | |
| >=60 µg/L | | | |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.
**No RFTS study subjects exposed above cutpoint during this exposure window.

**Table 6.19**
**Association between HAA5 exposure in window pertinent to development of uterine environment (4 weeks after LMP to 8 weeks after LMP) and subsequent pregnancy loss**

| HAA5 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| HAA5 water concentration (µg/L) | | | |
| [0, 0] | 70 | 1.0 | 1.0 |
| (0, 20.54] | 61 | 1.19 (0.84, 1.69) | 1.24 (0.87, 1.77) |
| (20.54,33.76] | 75 | 1.21 (0.87, 1.68) | 1.33 (0.95, 1.87) |
| >33.76 | 52 | 0.83 (0.58, 1.19) | 0.86 (0.59, 1.24) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 50 | 1.0 | 1.0 |
| (0, 20.54] | 41 | 1.14 (0.75, 1.74) | 1.21 (0.79, 1.85) |
| (20.54,33.76] | 51 | 1.14 (0.77, 1.68) | 1.26 (0.85, 1.89) |
| >33.76 | 41 | 0.90 (0.59, 1.36) | 0.93 (0.61, 1.43) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 20 | 1.0 | 1.0 |
| (0, 20.54] | 20 | 1.31 (0.70, 2.44) | 1.32 (0.70, 2.50) |
| (20.54,33.76] | 24 | 1.39 (0.77, 2.52) | 1.50 (0.82, 2.75) |
| >33.76 | 11 | 0.64 (0.31, 1.34) | 0.66 (0.32, 1.39) |
| HAA5 ingested amount (µg/day) | | | |
| All sites | | | |
| [0.0, 0.0] | 89 | 1.0 | 1.0 |
| (0.0, 8.62] | 33 | 1.35 (0.90, 2.02) | 1.22 (0.81, 1.83) |
| (8.62, 50.90] | 70 | 1.21 (0.88, 1.66) | 1.25 (0.90, 1.73) |
| >50.90 | 65 | 1.11 (0.81, 1.54) | 1.08 (0.78, 1.51) |
| Early losses (before 12 weeks) | | | |
| [0.0, 0.0] | 63 | 1.0 | 1.0 |
| (0.0, 8.62] | 23 | 1.35 (0.83, 2.18) | 1.19 (0.73, 1.95) |
| (8.62, 50.90] | 50 | 1.21 (0.83, 1.76) | 1.25 (0.85, 1.83) |
| >50.90 | 47 | 1.11 (0.76, 1.63) | 1.10 (0.74, 1.63) |
| Late losses (after 12 weeks) | | | |
| [0.0, 0.0] | 26 | 1.0 | 1.0 |
| (0.0, 8.62] | 10 | 1.36 (0.65, 2.83) | 1.27 (0.61, 2.65) |
| (8.62, 50.90] | 20 | 1.22 (0.68, 2.19) | 1.25 (0.70, 2.26) |
| >50.90 | 18 | 1.11 (0.61, 2.02) | 1.04 (0.56, 1.93) |
| HAA5 regulatory cutpoint | | ** | ** |
| <60 µg/L | | | |
| >= 60 µg/L | | | |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.
**Only 1 subject (had SAB) exposed above regulatory cutpoint.

**Table 6.20**
**Association between HAA5 exposure pertinent to direct fetal toxicity (9 weeks after LMP to 20 weeks after LMP) and subsequent pregnancy loss**

| HAA5 Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| HAA5 water concentration (µg/L) | | | |
| [0, 0] | 50 | 1.0 | 1.0 |
| (0, 20.45] | 44 | 1.34 (0.89, 2.02) | 1.54 (1.01, 2.33) |
| (20.45, 34.68] | 45 | 1.11 (0.74, 1.66) | 1.19 (0.79, 1.81) |
| >34.68 | 40 | 0.98 (0.65, 1.49) | 1.09 (0.71, 1.66) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 29 | 1.0 | 1.0 |
| (0, 20.45] | 22 | 1.27 (0.73, 2.23) | 1.43 (0.81, 2.54) |
| (20.45, 34.68] | 27 | 1.21 (0.72, 2.06) | 1.37 (0.80, 2.35) |
| >34.68 | 27 | 1.19 (0.70, 2.03) | 1.33 (0.88, 2.27) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 21 | 1.0 | 1.0 |
| (0, 20.45] | 22 | 1.40 (0.77, 2.55) | 1.61 (0.88, 2.95) |
| (20.45, 34.68] | 18 | 0.97 (0.51, 1.82) | 0.97 (0.50, 1.87) |
| >34.68 | 13 | 0.72 (0.36, 1.43) | 0.78 (0.39, 1.58) |
| HAA5 ingested amount (µg/day) | | | |
| All sites | | | |
| [0.0,0.0] | 60 | 1.0 | 1.0 |
| (0.0, 8.72] | 24 | 1.82 (1.13, 2.93) | 1.67 (1.03, 2.71) |
| (8.72, 49.73] | 52 | 1.41 (0.97, 2.05) | 1.52 (1.04, 2.22) |
| >49.73 | 43 | 1.16 (0.78, 1.72) | 1.15 (0.77, 1.73) |
| Early losses (before 12 weeks) | | | |
| [0.0,0.0] | 34 | 1.0 | 1.0 |
| (0.0, 8.72] | 15 | 2.46 (1.33, 4.56) | 2.20 (1.17, 4.12) |
| (8.72, 49.73] | 31 | 1.51 (0.92, 2.47) | 1.65 (1.00, 2.72) |
| >49.73 | 25 | 1.20 (0.72, 2.03) | 1.23 (0.73, 2.09) |
| Late losses (after 12 weeks) | | | |
| [0.0,0.0] | 26 | 1.0 | 1.0 |
| (0.0, 8.72] | 9 | 1.23 (0.58, 2.64) | 1.16 (0.54, 2.50) |
| (8.72, 49.73] | 21 | 1.27 (0.72, 2.27) | 1.35 (0.76, 2.42) |
| >49.73 | 18 | 1.09 (0.60, 2.00) | 1.05 (0.57, 1.95) |
| HAA5 regulatory cutpoint | | ** | ** |
| <60 µg/L | | | |
| >= 60 µg/L | | | |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.
**Only 6 subjects (0 had SAB) exposed above regulatory cutpoint.

**Table 6.21**
**Association between periconceptional (4 weeks prior to LMP to 3 weeks after LMP) HAA-Br exposure and subsequent pregnancy loss**

| HAA-Br Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| HAA-Br water concentration (µg/L) | | | |
| [0, 1.94] | 57 | 1.0 | 1.0 |
| (1.94, 7.81] | 41 | .72 (.48, 1.08) | .69 (.46, 1.04) |
| (7.81, 11.23] | 58 | .99 (.68, 1.43) | 1.07 (.73, 1.56) |
| (11.23, 17.24] | 48 | .8 (.55, 1.18) | .83 (.56, 1.24) |
| >17.24 | 54 | .95 (.65, 1.38) | 1.14 (.77, 1.69) |
| Early losses (before 12 weeks) | | | |
| [0, 1.94] | 42 | 1.0 | 1.0 |
| (1.94, 7.81] | 28 | .67 (.41, 1.08) | .65 (.4, 1.06) |
| (7.81, 11.23] | 40 | .9 (.58, 1.39) | .97 (.62, 1.51) |
| (11.23, 17.24] | 36 | .8 (.51, 1.25) | .82 (.52, 1.3) |
| >17.24 | 37 | .89 (.57, 1.38) | 1.07 (.68, 1.7) |
| Late losses (after 12 weeks) | | | |
| [0, 1.94] | 15 | 1.0 | 1.0 |
| (1.94, 7.81] | 13 | .86 (.41, 1.82) | .79 (.37, 1.7) |
| (7.81, 11.23] | 18 | 1.25 (.63, 2.49) | 1.36 (.68, 2.72) |
| (11.23, 17.24] | 12 | .81 (.38, 1.74) | .85 (.4, 1.84) |
| >17.24 | 17 | 1.12 (.56, 2.25) | 1.31 (.64, 2.69) |
| HAA-Br ingested amount (µg/day) | | | |
| All sites | | | |
| [0, .11] | 53 | 1.0 | 1.0 |
| (.11, 3.32] | 48 | .9 (.61, 1.33) | .78 (.52, 1.17) |
| (3.32, 8.5] | 42 | .77 (.52, 1.16) | .69 (.46, 1.05) |
| (8.5, 19.57] | 47 | .86 (.58, 1.28) | .84 (.56, 1.27) |
| >19.57 | 67 | 1.23 (.86, 1.77) | 1.2 (.83, 1.75) |
| Early losses (before 12 weeks) | | | |
| [0, .11] | 38 | 1.0 | 1.0 |
| (.11, 3.32] | 33 | .85 (.53, 1.37) | .74 (.46, 1.2) |
| (3.32, 8.5] | 28 | .71 (.43, 1.16) | .63 (.38, 1.04) |
| (8.5, 19.57] | 39 | .98 (.62, 1.53) | .97 (.61, 1.53) |
| >19.57 | 45 | 1.13 (.73, 1.75) | 1.11 (.71, 1.74) |
| Late losses (after 12 weeks) | | | |
| [0, .11] | 15 | 1.0 | 1.0 |
| (.11, 3.32] | 15 | 1.01 (.49, 2.07) | .89 (.43, 1.84) |
| (3.32, 8.5] | 14 | .95 (.46, 1.97) | .86 (.41, 1.8) |
| (8.5, 19.57] | 8 | .55 (.23, 1.29) | .53 (.22, 1.25) |
| >19.57 | 22 | 1.5 (.78, 2.9) | 1.45 (.74, 2.83) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

**Table 6.22**
**Association between HAA-Br exposure in window pertinent to development of uterine environment (4 weeks after LMP to 8 weeks after LMP) and subsequent pregnancy loss**

| HAA-Br Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| HAA-Br water concentration (µg/L) | | | |
| [0, 1.8] | 49 | 1.0 | 1.0 |
| (1.8, 7.52] | 56 | 1.14 (.77, 1.68) | 1.13 (.77, 1.67) |
| (7.52, 11.21] | 52 | 1.03 (.7, 1.53) | 1.07 (.71, 1.6) |
| (11.21, 17.96] | 42 | .83 (.55, 1.26) | .85 (.56, 1.3) |
| >17.96 | 59 | 1.21 (.83, 1.78) | 1.47 (.99, 2.18) |
| Early losses (before 12 weeks) | | | |
| [0, 1.8] | 36 | 1.0 | 1.0 |
| (1.8, 7.52] | 40 | 1.11 (.7, 1.74) | 1.1 (.69, 1.74) |
| (7.52, 11.21] | 33 | .87 (.54, 1.4) | .92 (.56, 1.5) |
| (11.21, 17.96] | 34 | .89 (.56, 1.43) | .93 (.58, 1.5) |
| >17.96 | 40 | 1.13 (.72, 1.78) | 1.38 (.86, 2.2) |
| Late losses (after 12 weeks) | | | |
| [0, 1.8] | 13 | 1.0 | 1.0 |
| (1.8, 7.52] | 16 | 1.23 (.59, 2.56) | 1.23 (.59, 2.56) |
| (7.52, 11.21] | 19 | 1.49 (.74, 3.03) | 1.47 (.72, 3.03) |
| (11.21, 17.96] | 8 | .63 (.26, 1.53) | .63 (.26, 1.54) |
| >17.96 | 19 | 1.43 (.71, 2.91) | 1.71 (.83, 3.53) |
| HAA-Br ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 53 | 1.0 | 1.0 |
| (0, 3.44] | 47 | 1.27 (.86, 1.89) | 1.07 (.71, 1.6) |
| (3.44, 10.03] | 46 | 1.01 (.68, 1.5) | .9 (.6, 1.35) |
| (10.03, 23.32] | 49 | 1.07 (.72, 1.58) | 1.01 (.68, 1.51) |
| >23.32 | 62 | 1.35 (.94, 1.96) | 1.26 (.86, 1.83) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 38 | 1.0 | 1.0 |
| (0, 3.44] | 33 | 1.25 (.78, 2) | 1.03 (.63, 1.66) |
| (3.44, 10.03] | 35 | 1.07 (.67, 1.7) | .94 (.59, 1.51) |
| (10.03, 23.32] | 35 | 1.05 (.66, 1.66) | 1 (.62, 1.6) |
| >23.32 | 42 | 1.26 (.81, 1.97) | 1.18 (.75, 1.85) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 15 | 1.0 | 1.0 |
| (0, 3.44] | 14 | 1.33 (.64, 2.76) | 1.17 (.56, 2.44) |
| (3.44, 10.03] | 11 | .86 (.4, 1.89) | .79 (.36, 1.73) |
| (10.03, 23.32] | 14 | 1.11 (.54, 2.31) | 1.06 (.51, 2.21) |
| >23.32 | 20 | 1.59 (.81, 3.11) | 1.46 (.74, 2.9) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

**Table 6.23**
**Association between HAA-Br exposure pertinent to direct fetal toxicity (9 weeks after LMP to 20 weeks after LMP) and subsequent pregnancy loss**

| HAA-Br Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| HAA-Br water concentration (µg/L) | | | |
| [0, 1.75] | 38 | 1.0 | 1.0 |
| (1.75, 7.38] | 36 | .96 (.61, 1.52) | .91 (.57, 1.44) |
| (7.38, 11.18] | 34 | .97 (.61, 1.55) | 1.02 (.64, 1.64) |
| (11.18, 17.57] | 31 | .82 (.51, 1.33) | .82 (.5, 1.35) |
| >17.57 | 40 | 1.07 (.69, 1.68) | 1.37 (.86, 2.18) |
| Early losses (before 12 weeks) | | | |
| [0, 1.75] | 22 | 1.0 | 1.0 |
| (1.75, 7.38] | 21 | .99 (.54, 1.81) | .91 (.49, 1.67) |
| (7.38, 11.18] | 23 | 1.21 (.67, 2.19) | 1.28 (.71, 2.34) |
| (11.18, 17.57] | 16 | .74 (.38, 1.41) | .76 (.39, 1.46) |
| >17.57 | 23 | 1.09 (.6, 1.96) | 1.38 (.75, 2.53) |
| Late losses (after 12 weeks) | | | |
| [0, 1.75] | 16 | 1.0 | 1.0 |
| (1.75, 7.38] | 15 | .93 (.46, 1.88) | .91 (.45, 1.85) |
| (7.38, 11.18] | 11 | .68 (.32, 1.47) | .72 (.33, 1.56) |
| (11.18, 17.57] | 15 | .94 (.46, 1.91) | .92 (.44, 1.9) |
| >17.57 | 17 | 1.05 (.53, 2.09) | 1.36 (.67, 2.76) |
| HAA-Br ingested amount (µg/day) | | | |
| All sites | | | |
| [0, 0] | 36 | 1.0 | 1.0 |
| (0, 3.34] | 30 | 1.45 (.89, 2.36) | 1.22 (.74, 1.99) |
| (3.34, 10.08] | 38 | 1.33 (.84, 2.11) | 1.23 (.77, 1.97) |
| (10.08, 22.86] | 30 | 1.06 (.65, 1.72) | .96 (.58, 1.57) |
| >22.86 | 45 | 1.57 (1.01, 2.45) | 1.54 (.98, 2.41) |
| Early losses (before 12 weeks) | | | |
| [0, 0] | 20 | 1.0 | 1.0 |
| (0, 3.34] | 18 | 1.68 (.88, 3.19) | 1.43 (.75, 2.73) |
| (3.34, 10.08] | 25 | 1.6 (.89, 2.9) | 1.46 (.8, 2.66) |
| (10.08, 22.86] | 17 | 1.11 (.58, 2.12) | 1.01 (.52, 1.96) |
| >22.86 | 25 | 1.59 (.88, 2.87) | 1.56 (.85, 2.83) |
| Late losses (after 12 weeks) | | | |
| [0, 0] | 16 | 1.0 | 1.0 |
| (0, 3.34] | 12 | 1.18 (.56, 2.51) | .98 (.46, 2.09) |
| (3.34, 10.08] | 13 | 1.01 (.48, 2.1) | .96 (.46, 2) |
| (10.08, 22.86] | 13 | .99 (.48, 2.07) | .89 (.42, 1.86) |
| >22.86 | 20 | 1.55 (.8, 3.01) | 1.52 (.78, 2.98) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

## RESULTS FOR TOTAL ORGANIC HALIDES AND PREGNANCY LOSS

In the first pregnancy time window (Table 6.24), concentration and ingested amount were essentially unrelated to risk of pregnancy loss, with the minor exception of the fourth quintile of ingested amount in relation to later pregnancy losses. For the second pregnancy window (Table 6.25), concentration was associated with slightly lower risk in the lowest quintile and similar risk across the upper four, somewhat enhanced for ingested amount in relation to later losses. In the third pregnancy window (Table 6.26), some stronger associations were found, particularly for early losses, but the overall associations for both concentration and ingested amount provided the clearest, strongest dose response gradient observed for any exposure in the study. For concentration, the odds ratios across the quintiles were 1.0 (referent), 1.5, 1.4, 1.6, and 1.6, and for ingested amount, 1.0 (referent), 1.3, 1.3, 1.6, and 1.6.

**Table 6.24**
**Association between periconceptional (4 weeks prior to LMP to 3 weeks after LMP) TOX exposure and subsequent pregnancy loss**

| TOX Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| TOX water concentration (µgCl/L) | | | |
| [0, 17.41] | 53 | 1.0 | 1.0 |
| (17.41, 145.23] | 45 | .83 (.56, 1.24) | .8 (.53, 1.2) |
| (145.23, 170.13] | 57 | 1.05 (.72, 1.53) | 1.18 (.8, 1.74) |
| (170.13, 182.36] | 50 | .91 (.62, 1.35) | .95 (.64, 1.42) |
| >182.36 | 53 | .97 (.66, 1.43) | 1.05 (.71, 1.56) |
| Early losses (before 12 weeks) | | | |
| [0, 17.41] | 37 | 1.0 | 1.0 |
| (17.41, 145.23] | 31 | .81 (.5, 1.31) | .77 (.47, 1.25) |
| (145.23, 170.13] | 41 | 1.07 (.68, 1.67) | 1.22 (.77, 1.94) |
| (170.13, 182.36] | 33 | .84 (.53, 1.35) | .89 (.55, 1.44) |
| >182.36 | 41 | 1.06 (.68, 1.66) | 1.14 (.72, 1.79) |
| Late losses (after 12 weeks) | | | |
| [0, 17.41] | 16 | 1.0 | 1.0 |
| (17.41, 145.23] | 14 | .89 (.43, 1.83) | .87 (.42, 1.79) |
| (145.23, 170.13] | 16 | 1.01 (.51, 2.03) | 1.08 (.53, 2.19) |
| (170.13, 182.36] | 17 | 1.09 (.55, 2.17) | 1.1 (.55, 2.21) |
| >182.36 | 12 | .76 (.36, 1.61) | .84 (.4, 1.79) |
| TOX ingested amount (µgCl/day) | | | |
| All sites | | | |
| [0, 12.26] | 42 | 1.0 | 1.0 |
| (12.26, 37.75] | 54 | 1.27 (.85, 1.91) | 1.06 (.7, 1.61) |
| (37.75, 101.6] | 41 | .95 (.61, 1.46) | .83 (.54, 1.29) |
| (101.6, 259.08] | 59 | 1.36 (.91, 2.03) | 1.36 (.91, 2.05) |
| >259.08 | 61 | 1.4 (.94, 2.09) | 1.31 (.87, 1.97) |
| Early losses (before 12 weeks) | | | |
| [0, 12.26] | 29 | 1.0 | 1.0 |
| (12.26, 37.75] | 39 | 1.31 (.81, 2.13) | 1.07 (.65, 1.76) |
| (37.75, 101.6] | 32 | 1.05 (.63, 1.74) | .91 (.55, 1.53) |
| (101.6, 259.08] | 38 | 1.24 (.76, 2.02) | 1.24 (.76, 2.04) |
| >259.08 | 45 | 1.46 (.91, 2.33) | 1.37 (.85, 2.22) |
| Late losses (after 12 weeks) | | | |
| [0, 12.26] | 13 | 1.0 | 1.0 |
| (12.26, 37.75] | 15 | 1.18 (.56, 2.48) | 1.04 (.49, 2.2) |
| (37.75, 101.6] | 9 | .71 (.3, 1.67) | .64 (.27, 1.51) |
| (101.6, 259.08] | 21 | 1.66 (.83, 3.32) | 1.66 (.82, 3.34) |
| >259.08 | 16 | 1.28 (.61, 2.66) | 1.16 (.55, 2.45) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

**Table 6.25**
**Association between TOX exposure in window pertinent to development of uterine environment (4 weeks after LMP to 8 weeks after LMP) and subsequent pregnancy loss**

| TOX Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| TOX water concentration (µgCl/L) | | | |
| [0, 17.43] | 44 | 1.0 | 1.0 |
| (17.43, 140.4] | 60 | 1.33 (.9, 1.97) | 1.33 (.89, 1.97) |
| (140.4, 171.82] | 54 | 1.18 (.79, 1.77) | 1.21 (.8, 1.83) |
| (171.82, 186.54] | 49 | 1.09 (.72, 1.64) | 1.18 (.78, 1.79) |
| >186.54 | 51 | 1.13 (.75, 1.69) | 1.36 (.9, 2.06) |
| Early losses (before 12 weeks) | | | |
| [0, 17.43] | 30 | 1.0 | 1.0 |
| (17.43, 140.4] | 43 | 1.37 (.86, 2.2) | 1.39 (.86, 2.23) |
| (140.4, 171.82] | 32 | 1 (.6, 1.65) | 1.07 (.64, 1.79) |
| (171.82, 186.54] | 42 | 1.36 (.84, 2.18) | 1.46 (.9, 2.37) |
| >186.54 | 36 | 1.14 (.7, 1.87) | 1.39 (.85, 2.28) |
| Late losses (after 12 weeks) | | | |
| [0, 17.43] | 14 | 1.0 | 1.0 |
| (17.43, 140.4] | 17 | 1.24 (.61, 2.52) | 1.2 (.59, 2.44) |
| (140.4, 171.82] | 22 | 1.62 (.83, 3.18) | 1.52 (.76, 3.03) |
| (171.82, 186.54] | 7 | .5 (.2, 1.25) | .55 (.22, 1.38) |
| >186.54 | 15 | 1.09 (.53, 2.27) | 1.3 (.62, 2.71) |
| TOX ingested amount (µgCl/day) | | | |
| All sites | | | |
| [0, 14.52] | 38 | 1.0 | 1.0 |
| (14.52, 40.44] | 54 | 1.41 (.93, 2.14) | 1.27 (.83, 1.94) |
| (40.44, 117.36] | 57 | 1.47 (.97, 2.23) | 1.32 (.87, 2.01) |
| (117.36, 298.63] | 49 | 1.25 (.82, 1.92) | 1.22 (.79, 1.88) |
| >298.63 | 59 | 1.51 (1, 2.28) | 1.47 (.97, 2.24) |
| Early losses (before 12 weeks) | | | |
| [0, 14.52] | 27 | 1.0 | 1.0 |
| (14.52, 40.44] | 36 | 1.31 (.79, 2.17) | 1.17 (.7, 1.94) |
| (40.44, 117.36] | 44 | 1.57 (.97, 2.55) | 1.39 (.85, 2.27) |
| (117.36, 298.63] | 36 | 1.27 (.77, 2.1) | 1.24 (.74, 2.07) |
| >298.63 | 40 | 1.41 (.86, 2.3) | 1.37 (.83, 2.26) |
| Late losses (after 12 weeks) | | | |
| [0, 14.52] | 11 | 1.0 | 1.0 |
| (14.52, 40.44] | 18 | 1.66 (.78, 3.53) | 1.53 (.72, 3.25) |
| (40.44, 117.36] | 13 | 1.21 (.54, 2.72) | 1.13 (.5, 2.54) |
| (117.36, 298.63] | 13 | 1.21 (.54, 2.71) | 1.16 (.52, 2.62) |
| >298.63 | 19 | 1.78 (.85, 3.75) | 1.73 (.81, 3.69) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

**Table 6.26**
**Association between TOX exposure pertinent to direct fetal toxicity (9 weeks after LMP to 20 weeks after LMP) and subsequent pregnancy loss**

| TOX Exposure | # Cases | Crude OR | Adjusted* OR |
|---|---|---|---|
| TOX water concentration (µgCl/L) | | | |
| [0, 17.26] | 28 | 1.0 | 1.0 |
| (17.26, 138.69] | 42 | 1.28 (.79, 2.07) | 1.31 (.8, 2.12) |
| (138.69, 172.47] | 34 | 1.12 (.68, 1.85) | 1.23 (.74, 2.06) |
| (172.47, 186.56] | 33 | 1.34 (.8, 2.22) | 1.6 (.96, 2.68) |
| >186.56 | 42 | 1.32 (.82, 2.14) | 1.56 (.95, 2.55) |
| Early losses (before 12 weeks) | | | |
| [0, 17.26] | 13 | 1.0 | 1.0 |
| (17.26, 138.69] | 27 | 1.55 (.79, 3.01) | 1.61 (.82, 3.15) |
| (138.69, 172.47] | 17 | 1.13 (.55, 2.34) | 1.31 (.63, 2.72) |
| (172.47, 186.56] | 19 | 1.94 (.95, 3.96) | 2.48 (1.21, 5.11) |
| >186.56 | 29 | 1.75 (.91, 3.38) | 2.11 (1.08, 4.12) |
| Late losses (after 12 weeks) | | | |
| [0, 17.26] | 15 | 1.0 | 1.0 |
| (17.26, 138.69] | 15 | 1.04 (.51, 2.13) | 1.05 (.51, 2.17) |
| (138.69, 172.47] | 17 | 1.14 (.57, 2.29) | 1.19 (.59, 2.44) |
| (172.47, 186.56] | 14 | .9 (.43, 1.86) | 1.01 (.49, 2.11) |
| >186.56 | 13 | .91 (.43, 1.92) | 1.04 (.48, 2.24) |
| TOX ingested amount (µgCl/day) | | | |
| All sites | | | |
| [0, 14.3] | 25 | 1.0 | 1.0 |
| (14.3, 40.66] | 38 | 1.52 (.92, 2.53) | 1.37 (.82, 2.29) |
| (40.66, 119.89] | 35 | 1.4 (.83, 2.34) | 1.26 (.75, 2.12) |
| (119.89, 299.37] | 39 | 1.52 (.91, 2.51) | 1.52 (.9, 2.54) |
| >299.37 | 42 | 1.68 (1.02, 2.77) | 1.66 (1, 2.77) |
| Early losses (before 12 weeks) | | | |
| [0, 14.3] | 14 | 1.0 | 1.0 |
| (14.3, 40.66] | 22 | 1.57 (.8, 3.08) | 1.4 (.71, 2.77) |
| (40.66, 119.89] | 20 | 1.42 (.71, 2.82) | 1.25 (.62, 2.5) |
| (119.89, 299.37] | 25 | 1.68 (.87, 3.25) | 1.68 (.86, 3.29) |
| >299.37 | 24 | 1.7 (.88, 3.31) | 1.72 (.88, 3.36) |
| Late losses (after 12 weeks) | | | |
| [0, 14.3] | 11 | 1.0 | 1.0 |
| (14.3, 40.66] | 16 | 1.47 (.68, 3.17) | 1.33 (.61, 2.89) |
| (40.66, 119.89] | 15 | 1.37 (.63, 2.99) | 1.27 (.58, 2.79) |
| (119.89, 299.37] | 14 | 1.29 (.59, 2.85) | 1.3 (.58, 2.89) |
| >299.37 | 18 | 1.66 (.78, 3.52) | 1.59 (.74, 3.43) |

*Adjusted for maternal age, black race, Hispanic ethnicity, education, marital status, alcohol use, age at menarche and vitamin use.

# CHAPTER 7
# INTERPRETATION

## STUDY APPROACH AND LIMITATIONS

Before discussing the results in the context of previous studies, it is important to review the features of the study that bear on its validity. One of the key strengths is the wide range of exposure available to study that result from our intentional selection of geographic sites with varying water quality characteristics. However, this strategy creates a very strong relationship between residential location and exposure, with the potential for many aspects of site other than water quality to affect pregnancy outcome. That is, if there are unmeasured and even unknown environmental or social influences on pregnancy loss that vary across our study sites, there would be the potential for those characteristics to bias our measured effects of drinking water DBPs on pregnancy outcome.

While our approach to measuring exposure is more extensive than others have attempted, with weekly system samples, we do recognize that there is unmeasured variability that remains within the water service area (though modest in magnitude) and variability over shorter time scales than our weekly values would reflect.

The behavioral data on water use, which contributes importantly to indices of ingested amount, integrated exposure, and bathing/showering exposures, is subject to the usual concerns with the accuracy of self-reported information. Beyond any overall error in reporting, the question of differential error in which high-risk women tend to over or under report water ingestion, filter use, and duration of bathing and showering is unknown.

Measurement of pregnancy onset and pregnancy loss is also challenging. We were able to address pregnancies in the range of 5–6 weeks or more gestation, missing pregnancies and losses that occur earlier and being susceptible to selectivity regarding which women are enrolled early in gestation. The actual timing of fetal demise is simply unknown, with the *recognition* of loss not the *occurrence* of loss ascertained. The ultrasound component of the protocol was valuable but could not consistently be administered prior to pregnancy loss and, regardless, would not be able to identify precisely when in calendar time the loss occurred even if the duration of gestation prior to loss could be evaluated.

We had limited ability to address heterogeneity in types of fetal loss. We could not distinguish those that were karyotypically normal or abnormal, or, for example, distinguish maternal from fetal influences. The only "handle" on heterogeneity we were able to consider was timing of loss, divided at 12 weeks' gestation, and our results do suggest some heterogeneity in the patterns of association for those two groups.

Finally, we have to acknowledge the imprecision even in a study as large as ours, particularly for subgroups. In generating and interpreting a substantial array of results, the role of random error should not be neglected or inappropriately underemphasized.

## SUMMARY OF PATTERN OF RESULTS

Given that the single study that was most critical in motivating the present research was that of Waller et al. (1998), the failure to replicate their findings of a fairly strong association between consumption of greater amounts of water with relatively high THMs is worthy of note.

There was no suggestion of a positive association for any of the THM indices they considered in their study, and the only point of compatibility was the shared observation that among the individual THMs, dibromochloromethane showed the strongest relationship to pregnancy loss. However, in absolute terms, the magnitude of association was much lower in our study (OR = 1.4, 95% CI = 0.9–2.2) than in their study (OR = 2.0, 95% CI = 1.2–3.5).

In trying to summarize a wide array of results, for multiple individual and groups of DBPs, multiple exposure measures, pregnancy windows, and subsets, there is a need for judgment regarding which of the many sporadically elevated (and reduced) relative risks are worthy of note and which should be downplayed as a result of random error. A key consideration was the extent to which there was any indication of a dose-response gradient of higher risk with higher exposure. Even when not fully monotonic, those instances in which a gradient was present were given more credence than those in which an isolated relative risk was elevated. The precision of the individual estimates is also quite important, but not in the sense of formal significance testing, which has little relevance in observational research and particularly in the context of many calculated measures of association. Consistency and regularity of results is also a factor, though the reason to have examined the multiple indices of exposure is to allow for the possibility that some, but not others, would be associated with pregnancy loss. The judgment about which findings are worthy of note and which are not is ultimately subjective, and thus we have tried to present the full array of data to allow others to make judgments independently, though we offer our interpretation as well.

Total THMs, the most extensively studied indicator of DBP exposure, was generally not associated with increased risk of pregnancy loss in our study. There were some indications that risk in the upper exposure ranges was increased for integrated exposure (driven by shower/bath exposure), with restriction to Sites 1 and 3 only, and for losses of 12 weeks' or more gestation. Dibromochloromethane showed no association except for a consistent, small increase for the upper quintiles of shower/bath and integrated exposure. Other THMs considered, chloroform and THM-Br, showed a similar small elevation in risk for integrated exposure driven by shower/bath exposure.

Some patterns can be noted in comparisons across exposure indices. There was some tendency for shower/bath and integrated exposure to show stronger associations for THMs (grouped and individual species) than tap water concentration or ingested amount. Given the rapid metabolism of ingested, but not dermally absorbed or inhaled THMs, such a pattern may be suggestive of an adverse effect of unmetabolized THMs.

HAA9 showed some larger elevations in risk in particular for exposure in later pregnancy with the indicator of ingested amount, among the most notable positive associations we identified. The regularity of the pattern should not be overstated, but overall the deviation from the null seems clear for these DBPs in that time window. A similar tendency was found for HAA-Br and HAA5. Results for total organic halides provided support for an association of both concentration and ingested amount in the second and third pregnancy window with risk of pregnancy loss. There was more support for a dose-response gradient than found for the other individual DBPs, and reasonable consistency across the indicators of concentration and ingested amount, with odds ratios in the uppermost quintile of 1.3 to 1.9.

For HAAs and TOX, the later pregnancy windows consistently showed stronger associations than the earlier pregnancy window, suggesting any effect that might be occurring is a result of fetal toxicity. Ingested amount was generally more suggestive of an association than concentration, and should serve as a more accurate marker of actual exposure received.

## CONTRIBUTION OF STUDY

Methodologically, there were a number of important refinements to the study with regard to exposure assessment, refined pregnancy dating, and analytic methods to fully account for the temporal nature of exposure and pregnancy outcome. The opportunity to consider the multiple exposure indices allows simultaneous exploration of a number of hypothesized pathways by which DBPs could affect the health of pregnancy. The study settings and diversity of water use patterns among women ensured a wide range of exposure could be evaluated.

If forced to dichotomize the results as positive or negative, which is inevitably an oversimplification of a complex pattern, the results would have to be summarized as negative, not supporting an association between DBPs and pregnancy outcome. Relative to past studies that focused on THMs and pregnancy loss (Aschengrau et al. 1989, Swan et al. 1992, Deane et al. 1992, Wrensch et al. 1992, Savitz et al. 1995, Swan et al. 1998, Waller et al. 1998), which themselves generated mixed but weakly supportive positive findings, our study adds mixed but generally negative findings. If, in fact, the previous studies are viewed as having provided a "signal" that was diluted through imprecision in exposure (regarding which agent, insufficient behavioral details on water use, which time window of pregnancy, etc.), then our study should have been able to zero in on the etiologically important exposure. Our failure to find such a strong signal makes the results even more influentially negative in light of the ability to search so thoroughly for the appropriate exposure index and metric. When the methods get stronger and the results get weaker, if anything, that may be indicative of where the findings are headed.

Reconciliation of our results with those of Waller et al. (1998) in particular is called for and there is no obvious explanation. Our studies were carried out in very different geographic settings, with notably different source populations, and using completely different approaches to exposure assessment. Among our future plans, we will examine more fully the implications of how women in the study may be a biased sample of women in the community with regard to basic demographic features, and also consider what we would have found had we applied the simplest of indices, quarterly monitoring data on THM levels for each of the study sites. We will be conducting further analyses on other endpoints, preterm birth, birth weight, and time to conception, as well as a full sensitivity analysis of the study methods and results. The rich array of data we have collected lends itself to more scrutiny and self-examination, which should be fully exploited.

Insofar as our results are useful in shaping the more general research agenda on DBPs, some directions can be proposed. The suggestion that shower/bath THMs may be more strongly associated with pregnancy loss than other exposure indicators provides further encouragement to learn how to more accurately capture the exposures received. Duration alone is surely an incomplete exposure indicator and there are a range of other aspects that could be considered, including temperature, time in the bathroom before and after bathing or showering, accuracy of self-reported duration, water flow rate, and shower droplet size and volatilization. The HAAs point more toward fetal toxicity, and much of the previous toxicology of DBPs has focused on earlier events in conception and pregnancy survival. Some encouragement to focus more on fetal than maternal toxicity could be inferred.

# CHAPTER 8
# ANALYSES OF LIVE BIRTH OUTCOMES

## EXPOSURE AND OUTCOME ASSESSMENT

The approach to the analysis of live birth outcomes was conducted in a parallel manner to the analysis of pregnancy loss, using the same population resource as described previously (Chapter 2). Specifically, we sought to relate the same indices of DBP exposure, concentration, ingested amount, total integrated exposure, and shower/bath exposure (the latter two for THMs only) to the risk of having a live birth that was born prior to term (< 37 weeks' completed gestation following the LMP) or small-for-gestational-age (SGA), and conduct an analysis of birth weight among term births as a continuous outcome measure. Although there are other indices that can be examined, e.g., low birth weight, these three measures capture influences on early delivery and on fetal growth well. Details of the methods for assigning water exposure indices are provided in Chapter 3.

A number of modifications had to be made given the nature of these outcomes, which are restricted to live births. A total of 1,934 women were available for analyses of the association between DBP exposure and live birth outcomes (preterm birth, small for gestational age infant and term birth weight), excluding women who had a pregnancy loss. The pregnancy windows chosen for the study of pregnancy loss are not applicable, so we chose time windows for the live birth outcome analyses that correspond to the three trimesters of pregnancy (weeks 0 to 12, weeks 13 to 26, and week 27 until birth). Although the most relevant time period for a potential adverse effect of DBPs is unclear, these time windows should reflect early, middle, and late pregnancy exposures.

The algorithm for quantifying ingestion of cold and hot tap water, filtered and unfiltered, was identical to that described for the analysis of pregnancy loss. The same strategy was also used for addressing changes in exposure over the course of the pregnancy interval. However, the shift to interest in later phases of pregnancy resulted in some changes of implementation, if not of strategy. Women who had complete outcome information including delivery date, child's birth weight and gender were included in the live birth outcomes analyses. Participants completed a follow-up interview around 20 weeks' gestation, during which time they were asked about their water use behavior again. If a woman reported a change in water use behavior, we assumed the change occurred midway between the date of the intake interview and the follow-up interview and incorporated the change into the estimation of exposure metrics (2), (3) and (4) by taking a weighted average of the two measures. This affected estimation of exposure primarily during the second time window of interest since the follow-up interview was completed between 20 and 25 weeks' gestation.

Gestational age was estimated as follows: We calculated the interval between the date of their LMP, corrected as feasible based on ultrasound, and the date of delivery, as identified in the medical record, birth record, or by the woman's self-report. Birth weight used the same data sources as for gestational age, namely the medical record (N = 805), vital records (N = 1,106) birth record, or self-report (N = 23).

## PRETERM BIRTH AND SMALL FOR GESTATIONAL AGE ANALYSIS

For statistical modeling, preterm birth was dichotomized as birth to an infant before 37 weeks gestation ("preterm") versus birth to an infant at or later than 37 weeks gestation ("term"). Small for gestational age (SGA) was defined as birth to a infant with a birth weight below ("SGA") or above ("not SGA") the tenth percentile for his/her gestational age according to infant gender, maternal race, and parity-specific birth weight curves derived by Zhang and Bowes (1995) using birth certificates data from the entire US population for the year 1989. For both preterm birth and SGA, logistic regression models were constructed to model the log odds of each outcome separately in relation to DBP exposure. Selection of confounders to include in final models used the same algorithm as for the pregnancy loss analysis: covariates were retained if found to be predictive of the outcome based on a p-value $< 0.20$ and/or changed the effect estimates for the of exposure interest by 10% or greater when excluded from the model. However, the list of confounders considered was slightly different. Age at menarche and history of induced abortion were not considered potential confounders and pregnancy history was redefined as no prior live birth, one or more prior live births but none preterm or SGA, or at least one prior preterm/SGA live birth. In addition, infant gender was added to the list of potential confounders for the SGA analysis only. Maternal caffeine consumption (0 mg/day, 1–150 mg/day, 151–300 mg/day, and > 300 mg/day), income (< 40,000/year, 40,000–80,000/year, > 80,000/year), body mass index (BMI) (underweight, normal, overweight, obese) and live birth history were included as covariates in all adjusted preterm birth models. Black race, education, (high school, some college, college or greater), smoking (< 10 cigarettes per day, ≥ 10 cigarettes per day), BMI and live birth history were included as covariates in all adjusted SGA models.

## TERM BIRTH WEIGHT

For statistical modeling, birth weight was coded continuously (in grams) and subjects were restricted to those that gave birth to an infant greater than or equal to 37 weeks gestational age. The association between term birth weight and DBP exposure was modeled using linear regression, controlling tightly for gestational age using a quadratic model (both gestational age and gestational age$^2$ were included in all models). Of note, we also constructed models that controlled for gestational age using linear and quadratic splines; however, the quadratic model performed equivalently to the more complex spline models (based upon the adjusted $R^2$ value of models), so we chose to use a quadratic model for simplicity.

The same list of potential confounders used in the preterm birth and SGA analyses were considered in the term birth weight analysis; however, maternal race, parity, infant gender and gestational age were included regardless of predictive value or impact on the exposure of interest so that results of the term birth weight analysis would be comparable to the SGA analysis which is already "adjusted" for these variables. Other covariates were retained only if found to be predictive of term birth weight based upon a p-value $< 0.20$ and/or they changed the effect estimates for the of exposure interest by 10% or greater when excluded from the model. Maternal caffeine consumption, Black race, education, income, smoking, BMI, employment (yes/no), diabetes status (none, gestational, chronic), live birth history, gestational age (continuous) and gestational age$^2$ were included as covariates in all adjusted term birth weight models.

## RESULTS FOR PRETERM BIRTH

Analysis of THM4 in relation to preterm birth (Table 8.1) provides a rather consistent indication of reduced risk associated with higher levels of exposure, somewhat more strongly so for concentration and ingested amount than for integrated exposure and shower/bath exposure. The pregnancy interval with the most notable inverse association varied across the indices of exposure. In the uppermost quintiles, adjusted odds ratios were in the range of 0.6–0.9, with inconsistent support for a dose-response gradient. Restriction to Sites 1 and 3 only (Table 8.2) and to Site 1 only (Table 8.3) enhanced the inverse association for concentration and ingested amount in the first and second trimesters slightly, but eliminated the inverse association for integrated exposure and ingested amount

BDCM analysis (Table 8.4) yielded results closer to the null than was found for THM4, but with some weak inverse associations between concentration and preterm birth, especially for the first trimester for both concentration and ingested amount. HAA9 (Table 8.5) also yielded indications of an inverse association for both concentration and to a lesser extent for ingested amount. There was not a monotonic gradient, but a reduced odds ratio in the uppermost quintile. Restriction to Sites 1 and 3 (Table 8.6) and more clearly Site 1 alone (Table 8.7) strengthened the inverse association with HAA9 slightly.

Chloroform exposure was similarly and more strongly inversely associated with risk of preterm birth (Table 8.8), especially for concentration and ingested amount, following the same pattern as for THM4. Brominated THMs were less consistently associated with decreased risk than other THMs discussed previously (Table 8.9) (at least in the highest quintile of exposure). HAA5 (Table 8.10) followed largely the same pattern as HAA9. HAA-Br yielded highly irregular dose-response patterns (Table 8.11), with lower odds ratios in the middle quintiles and somewhat higher odds ratios in the uppermost one. TOX concentrations were unrelated to preterm birth (Table 8.12), whereas ingested amounts of TOX were associated with reduced odds ratios.

**Table 8.1**
**Association between THM4 exposure and preterm birth, all RFTS sites**

| THM4 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| THM4 water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 3.3] | 49 | 337 | 1.00 | 1.00 |
| (3.3, 45.3] | 43 | 344 | 0.86 (0.56, 1.33) | 0.81 (0.50, 1.31) |
| (45.3, 60.2] | 49 | 337 | 1.00 (0.66, 1.53) | 1.06 (0.67, 1.70) |
| (60.2, 74.6] | 28 | 360 | 0.54 (0.33, 0.87) | 0.53 (0.31, 0.92) |
| >74.6 | 27 | 360 | 0.52 (0.32, 0.84) | 0.59 (0.35, 1.01) |
| Weeks 13 to 26 | | | | |
| [0.0, 3.3] | 39 | 349 | 1.00 | 1.00 |
| (3.3, 45.6] | 54 | 334 | 1.45 (0.93, 2.24) | 1.37 (0.85, 2.21) |
| (45.6, 62.2] | 47 | 337 | 1.25 (0.80, 1.96) | 1.34 (0.83, 2.18) |
| (62.2, 74.4] | 29 | 359 | 0.72 (0.44, 1.20) | 0.77 (0.44, 1.34) |
| >74.4 | 27 | 359 | 0.67 (0.40, 1.12) | 0.65 (0.37, 1.15) |
| Week 27 until birth | | | | |
| [0.0, 3.5] | 50 | 326 | 1.00 | 1.00 |
| (3.5, 45.2] | 34 | 341 | 0.65 (0.41, 1.03) | 0.57 (0.34, 0.94) |
| (45.2, 60.8] | 27 | 348 | 0.51 (0.31, 0.83) | 0.59 (0.35, 1.00) |
| (60.8, 74.1] | 37 | 339 | 0.71 (0.45, 1.12) | 0.66 (0.40, 1.08) |
| >74.1 | 37 | 338 | 0.71 (0.45, 1.12) | 0.74 (0.45, 1.21) |
| THM4 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.0] | 40 | 354 | 1.00 | 1.00 |
| (0, 5.3] | 36 | 342 | 0.93 (0.58, 1.50) | 0.91 (0.54, 1.52) |
| (5.3, 29.8] | 55 | 331 | 1.47 (0.95, 2.27) | 1.29 (0.80, 2.09) |
| (29.8, 92] | 36 | 350 | 0.91 (0.57, 1.46) | 0.91 (0.54, 1.54) |
| >92 | 29 | 358 | 0.72 (0.44, 1.18) | 0.71 (0.41, 1.22) |
| Weeks 13 to 26 | | | | |
| [0.0, 2.0] | 41 | 345 | 1.00 | 1.00 |
| (2, 6.9] | 43 | 343 | 1.06 (0.67, 1.66) | 1.03 (0.63, 1.68) |
| (6.9, 21.6] | 51 | 336 | 1.28 (0.82, 1.98) | 1.05 (0.64, 1.71) |
| (21.6, 60.2] | 30 | 355 | 0.71 (0.43, 1.17) | 0.69 (0.4, 1.20) |
| >60.2 | 31 | 356 | 0.73 (0.45, 1.20) | 0.72 (0.42, 1.21) |
| Week 27 until birth | | | | |
| [0.0, 1.2] | 40 | 336 | 1.00 | 1.00 |
| (1.2, 7.1] | 42 | 334 | 1.06 (0.67, 1.67) | 1.00 (0.61, 1.66) |
| (7.1, 35.1] | 43 | 332 | 1.09 (0.69, 1.72) | 0.95 (0.57, 1.59) |
| (35.1, 103.7] | 34 | 341 | 0.84 (0.52, 1.36) | 0.85 (0.50, 1.45) |
| >103.7 | 26 | 349 | 0.63 (0.37, 1.05) | 0.68 (0.39, 1.18) |

(continued)

**Table 8.1 (continued)**

| THM4 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| THM4 total integrated exposure (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.1] | 47 | 338 | 1.00 | 1.00 |
| (0.1, 0.7] | 41 | 344 | 0.86 (0.55, 1.34) | 0.72 (0.44, 1.19) |
| (0.7, 1.4] | 32 | 354 | 0.65 (0.41, 1.04) | 0.73 (0.43, 1.21) |
| (1.4, 2.2] | 26 | 360 | 0.52 (0.32, 0.86) | 0.51 (0.29, 0.88) |
| >2.2 | 50 | 335 | 1.07 (0.7, 1.64) | 0.91 (0.56, 1.48) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.1] | 41 | 345 | 1.00 | 1.00 |
| (0.1, 0.3] | 47 | 338 | 1.17 (0.75, 1.83) | 0.97 (0.59, 1.59) |
| (0.3, 0.7] | 30 | 356 | 0.71 (0.43, 1.16) | 0.79 (0.47, 1.34) |
| (0.7, 1.4] | 29 | 355 | 0.69 (0.42, 1.13) | 0.77 (0.46, 1.31) |
| >1.4 | 49 | 337 | 1.22 (0.79, 1.90) | 0.89 (0.54, 1.47) |
| Week 27 until birth | | | | |
| [0.0, 0.1] | 45 | 330 | 1.00 | 1.00 |
| (0.1, 0.6] | 51 | 325 | 1.15 (0.75, 1.77) | 1.00 (0.62, 1.61) |
| (0.6, 1.3] | 25 | 350 | 0.52 (0.31, 0.87) | 0.57 (0.33, 0.99) |
| (1.3, 2.1] | 24 | 352 | 0.50 (0.30, 0.84) | 0.62 (0.36, 1.06) |
| >2.1 | 40 | 335 | 0.88 (0.56, 1.38) | 0.72 (0.43, 1.19) |
| THM4 shower/bath (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.1] | 46 | 340 | 1.00 | 1.00 |
| (0.1, 0.6] | 41 | 345 | 0.88 (0.56, 1.37) | 0.75 (0.46, 1.24) |
| (0.6, 1.2] | 32 | 354 | 0.67 (0.42, 1.07) | 0.72 (0.43, 1.22) |
| (1.2, 1.9] | 24 | 362 | 0.49 (0.29, 0.82) | 0.50 (0.29, 0.88) |
| >1.9 | 53 | 333 | 1.18 (0.77, 1.8) | 0.98 (0.60, 1.58) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.1] | 41 | 345 | 1.00 | 1.00 |
| (0.1, 0.3] | 47 | 339 | 1.17 (0.75, 1.82) | 1.00 (0.61, 1.63) |
| (0.3, 0.6] | 25 | 361 | 0.58 (0.35, 0.98) | 0.59 (0.34, 1.04) |
| (0.6, 1.2] | 34 | 352 | 0.81 (0.50, 1.31) | 0.94 (0.56, 1.56) |
| >1.2 | 49 | 337 | 1.22 (0.79, 1.9) | 0.90 (0.54, 1.48) |
| Week 27 until birth | | | | |
| [0.0, 0.1] | 47 | 328 | 1.00 | 1.00 |
| (0.1, 0.4] | 48 | 327 | 1.02 (0.67, 1.58) | 0.88 (0.55, 1.42) |
| (0.4, 1] | 23 | 353 | 0.46 (0.27, 0.77) | 0.50 (0.28, 0.88) |
| (1, 1.7] | 26 | 349 | 0.52 (0.32, 0.86) | 0.62 (0.37, 1.06) |
| >1.7 | 41 | 335 | 0.85 (0.55, 1.33) | 0.73 (0.44, 1.21) |

(continued)

**Table 8.1 (continued)**

| THM4 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| THM4 regulatory cutpoint | | | | |
| Weeks 0 to 12 | | | | |
| <80 µg/L | 178 | 1508 | 1.00 | 1.00 |
| >=80 µg/L | 18 | 230 | 0.66 (0.40, 1.10) | 0.80 (0.47, 1.37) |
| Weeks 13 to 26 | | | | |
| <80 µg/L | 186 | 1553 | 1.00 | 1.00 |
| >=80 µg/L | 10 | 185 | 0.45 (0.24, 0.87) | 0.50 (0.25, 1.00) |
| Week 27 until birth | | | | |
| <80 µg/L | 170 | 1548 | 1.00 | 1.00 |
| >=80 µg/L | 15 | 144 | 0.95 (0.55, 1.65) | 0.97 (0.52, 1.82) |

*Adjusted for maternal caffeine intake, income, body mass index (BMI) and live birth history.

**Table 8.2**
**Association between THM4 exposure and preterm birth, all RFTS sites 1 and 3 only**

| THM4 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| THM4 water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 53.9] | 42 | 267 | 1.00 | 1.00 |
| (53.9, 66] | 27 | 281 | 0.61 (0.37, 1.02) | 0.59 (0.33, 1.05) |
| (66, 77.2] | 20 | 288 | 0.44 (0.25, 0.77) | 0.39 (0.21, 0.74) |
| >77.2 | 22 | 288 | 0.49 (0.28, 0.84) | 0.52 (0.29, 0.93) |
| Weeks 13 to 26 | | | | |
| [0.0, 57.2] | 35 | 272 | 1.00 | 1.00 |
| (57.2, 66.8] | 31 | 280 | 0.86 (0.52, 1.44) | 0.92 (0.53, 1.62) |
| (66.8, 77] | 24 | 283 | 0.66 (0.38, 1.14) | 0.60 (0.32, 1.11) |
| >77 | 21 | 289 | 0.57 (0.32, 0.99) | 0.53 (0.28, 1.00) |
| Week 27 until birth | | | | |
| [0.0, 57.5] | 22 | 279 | 1.00 | 1.00 |
| (57.5, 65.6] | 22 | 278 | 1.00 (0.54, 1.85) | 1.03 (0.53, 1.99) |
| (65.6, 75.9] | 33 | 269 | 1.56 (0.89, 2.74) | 1.27 (0.68, 2.41) |
| >75.9 | 27 | 273 | 1.25 (0.70, 2.26) | 1.13 (0.59, 2.17) |
| THM4 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 30 | 296 | 1.00 | 1.00 |
| (0, 51.8] | 29 | 262 | 1.09 (0.64, 1.87) | 1.10 (0.60, 2.01) |
| (51.8, 112.5] | 29 | 280 | 1.02 (0.60, 1.75) | 1.06 (0.59, 1.93) |
| >112.5 | 23 | 286 | 0.79 (0.45, 1.40) | 0.74 (0.39, 1.40) |

(continued)

**Table 8.2 (continued)**

| THM4 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| Weeks 13 to 26 | | | | |
| [0.0, 9] | 34 | 275 | 1.00 | 1.00 |
| (9, 33.6] | 28 | 280 | 0.81 (0.48, 1.37) | 0.74 (0.41, 1.35) |
| (33.6, 72] | 25 | 284 | 0.71 (0.41, 1.22) | 0.72 (0.39, 1.33) |
| >72 | 24 | 285 | 0.68 (0.39, 1.18) | 0.60 (0.33, 1.10) |
| Week 27 until birth | | | | |
| [0.0, 10.9] | 34 | 266 | 1.00 | 1.00 |
| (10.9, 60.4] | 24 | 278 | 0.68 (0.39, 1.17) | 0.70 (0.38, 1.30) |
| (60.4, 124.4] | 26 | 274 | 0.74 (0.43, 1.27) | 0.73 (0.40, 1.34) |
| >124.4 | 20 | 281 | 0.56 (0.31, 0.99) | 0.55 (0.29, 1.04) |
| | | | | |
| THM4 total integrated exposure (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 1.2] | 22 | 287 | 1.00 | 1.00 |
| (1.2, 1.7] | 23 | 285 | 1.05 (0.57, 1.93) | 1.04 (0.54, 2.00) |
| (1.7, 2.4] | 27 | 281 | 1.25 (0.70, 2.25) | 1.09 (0.57, 2.07) |
| >2.4 | 39 | 269 | 1.89 (1.09, 3.27) | 1.22 (0.65, 2.30) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.6] | 19 | 289 | 1.00 | 1.00 |
| (0.6, 0.9] | 25 | 283 | 1.34 (0.72, 2.49) | 1.15 (0.59, 2.22) |
| (0.9, 1.6] | 28 | 280 | 1.52 (0.83, 2.79) | 1.28 (0.66, 2.47) |
| >1.6 | 39 | 270 | 2.20 (1.24, 3.90) | 1.15 (0.59, 2.25) |
| Week 27 until birth | | | | |
| [0.0, 1] | 30 | 271 | 1.00 | 1.00 |
| (1, 1.5] | 21 | 279 | 0.68 (0.38, 1.22) | 0.92 (0.49, 1.73) |
| (1.5, 2.3] | 18 | 283 | 0.58 (0.31, 1.06) | 0.69 (0.36, 1.33) |
| >2.3 | 35 | 266 | 1.19 (0.71, 1.99) | 0.83 (0.45, 1.55) |
| THM4 shower/bath (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 1] | 24 | 284 | 1.00 | 1.00 |
| (1, 1.4] | 20 | 288 | 0.82 (0.44, 1.52) | 0.71 (0.36, 1.41) |
| (1.4, 2.2] | 25 | 284 | 1.04 (0.58, 1.87) | 0.95 (0.50, 1.78) |
| >2.2 | 42 | 266 | 1.87 (1.10, 3.17) | 1.16 (0.63, 2.14) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.5] | 18 | 290 | 1.00 | 1.00 |
| (0.5, 0.8] | 26 | 282 | 1.49 (0.80, 2.77) | 1.36 (0.70, 2.64) |
| (0.8, 1.4] | 26 | 282 | 1.49 (0.80, 2.77) | 1.21 (0.62, 2.37) |
| >1.4 | 41 | 268 | 2.47 (1.38, 4.40) | 1.26 (0.64, 2.49) |
| Week 27 until birth | | | | |
| [0.0, 0.9] | 27 | 273 | 1.00 | 1.00 |
| (0.9, 1.2] | 20 | 281 | 0.72 (0.39, 1.31) | 0.78 (0.40, 1.51) |
| (1.2, 2] | 19 | 282 | 0.68 (0.37, 1.25) | 0.74 (0.39, 1.43) |
| >2 | 38 | 263 | 1.46 (0.87, 2.46) | 1.02 (0.56, 1.88) |

(continued)

**Table 8.2 (continued)**

| THM4 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| THM4 regulatory cutpoint | | | | |
| Weeks 0 to 12 | | | | |
| <80 µg/L | 93 | 894 | 1.00 | 1.00 |
| >=80 µg/L | 18 | 230 | 0.75 (0.45, 1.27) | 0.90 (0.51, 1.57) |
| Weeks 13 to 26 | | | | |
| <80 µg/L | 101 | 939 | 1.00 | 1.00 |
| >=80 µg/L | 10 | 185 | 0.50 (0.26, 0.98) | 0.53 (0.26, 1.10) |
| Week 27 until birth | | | | |
| <80 µg/L | 89 | 955 | 1.00 | 1.00 |
| >=80 µg/L | 15 | 144 | 1.12 (0.63, 1.99) | 1.12 (0.58, 2.15) |

*Adjusted for maternal caffeine intake, income, body mass index (BMI) and live birth history.

**Table 8.3**
**Association between THM4 exposure and preterm birth, Site1 only**

| THM4 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| THM4 water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 57.6] | 23 | 205 | 1.00 | 1.00 |
| (57.6, 66.5] | 20 | 209 | 0.85 (0.46, 1.60) | 0.75 (0.37, 1.50) |
| (66.5, 77.2] | 11 | 218 | 0.45 (0.21, 0.95) | 0.34 (0.14, 0.80) |
| >77.2 | 9 | 220 | 0.37 (0.17, 0.81) | 0.33 (0.13, 0.80) |
| Weeks 13 to 26 | | | | |
| [0.0, 58.1] | 20 | 208 | 1.00 | 1.00 |
| (58.1, 66.8] | 18 | 211 | 0.89 (0.46, 1.73) | 0.87 (0.42, 1.81) |
| (66.8, 77] | 14 | 217 | 0.67 (0.33, 1.36) | 0.55 (0.24, 1.26) |
| >77 | 11 | 216 | 0.53 (0.25, 1.13) | 0.48 (0.21, 1.12) |
| Week 27 until birth | | | | |
| [0.0, 56.4] | 12 | 211 | 1.00 | 1.00 |
| (56.4, 64.5] | 12 | 211 | 1.00 (0.44, 2.28) | 0.85 (0.34, 2.14) |
| (64.5, 74.6] | 17 | 206 | 1.45 (0.68, 3.11) | 1.26 (0.53, 2.98) |
| >74.6 | 17 | 206 | 1.45 (0.68, 3.11) | 1.42 (0.61, 3.35) |
| THM4 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 15.2] | 16 | 212 | 1.00 | 1.00 |
| (15.2, 61.9] | 20 | 210 | 1.26 (0.64, 2.50) | 1.20 (0.57, 2.53) |
| (61.9, 118] | 15 | 214 | 0.93 (0.45, 1.93) | 0.75 (0.34, 1.68) |
| >118 | 12 | 216 | 0.74 (0.34, 1.59) | 0.58 (0.24, 1.40) |
| Weeks 13 to 26 | | | | |
| [0.0, 12.7] | 18 | 210 | 1.00 | 1.00 |
| (12.7, 34.3] | 17 | 213 | 0.93 (0.47, 1.86) | 1.01 (0.47, 2.17) |
| (34.3, 68.3] | 13 | 215 | 0.71 (0.34, 1.48) | 0.62 (0.26, 1.49) |
| >68.3 | 15 | 214 | 0.82 (0.40, 1.67) | 0.77 (0.35, 1.72) |
| Week 27 until birth | | | | |
| [0.0, 16.4] | 18 | 205 | 1.00 | 1.00 |
| (16.4, 63.5] | 13 | 210 | 0.71 (0.34, 1.48) | 0.71 (0.31, 1.64) |
| (63.5, 127.1] | 14 | 209 | 0.76 (0.37, 1.57) | 0.68 (0.29, 1.57) |
| >127.1 | 13 | 210 | 0.71 (0.34, 1.48) | 0.68 (0.29, 1.57) |
| THM4 total integrated exposure (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 1.1] | 11 | 218 | 1.00 | 1.00 |
| (1.1, 1.6] | 15 | 213 | 1.40 (0.63, 3.11) | 1.23 (0.54, 2.84) |
| (1.6, 2.4] | 17 | 211 | 1.60 (0.73, 3.49) | 1.34 (0.58, 3.08) |
| >2.4 | 20 | 209 | 1.90 (0.89, 4.05) | 1.09 (0.45, 2.61) |

(continued)

**Table 8.3 (continued)**

| THM4 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| Weeks 13 to 26 | | | | |
| [0.0, 0.5] | 11 | 217 | 1.00 | 1.00 |
| (0.5, 0.8] | 15 | 214 | 1.38 (0.62, 3.08) | 1.57 (0.66, 3.72) |
| (0.8, 1.2] | 14 | 214 | 1.29 (0.57, 2.91) | 1.58 (0.66, 3.81) |
| >1.2 | 23 | 206 | 2.20 (1.05, 4.63) | 1.56 (0.65, 3.73) |
| Week 27 until birth | | | | |
| [0.0, 1] | 11 | 212 | 1.00 | 1.00 |
| (1, 1.5] | 15 | 208 | 1.39 (0.62, 3.10) | 1.99 (0.83, 4.80) |
| (1.5, 2.2] | 11 | 212 | 1.00 (0.42, 2.36) | 1.40 (0.55, 3.55) |
| >2.2 | 21 | 202 | 2.00 (0.94, 4.26) | 1.52 (0.61, 3.81) |
| THM4 shower/bath (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.9] | 10 | 219 | 1.00 | 1.00 |
| (0.9, 1.3] | 17 | 211 | 1.76 (0.79, 3.94) | 1.52 (0.64, 3.57) |
| (1.3, 2] | 11 | 217 | 1.11 (0.46, 2.67) | 0.99 (0.39, 2.49) |
| >2 | 25 | 204 | 2.68 (1.26, 5.73) | 1.72 (0.74, 3.99) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.4] | 13 | 216 | 1.00 | 1.00 |
| (0.4, 0.6] | 11 | 217 | 0.84 (0.37, 1.92) | 0.94 (0.39, 2.29) |
| (0.6, 1.1] | 13 | 216 | 1.00 (0.45, 2.21) | 1.19 (0.51, 2.80) |
| >1.1 | 26 | 202 | 2.14 (1.07, 4.28) | 1.62 (0.72, 3.65) |
| Week 27 until birth | | | | |
| [0.0, 0.8] | 13 | 210 | 1.00 | 1.00 |
| (0.8, 1.1] | 9 | 214 | 0.68 (0.28, 1.62) | 0.79 (0.31, 2.01) |
| (1.1, 1.8] | 16 | 207 | 1.25 (0.59, 2.66) | 1.58 (0.70, 3.6) |
| >1.8 | 20 | 203 | 1.59 (0.77, 3.28) | 1.14 (0.48, 2.71) |
| THM4 regulatory cutpoint | | | | |
| Weeks 0 to 12 | | | | |
| <80 µg/L | 56 | 670 | 1.00 | 1.00 |
| >=80 µg/L | 7 | 182 | 0.46 (0.21, 1.03) | 0.51 (0.21, 1.23) |
| Weeks 13 to 26 | | | | |
| <80 µg/L | 58 | 698 | 1.00 | 1.00 |
| >=80 µg/L | 5 | 154 | 0.39 (0.15, 0.99) | 0.37 (0.13, 1.07) |
| Week 27 until birth | | | | |
| <80 µg/L | 50 | 735 | 1.00 | 1.00 |
| >=80 µg/L | 8 | 99 | 1.19 (0.55, 2.58) | 1.16 (0.46, 2.88) |

*Adjusted for maternal caffeine intake, income, body mass index (BMI) and live birth history.

**Table 8.4**
**Association between $CHBrCl_2$ exposure and preterm birth, all RFTS sites**

| $CHBrCl_2$ Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| $CHBrCl_2$ water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 1.1] | 49 | 333 | 1.00 | 1.00 |
| (1.1, 11] | 43 | 349 | 0.84 (0.54, 1.30) | 0.78 (0.48, 1.26) |
| (11, 14] | 35 | 351 | 0.68 (0.43, 1.07) | 0.78 (0.47, 1.28) |
| (14, 18.6] | 32 | 357 | 0.61 (0.38, 0.97) | 0.58 (0.34, 0.98) |
| >18.6 | 37 | 348 | 0.72 (0.46, 1.14) | 0.73 (0.45, 1.21) |
| Weeks 13 to 26 | | | | |
| [0.0, 1.1] | 35 | 353 | 1.00 | 1.00 |
| (1.1, 11] | 57 | 326 | 1.76 (1.13, 2.76) | 1.66 (1.02, 2.70) |
| (11, 13.7] | 28 | 361 | 0.78 (0.47, 1.31) | 0.79 (0.45, 1.40) |
| (13.7, 20.1] | 36 | 350 | 1.04 (0.64, 1.69) | 1.13 (0.66, 1.91) |
| >20.1 | 40 | 348 | 1.16 (0.72, 1.87) | 1.06 (0.63, 1.78) |
| Week 27 until birth | | | | |
| [0.0, 1.1] | 48 | 328 | 1.00 | 1.00 |
| (1.1, 10.8] | 35 | 340 | 0.70 (0.44, 1.12) | 0.63 (0.38, 1.04) |
| (10.8, 13.2] | 23 | 353 | 0.45 (0.27, 0.75) | 0.47 (0.27, 0.83) |
| (13.2, 19.7] | 32 | 342 | 0.64 (0.40, 1.03) | 0.69 (0.41, 1.15) |
| >19.7 | 47 | 329 | 0.98 (0.64, 1.50) | 0.96 (0.60, 1.54) |
| $CHBrCl_2$ ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 40 | 354 | 1.00 | 1.00 |
| (0, 1.7] | 35 | 343 | 0.90 (0.56, 1.46) | 0.89 (0.53, 1.50) |
| (1.7, 7] | 57 | 330 | 1.53 (0.99, 2.35) | 1.33 (0.83, 2.14) |
| (7, 22.8] | 33 | 352 | 0.83 (0.51, 1.35) | 0.84 (0.49, 1.43) |
| >22.8 | 31 | 356 | 0.77 (0.47, 1.26) | 0.76 (0.44, 1.29) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.6] | 41 | 346 | 1.00 | 1.00 |
| (0.6, 2.2] | 41 | 344 | 1.01 (0.64, 1.59) | 0.96 (0.58, 1.57) |
| (2.2, 9.1] | 55 | 332 | 1.40 (0.91, 2.15) | 1.17 (0.72, 1.88) |
| (9.1, 25.1] | 30 | 355 | 0.71 (0.44, 1.17) | 0.67 (0.39, 1.16) |
| >25.1 | 29 | 358 | 0.68 (0.42, 1.13) | 0.67 (0.39, 1.14) |
| Week 27 until birth | | | | |
| [0.0, 0.3] | 40 | 336 | 1.00 | 1.00 |
| (0.3, 2.2] | 43 | 331 | 1.09 (0.69, 1.72) | 1.02 (0.61, 1.68) |
| (2.2, 8.7] | 38 | 338 | 0.94 (0.59, 1.51) | 0.89 (0.53, 1.49) |
| (8.7, 25.5] | 31 | 345 | 0.76 (0.46, 1.24) | 0.69 (0.40, 1.19) |
| >25.5 | 33 | 342 | 0.81 (0.50, 1.32) | 0.90 (0.54, 1.52) |

(continued)

**Table 8.4 (continued)**

| $CHBrCl_2$ Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| $CHBrCl_2$ total integrated exposure (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 45 | 341 | 1.00 | 1.00 |
| (0, 0.1] | 43 | 341 | 0.96 (0.61, 1.49) | 0.87 (0.54, 1.43) |
| (0.1, 0.3] | 27 | 359 | 0.57 (0.35, 0.94) | 0.61 (0.36, 1.06) |
| (0.3, 0.5] | 27 | 359 | 0.57 (0.35, 0.94) | 0.62 (0.36, 1.06) |
| >0.5 | 54 | 331 | 1.24 (0.81, 1.89) | 0.99 (0.61, 1.62) |
| Weeks 13 to 26 | | | | |
| [0.0, 0] | 38 | 347 | 1.00 | 1.00 |
| (0, 0.1] | 49 | 336 | 1.33 (0.85, 2.09) | 1.12 (0.68, 1.84) |
| (0.1, 0.3] | 30 | 357 | 0.77 (0.47, 1.27) | 0.86 (0.51, 1.47) |
| (0.3, 0.5] | 31 | 354 | 0.80 (0.49, 1.31) | 0.85 (0.50, 1.44) |
| >0.5 | 48 | 337 | 1.3 (0.83, 2.04) | 0.96 (0.57, 1.60) |
| Week 27 until birth | | | | |
| [0.0, 0] | 47 | 328 | 1.00 | 1.00 |
| (0, 0.1] | 43 | 333 | 0.90 (0.58, 1.40) | 0.77 (0.47, 1.26) |
| (0.1, 0.3] | 27 | 349 | 0.54 (0.33, 0.89) | 0.65 (0.38, 1.11) |
| (0.3, 0.4] | 26 | 349 | 0.52 (0.32, 0.86) | 0.60 (0.35, 1.03) |
| >0.4 | 42 | 333 | 0.88 (0.57, 1.37) | 0.76 (0.46, 1.26) |
| $CHBrCl_2$ shower/bath (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 44 | 342 | 1.00 | 1.00 |
| (0, 0.1] | 42 | 344 | 0.95 (0.61, 1.49) | 0.87 (0.53, 1.42) |
| (0.1, 0.3] | 29 | 357 | 0.63 (0.39, 1.03) | 0.68 (0.40, 1.17) |
| (0.3, 0.5] | 26 | 360 | 0.56 (0.34, 0.93) | 0.59 (0.34, 1.03) |
| >0.5 | 55 | 331 | 1.29 (0.85, 1.97) | 1.06 (0.65, 1.73) |
| Weeks 13 to 26 | | | | |
| [0.0, 0] | 37 | 349 | 1.00 | 1.00 |
| (0, 0.1] | 53 | 333 | 1.50 (0.96, 2.35) | 1.27 (0.77, 2.07) |
| (0.1, 0.3] | 24 | 362 | 0.63 (0.37, 1.07) | 0.72 (0.41, 1.27) |
| (0.3, 0.5] | 34 | 352 | 0.91 (0.56, 1.49) | 0.96 (0.57, 1.62) |
| >0.5 | 48 | 338 | 1.34 (0.85, 2.11) | 0.98 (0.58, 1.65) |
| Week 27 until birth | | | | |
| [0.0, 0] | 47 | 329 | 1.00 | 1.00 |
| (0, 0.1] | 45 | 329 | 0.96 (0.62, 1.48) | 0.80 (0.49, 1.31) |
| (0.1, 0.2] | 26 | 351 | 0.52 (0.31, 0.86) | 0.61 (0.35, 1.04) |
| (0.2, 0.4] | 25 | 350 | 0.50 (0.30, 0.83) | 0.55 (0.32, 0.95) |
| >0.4 | 42 | 333 | 0.88 (0.57, 1.38) | 0.76 (0.46, 1.26) |

**Table 8.5**
**Association between HAA9 exposure and preterm birth, all RFTS sites**

| HAA9 Exposure | Cases | Non-cases | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| HAA9 water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 1.9] | 40 | 346 | 1.00 | 1.00 |
| (1.9, 30.1] | 48 | 339 | 1.23 (0.78, 1.91) | 1.33 (0.81, 2.16) |
| (30.1, 43.8] | 36 | 352 | 0.89 (0.55, 1.42) | 0.94 (0.55, 1.58) |
| (43.8, 51.7] | 47 | 344 | 1.18 (0.76, 1.85) | 1.32 (0.80, 2.15) |
| >51.7 | 25 | 357 | 0.61 (0.36, 1.02) | 0.65 (0.36, 1.16) |
| Weeks 13 to 26 | | | | |
| [0.0, 1.8] | 37 | 350 | 1.00 | 1.00 |
| (1.8, 29.3] | 54 | 332 | 1.54 (0.99, 2.40) | 1.38 (0.85, 2.24) |
| (29.3, 44.9] | 42 | 345 | 1.15 (0.72, 1.84) | 1.15 (0.70, 1.91) |
| (44.9, 51.7] | 42 | 344 | 1.16 (0.73, 1.84) | 1.10 (0.66, 1.82) |
| >51.7 | 21 | 367 | 0.54 (0.31, 0.94) | 0.53 (0.29, 0.98) |
| Week 27 until birth | | | | |
| [0.0, 1.1] | 40 | 335 | 1.00 | 1.00 |
| (1.1, 28.5] | 45 | 330 | 1.14 (0.73, 1.80) | 0.98 (0.60, 1.62) |
| (28.5, 44.7] | 37 | 340 | 0.91 (0.57, 1.46) | 1.02 (0.62, 1.68) |
| (44.7, 52.3] | 45 | 330 | 1.14 (0.73, 1.80) | 1.08 (0.66, 1.78) |
| >52.3 | 18 | 357 | 0.42 (0.24, 0.75) | 0.42 (0.22, 0.80) |
| HAA9 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.1] | 40 | 346 | 1.00 | 1.00 |
| (0.1, 5.6] | 45 | 342 | 1.14 (0.73, 1.79) | 1.17 (0.72, 1.91) |
| (5.6, 36.4] | 44 | 342 | 1.11 (0.71, 1.75) | 0.94 (0.57, 1.57) |
| (36.4, 81.7] | 34 | 352 | 0.84 (0.52, 1.35) | 0.92 (0.55, 1.56) |
| >81.7 | 33 | 353 | 0.81 (0.50, 1.31) | 0.84 (0.49, 1.43) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.2] | 38 | 349 | 1.00 | 1.00 |
| (0.2, 7.1] | 52 | 334 | 1.43 (0.92, 2.23) | 1.42 (0.87, 2.32) |
| (7.1, 42.3] | 48 | 338 | 1.30 (0.83, 2.05) | 1.19 (0.72, 1.98) |
| (42.3, 88.4] | 28 | 357 | 0.72 (0.43, 1.20) | 0.86 (0.50, 1.50) |
| >88.4 | 30 | 357 | 0.77 (0.47, 1.27) | 0.86 (0.50, 1.47) |
| Week 27 until birth | | | | |
| [0.0, 0] | 57 | 442 | 1.00 | 1.00 |
| (0, 6] | 31 | 220 | 1.09 (0.69, 1.74) | 1.06 (0.63, 1.79) |
| (6, 42] | 44 | 333 | 1.03 (0.67, 1.56) | 1.00 (0.63, 1.60) |
| (42, 92.7] | 27 | 347 | 0.60 (0.37, 0.97) | 0.70 (0.42, 1.19) |
| >92.7 | 26 | 350 | 0.58 (0.36, 0.94) | 0.67 (0.40, 1.13) |

*Adjusted for maternal caffeine intake, income, body mass index (BMI) and live birth history.

**Table 8.6**
**Association between HAA9 exposure and preterm birth, all RFTS sites 1 and 3 only**

| HAA9 Exposure | Cases | Non-cases | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| HAA9 water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 40.9] | 23 | 285 | 1.00 | 1.00 |
| (40.9, 46.1] | 35 | 275 | 1.58 (0.91, 2.74) | 1.43 (0.78, 2.64) |
| (46.1, 53] | 35 | 273 | 1.59 (0.92, 2.76) | 1.29 (0.70, 2.39) |
| >53 | 18 | 291 | 0.77 (0.41, 1.45) | 0.77 (0.38, 1.56) |
| Weeks 13 to 26 | | | | |
| [0.0, 42.1] | 27 | 282 | 1.00 | 1.00 |
| (42.1, 48.7] | 44 | 264 | 1.74 (1.05, 2.89) | 1.31 (0.75, 2.32) |
| (48.7, 52.9] | 24 | 283 | 0.89 (0.50, 1.57) | 0.85 (0.46, 1.58) |
| >52.9 | 16 | 295 | 0.57 (0.30, 1.07) | 0.53 (0.26, 1.07) |
| Week 27 until birth | | | | |
| [0.0, 41.9] | 25 | 277 | 1.00 | 1.00 |
| (41.9, 47] | 39 | 261 | 1.66 (0.98, 2.81) | 1.34 (0.74, 2.42) |
| (47, 53.4] | 24 | 276 | 0.96 (0.54, 1.73) | 0.85 (0.45, 1.63) |
| >53.4 | 16 | 285 | 0.62 (0.33, 1.19) | 0.58 (0.28, 1.20) |
| HAA9 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 20] | 31 | 278 | 1.00 | 1.00 |
| (20, 53.4] | 29 | 279 | 0.93 (0.55, 1.59) | 1.10 (0.60, 2.02) |
| (53.4, 91.8] | 28 | 281 | 0.89 (0.52, 1.53) | 1.18 (0.64, 2.16) |
| >91.8 | 23 | 286 | 0.72 (0.41, 1.27) | 0.81 (0.43, 1.54) |
| Weeks 13 to 26 | | | | |
| [0.0, 24.3] | 41 | 267 | 1.00 | 1.00 |
| (24.3, 58.8] | 22 | 288 | 0.50 (0.29, 0.86) | 0.71 (0.38, 1.32) |
| (58.8, 99.2] | 26 | 282 | 0.60 (0.36, 1.01) | 0.93 (0.52, 1.67) |
| >99.2 | 22 | 287 | 0.50 (0.29, 0.86) | 0.60 (0.32, 1.11) |
| Week 27 until birth | | | | |
| [0.0, 22.8] | 35 | 266 | 1.00 | 1.00 |
| (22.8, 58.7] | 22 | 278 | 0.60 (0.34, 1.05) | 0.82 (0.43, 1.55) |
| (58.7, 103.9] | 25 | 277 | 0.69 (0.40, 1.18) | 1.03 (0.56, 1.91) |
| >103.9 | 22 | 278 | 0.60 (0.34, 1.05) | 0.75 (0.40, 1.41) |

*Adjusted for maternal caffeine intake, income, body mass index (BMI) and live birth history.

**Table 8.7**
**Association between HAA9 exposure and preterm birth, RFTS sites 1 only**

| HAA9 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| HAA9 water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 2.4] | 20 | 209 | 1.00 | 1.00 |
| (2.4, 39.9] | 17 | 211 | 0.84 (0.43, 1.65) | 0.81 (0.38, 1.72) |
| (39.9, 50.2] | 11 | 217 | 0.53 (0.25, 1.13) | 0.45 (0.19, 1.08) |
| >50.2 | 15 | 215 | 0.73 (0.36, 1.46) | 0.68 (0.32, 1.46) |
| Weeks 13 to 26 | | | | |
| [0.0, 2.7] | 23 | 207 | 1.00 | 1.00 |
| (2.7, 40.8] | 14 | 213 | 0.59 (0.30, 1.18) | 0.50 (0.23, 1.12) |
| (40.8, 50.9] | 16 | 214 | 0.67 (0.35, 1.31) | 0.57 (0.27, 1.20) |
| >50.9 | 10 | 218 | 0.41 (0.19, 0.89) | 0.40 (0.18, 0.93) |
| Week 27 until birth | | | | |
| [0.0, 2.2] | 18 | 205 | 1.00 | 1.00 |
| (2.2, 40.1] | 18 | 205 | 1.00 (0.51, 1.98) | 0.97 (0.45, 2.07) |
| (40.1, 50.7] | 8 | 215 | 0.42 (0.18, 1.00) | 0.41 (0.16, 1.05) |
| >50.7 | 14 | 209 | 0.76 (0.37, 1.57) | 0.63 (0.27, 1.44) |
| HAA9 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.9] | 18 | 211 | 1.00 | 1.00 |
| (0.9, 16.3] | 16 | 212 | 0.89 (0.44, 1.78) | 0.85 (0.38, 1.87) |
| (16.3, 68.2] | 12 | 218 | 0.65 (0.30, 1.37) | 0.79 (0.35, 1.77) |
| >68.2 | 17 | 211 | 0.94 (0.47, 1.88) | 0.95 (0.43, 2.09) |
| Weeks 13 to 26 | | | | |
| [0.0, 1.3] | 19 | 209 | 1.00 | 1.00 |
| (1.3, 20.7] | 16 | 213 | 0.83 (0.41, 1.65) | 1.18 (0.54, 2.60) |
| (20.7, 74.7] | 14 | 216 | 0.71 (0.35, 1.46) | 0.96 (0.43, 2.15) |
| >74.7 | 14 | 214 | 0.72 (0.35, 1.47) | 0.78 (0.34, 1.8) |
| Week 27 until birth | | | | |
| [0.0, 0] | 17 | 206 | 1.00 | 1.00 |
| (0, 20.3] | 17 | 206 | 1.00 (0.50, 2.01) | 1.06 (0.47, 2.39) |
| (20.3, 77] | 14 | 209 | 0.81 (0.39, 1.69) | 0.98 (0.42, 2.25) |
| >77 | 10 | 213 | 0.57 (0.26, 1.27) | 0.62 (0.25, 1.52) |

*Adjusted for maternal caffeine intake, income, body mass index (BMI) and live birth history.

**Table 8.8**
**Association between $CHCl_3$ exposure and preterm birth, all RFTS sites**

| $CHCl_3$ Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| CHCl3 water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.1] | 52 | 336 | 1.00 | 1.00 |
| (0.1, 9.7] | 40 | 345 | 0.75 (0.48, 1.16) | 0.83 (0.52, 1.35) |
| (9.7, 32.8] | 53 | 335 | 1.02 (0.68, 1.54) | 1.10 (0.69, 1.74) |
| (32.8, 48.6] | 32 | 355 | 0.58 (0.37, 0.93) | 0.64 (0.38, 1.07) |
| >48.6 | 19 | 367 | 0.34 (0.19, 0.58) | 0.36 (0.19, 0.67) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.1] | 36 | 351 | 1.00 | 1.00 |
| (0.1, 12.2] | 63 | 324 | 1.90 (1.23, 2.93) | 1.64 (1.02, 2.66) |
| (12.2, 30.7] | 49 | 338 | 1.41 (0.90, 2.23) | 1.43 (0.88, 2.32) |
| (30.7, 48.7] | 22 | 365 | 0.59 (0.34, 1.02) | 0.65 (0.36, 1.17) |
| >48.7 | 26 | 360 | 0.70 (0.42, 1.19) | 0.67 (0.37, 1.21) |
| Week 27 until birth | | | | |
| [0.0, 0.1] | 50 | 331 | 1.00 | 1.00 |
| (0.1, 10.9] | 41 | 329 | 0.83 (0.53, 1.28) | 0.68 (0.42, 1.11) |
| (10.9, 30.4] | 40 | 336 | 0.79 (0.51, 1.23) | 0.76 (0.47, 1.24) |
| (30.4, 48.2] | 26 | 349 | 0.49 (0.30, 0.81) | 0.52 (0.31, 0.90) |
| >48.2 | 28 | 347 | 0.53 (0.33, 0.87) | 0.54 (0.31, 0.92) |
| CHCl3 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 44 | 382 | 1.00 | 1.00 |
| (0, 0.2] | 41 | 304 | 1.17 (0.75, 1.84) | 1.11 (0.68, 1.81) |
| (0.2, 12.5] | 49 | 339 | 1.26 (0.81, 1.93) | 1.12 (0.70, 1.80) |
| (12.5, 53.5] | 38 | 347 | 0.95 (0.60, 1.50) | 0.95 (0.58, 1.58) |
| >53.5 | 24 | 363 | 0.57 (0.34, 0.96) | 0.54 (0.30, 0.96) |
| Weeks 13 to 26 | | | | |
| [0.0, 0] | 44 | 342 | 1.00 | 1.00 |
| (0, 0.1] | 40 | 347 | 0.90 (0.57, 1.41) | 0.83 (0.50, 1.37) |
| (0.1, 4.6] | 51 | 334 | 1.19 (0.77, 1.83) | 1.06 (0.66, 1.70) |
| (4.6, 17.8] | 35 | 351 | 0.78 (0.49, 1.24) | 0.74 (0.44, 1.24) |
| >17.8 | 26 | 361 | 0.56 (0.34, 0.93) | 0.55 (0.32, 0.95) |
| Week 27 until birth | | | | |
| [0.0, 0] | 56 | 384 | 1.00 | 1.00 |
| (0, 0.3] | 29 | 281 | 0.71 (0.44, 1.14) | 0.75 (0.45, 1.25) |
| (0.3, 15.8] | 46 | 331 | 0.95 (0.63, 1.45) | 0.86 (0.54, 1.37) |
| (15.8, 57.5] | 28 | 346 | 0.56 (0.35, 0.89) | 0.59 (0.35, 1.00) |
| >57.5 | 26 | 350 | 0.51 (0.31, 0.83) | 0.56 (0.33, 0.95) |

(continued)

**Table 8.8 (continued)**

| $CHCl_3$ Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| CHCl3 total integrated exposure (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 53 | 333 | 1.00 | 1.00 |
| (0, 0.3] | 40 | 345 | 0.73 (0.47, 1.13) | 0.64 (0.39, 1.04) |
| (0.3, 0.8] | 36 | 350 | 0.65 (0.41, 1.01) | 0.65 (0.39, 1.06) |
| (0.8, 1.4] | 31 | 354 | 0.55 (0.35, 0.88) | 0.64 (0.39, 1.06) |
| >1.4 | 36 | 349 | 0.65 (0.41, 1.02) | 0.54 (0.33, 0.91) |
| Weeks 13 to 26 | | | | |
| [0.0, 0] | 38 | 348 | 1.00 | 1.00 |
| (0, 0] | 56 | 329 | 1.56 (1.01, 2.42) | 1.48 (0.91, 2.40) |
| (0, 0.2] | 26 | 360 | 0.66 (0.39, 1.11) | 0.74 (0.42, 1.29) |
| (0.2, 0.5] | 40 | 345 | 1.06 (0.67, 1.70) | 1.10 (0.66, 1.84) |
| >0.5 | 36 | 349 | 0.95 (0.59, 1.53) | 0.96 (0.56, 1.63) |
| Week 27 until birth | | | | |
| [0.0, 0] | 46 | 329 | 1.00 | 1.00 |
| (0, 0.2] | 51 | 325 | 1.12 (0.73, 1.72) | 1.03 (0.65, 1.66) |
| (0.2, 0.8] | 26 | 349 | 0.53 (0.32, 0.88) | 0.56 (0.32, 0.96) |
| (0.8, 1.3] | 30 | 345 | 0.62 (0.38, 1.01) | 0.82 (0.49, 1.37) |
| >1.3 | 32 | 344 | 0.67 (0.41, 1.07) | 0.59 (0.34, 1.01) |
| | | | | |
| CHCl3 shower/bath (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 53 | 335 | 1.00 | 1.00 |
| (0, 0.2] | 41 | 343 | 0.76 (0.49, 1.17) | 0.68 (0.42, 1.10) |
| (0.2, 0.7] | 32 | 354 | 0.57 (0.36, 0.91) | 0.61 (0.37, 1.00) |
| (0.7, 1.1] | 33 | 353 | 0.59 (0.37, 0.94) | 0.69 (0.42, 1.13) |
| >1.1 | 37 | 349 | 0.67 (0.43, 1.05) | 0.58 (0.35, 0.97) |
| Weeks 13 to 26 | | | | |
| [0.0, 0] | 39 | 347 | 1.00 | 1.00 |
| (0, 0] | 55 | 331 | 1.48 (0.96, 2.29) | 1.48 (0.91, 2.40) |
| (0, 0.2] | 26 | 360 | 0.64 (0.38, 1.08) | 0.74 (0.42, 1.31) |
| (0.2, 0.4] | 34 | 352 | 0.86 (0.53, 1.39) | 0.93 (0.55, 1.59) |
| >0.4 | 42 | 344 | 1.09 (0.69, 1.72) | 1.13 (0.67, 1.88) |
| Week 27 until birth | | | | |
| [0.0, 0] | 52 | 324 | 1.00 | 1.00 |
| (0, 0.2] | 47 | 327 | 0.9 (0.59, 1.37) | 0.88 (0.55, 1.41) |
| (0.2, 0.6] | 27 | 349 | 0.48 (0.3, 0.79) | 0.53 (0.31, 0.90) |
| (0.6, 1] | 28 | 348 | 0.5 (0.31, 0.81) | 0.68 (0.41, 1.14) |
| >1 | 31 | 344 | 0.56 (0.35, 0.9) | 0.52 (0.30, 0.89) |

*Adjusted for maternal caffeine intake, income, body mass index (BMI) and live birth history.

**Table 8.9**
**Association between THM-Br exposure and preterm birth, all RFTS sites**

| THM-Br Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| THM-Br water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 3.1] | 47 | 341 | 1.00 | 1.00 |
| (3.1, 12.8] | 44 | 343 | 0.93 (0.60, 1.44) | 0.90 (0.56, 1.45) |
| (12.8, 17.9] | 31 | 356 | 0.63 (0.39, 1.02) | 0.69 (0.41, 1.16) |
| (17.9, 31.6] | 25 | 361 | 0.50 (0.30, 0.83) | 0.48 (0.27, 0.84) |
| >31.6 | 49 | 337 | 1.06 (0.69, 1.62) | 1.01 (0.63, 1.62) |
| Weeks 13 to 26 | | | | |
| [0.0, 3.2] | 40 | 349 | 1.00 | 1.00 |
| (3.2, 12.7] | 54 | 331 | 1.42 (0.92, 2.20) | 1.38 (0.86, 2.21) |
| (12.7, 17.6] | 24 | 363 | 0.58 (0.34, 0.98) | 0.56 (0.31, 1.01) |
| (17.6, 32.7] | 28 | 359 | 0.68 (0.41, 1.13) | 0.71 (0.40, 1.23) |
| >32.7 | 50 | 336 | 1.30 (0.84, 2.02) | 1.24 (0.77, 2.01) |
| Week 27 until birth | | | | |
| [0.0, 3.4] | 50 | 326 | 1.00 | 1.00 |
| (3.4, 12.7] | 36 | 338 | 0.69 (0.44, 1.09) | 0.58 (0.35, 0.97) |
| (12.7, 17.1] | 21 | 355 | 0.39 (0.23, 0.66) | 0.45 (0.25, 0.78) |
| (17.1, 32.5] | 25 | 350 | 0.47 (0.28, 0.77) | 0.51 (0.29, 0.88) |
| >32.5 | 53 | 323 | 1.07 (0.71, 1.62) | 1.03 (0.65, 1.63) |
| THM-Br ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 40 | 354 | 1.00 | 1.00 |
| (0, 4.6] | 34 | 344 | 0.88 (0.54, 1.42) | 0.86 (0.51, 1.45) |
| (4.6, 11.4] | 52 | 335 | 1.37 (0.89, 2.13) | 1.24 (0.76, 2.01) |
| (11.4, 31.7] | 35 | 350 | 0.89 (0.55, 1.43) | 0.89 (0.53, 1.50) |
| >31.7 | 35 | 352 | 0.88 (0.55, 1.42) | 0.84 (0.50, 1.42) |
| Weeks 13 to 26 | | | | |
| [0.0, 1.9] | 41 | 346 | 1.00 | 1.00 |
| (1.9, 5.8] | 44 | 341 | 1.09 (0.69, 1.71) | 0.95 (0.58, 1.56) |
| (5.8, 13.8] | 48 | 339 | 1.20 (0.77, 1.86) | 1.16 (0.71, 1.89) |
| (13.8, 36] | 30 | 356 | 0.71 (0.43, 1.17) | 0.63 (0.37, 1.09) |
| >36 | 33 | 353 | 0.79 (0.49, 1.28) | 0.74 (0.44, 1.25) |
| Week 27 until birth | | | | |
| [0.0, 1.2] | 40 | 336 | 1.00 | 1.00 |
| (1.2, 5.8] | 40 | 335 | 1.00 (0.63, 1.6) | 0.94 (0.56, 1.58) |
| (5.8, 13.7] | 41 | 334 | 1.03 (0.65, 1.64) | 1.01 (0.61, 1.69) |
| (13.7, 36.4] | 28 | 347 | 0.68 (0.41, 1.12) | 0.59 (0.33, 1.03) |
| >36.4 | 36 | 340 | 0.89 (0.55, 1.43) | 0.95 (0.57, 1.59) |

(continued)

**Table 8.9 (continued)**

| THM-Br Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| THM-Br total integrated exposure (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.1] | 45 | 341 | 1.00 | 1.00 |
| (0.1, 0.2] | 40 | 345 | 0.88 (0.56, 1.38) | 0.84 (0.51, 1.38) |
| (0.2, 0.4] | 23 | 363 | 0.48 (0.28, 0.81) | 0.49 (0.27, 0.86) |
| (0.4, 0.8] | 37 | 348 | 0.81 (0.51, 1.28) | 0.81 (0.49, 1.34) |
| >0.8 | 51 | 334 | 1.16 (0.75, 1.78) | 0.92 (0.56, 1.51) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.1] | 41 | 345 | 1.00 | 1.00 |
| (0.1, 0.2] | 41 | 343 | 1.01 (0.64, 1.59) | 0.91 (0.55, 1.49) |
| (0.2, 0.4] | 31 | 356 | 0.73 (0.45, 1.20) | 0.78 (0.46, 1.32) |
| (0.4, 0.8] | 33 | 351 | 0.79 (0.49, 1.28) | 0.83 (0.5, 1.4) |
| >0.8 | 50 | 336 | 1.25 (0.81, 1.94) | 0.9 (0.54, 1.49) |
| Week 27 until birth | | | | |
| [0.0, 0.1] | 46 | 329 | 1.00 | 1.00 |
| (0.1, 0.2] | 39 | 337 | 0.83 (0.53, 1.30) | 0.78 (0.47, 1.28) |
| (0.2, 0.3] | 28 | 348 | 0.58 (0.35, 0.94) | 0.60 (0.35, 1.04) |
| (0.3, 0.7] | 30 | 345 | 0.62 (0.38, 1.01) | 0.68 (0.40, 1.15) |
| >0.7 | 42 | 333 | 0.90 (0.58, 1.41) | 0.76 (0.46, 1.26) |
| THM-Br shower/bath (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.1] | 45 | 341 | 1.00 | 1.00 |
| (0.1, 0.2] | 40 | 346 | 0.88 (0.56, 1.38) | 0.85 (0.52, 1.39) |
| (0.2, 0.4] | 22 | 364 | 0.46 (0.27, 0.78) | 0.46 (0.26, 0.82) |
| (0.4, 0.8] | 37 | 349 | 0.80 (0.51, 1.27) | 0.83 (0.50, 1.37) |
| >0.8 | 52 | 334 | 1.18 (0.77, 1.81) | 0.93 (0.57, 1.52) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.1] | 42 | 344 | 1.00 | 1.00 |
| (0.1, 0.2] | 42 | 344 | 1.00 (0.64, 1.57) | 0.91 (0.55, 1.49) |
| (0.2, 0.3] | 24 | 362 | 0.54 (0.32, 0.92) | 0.55 (0.31, 0.96) |
| (0.3, 0.7] | 40 | 346 | 0.95 (0.60, 1.50) | 1.01 (0.62, 1.65) |
| >0.7 | 48 | 338 | 1.16 (0.75, 1.81) | 0.81 (0.49, 1.35) |
| Week 27 until birth | | | | |
| [0.0, 0.1] | 46 | 329 | 1.00 | 1.00 |
| (0.1, 0.2] | 38 | 338 | 0.80 (0.51, 1.27) | 0.78 (0.47, 1.28) |
| (0.2, 0.3] | 27 | 349 | 0.55 (0.34, 0.91) | 0.60 (0.35, 1.03) |
| (0.3, 0.7] | 31 | 343 | 0.65 (0.40, 1.05) | 0.71 (0.42, 1.20) |
| >0.7 | 43 | 333 | 0.92 (0.59, 1.44) | 0.80 (0.49, 1.32) |

*Adjusted for maternal caffeine intake, income, body mass index (BMI) and live birth history.

**Table 8.10**
**Association between HAA5 exposure and preterm birth, all RFTS sites**

| HAA5 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| HAA5 water concentration (µg/L)** | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 36 | 353 | 1.00 | 1.00 |
| (0, 19.1] | 57 | 328 | 1.70 (1.09, 2.66) | 2.17 (1.32, 3.56) |
| (19.1, 26.2] | 48 | 338 | 1.39 (0.88, 2.20) | 1.64 (0.98, 2.74) |
| (26.2, 38] | 31 | 358 | 0.85 (0.51, 1.40) | 1.00 (0.56, 1.77) |
| >38 | 24 | 361 | 0.65 (0.38, 1.12) | 0.76 (0.41, 1.41) |
| Weeks 13 to 26 | | | | |
| [0.0, 0] | 43 | 367 | 1.00 | 1.00 |
| (0, 19.1] | 51 | 310 | 1.40 (0.91, 2.17) | 1.20 (0.74, 1.94) |
| (19.1, 26.1] | 53 | 335 | 1.35 (0.88, 2.07) | 1.35 (0.85, 2.13) |
| (26.1, 38.4] | 29 | 360 | 0.69 (0.42, 1.13) | 0.63 (0.36, 1.09) |
| >38.4 | 20 | 366 | 0.47 (0.27, 0.81) | 0.50 (0.27, 0.90) |
| Week 27 until birth | | | | |
| [0.0, 0] | 68 | 483 | 1.00 | 1.00 |
| (0, 18.6] | 26 | 173 | 1.07 (0.66, 1.73) | 1.02 (0.60, 1.75) |
| (18.6, 24.6] | 39 | 338 | 0.82 (0.54, 1.24) | 0.83 (0.53, 1.32) |
| (24.6, 40] | 30 | 345 | 0.62 (0.39, 0.97) | 0.78 (0.48, 1.27) |
| >40 | 22 | 353 | 0.44 (0.27, 0.73) | 0.45 (0.25, 0.79) |
| HAA5 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 61 | 535 | 1.00 | 1.00 |
| (0, 0.5] | 22 | 154 | 1.25 (0.75, 2.11) | 1.59 (0.92, 2.75) |
| (0.5, 25.5] | 51 | 335 | 1.34 (0.90, 1.98) | 1.37 (0.88, 2.14) |
| (25.5, 58.8] | 33 | 353 | 0.82 (0.53, 1.28) | 0.99 (0.61, 1.62) |
| >58.8 | 29 | 358 | 0.71 (0.45, 1.13) | 0.84 (0.51, 1.40) |
| Weeks 13 to 26 | | | | |
| [0.0, 0] | 59 | 473 | 1.00 | 1.00 |
| (0, 0.7] | 34 | 207 | 1.32 (0.84, 2.07) | 1.15 (0.69, 1.91) |
| (0.7, 31.5] | 46 | 339 | 1.09 (0.72, 1.64) | 0.92 (0.58, 1.46) |
| (31.5, 63.1] | 34 | 352 | 0.77 (0.50, 1.21) | 0.91 (0.56, 1.46) |
| >63.1 | 23 | 364 | 0.51 (0.31, 0.84) | 0.54 (0.32, 0.92) |
| Week 27 until birth | | | | |
| [0.0, 0] | 92 | 629 | 1.00 | 1.00 |
| (0, 0.2] | 3 | 27 | 0.76 (0.23, 2.55) | 1.04 (0.30, 3.64) |
| (0.2, 30] | 36 | 340 | 0.72 (0.48, 1.09) | 0.75 (0.48, 1.19) |
| (30, 65.1] | 32 | 343 | 0.64 (0.42, 0.97) | 0.78 (0.49, 1.24) |
| >65.1 | 22 | 353 | 0.43 (0.26, 0.69) | 0.52 (0.31, 0.87) |

*Adjusted for maternal caffeine intake, income, body mass index (BMI) and live birth history/
**No RFTS study subjects exposed above regulatory cutpoint (>= 60 µg/L)/

**Table 8.11**
**Association between HAA-Br exposure and preterm birth, all RFTS sites**

| HAA-Br Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| HAA-Br water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 1.9] | 37 | 348 | 1.00 | 1.00 |
| (1.9, 8.3] | 54 | 333 | 1.53 (0.98, 2.38) | 1.46 (0.90, 2.37) |
| (8.3, 11.3] | 31 | 356 | 0.82 (0.50, 1.35) | 0.80 (0.46, 1.41) |
| (11.3, 17.1] | 24 | 364 | 0.62 (0.36, 1.06) | 0.69 (0.39, 1.24) |
| >17.1 | 50 | 337 | 1.40 (0.89, 2.19) | 1.35 (0.82, 2.20) |
| Weeks 13 to 26 | | | | |
| [0.0, 1.8] | 35 | 352 | 1.00 | 1.00 |
| (1.8, 8.1] | 57 | 331 | 1.73 (1.11, 2.71) | 1.46 (0.9, 2.37) |
| (8.1, 11.1] | 31 | 355 | 0.88 (0.53, 1.46) | 0.92 (0.54, 1.58) |
| (11.1, 17.1] | 22 | 365 | 0.61 (0.35, 1.05) | 0.53 (0.28, 0.99) |
| >17.1 | 51 | 335 | 1.53 (0.97, 2.41) | 1.4 (0.86, 2.29) |
| Week 27 until birth | | | | |
| [0.0, 1.1] | 40 | 335 | 1.00 | 1.00 |
| (1.1, 7.9] | 45 | 332 | 1.14 (0.72, 1.78) | 0.98 (0.59, 1.61) |
| (7.9, 11] | 25 | 350 | 0.60 (0.36, 1.01) | 0.70 (0.40, 1.22) |
| (11, 16.9] | 23 | 352 | 0.55 (0.32, 0.93) | 0.57 (0.32, 1.01) |
| >16.9 | 52 | 323 | 1.35 (0.87, 2.09) | 1.28 (0.79, 2.08) |
| HAA-Br ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.1] | 40 | 346 | 1.00 | 1.00 |
| (0.1, 3.6] | 38 | 349 | 0.94 (0.59, 1.50) | 0.98 (0.59, 1.62) |
| (3.6, 10] | 46 | 339 | 1.17 (0.75, 1.84) | 1.12 (0.68, 1.84) |
| (10, 21.2] | 28 | 359 | 0.68 (0.41, 1.12) | 0.66 (0.38, 1.16) |
| >21.2 | 44 | 342 | 1.11 (0.71, 1.75) | 1.13 (0.69, 1.86) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.1] | 38 | 348 | 1.00 | 1.00 |
| (0.1, 4.5] | 46 | 340 | 1.24 (0.79, 1.95) | 1.33 (0.81, 2.19) |
| (4.5, 11.1] | 43 | 343 | 1.15 (0.72, 1.82) | 1.14 (0.68, 1.91) |
| (11.1, 23.1] | 34 | 352 | 0.89 (0.54, 1.44) | 0.89 (0.52, 1.53) |
| >23.1 | 35 | 352 | 0.91 (0.56, 1.48) | 0.96 (0.57, 1.62) |
| Week 27 until birth | | | | |
| [0.0, 0] | 57 | 442 | 1.00 | 1.00 |
| (0, 3.7] | 27 | 224 | 0.94 (0.58, 1.52) | 0.92 (0.54, 1.59) |
| (3.7, 11.1] | 36 | 341 | 0.82 (0.53, 1.27) | 0.93 (0.57, 1.50) |
| (11.1, 24.1] | 29 | 345 | 0.65 (0.41, 1.04) | 0.64 (0.38, 1.08) |
| >24.1 | 36 | 340 | 0.82 (0.53, 1.28) | 0.92 (0.57, 1.48) |

*Adjusted for maternal caffeine intake, income, body mass index (BMI) and live birth history.

**Table 8.12**
**Association between TOX exposure and preterm birth, all RFTS sites**

| TOX Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| TOX water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 16.9] | 37 | 331 | 1.00 | 1.00 |
| (16.9, 150.7] | 54 | 352 | 1.37 (0.88, 2.14) | 1.26 (0.78, 2.04) |
| (150.7, 172] | 38 | 347 | 0.98 (0.61, 1.58) | 1.03 (0.61, 1.73) |
| (172, 181.8] | 33 | 355 | 0.83 (0.51, 1.36) | 0.79 (0.46, 1.36) |
| >181.8 | 34 | 353 | 0.86 (0.53, 1.41) | 0.84 (0.49, 1.43) |
| Weeks 13 to 26 | | | | |
| [0.0, 17.7] | 37 | 349 | 1.00 | 1.00 |
| (17.7, 149.1] | 56 | 331 | 1.6o (1.03, 2.48) | 1.56 (0.96, 2.53) |
| (149.1, 173.6] | 31 | 355 | 0.82 (0.50, 1.36) | 0.98 (0.57, 1.68) |
| (173.6, 186.5] | 26 | 363 | 0.68 (0.40, 1.14) | 0.66 (0.37, 1.18) |
| >186.5 | 46 | 340 | 1.28 (0.81, 2.02) | 1.26 (0.76, 2.08) |
| Week 27 until birth | | | | |
| [0.0, 18.7] | 49 | 326 | 1.00 | 1.00 |
| (18.7, 146] | 37 | 338 | 0.73 (0.46, 1.15) | 0.75 (0.45, 1.24) |
| (146, 173.9] | 24 | 353 | 0.45 (0.27, 0.75) | 0.57 (0.33, 1.00) |
| (173.9, 188.1] | 30 | 345 | 0.58 (0.36, 0.93) | 0.60 (0.35, 1.03) |
| >188.1 | 45 | 330 | 0.91 (0.59, 1.40) | 0.99 (0.62, 1.59) |
| TOX ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 14.9] | 39 | 348 | 1.00 | 1.00 |
| (14.9, 41.7] | 42 | 343 | 1.09 (0.69, 1.73) | 1.26 (0.77, 2.09) |
| (41.7, 116.9] | 48 | 339 | 1.26 (0.81, 1.98) | 1.22 (0.74, 2.01) |
| (116.9, 279.1] | 32 | 353 | 0.81 (0.50, 1.32) | 0.92 (0.53, 1.58) |
| >279.1 | 35 | 352 | 0.89 (0.55, 1.43) | 0.93 (0.55, 1.58) |
| Weeks 13 to 26 | | | | |
| [0.0, 21.2] | 47 | 339 | 1.00 | 1.00 |
| (21.2, 51.7] | 43 | 344 | 0.90 (0.58, 1.40) | 0.84 (0.51, 1.36) |
| (51.7, 141.4] | 46 | 340 | 0.98 (0.63, 1.51) | 0.91 (0.56, 1.48) |
| (141.4, 315.8] | 29 | 357 | 0.59 (0.36, 0.95) | 0.65 (0.38, 1.10) |
| >315.8 | 31 | 355 | 0.63 (0.39, 1.02) | 0.69 (0.41, 1.15) |
| Week 27 until birth | | | | |
| [0.0, 19.8] | 50 | 325 | 1.00 | 1.00 |
| (19.8, 50.7] | 36 | 340 | 0.69 (0.44, 1.08) | 0.64 (0.38, 1.07) |
| (50.7, 145.7] | 42 | 334 | 0.82 (0.53, 1.27) | 0.90 (0.56, 1.46) |
| (145.7, 329.3] | 27 | 347 | 0.51 (0.31, 0.83) | 0.59 (0.35, 1.02) |
| >329.3 | 30 | 346 | 0.56 (0.35, 0.91) | 0.63 (0.38, 1.06) |

*Adjusted for maternal caffeine intake, income, body mass index (BMI) and live birth history.

## RESULTS FOR SGA BIRTHS

THM4 concentration in the second and third trimester had a weak positive association with SGA (Table 8.13), with a more apparent association in the third trimester using the regulatory dichotomy of 80 µg/L, for which the adjusted odds ratio was 2.1 (1.1–3.8). With restriction to Sites 1 and 3 and Site 1 alone, the associations were more notable for integrated exposure and for shower/bath exposure than for concentration or ingested amounts (Tables 8.14 and 8.15). BDCM concentration in the second and third trimester was related to increased risk of SGA births, also found less clearly for integrated exposure and shower/bath exposure, but not for ingested amount. (Table 8.16)

Except for isolated inverse associations for Sites 1 and 3 and Site 1 with first trimester exposure and for Site 1 alone for second trimester exposure, the results for HAA9 were consistently null (Tables 8.17–19). Chloroform (Table 8.20) exposure was not associated with SGA births. THM-Br (Table 8.21) exposure showed weak positive associations in relation to concentration in the second and third trimesters, also found for shower/bath and ingested exposure but not ingested amount. HAA5, (Table 8.22), HAA-Br (8.23), and TOX (Table 8.24) were essentially unrelated to SGA births after adjustment for potential confounders.

**Table 8.13**
**Association between THM4 exposure and SGA, all RFTS sites**

| THM4 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| THM4 water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 57.6] | 23 | 429 | 1.00 | 1.00 |
| (57.6, 66.5] | 27 | 448 | 1.12 (0.64, 1.99) | 1.16 (0.63, 2.10) |
| (66.5, 77.2] | 31 | 428 | 1.35 (0.78, 2.36) | 1.40 (0.78, 2.49) |
| >77.2 | 21 | 428 | 0.92 (0.50, 1.68) | 0.87 (0.46, 1.65) |
| Weeks 13 to 26 | | | | |
| [0.0, 58.1] | 24 | 442 | 1.00 | 1.00 |
| (58.1, 66.8] | 23 | 434 | 0.98 (0.54, 1.76) | 0.92 (0.5, 1.7) |
| (66.8, 77] | 20 | 443 | 0.83 (0.45, 1.53) | 0.89 (0.48, 1.66) |
| >77 | 35 | 414 | 1.56 (0.91, 2.66) | 1.46 (0.83, 2.58) |
| Week 27 until birth | | | | |
| [0.0, 56.4] | 22 | 429 | 1.00 | 1.00 |
| (56.4, 64.5] | 26 | 410 | 1.24 (0.69, 2.22) | 1.35 (0.73, 2.49) |
| (64.5, 74.6] | 23 | 418 | 1.07 (0.59, 1.96) | 1.00 (0.52, 1.92) |
| >74.6 | 27 | 424 | 1.24 (0.70, 2.22) | 1.39 (0.76, 2.54) |
| THM4 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 15.2] | 27 | 433 | 1.00 | 1.00 |
| (15.2, 61.9] | 24 | 439 | 0.88 (0.50, 1.54) | 0.79 (0.44, 1.44) |
| (61.9, 118] | 24 | 437 | 0.88 (0.50, 1.55) | 0.84 (0.46, 1.53) |
| >118 | 27 | 421 | 1.03 (0.59, 1.78) | 0.99 (0.56, 1.76) |
| Weeks 13 to 26 | | | | |
| [0.0, 12.7] | 30 | 434 | 1.00 | 1.00 |
| (12.7, 34.3] | 18 | 439 | 0.59 (0.33, 1.08) | 0.57 (0.31, 1.07) |
| (34.3, 68.3] | 28 | 428 | 0.95 (0.56, 1.61) | 0.94 (0.53, 1.65) |
| >68.3 | 26 | 429 | 0.88 (0.51, 1.51) | 0.82 (0.46, 1.45) |
| Week 27 until birth | | | | |
| [0.0, 16.4] | 30 | 414 | 1.00 | 1.00 |
| (16.4, 63.5] | 18 | 428 | 0.58 (0.32, 1.06) | 0.56 (0.30, 1.04) |
| (63.5, 127.1] | 24 | 419 | 0.79 (0.45, 1.38) | 0.76 (0.42, 1.37) |
| >127.1 | 26 | 420 | 0.85 (0.50, 1.47) | 0.86 (0.49, 1.51) |
| THM4 total integrated exposure (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 1.1] | 22 | 436 | 1.00 | 1.00 |
| (1.1, 1.6] | 23 | 440 | 1.04 (0.57, 1.89) | 0.96 (0.51, 1.8) |
| (1.6, 2.4] | 25 | 427 | 1.16 (0.64, 2.09) | 1.18 (0.63, 2.19) |
| >2.4 | 31 | 424 | 1.45 (00.83, 2.54) | 1.22 (0.68, 2.2) |

(continued)

**Table 8.13 (continued)**

| THM4 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| Weeks 13 to 26 | | | | |
| [0.0, 0.5] | 21 | 438 | 1.00 | 1.00 |
| (0.5, 0.8] | 21 | 442 | 0.99 (0.53, 1.84) | 1.06 (0.56, 2.00) |
| (0.8, 1.2] | 27 | 429 | 1.31 (0.73, 2.36) | 1.30 (0.70, 2.41) |
| >1.2 | 32 | 418 | 1.60 (0.91, 2.81) | 1.28 (0.70, 2.33) |
| Week 27 until birth | | | | |
| [0.0, 1] | 25 | 421 | 1.00 | 1.00 |
| (1, 1.5] | 25 | 421 | 1.00 (0.57, 1.77) | 0.95 (0.51, 1.76) |
| (1.5, 2.2] | 20 | 427 | 0.79 (0.43, 1.44) | 0.96 (0.51, 1.82) |
| >2.2 | 28 | 412 | 1.15 (0.66, 2.00) | 1.15 (0.64, 2.05) |
| THM4 shower/bath (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.9] | 22 | 437 | 1.00 | 1.00 |
| (0.9, 1.3] | 22 | 441 | 0.99 (0.54, 1.82) | 0.96 (0.51, 1.81) |
| (1.3, 2] | 26 | 430 | 1.20 (0.67, 2.15) | 1.17 (0.63, 2.18) |
| >2 | 31 | 422 | 1.46 (0.83, 2.56) | 1.20 (0.67, 2.17) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.4] | 20 | 442 | 1.00 | 1.00 |
| (0.4, 0.6] | 22 | 439 | 1.11 (0.60, 2.06) | 1.18 (0.62, 2.23) |
| (0.6, 1.1] | 24 | 431 | 1.23 (0.67, 2.26) | 1.25 (0.66, 2.38) |
| >1.1 | 35 | 418 | 1.85 (1.05, 3.26) | 1.45 (0.79, 2.66) |
| Week 27 until birth | | | | |
| [0.0, 0.8] | 24 | 422 | 1.00 | 1.00 |
| (0.8, 1.1] | 24 | 424 | 1.00 (0.56, 1.78) | 1.04 (0.56, 1.96) |
| (1.1, 1.8] | 22 | 422 | 0.92 (0.51, 1.66) | 1.17 (0.62, 2.19) |
| >1.8 | 28 | 413 | 1.19 (0.68, 2.09) | 1.24 (0.69, 2.23) |
| THM4 regulatory cutpoint | | | | |
| Weeks 0 to 12 | | | | |
| <80 µg/L | 94 | 1507 | 1.00 | 1.00 |
| >=80 µg/L | 8 | 226 | 0.57 (0.27, 1.18) | 0.54 (0.25, 1.20) |
| Weeks 13 to 26 | | | | |
| <80 µg/L | 89 | 1567 | 1.00 | 1.00 |
| >=80 µg/L | 13 | 166 | 1.38 (0.75, 2.52) | 1.31 (0.69, 2.51) |
| Week 27 until birth | | | | |
| <80 µg/L | 84 | 1544 | 1.00 | 1.00 |
| >=80 µg/L | 14 | 137 | 1.88 (1.04, 3.40) | 2.07 (1.12, 3.82) |

*Adjusted for maternal race, education, smoking, body mass index (BMI) and live birth history.

**Table 8.14**
**Association between THM4 exposure and SGA, all RFTS Sites 1 and 3 only**

| THM4 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| THM4 water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 59.1] | 25 | 367 | 1.00 | 1.00 |
| (59.1, 74.4] | 26 | 363 | 1.05 (0.6, 1.86) | 1.01 (0.55, 1.84) |
| >74.4 | 16 | 368 | 0.64 (0.34, 1.22) | 0.58 (0.3, 1.15) |
| Weeks 13 to 26 | | | | |
| [0.0, 60.3] | 19 | 374 | 1.00 | 1.00 |
| (60.3, 74] | 20 | 368 | 1.07 (0.56, 2.04) | 1.18 (0.61, 2.29) |
| >74 | 28 | 356 | 1.55 (0.85, 2.82) | 1.37 (0.72, 2.6) |
| Week 27 until birth | | | | |
| [0.0, 60] | 25 | 346 | 1.00 | 1.00 |
| (60, 73.5] | 17 | 361 | 0.65 (0.35, 1.23) | 0.52 (0.26, 1.05) |
| >73.5 | 23 | 362 | 0.88 (0.49, 1.58) | 0.91 (0.5, 1.68) |
| THM4 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 21] | 22 | 366 | 1.00 | 1.00 |
| (21, 87.4] | 22 | 374 | 0.98 (0.53, 1.8) | 1 (0.53, 1.91) |
| >87.4 | 23 | 358 | 1.07 (0.59, 1.95) | 1.07 (0.56, 2.02) |
| Weeks 13 to 26 | | | | |
| [0.0, 17.1] | 22 | 368 | 1.00 | 1.00 |
| (17.1, 56.5] | 21 | 365 | 0.96 (0.52, 1.78) | 0.95 (0.49, 1.82) |
| >56.5 | 24 | 365 | 1.1 (0.61, 2) | 1 (0.53, 1.89) |
| Week 27 until birth | | | | |
| [0.0, 26.9] | 26 | 351 | 1.00 | 1.00 |
| (26.9, 97.9] | 17 | 361 | 0.64 (0.34, 1.19) | 0.57 (0.29, 1.13) |
| >97.9 | 22 | 357 | 0.83 (0.46, 1.5) | 0.9 (0.49, 1.65) |
| THM4 total integrated exposure (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 1.3] | 15 | 377 | 1.00 | 1.00 |
| (1.3, 2.2] | 22 | 358 | 1.55 (0.79, 3.02) | 1.57 (0.76, 3.24) |
| >2.2 | 29 | 362 | 2.01 (1.06, 3.82) | 1.76 (0.86, 3.61) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.7] | 13 | 380 | 1.00 | 1.00 |
| (0.7, 1.3] | 23 | 365 | 1.84 (0.92, 3.69) | 1.74 (0.84, 3.62) |
| >1.3 | 30 | 352 | 2.49 (1.28, 4.85) | 1.84 (0.86, 3.95) |
| Week 27 until birth | | | | |
| [0.0, 1.2] | 26 | 349 | 1.00 | 1.00 |
| (1.2, 2] | 13 | 368 | 0.47 (0.24, 0.94) | 0.59 (0.29, 1.2) |
| >2 | 26 | 352 | 0.99 (0.56, 1.74) | 1.03 (0.55, 1.92) |

(continued)

**Table 8.14 (continued)**

| THM4 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| THM4 shower/bath (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 1.1] | 14 | 375 | 1.00 | 1.00 |
| (1.1, 1.9] | 23 | 364 | 1.69 (0.86, 3.34) | 1.75 (0.84, 3.66) |
| >1.9 | 29 | 358 | 2.17 (1.13, 4.17) | 1.87 (0.89, 3.96) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.6] | 13 | 380 | 1.00 | 1.00 |
| (0.6, 1.2] | 23 | 362 | 1.86 (0.93, 3.72) | 1.69 (0.81, 3.52) |
| >1.2 | 30 | 355 | 2.47 (1.27, 4.81) | 1.87 (0.87, 4.01) |
| Week 27 until birth | | | | |
| [0.0, 1] | 20 | 357 | 1.00 | 1.00 |
| (1, 1.7] | 18 | 364 | 0.88 (0.46, 1.7) | 1.22 (0.6, 2.46) |
| >1.7 | 27 | 348 | 1.39 (0.76, 2.52) | 1.51 (0.77, 2.96) |
| THM4 regulatory cutpoint | | | | |
| Weeks 0 to 12 | | | | |
| <80 µg/L | 59 | 872 | 1.00 | 1.00 |
| >=80 µg/L | 8 | 226 | 0.52 (0.25, 1.11) | 0.49 (0.22, 1.11) |
| Weeks 13 to 26 | | | | |
| <80 µg/L | 54 | 932 | 1.00 | 1.00 |
| >=80 µg/L | 13 | 166 | 1.35 (0.72, 2.53) | 1.23 (0.62, 2.41) |
| Week 27 until birth | | | | |
| <80 µg/L | 51 | 932 | 1.00 | 1.00 |
| >=80 µg/L | 14 | 137 | 1.87 (1.01, 3.46) | 2.07 (1.09, 3.91) |

*Adjusted for maternal race, education, smoking, body mass index (BMI) and live birth history.

**Table 8.15**
**Association between THM4 exposure and SGA, Site 1 only**

| THM4 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| THM4 water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 4.5] | 16 | 271 | 1.00 | 1.00 |
| (4.5, 65.4] | 17 | 269 | 1.07 (0.53, 2.16) | 1.06 (0.50, 2.25) |
| >65.4 | 6 | 280 | 0.36 (0.14, 0.94) | 0.39 (0.15, 1.04) |
| Weeks 13 to 26 | | | | |
| [0.0, 4.3] | 11 | 279 | 1.00 | 1.00 |
| (4.3, 66.3] | 12 | 273 | 1.07 (0.53, 2.16) | 1.11 (0.47, 2.60) |
| >66.3 | 16 | 268 | 0.36 (0.14, 0.94) | 1.30 (0.57, 2.96) |
| Week 27 until birth | | | | |
| [0.0, 4.6] | 14 | 260 | 1.00 | 1.00 |
| (4.6, 65.2] | 9 | 271 | 0.62 (0.26, 1.45) | 0.53 (0.21, 1.33) |
| >65.2 | 15 | 268 | 1.04 (0.49, 2.20) | 0.99 (0.45, 2.14) |
| THM4 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 3.5] | 13 | 272 | 1.00 | 1.00 |
| (3.5, 47.2] | 14 | 276 | 1.06 (0.49, 2.30) | 0.91 (0.40, 2.04) |
| >47.2 | 12 | 272 | 0.92 (0.41, 2.06) | 0.93 (0.41, 2.11) |
| Weeks 13 to 26 | | | | |
| [0.0, 5] | 13 | 273 | 1.00 | 1.00 |
| (5, 32.2] | 14 | 274 | 1.07 (0.50, 2.33) | 0.93 (0.41, 2.10) |
| >32.2 | 12 | 273 | 0.92 (0.41, 2.06) | 0.84 (0.37, 1.91) |
| Week 27 until birth | | | | |
| [0.0, 4.7] | 14 | 265 | 1.00 | 1.00 |
| (4.7, 56.4] | 12 | 266 | 0.85 (0.39, 1.88) | 0.62 (0.26, 1.47) |
| >56.4 | 12 | 268 | 0.85 (0.39, 1.87) | 0.85 (0.38, 1.90) |
| THM4 total integrated exposure (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.2] | 9 | 282 | 1.00 | 1.00 |
| (0.2, 1.6] | 16 | 264 | 1.90 (0.83, 4.37) | 1.96 (0.81, 4.75) |
| >1.6 | 14 | 273 | 1.61 (0.68, 3.77) | 1.44 (0.56, 3.72) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.2] | 8 | 282 | 1.00 | 1.00 |
| (0.2, 0.9] | 17 | 269 | 2.23 (0.95, 5.25) | 1.9 (0.79, 4.59) |
| >0.9 | 14 | 268 | 1.84 (0.76, 4.46) | 1.36 (0.52, 3.56) |
| Week 27 until birth | | | | |
| [0.0, 0.2] | 14 | 263 | 1.00 | 1.00 |
| (0.2, 1.5] | 10 | 272 | 0.69 (0.3, 1.58) | 0.68 (0.28, 1.63) |
| >1.5 | 14 | 264 | 1.00 (0.47, 2.13) | 1.04 (0.46, 2.34) |

(continued)

**Table 8.15 (continued)**

| THM4 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| THM4 shower/bath (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.2] | 8 | 282 | 1.00 | 1.00 |
| (0.2, 1.4] | 18 | 266 | 2.39 (1.02, 5.58) | 2.56 (1.03, 6.35) |
| >1.4 | 13 | 271 | 1.69 (0.69, 4.14) | 1.50 (0.55, 4.13) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.2] | 9 | 280 | 1.00 | 1.00 |
| (0.2, 0.8] | 16 | 274 | 1.82 (0.79, 4.18) | 1.54 (0.65, 3.65) |
| >0.8 | 14 | 265 | 1.64 (0.70, 3.86) | 1.23 (0.48, 3.16) |
| Week 27 until birth | | | | |
| [0.0, 0.1] | 13 | 266 | 1.00 | 1.00 |
| (0.1, 1.2] | 11 | 271 | 0.83 (0.37, 1.89) | 0.91 (0.38, 2.15) |
| >1.2 | 14 | 262 | 1.09 (0.50, 2.37) | 1.11 (0.48, 2.56) |
| THM4 regulatory cutpoint | | | | |
| Weeks 0 to 12 | | | | |
| <80 µg/L | 35 | 645 | 1.00 | 1.00 |
| >=80 µg/L | 4 | 175 | 0.42 (0.15, 1.20) | 0.47 (0.16, 1.36) |
| Weeks 13 to 26 | | | | |
| <80 µg/L | 31 | 681 | 1.00 | 1.00 |
| >=80 µg/L | 8 | 139 | 1.26 (0.57, 2.81) | 1.12 (0.47, 2.68) |
| Week 27 until birth | | | | |
| <80 µg/L | 29 | 709 | 1.00 | 1.00 |
| >=80 µg/L | 9 | 90 | 2.45 (1.12, 5.33) | 2.45 (1.09, 5.50) |

*Adjusted for maternal race, education, smoking, body mass index (BMI) and live birth history

**Table 8.16**
**Association between $CHBrCl_2$ exposure and SGA, all RFTS sites**

| $CHBrCl_2$ Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| $CHBrCl_2$ water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 1.2] | 31 | 437 | 1.00 | 1.00 |
| (1.2, 12.5] | 14 | 437 | 0.45 (0.24, 0.86) | 0.51 (0.26, 0.99) |
| (12.5, 16.9] | 24 | 433 | 0.78 (0.45, 1.35) | 0.89 (0.50, 1.59) |
| >16.9 | 33 | 426 | 1.09 (0.66, 1.82) | 1.04 (0.60, 1.8) |
| Weeks 13 to 26 | | | | |
| [0.0, 1.1] | 21 | 443 | 1.00 | 1.00 |
| (1.1, 12.3] | 22 | 439 | 1.06 (0.57, 1.95) | 1.09 (0.58, 2.06) |
| (12.3, 18.2] | 21 | 430 | 1.03 (0.56, 1.91) | 1.25 (0.66, 2.36) |
| >18.2 | 38 | 421 | 1.90 (1.10, 3.30) | 1.71 (0.95, 3.08) |
| Week 27 until birth | | | | |
| [0.0, 1.2] | 22 | 424 | 1.00 | 1.00 |
| (1.2, 11.5] | 20 | 429 | 0.90 (0.48, 1.67) | 1.06 (0.55, 2.02) |
| (11.5, 17.7] | 19 | 416 | 0.88 (0.47, 1.65) | 1.07 (0.56, 2.07) |
| >17.7 | 37 | 412 | 1.73 (1.00, 2.98) | 1.63 (0.90, 2.96) |
| $CHBrCl_2$ ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.5] | 27 | 433 | 1.00 | 1.00 |
| (0.5, 3.1] | 24 | 435 | 0.89 (0.50, 1.56) | 0.82 (0.45, 1.48) |
| (3.1, 17.9] | 23 | 442 | 0.84 (0.47, 1.48) | 0.79 (0.43, 1.45) |
| >17.9 | 28 | 420 | 1.07 (0.62, 1.85) | 1.04 (0.59, 1.83) |
| Weeks 13 to 26 | | | | |
| [0.0, 1] | 27 | 436 | 1.00 | 1.00 |
| (1, 3.9] | 22 | 436 | 0.82 (0.46, 1.45) | 0.8 (0.44, 1.47) |
| (3.9, 20.4] | 28 | 426 | 1.06 (0.62, 1.83) | 1.06 (0.59, 1.9) |
| >20.4 | 25 | 432 | 0.93 (0.53, 1.64) | 0.9 (0.50, 1.61) |
| Week 27 until birth | | | | |
| [0.0, 0.9] | 29 | 415 | 1.00 | 1.00 |
| (0.9, 3.8] | 22 | 424 | 0.74 (0.42, 1.31) | 0.70 (0.38, 1.28) |
| (3.8, 19.8] | 20 | 423 | 0.68 (0.38, 1.22) | 0.68 (0.37, 1.26) |
| >19.8 | 27 | 419 | 0.92 (0.54, 1.59) | 0.91 (0.51, 1.60) |
| $CHBrCl_2$ total integrated exposure (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 22 | 435 | 1.00 | 1.00 |
| (0, 0.2] | 20 | 446 | 0.89 (0.48, 1.65) | 0.92 (0.49, 1.73) |
| (0.2, 0.4] | 29 | 421 | 1.36 (0.77, 2.41) | 1.34 (0.73, 2.46) |
| >0.4 | 30 | 425 | 1.40 (0.79, 2.46) | 1.11 (0.61, 2.02) |

(continued)

**Table 8.16 (continued)**

| $CHBrCl_2$ Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| Weeks 13 to 26 | | | | |
| [0.0, 0] | 21 | 440 | 1.00 | 1.00 |
| (0, 0.2] | 23 | 436 | 1.11 (0.60, 2.03) | 1.14 (0.61, 2.15) |
| (0.2, 0.4] | 24 | 432 | 1.16 (0.64, 2.12) | 1.15 (0.61, 2.18) |
| >0.4 | 33 | 419 | 1.65 (0.94, 2.90) | 1.35 (0.74, 2.46) |
| Week 27 until birth | | | | |
| [0.0, 0] | 23 | 423 | 1.00 | 1.00 |
| (0, 0.2] | 25 | 426 | 1.08 (0.60, 1.93) | 1.15 (0.62, 2.14) |
| (0.2, 0.4] | 20 | 418 | 0.88 (0.48, 1.63) | 1.05 (0.54, 2.02) |
| >0.4 | 30 | 414 | 1.33 (0.76, 2.33) | 1.35 (0.75, 2.43) |
| $CHBrCl_2$ shower/bath (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 22 | 437 | 1.00 | 1.00 |
| (0, 0.2] | 20 | 445 | 0.89 (0.48, 1.66) | 0.91 (0.48, 1.72) |
| (0.2, 0.4] | 29 | 424 | 1.36 (0.77, 2.40) | 1.36 (0.74, 2.49) |
| >0.4 | 30 | 424 | 1.41 (0.80, 2.48) | 1.10 (0.60, 2.00) |
| Weeks 13 to 26 | | | | |
| [0.0, 0] | 21 | 439 | 1.00 | 1.00 |
| (0, 0.2] | 21 | 439 | 1.00 (0.54, 1.86) | 1.05 (0.55, 2.00) |
| (0.2, 0.4] | 25 | 432 | 1.21 (0.67, 2.19) | 1.22 (0.65, 2.29) |
| >0.4 | 34 | 420 | 1.69 (0.97, 2.96) | 1.40 (0.77, 2.53) |
| Week 27 until birth | | | | |
| [0.0, 0] | 23 | 423 | 1.00 | 1.00 |
| (0, 0.2] | 24 | 427 | 1.03 (0.57, 1.86) | 1.13 (0.60, 2.12) |
| (0.2, 0.3] | 18 | 419 | 0.79 (0.42, 1.49) | 0.94 (0.47, 1.85) |
| >0.3 | 33 | 412 | 1.47 (0.85, 2.55) | 1.52 (0.85, 2.72) |

**Table 8.17**
**Association between HAA9 exposure and SGA, all RFTS sites**

| HAA9 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| HAA9 water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 2.4] | 22 | 441 | 1.00 | 1.00 |
| (2.4, 39.9] | 30 | 428 | 1.41 (0.80, 2.48) | 1.59 (0.88, 2.89) |
| (39.9, 50.2] | 32 | 428 | 1.50 (0.86, 2.62) | 1.59 (0.87, 2.89) |
| >50.2 | 18 | 436 | 0.83 (0.44, 1.56) | 0.89 (0.45, 1.76) |
| Weeks 13 to 26 | | | | |
| [0.0, 2.7] | 28 | 438 | 1.00 | 1.00 |
| (2.7, 40.8] | 18 | 438 | 0.64 (0.35, 1.18) | 0.77 (0.41, 1.44) |
| (40.8, 50.9] | 38 | 427 | 1.39 (0.84, 2.31) | 1.33 (0.77, 2.29) |
| >50.9 | 18 | 430 | 0.66 (0.36, 1.20) | 0.75 (0.40, 1.42) |
| Week 27 until birth | | | | |
| [0.0, 2.2] | 27 | 422 | 1.00 | 1.00 |
| (2.2, 40.1] | 20 | 421 | 0.74 (0.41, 1.35) | 0.89 (0.48, 1.65) |
| (40.1, 50.7] | 29 | 417 | 1.09 (0.63, 1.87) | 0.94 (0.52, 1.71) |
| >50.7 | 22 | 421 | 0.82 (0.46, 1.46) | 0.97 (0.53, 1.77) |
| HAA9 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.9] | 30 | 432 | 1.00 | 1.00 |
| (0.9, 16.3] | 19 | 441 | 0.62 (0.34, 1.12) | 0.69 (0.37, 1.27) |
| (16.3, 68.2] | 31 | 427 | 1.05 (0.62, 1.76) | 1.24 (0.71, 2.16) |
| >68.2 | 22 | 430 | 0.74 (0.42, 1.30) | 0.80 (0.44, 1.45) |
| Weeks 13 to 26 | | | | |
| [0.0, 1.3] | 29 | 436 | 1.00 | 1.00 |
| (1.3, 20.7] | 22 | 433 | 0.76 (0.43, 1.35) | 0.80 (0.44, 1.46) |
| (20.7, 74.7] | 24 | 434 | 0.83 (0.48, 1.45) | 0.91 (0.50, 1.66) |
| >74.7 | 27 | 427 | 0.95 (0.55, 1.63) | 1.10 (0.63, 1.94) |
| Week 27 until birth | | | | |
| [0.0, 0] | 33 | 441 | 1.00 | 1.00 |
| (0, 20.3] | 20 | 399 | 0.67 (0.38, 1.19) | 0.67 (0.36, 1.22) |
| (20.3, 77] | 21 | 422 | 0.67 (0.38, 1.17) | 0.70 (0.39, 1.28) |
| >77 | 24 | 419 | 0.77 (0.45, 1.32) | 0.87 (0.50, 1.54) |

*Adjusted for maternal race, education, smoking, body mass index (BMI) and live birth history.

**Table 8.18**
**Association between HAA9 exposure and SGA, all RFTS Sites 1 and 3 only**

| HAA9 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| HAA9 water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 42.9] | 25 | 361 | 1.00 | 1.00 |
| (42.9, 51.4] | 29 | 364 | 1.15 (0.66, 2.00) | 1.03 (0.57, 1.86) |
| >51.4 | 13 | 373 | 0.50 (0.25, 1.00) | 0.45 (0.21, 0.93) |
| Weeks 13 to 26 | | | | |
| [0.0, 44.3] | 25 | 363 | 1.00 | 1.00 |
| (44.3, 51.5] | 25 | 368 | 0.99 (0.56, 1.75) | 0.80 (0.43, 1.49) |
| >51.5 | 17 | 367 | 0.67 (0.36, 1.27) | 0.69 (0.36, 1.34) |
| Week 27 until birth | | | | |
| [0.0, 43.9] | 21 | 351 | 1.00 | 1.00 |
| (43.9, 52] | 24 | 361 | 1.11 (0.61, 2.03) | 0.85 (0.44, 1.62) |
| >52 | 20 | 357 | 0.94 (0.50, 1.76) | 1.02 (0.53, 1.94) |
| HAA9 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 29.6] | 23 | 366 | 1.00 | 1.00 |
| (29.6, 7] | 26 | 363 | 1.14 (0.64, 2.04) | 1.41 (0.76, 2.64) |
| >79.5 | 18 | 369 | 0.78 (0.41, 1.46) | 0.78 (0.39, 1.54) |
| Weeks 13 to 26 | | | | |
| [0.0, 36.7] | 29 | 355 | 1.00 | 1.00 |
| (36.7, 86.2] | 14 | 380 | 0.45 (0.23, 0.87) | 0.40 (0.20, 0.82) |
| >86.2 | 24 | 363 | 0.81 (0.46, 1.42) | 0.84 (0.47, 1.52) |
| Week 27 until birth | | | | |
| [0.0, 35.6] | 25 | 352 | 1.00 | 1.00 |
| (35.6, 87.8] | 18 | 360 | 0.70 (0.38, 1.31) | 0.69 (0.35, 1.35) |
| >87.8 | 22 | 357 | 0.87 (0.48, 1.57) | 0.98 (0.53, 1.81) |

*Adjusted for maternal race, education, smoking, body mass index (BMI) and live birth history.

**Table 8.19**
**Association between HAA9 exposure and SGA, RFTS Sites 1 only**

| HAA9 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| HAA9 water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 3.7] | 20 | 266 | 1.00 | 1.00 |
| (3.7, 45.8] | 13 | 270 | 0.64 (0.31, 1.31) | 0.68 (0.32, 1.44) |
| >45.8 | 6 | 284 | 0.28 (0.11, 0.71) | 0.31 (0.12, 0.80) |
| Weeks 13 to 26 | | | | |
| [0.0, 3.6] | 13 | 274 | 1.00 | 1.00 |
| (3.6, 47.6] | 11 | 276 | 0.84 (0.37, 1.91) | 0.69 (0.29, 1.64) |
| >47.6 | 15 | 270 | 1.17 (0.55, 2.51) | 1.08 (0.49, 2.37) |
| Week 27 until birth | | | | |
| [0.0, 3.8] | 13 | 260 | 1.00 | 1.00 |
| (3.8, 46.6] | 12 | 272 | 0.88 (0.40, 1.97) | 0.77 (0.33, 1.80) |
| >46.6 | 13 | 267 | 0.97 (0.44, 2.14) | 1.00 (0.45, 2.26) |
| HAA9 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 2.7] | 15 | 272 | 1.00 | 1.00 |
| (2.7, 5] | 15 | 271 | 1.00 (0.48, 2.09) | 1.05 (0.48, 2.27) |
| >50.3 | 9 | 277 | 0.59 (0.25, 1.37) | 0.60 (0.25, 1.45) |
| Weeks 13 to 26 | | | | |
| [0.0, 3.7] | 18 | 266 | 1.00 | 1.00 |
| (3.7, 56.4] | 11 | 277 | 0.59 (0.27, 1.27) | 0.57 (0.26, 1.28) |
| >56.4 | 10 | 277 | 0.53 (0.24, 1.18) | 0.48 (0.21, 1.10) |
| Week 27 until birth | | | | |
| [0.0, 2.4] | 13 | 264 | 1.00 | 1.00 |
| (2.4, 56] | 14 | 267 | 1.07 (0.49, 2.31) | 1.00 (0.44, 2.28) |
| >56 | 11 | 268 | 0.83 (0.37, 1.89) | 0.82 (0.35, 1.92) |

*Adjusted for maternal race, education, smoking, body mass index (BMI) and live birth history.

**Table 8.20**
**Association between $CHCl_3$ exposure and SGA, all RFTS sites**

| $CHCl_3$ Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| CHCl3 water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.2] | 26 | 440 | 1.00 | 1.00 |
| (0.2, 17.3] | 32 | 429 | 1.26 (0.74, 2.15) | 1.11 (0.63, 1.96) |
| (17.3, 47.8] | 26 | 432 | 1.02 (0.58, 1.78) | 1.00 (0.55, 1.80) |
| >47.8 | 18 | 432 | 0.71 (0.38, 1.31) | 0.84 (0.45, 1.59) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.2] | 26 | 439 | 1.00 | 1.00 |
| (0.2, 18.1] | 32 | 429 | 1.26 (0.74, 2.15) | 1.09 (0.62, 1.93) |
| (18.1, 47.4] | 21 | 439 | 0.81 (0.45, 1.46) | 0.84 (0.45, 1.56) |
| >47.4 | 23 | 426 | 0.91 (0.51, 1.62) | 0.96 (0.53, 1.75) |
| Week 27 until birth | | | | |
| [0.0, 0.2] | 22 | 429 | 1.00 | 1.00 |
| (0.2, 19.2] | 33 | 412 | 1.56 (0.90, 2.72) | 1.45 (0.79, 2.64) |
| (19.2, 47.1] | 24 | 415 | 1.13 (0.62, 2.04) | 1.33 (0.71, 2.49) |
| >47.1 | 19 | 425 | 0.87 (0.47, 1.63) | 1.05 (0.54, 2.01) |
| CHCl3 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 23 | 436 | 1.00 | 1.00 |
| (0, 1.2] | 29 | 435 | 1.26 (0.72, 2.22) | 1.19 (0.66, 2.14) |
| (1.2, 42.2] | 28 | 430 | 1.23 (0.70, 2.18) | 1.09 (0.60, 2.00) |
| >42.2 | 22 | 429 | 0.97 (0.53, 1.77) | 1.03 (0.56, 1.92) |
| Weeks 13 to 26 | | | | |
| [0.0, 0] | 27 | 438 | 1.00 | 1.00 |
| (0, 1] | 23 | 438 | 0.85 (0.48, 1.51) | 0.73 (0.40, 1.33) |
| (1, 13.4] | 25 | 435 | 0.93 (0.53, 1.63) | 0.85 (0.47, 1.53) |
| >13.4 | 27 | 419 | 1.05 (0.60, 1.81) | 0.97 (0.54, 1.72) |
| Week 27 until birth | | | | |
| [0.0, 0] | 28 | 414 | 1.00 | 1.00 |
| (0, 1.6] | 19 | 432 | 0.65 (0.36, 1.18) | 0.67 (0.36, 1.25) |
| (1.6, 45.2] | 29 | 414 | 1.04 (0.61, 1.77) | 1.03 (0.58, 1.83) |
| >45.2 | 22 | 421 | 0.77 (0.44, 1.37) | 0.86 (0.47, 1.56) |
| CHCl3 total integrated exposure (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 26 | 435 | 1.00 | 1.00 |
| (0, 0.5] | 25 | 437 | 0.96 (0.54, 1.68) | 0.85 (0.46, 1.55) |
| (0.5, 1.2] | 25 | 428 | 0.98 (0.56, 1.72) | 1.02 (0.56, 1.84) |
| >1.2 | 25 | 427 | 0.98 (0.56, 1.72) | 0.99 (0.55, 1.76) |

(continued)

**Table 8.20 (continued)**

| $CHCl_3$ Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| Weeks 13 to 26 | | | | |
| [0.0, 0] | 24 | 442 | 1.00 | 1.00 |
| (0, 0.1] | 24 | 434 | 1.02 (0.57, 1.82) | 1.04 (0.57, 1.89) |
| (0.1, 0.4] | 26 | 436 | 1.10 (0.62, 1.94) | 0.98 (0.53, 1.80) |
| >0.4 | 27 | 415 | 1.20 (0.68, 2.11) | 1.15 (0.64, 2.07) |
| Week 27 until birth | | | | |
| [0.0, 0] | 24 | 426 | 1.00 | 1.00 |
| (0, 0.5] | 28 | 418 | 1.19 (0.68, 2.09) | 1.16 (0.63, 2.14) |
| (0.5, 1.2] | 23 | 419 | 0.97 (0.54, 1.75) | 1.26 (0.68, 2.33) |
| >1.2 | 23 | 418 | 0.98 (0.54, 1.76) | 1.14 (0.62, 2.09) |
| CHCl3 shower/bath (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 25 | 438 | 1.00 | 1.00 |
| (0, 0.4] | 25 | 438 | 1.00 (0.57, 1.77) | 0.89 (0.48, 1.63) |
| (0.4, 1] | 26 | 430 | 1.06 (0.60, 1.86) | 1.10 (0.61, 1.98) |
| >1 | 25 | 424 | 1.03 (0.58, 1.83) | 1.02 (0.57, 1.84) |
| Weeks 13 to 26 | | | | |
| [0.0, 0] | 24 | 443 | 1.00 | 1.00 |
| (0, 0.1] | 25 | 434 | 1.06 (0.60, 1.89) | 1.04 (0.57, 1.89) |
| (0.1, 0.3] | 24 | 436 | 1.02 (0.57, 1.82) | 0.98 (0.53, 1.81) |
| >0.3 | 28 | 417 | 1.24 (0.71, 2.17) | 1.13 (0.63, 2.03) |
| Week 27 until birth | | | | |
| [0.0, 0] | 25 | 425 | 1.00 | 1.00 |
| (0, 0.4] | 28 | 418 | 1.14 (0.65, 1.99) | 1.33 (0.72, 2.44) |
| (0.4, 0.8] | 21 | 421 | 0.85 (0.47, 1.54) | 1.21 (0.64, 2.29) |
| >0.8 | 24 | 417 | 0.98 (0.55, 1.74) | 1.21 (0.66, 2.22) |

*Adjusted for maternal race, education, smoking, body mass index (BMI) and live birth history.

**Table 8.21**
**Association between THM-Br exposure and SGA, all RFTS sites**

| THM-Br Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| THM-Br water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 3.3] | 26 | 436 | 1.00 | 1.00 |
| (3.3, 16.3] | 22 | 435 | 0.85 (0.47, 1.52) | 0.98 (0.54, 1.79) |
| (16.3, 25.9] | 22 | 434 | 0.85 (0.47, 1.52) | 1.00 (0.54, 1.86) |
| >25.9 | 32 | 428 | 1.25 (0.74, 2.14) | 1.17 (0.65, 2.09) |
| Weeks 13 to 26 | | | | |
| [0.0, 3.3] | 22 | 443 | 1.00 | 1.00 |
| (3.3, 15.5] | 20 | 440 | 0.92 (0.49, 1.70) | 0.94 (0.49, 1.78) |
| (15.5, 26.8] | 25 | 426 | 1.18 (0.66, 2.13) | 1.43 (0.78, 2.63) |
| >26.8 | 35 | 424 | 1.66 (0.96, 2.88) | 1.43 (0.79, 2.59) |
| Week 27 until birth | | | | |
| [0.0, 3.6] | 23 | 425 | 1.00 | 1.00 |
| (3.6, 14.2] | 18 | 431 | 0.77 (0.41, 1.45) | 0.86 (0.45, 1.66) |
| (14.2, 25.4] | 19 | 416 | 0.84 (0.45, 1.57) | 1.03 (0.54, 1.97) |
| >25.4 | 38 | 409 | 1.72 (1.01, 2.93) | 1.58 (0.88, 2.83) |
| THM-Br ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 1.5] | 27 | 433 | 1.00 | 1.00 |
| (1.5, 7] | 25 | 432 | 0.93 (0.53, 1.63) | 0.88 (0.49, 1.58) |
| (7, 25.9] | 24 | 438 | 0.88 (0.50, 1.55) | 0.84 (0.46, 1.52) |
| >25.9 | 26 | 427 | 0.98 (0.56, 1.70) | 0.91 (0.51, 1.62) |
| Weeks 13 to 26 | | | | |
| [0.0, 2.8] | 28 | 437 | 1.00 | 1.00 |
| (2.8, 8.5] | 22 | 431 | 0.80 (0.45, 1.41) | 0.75 (0.41, 1.37) |
| (8.5, 29] | 27 | 429 | 0.98 (0.57, 1.69) | 0.96 (0.54, 1.71) |
| >29 | 25 | 433 | 0.90 (0.52, 1.57) | 0.83 (0.46, 1.49) |
| Week 27 until birth | | | | |
| [0.0, 2.6] | 29 | 415 | 1.00 | 1.00 |
| (2.6, 8.9] | 20 | 423 | 0.68 (0.38, 1.22) | 0.71 (0.39, 1.30) |
| (8.9, 28.6] | 23 | 423 | 0.78 (0.44, 1.37) | 0.68 (0.37, 1.25) |
| >28.6 | 26 | 420 | 0.89 (0.51, 1.53) | 0.86 (0.49, 1.53) |
| THM-Br total integrated exposure (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.1] | 22 | 435 | 1.00 | 1.00 |
| (0.1, 0.3] | 18 | 444 | 0.80 (0.42, 1.52) | 0.84 (0.44, 1.61) |
| (0.3, 0.6] | 27 | 427 | 1.25 (0.7, 2.23) | 1.33 (0.73, 2.42) |
| >0.6 | 34 | 421 | 1.60 (0.92, 2.78) | 1.15 (0.63, 2.09) |

(continued)

**Table 8.21 (continued)**

| THM-Br Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| Weeks 13 to 26 | | | | |
| [0.0, 0.1] | 23 | 437 | 1.00 | 1.00 |
| (0.1, 0.3] | 19 | 439 | 0.82 (0.44, 1.53) | 0.88 (0.46, 1.67) |
| (0.3, 0.6] | 23 | 430 | 1.02 (0.56, 1.84) | 1.02 (0.55, 1.90) |
| >0.6 | 36 | 421 | 1.63 (0.95, 2.79) | 1.34 (0.75, 2.40) |
| Week 27 until birth | | | | |
| [0.0, 0.1] | 23 | 422 | 1.00 | 1.00 |
| (0.1, 0.2] | 22 | 428 | 0.94 (0.52, 1.72) | 1.02 (0.54, 1.95) |
| (0.2, 0.6] | 16 | 425 | 0.69 (0.36, 1.33) | 0.89 (0.45, 1.75) |
| >0.6 | 37 | 406 | 1.67 (0.98, 2.86) | 1.65 (0.93, 2.94) |
| THM-Br shower/bath (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.1] | 22 | 436 | 1.00 | 1.00 |
| (0.1, 0.3] | 19 | 445 | 0.85 (0.45, 1.59) | 0.90 (0.47, 1.71) |
| (0.3, 0.6] | 25 | 428 | 1.16 (0.64, 2.09) | 1.23 (0.67, 2.26) |
| >0.6 | 35 | 421 | 1.65 (0.95, 2.86) | 1.19 (0.66, 2.16) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.1] | 22 | 439 | 1.00 | 1.00 |
| (0.1, 0.3] | 17 | 443 | 0.77 (0.40, 1.46) | 0.85 (0.44, 1.64) |
| (0.3, 0.6] | 26 | 426 | 1.22 (0.68, 2.18) | 1.18 (0.64, 2.18) |
| >0.6 | 36 | 422 | 1.70 (0.99, 2.94) | 1.38 (0.77, 2.49) |
| Week 27 until birth | | | | |
| [0.0, 0.1] | 24 | 423 | 1.00 | 1.00 |
| (0.1, 0.2] | 20 | 429 | 0.82 (0.45, 1.51) | 0.89 (0.46, 1.71) |
| (0.2, 0.5] | 16 | 423 | 0.67 (0.35, 1.27) | 0.86 (0.44, 1.68) |
| >0.5 | 38 | 406 | 1.65 (0.97, 2.80) | 1.63 (0.93, 2.88) |

*Adjusted for maternal race, education, smoking, body mass index (BMI) and live birth history.

**Table 8.22**
**Association between HAA5 exposure and SGA, all RFTS sites**

| HAA-5 Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| HAA5 water concentration (µg/L)** | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.2] | 25 | 505 | 1.00 | 1.00 |
| (0.2, 21.9] | 28 | 366 | 1.55 (0.89, 2.69) | 1.46 (0.81, 2.62) |
| (21.9, 36.3] | 34 | 421 | 1.63 (0.96, 2.78) | 1.63 (0.93, 2.85) |
| >36.3 | 15 | 441 | 0.69 (0.36, 1.32) | 0.80 (0.41, 1.57) |
| Weeks 13 to 26 | | | | |
| [0.0, 0.2] | 29 | 438 | 1.00 | 1.00 |
| (0.2, 21.6] | 28 | 433 | 0.98 (0.57, 1.67) | 0.77 (0.43, 1.36) |
| (21.6, 37.7] | 27 | 430 | 0.95 (0.55, 1.63) | 0.93 (0.53, 1.63) |
| >37.7 | 18 | 432 | 0.63 (0.34, 1.15) | 0.65 (0.35, 1.21) |
| Week 27 until birth | | | | |
| [0.0, 0] | 25 | 502 | 1.00 | 1.00 |
| (0, 20.5] | 29 | 341 | 1.71 (0.98, 2.97) | 1.47 (0.81, 2.66) |
| (20.5, 37.8] | 28 | 409 | 1.38 (0.79, 2.39) | 1.43 (0.80, 2.55) |
| >37.8 | 16 | 429 | 0.75 (0.40, 1.42) | 0.87 (0.45, 1.69) |
| HAA5 ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0] | 31 | 539 | 1.00 | 1.00 |
| (0, 10.1] | 20 | 333 | 1.04 (0.59, 1.86) | 1.13 (0.62, 2.07) |
| (10.1, 49.6] | 30 | 424 | 1.23 (0.73, 2.07) | 1.41 (0.81, 2.44) |
| >49.6 | 21 | 434 | 0.84 (0.48, 1.49) | 0.93 (0.51, 1.70) |
| Weeks 13 to 26 | | | | |
| [0.0, 0] | 35 | 479 | 1.00 | 1.00 |
| (0, 13.1] | 18 | 390 | 0.63 (0.35, 1.13) | 0.53 (0.28, 1.00) |
| (13.1, 54.4] | 27 | 431 | 0.86 (0.51, 1.44) | 0.89 (0.52, 1.55) |
| >54.4 | 22 | 430 | 0.70 (0.40, 1.21) | 0.78 (0.44, 1.37) |
| Week 27 until birth | | | | |
| [0.0, 0] | 38 | 647 | 1.00 | 1.00 |
| (0, 12.5] | 13 | 195 | 1.14 (0.59, 2.17) | 1.14 (0.57, 2.26) |
| (12.5, 53.9] | 26 | 418 | 1.06 (0.63, 1.77) | 1.16 (0.67, 2.01) |
| >53.9 | 21 | 421 | 0.85 (0.49, 1.47) | 1.01 (0.57, 1.78) |

*Adjusted for maternal race, education, smoking, body mass index (BMI) and live birth history.
**No RFTS study subjects exposed above regulatory cutpoint (>= 60 µg/L).

**Table 8.23**
**Association between HAA-Br exposure and SGA, all RFTS sites**

| HAA-Br Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| HAA-Br water concentration (µg/L) | | | | |
| Weeks 0 to 12 | | | | |
| [ 0.0, 2.3] | 23 | 440 | 1.00 | 1.00 |
| (2.3, 9.4] | 28 | 431 | 1.24 (0.71, 2.19) | 1.44 (0.80, 2.61) |
| (9.4, 15] | 19 | 430 | 0.85 (0.45, 1.57) | 1.00 (0.52, 1.93) |
| >15 | 32 | 432 | 1.42 (0.82, 2.46) | 1.36 (0.74, 2.48) |
| Weeks 13 to 26 | | | | |
| [0.0, 2.6] | 28 | 436 | 1.00 | 1.00 |
| (2.6, 9.1] | 18 | 440 | 0.64 (0.35, 1.17) | 0.77 (0.41, 1.44) |
| (9.1, 14.6] | 20 | 431 | 0.72 (0.40, 1.30) | 0.89 (0.48, 1.64) |
| >14.6 | 36 | 426 | 1.32 (0.79, 2.20) | 1.21 (0.69, 2.12) |
| Week 27 until birth | | | | |
| [0.0, 2.2] | 27 | 423 | 1.00 | 1.00 |
| (2.2, 8.9] | 17 | 426 | 0.63 (0.34, 1.16) | 0.72 (0.38, 1.37) |
| (8.9, 13.9] | 17 | 424 | 0.63 (0.34, 1.17) | 0.76 (0.40, 1.45) |
| >13.9 | 37 | 408 | 1.42 (0.85, 2.38) | 1.30 (0.74, 2.27) |
| HAA-Br ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 0.8] | 31 | 430 | 1.00 | 1.00 |
| (0.8, 6.2] | 21 | 438 | 0.67 (0.38, 1.18) | 0.76 (0.42, 1.38) |
| (6.2, 17.8] | 28 | 433 | 0.90 (0.53, 1.52) | 1.01 (0.57, 1.76) |
| >17.8 | 22 | 429 | 0.71 (0.41, 1.25) | 0.75 (0.41, 1.35) |
| Weeks 13 to 26 | | | | |
| [0.0, 1.1] | 27 | 438 | 1.00 | 1.00 |
| (1.1, 7.2] | 23 | 427 | 0.87 (0.49, 1.55) | 1.01 (0.56, 1.84) |
| (7.2, 18.8] | 25 | 435 | 0.93 (0.53, 1.63) | 1.00 (0.55, 1.83) |
| >18.8 | 27 | 430 | 1.02 (0.59, 1.77) | 1.05 (0.59, 1.87) |
| Week 27 until birth | | | | |
| [0.0, 0] | 33 | 441 | 1.00 | 1.00 |
| (0, 6.9] | 16 | 399 | 0.54 (0.29, 0.99) | 0.59 (0.31, 1.12) |
| (6.9, 18.9] | 23 | 422 | 0.73 (0.42, 1.26) | 0.75 (0.41, 1.34) |
| >18.9 | 26 | 419 | 0.83 (0.49, 1.41) | 0.89 (0.51, 1.55) |

*Adjusted for maternal race, education, smoking, body mass index (BMI) and live birth history.

**Table 8.24**
**Association between TOX exposure and SGA, all RFTS sites**

| TOX Exposure | Cases (n) | Non-cases (n) | Crude OR | Adjusted* OR |
|---|---|---|---|---|
| TOX water concentration (µg/L) | | | | |
| Weeks 0 to 1 2 | | | | |
| [0.0, 19.3] | 29 | 437 | 1.00 | 1.00 |
| (19.3, 166.2] | 19 | 441 | 0.65 (0.36, 1.18) | 0.72 (0.39, 1.34) |
| (166.2, 17.6] | 23 | 433 | 0.80 (0.46, 1.41) | 0.89 (0.49, 1.61) |
| >178.6 | 31 | 422 | 1.11 (0.66, 1.87) | 1.10 (0.63, 1.93) |
| Weeks 13 to 26 | | | | |
| [0.0, 19.2] | 24 | 440 | 1.00 | 1.00 |
| (19.2, 168.4] | 21 | 438 | 0.88 (0.48, 1.6) | 0.92 (0.49, 1.72) |
| (168.4, 180.5] | 27 | 428 | 1.16 (0.66, 2.04) | 1.22 (0.68, 2.22) |
| >180.5 | 30 | 427 | 1.29 (0.74, 2.24) | 1.20 (0.66, 2.16) |
| Week 27 until birth | | | | |
| [0.0, 20] | 21 | 427 | 1.00 | 1.00 |
| (20, 167] | 23 | 419 | 1.12 (0.61, 2.05) | 1.27 (0.67, 2.39) |
| (167, 181.8] | 31 | 412 | 1.53 (0.87, 2.71) | 1.65 (0.90, 3.00) |
| >181.8 | 23 | 423 | 1.11 (0.60, 2.03) | 1.03 (0.54, 1.96) |
| TOX ingested amount (µg/day) | | | | |
| Weeks 0 to 12 | | | | |
| [0.0, 20.3] | 33 | 429 | 1.00 | 1.00 |
| (20.3, 70.9] | 18 | 440 | 0.53 (0.30, 0.96) | 0.52 (0.28, 0.97) |
| (70.9, 241.8] | 23 | 438 | 0.68 (0.39, 1.18) | 0.81 (0.45, 1.44) |
| >241.8 | 28 | 423 | 0.86 (0.51, 1.45) | 0.89 (0.51, 1.54) |
| Weeks 13 to 26 | | | | |
| [0.0, 27] | 32 | 430 | 1.00 | 1.00 |
| (27, 80.9] | 23 | 435 | 0.71 (0.41, 1.23) | 0.70 (0.39, 1.25) |
| (80.9, 268.1] | 19 | 439 | 0.58 (0.33, 1.04) | 0.61 (0.33, 1.13) |
| >268.1 | 28 | 426 | 0.88 (0.52, 1.49) | 0.89 (0.51, 1.54) |
| Week 27 until birth | | | | |
| [0.0, 25.8] | 30 | 412 | 1.00 | 1.00 |
| (25.8, 83.2] | 22 | 428 | 0.71 (0.40, 1.24) | 0.70 (0.39, 1.28) |
| (83.2, 266.7] | 19 | 424 | 0.62 (0.34, 1.11) | 0.68 (0.36, 1.27) |
| >266.7 | 27 | 417 | 0.89 (0.52, 1.52) | 0.93 (0.53, 1.65) |

*Adjusted for maternal race, education, smoking, body mass index (BMI) and live birth history.

## RESULTS FOR TERM BIRTH WEIGHT

With some sporadic fluctuations, THM4 exposure was largely unrelated to notable shifts in term birth weight after adjustment for confounders (Table 8.25). Using the dichotomy of the regulatory cutpoint yielded evidence of modestly lower birth weight associated with higher exposures in the second and especially third trimester. This pattern was enhanced somewhat for Sites 1 and 3 only and Site 1 only (Tables 8.26 and 8.27, respectively). Analysis of birth weight in relation to BDCM exposure (Table 8.28) did not show any notable increases or decreases and an absence of monotonic gradients. HAA9 indices were associated with increased birth weight, particularly in analyses restricted to Sites 1 and 3 or Site 1 only (Tables 8.29–31). The other agents considered, chloroform (Table 8.32), THM-Br (Table 8.33), HAA5 (Table 8.34), HAA-Br (Table 8.35), and TOX (Table 8.36) were not associated in any consistent or substantial manner with changes in term birth weight.

**Table 8.25**
**Association between THM4 exposure and term birth weight, all RFTS sites**

| THM4 Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| THM4 water concentration (µg/L) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 3.3] | 337 | 0 | 0 |
| (3.3, 45.3] | 344 | –15 (–85, 55) | –29 (–96, 38) |
| (45.3, 60.2] | 337 | 32 (–39, 102) | –24 (–92, 44) |
| (60.2, 74.6] | 360 | 27 (–42, 97) | –24 (–90, 41) |
| >74.6 | 360 | 77 (7, 146) | 31 (–35, 98) |
| Weeks 13 to 26 | | | |
| [0.0, 3.3] | 349 | 0 | 0 |
| (3.3, 45.6] | 334 | 14 (–56, 84) | 33 (–33, 100) |
| (45.6, 62.2] | 337 | 90 (20, 160) | 25 (–41, 92) |
| (62.2, 74.4] | 359 | 74 (5, 143) | 42 (–24, 108) |
| >74.4 | 359 | 22 (–47, 91) | –9 (–75, 57) |
| Week 27 until birth | | | |
| [0.0, 3.5] | 326 | 0 | 0 |
| (3.5, 45.2] | 341 | 42 (–29, 113) | 0 (–67, 67) |
| (45.2, 60.8] | 348 | 72 (1, 143) | –12 (–81, 56) |
| (60.8, 74.1] | 339 | 92 (20, 163) | 31 (–38, 99) |
| >74.1 | 338 | 51 (–20, 122) | –23 (–92, 46) |
| THM4 ingested amount (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0.0] | 354 | 0 | 0 |
| (0, 5.3] | 342 | –32 (–102, 37) | 13 (–54, 81) |
| (5.3, 29.8] | 331 | –23 (–93, 47) | 6 (–62, 74) |
| (29.8, 92] | 350 | 55 (–14, 124) | 53 (–14, 120) |
| >92 | 358 | 52 (–17, 120) | 37 (–30, 104) |
| Weeks 13 to 26 | | | |
| [0.0, 2.0] | 345 | 0 | 0 |
| (2, 6.9] | 343 | –43 (–113, 27) | 3 (–65, 70) |
| (6.9, 21.6] | 336 | –51 (–121, 19) | –9 (–77, 58) |
| (21.6, 60.2] | 355 | 5 (–65, 74) | 11 (–57, 79) |
| >60.2 | 356 | 8 (–62, 77) | 10 (–57, 78) |
| Week 27 until birth | | | |
| [0.0, 1.2] | 336 | 0 | 0 |
| (1.2, 7.1] | 334 | –49 (–120, 22) | 3 (–66, 71) |
| (7.1, 35.1] | 332 | –84 (–155, –13) | –48 (–117, 20) |
| (35.1, 103.7] | 341 | 15 (–55, 86) | 44 (–25, 112) |
| >103.7 | 349 | –10 (–80, 60) | –4 (–73, 64) |

(continued)

**Table 8.25 (continued)**

| THM4 Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| THM4 total integrated exposure (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0.1] | 338 | 0 | 0 |
| (0.1, 0.7] | 344 | –98 (–168, –28) | –17 (–84, 51) |
| (0.7, 1.4] | 354 | 35 (–35, 104) | –3 (–69, 64) |
| (1.4, 2.2] | 360 | 28 (–41, 97) | 8 (–58, 74) |
| >2.2 | 335 | –54 (–125, 16) | –19 (–88, 50) |
| Weeks 13 to 26 | | | |
| [0.0, 0.1] | 345 | 0 | 0 |
| (0.1, 0.3] | 338 | –83 (–153, –13) | –24 (–91, 43) |
| (0.3, 0.7] | 356 | 13 (–56, 82) | –14 (–79, 52) |
| (0.7, 1.4] | 355 | 9 (–60, 78) | –1 (–66, 65) |
| >1.4 | 337 | –77 (–147, –7) | –31 (–102, 40) |
| Week 27 until birth | | | |
| [0.0, 0.1] | 330 | 0 | 0 |
| (0.1, 0.6] | 325 | –85 (–157, –14) | –41 (–109, 28) |
| (0.6, 1.3] | 350 | 29 (–41, 100) | –26 (–93, 41) |
| (1.3, 2.1] | 352 | 75 (5, 146) | 25 (–43, 92) |
| >2.1 | 335 | –10 (–81, 61) | –5 (–74, 63) |
| THM4 shower/bath (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0.1] | 340 | 0 | 0 |
| (0.1, 0.6] | 345 | –109 (–178, –40) | –23 (–91, 44) |
| (0.6, 1.2] | 354 | 64 (–5, 133) | 16 (–50, 82) |
| (1.2, 1.9] | 362 | 14 (–55, 82) | –3 (–69, 62) |
| >1.9 | 333 | –87 (–157, –17) | –38 (–107, 31) |
| Weeks 13 to 26 | | | |
| [0.0, 0.1] | 345 | 0 | 0 |
| (0.1, 0.3] | 339 | –82 (–152, –13) | –22 (–89, 45) |
| (0.3, 0.6] | 361 | 31 (–37, 100) | 3 (–62, 68) |
| (0.6, 1.2] | 352 | –13 (–83, 56) | –19 (–85, 46) |
| >1.2 | 337 | –95 (–165, –25) | –43 (–113, 28) |
| Week 27 until birth | | | |
| [0.0, 0.1] | 328 | 0 | 0 |
| (0.1, 0.4] | 327 | –70 (–141, 2) | –30 (–99, 38) |
| (0.4, 1] | 353 | 47 (–23, 117) | –13 (–80, 54) |
| (1, 1.7] | 349 | 67 (–3, 138) | 6 (–61, 73) |
| >1.7 | 335 | –19 (–90, 52) | –15 (–84, 55) |

(continued)

**Table 8.25 (continued)**

| THM4 Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| THM4 regulatory cutpoint | | | |
| Weeks 0 to 12 | | | |
| <80 µg/L | 1508 | 0 | 0 |
| >=80 µg/L | 230 | 31 (–47, 108) | 40 (–22, 103) |
| Weeks 13 to 26 | | | |
| <80 µg/L | 1553 | 0 | 0 |
| >=80 µg/L | 185 | –58 (–140, 25) | –36 (–105, 33) |
| Week 27 until birth | | | |
| <80 µg/L | 1548 | 0 | 0 |
| >=80 µg/L | 144 | –91 (–190, 9) | –71 (–148, 7) |

*Adjusted for maternal caffeine intake, race, education, income, smoking, body mass index (BMI), employment, diabetes status, live birth history, gestational age and gestational age$^2$.

**Table 8.26**
**Association between THM4 exposure and term birth weight, RFTS Sites 1 and 3 only**

| THM4 Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| THM4 water concentration (µg/L) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 50.7] | 223 | 0 | 0 |
| (50.7, 61] | 210 | –61 (–150, 28) | 26 (–61, 113) |
| (61, 71.5] | 233 | –67 (–154, 20) | –24 (–107, 59) |
| (71.5, 80.1] | 229 | –2 (–89, 85) | 61 (–24, 146) |
| >80.1 | 229 | 2 (–85, 89) | 47 (–37, 131) |
| Weeks 13 to 26 | | | |
| [0.0, 53.4] | 221 | 0 | 0 |
| (53.4, 62.8] | 217 | 4 (–85, 92) | 19 (–65, 104) |
| (62.8, 71] | 230 | 16 (–72, 103) | 37 (–47, 121) |
| (71, 78.5] | 224 | –67 (–155, 21) | –34 (–119, 51) |
| >78.5 | 232 | –64 (–151, 23) | –25 (–108, 59) |
| Week 27 until birth | | | |
| [0.0, 54.1] | 225 | 0 | 0 |
| (54.1, 61.8] | 224 | 34 (–54, 122) | 0 (–84, 84) |
| (61.8, 70.9] | 219 | 22 (–67, 111) | 18 (–66, 102) |
| (70.9, 77.3] | 212 | 16 (–74, 105) | 3 (–82, 89) |
| >77.3 | 219 | –12 (–101, 76) | –22 (–108, 64) |

(continued)

**Table 8.26 (continued)**

| THM4 Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| THM4 ingested amount (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0] | 296 | 0 | 0 |
| (0, 32.7] | 149 | –7 (–100, 86) | 12 (–80, 103) |
| (32.7, 72.2] | 224 | 85 (3, 168) | 82 (2, 162) |
| (72.2, 125.4] | 225 | 36 (–46, 118) | 17 (–63, 96) |
| >125.4 | 230 | 58 (–24, 139) | 74 (–6, 154) |
| Weeks 13 to 26 | | | |
| [0.0, 2.9] | 220 | 0 | 0 |
| (2.9, 23.5] | 222 | –20 (–109, 68) | 13 (–73, 100) |
| (23.5, 46.2] | 223 | –13 (–101, 75) | 12 (–75, 100) |
| (46.2, 86.3] | 233 | –49 (–137, 38) | 5 (–81, 91) |
| >86.3 | 226 | 8 (–80, 96) | 34 (–53, 121) |
| Week 27 until birth | | | |
| [0.0, 0] | 250 | 0 | 0 |
| (0, 37.9] | 182 | –39 (–130, 51) | –16 (–104, 71) |
| (37.9, 80] | 221 | 9 (–77, 95) | 66 (–18, 150) |
| (80, 144.5] | 220 | –59 (–145, 27) | –13 (–96, 71) |
| >144.5 | 226 | 31 (–54, 117) | 50 (–33, 134) |
| THM4 total integrated exposure (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 1.1] | 228 | 0 | 0 |
| (1.1, 1.5] | 228 | –15 (–102, 72) | 2 (–82, 85) |
| (1.5, 1.9] | 234 | 13 (–73, 99) | 29 (–53, 112) |
| (1.9, 2.8] | 218 | –71 (–159, 17) | –55 (–140, 31) |
| >2.8 | 214 | –87 (–175, 1) | 21 (–70, 112) |
| Weeks 13 to 26 | | | |
| [0.0, 0.5] | 235 | 0 | 0 |
| (0.5, 0.8] | 222 | 7 (–80, 93) | 58 (–25, 140) |
| (0.8, 1.1] | 230 | –22 (–108, 64) | 9 (–73, 91) |
| (1.1, 1.8] | 224 | –108 (–195, –22) | –19 (–104, 67) |
| >1.8 | 211 | –123 (–211, –36) | –8 (–104, 87) |
| Week 27 until birth | | | |
| [0.0, 0.9] | 215 | 0 | 0 |
| (0.9, 1.3] | 224 | –17 (–106, 72) | –32 (–117, 52) |
| (1.3, 1.8] | 224 | 72 (–17, 161) | 41 (–44, 125) |
| (1.8, 2.6] | 225 | 3 (–86, 91) | 9 (–76, 94) |
| >2.6 | 211 | –16 (–106, 74) | 28 (–62, 117) |

(continued)

**Table 8.26 (continued)**

| THM4 Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| THM4 shower/bath (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0.9] | 230 | 0 | 0 |
| (0.9, 1.2] | 227 | 18 (–68, 105) | 1 (–83, 84) |
| (1.2, 1.7] | 231 | –61 (–147, 25) | –67 (–150, 15) |
| (1.7, 2.5] | 222 | –68 (–155, 19) | –30 (–116, 55) |
| >2.5 | 212 | –94 (–182, –6) | 2 (–88, 93) |
| Weeks 13 to 26 | | | |
| [0.0, 0.4] | 232 | 0 | 0 |
| (0.4, 0.6] | 231 | 20 (–65, 106) | 55 (–26, 137) |
| (0.6, 1] | 226 | –28 (–114, 58) | 13 (–70, 95) |
| (1, 1.6] | 222 | –134 (–220, –47) | –46 (–133, 41) |
| >1.6 | 211 | –134 (–222, –47) | –30 (–126, 66) |
| Week 27 until birth | | | |
| [0.0, 0.7] | 219 | 0 | 0 |
| (0.7, 1.1] | 224 | 29 (–60, 118) | –6 (–89, 78) |
| (1.1, 1.5] | 220 | 18 (–71, 107) | –10 (–95, 76) |
| (1.5, 2.3] | 229 | 7 (–81, 96) | –15 (–100, 69) |
| >2.3 | 207 | –46 (–137, 44) | 14 (–76, 105) |
| THM4 regulatory cutpoint | | | |
| Weeks 0 to 12 | | | |
| <80 µg/L | 894 | 0 | 0 |
| >=80 µg/L | 230 | 35 (–33, 104) | 41 (–25, 107) |
| Weeks 13 to 26 | | | |
| <80 µg/L | 939 | 0 | 0 |
| >=80 µg/L | 185 | –58 (–132, 17) | –41 (–113, 31) |
| Week 27 until birth | | | |
| <80 µg/L | 955 | 0 | 0 |
| >=80 µg/L | 144 | –78 (–161, 5) | –72 (–152, 8) |

*Adjusted for maternal caffeine intake, race, education, income, smoking, body mass index (BMI), employment, diabetes status, live birth history, gestational age and gestational age$^2$.

**Table 8.27**
**Association between THM4 exposure and term birth weight, RFTS Sites 1 only**

| THM4 Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| THM4 water concentration (µg/L) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 3.3] | 166 | 0 | 0 |
| (3.3, 45.3] | 162 | –8 (–110, 94) | 45 (–55, 145) |
| (45.3, 60.2] | 174 | –91 (–191, 9) | –28 (–126, 70) |
| (60.2, 74.6] | 174 | 25 (–75, 126) | 85 (–14, 184) |
| >74.6 | 176 | 20 (–80, 120) | 53 (–44, 150) |
| Weeks 13 to 26 | | | |
| [0.0, 3.3] | 165 | 0 | 0 |
| (3.3, 45.6] | 168 | 21 (–80, 123) | 25 (–73, 122) |
| (45.6, 62.2] | 177 | 21 (–79, 121) | 34 (–62, 131) |
| (62.2, 74.4] | 165 | –59 (–160, 43) | –37 (–137, 62) |
| >74.4 | 177 | –48 (–148, 52) | –16 (–112, 81) |
| Week 27 until birth | | | |
| [0.0, 3.5] | 168 | 0 | 0 |
| (3.5, 45.2] | 170 | 30 (–71, 131) | –4 (–102, 94) |
| (45.2, 60.8] | 170 | 38 (–63, 139) | 18 (–80, 116) |
| (60.8, 74.1] | 160 | 3 (–100, 106) | –11 (–109, 88) |
| >74.1 | 166 | –19 (–121, 83) | –28 (–127, 71) |
| THM4 ingested amount (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0] | 183 | 0 | 0 |
| (0, 5.3] | 156 | 25 (–76, 126) | 57 (–43, 157) |
| (5.3, 29.8] | 171 | 19 (–80, 117) | 29 (–68, 126) |
| (29.8, 92] | 169 | 36 (–63, 135) | 43 (–54, 140) |
| >92 | 173 | 54 (–44, 153) | 81 (–16, 178) |
| Weeks 13 to 26 | | | |
| [0.0, 2] | 168 | 0 | 0 |
| (2, 6.9] | 169 | 2 (–99, 103) | 46 (–52, 144) |
| (6.9, 21.6] | 169 | –20 (–121, 81) | 24 (–75, 124) |
| (21.6, 60.2] | 176 | –37 (–137, 63) | 19 (–79, 118) |
| >60.2 | 170 | 6 (–95, 107) | 62 (–38, 162) |
| Week 27 until birth | | | |
| [0.0, 1.2] | 162 | 0 | 0 |
| (1.2, 7.1] | 166 | –70 (–172, 33) | –24 (–124, 76) |
| (7.1, 35.1] | 171 | 1 (–101, 102) | 79 (–21, 179) |
| (35.1, 103.7] | 164 | –47 (–150, 56) | 13 (–87, 113) |
| >103.7 | 171 | 17 (–85, 119) | 55 (–46, 155) |

(continued)

**Table 8.27 (continued)**

| THM4 Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| THM4 total integrated exposure (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0.1] | 175 | 0 | 0 |
| (0.1, 0.7] | 169 | –28 (–127, 72) | 11 (–85, 107) |
| (0.7, 1.4] | 173 | 12 (–87, 111) | 14 (–82, 110) |
| (1.4, 2.2] | 170 | –83 (–183, 16) | –56 (–153, 41) |
| >2.2 | 164 | –94 (–194, 7) | 31 (–72, 135) |
| Weeks 13 to 26 | | | |
| [0.0, 0.1] | 173 | 0 | 0 |
| (0.1, 0.3] | 171 | 8 (–92, 107) | 40 (–56, 137) |
| (0.3, 0.7] | 174 | –6 (–105, 94) | 47 (–49, 142) |
| (0.7, 1.4] | 170 | –49 (–148, 51) | –9 (–106, 88) |
| >1.4 | 163 | –110 (–211, –9) | –8 (–115, 98) |
| Week 27 until birth | | | |
| [0.0, 0.1] | 169 | 0 | 0 |
| (0.1, 0.6] | 167 | 53 (–48, 155) | 39 (–58, 136) |
| (0.6, 1.3] | 169 | 45 (–56, 146) | 53 (–43, 150) |
| (1.3, 2.1] | 169 | 39 (–62, 140) | 55 (–42, 152) |
| >2.1 | 160 | 4 (–98, 107) | 66 (–36, 168) |
| THM4 shower/bath (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0.1] | 176 | 0 | 0 |
| (0.1, 0.6] | 170 | 23 (–76, 122) | 0 (–96, 96) |
| (0.6, 1.2] | 172 | –43 (–141, 56) | –59 (–154, 36) |
| (1.2, 1.9] | 169 | –68 (–167, 32) | –50 (–148, 48) |
| >1.9 | 164 | –119 (–220, –19) | –34 (–137, 68) |
| Weeks 13 to 26 | | | |
| [0.0, 0.1] | 174 | 0 | 0 |
| (0.1, 0.3] | 171 | 52 (–47, 152) | 83 (–13, 179) |
| (0.3, 0.6] | 174 | –13 (–111, 86) | 45 (–50, 139) |
| (0.6, 1.2] | 170 | –23 (–122, 76) | 15 (–81, 111) |
| >1.2 | 162 | –124 (–225, –24) | –12 (–118, 94) |
| Week 27 until birth | | | |
| [0.0, 0.1] | 168 | 0 | 0 |
| (0.1, 0.4] | 170 | 28 (–73, 129) | –8 (–106, 89) |
| (0.4, 1] | 170 | 28 (–74, 129) | –16 (–113, 81) |
| (1, 1.7] | 166 | 9 (–93, 110) | –1 (–100, 97) |
| >1.7 | 160 | –49 (–151, 54) | 3 (–99, 105) |

(continued)

**Table 8.27 (continued)**

| THM4 Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| THM4 regulatory cutpoint | | | |
| Weeks 0 to 12 | | | |
| <80 µg/L | 670 | 0 | 0 |
| >=80 µg/L | 182 | 31 (–47, 108) | 35 (–40, 110) |
| Weeks 13 to 26 | | | |
| <80 µg/L | 698 | 0 | 0 |
| >=80 µg/L | 154 | –58 (–140, 25) | –31 (–112, 50) |
| Week 27 until birth | | | |
| <80 µg/L | 735 | 0 | 0 |
| >=80 µg/L | 99 | –91 (–190, 9) | –89 (–187, 9) |

*Adjusted for maternal caffeine intake, race, education, income, smoking, body mass index (BMI), employment, diabetes status, live birth history, gestational age and gestational age$^2$.

**Table 8.28**
**Association between $CHBrCl_2$ exposure and term birth weight, all RFTS sites**

| $CHBrCl_2$ Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| $CHBrCl_2$ water concentration (µg/L) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 1.1] | 333 | 0 | 0 |
| (1.1, 11] | 349 | 53 (–17, 123) | 34 (–33, 100) |
| (11, 14] | 351 | 136 (66, 206) | 63 (–4, 130) |
| (14, 18.6] | 357 | 48 (–22, 117) | –12 (–78, 55) |
| >18.6 | 348 | 69 (–1, 139) | 38 (–30, 106) |
| Weeks 13 to 26 | | | |
| [0.0, 1.1] | 353 | 0 | 0 |
| (1.1, 11] | 326 | –8 (–78, 62) | 47 (–19, 113) |
| (11, 13.7] | 361 | 112 (44, 181) | 60 (–6, 125) |
| (13.7, 20.1] | 350 | 26 (–43, 95) | –3 (–69, 63) |
| >20.1 | 348 | –17 (–86, 52) | –21 (–88, 45) |
| Week 27 until birth | | | |
| [0.0, 1.1] | 328 | 0 | 0 |
| (1.1, 10.8] | 340 | 24 (–47, 95) | –15 (–82, 52) |
| (10.8, 13.2] | 353 | 136 (66, 206) | 42 (–26, 110) |
| (13.2, 19.7] | 342 | 63 (–8, 133) | –10 (–78, 58) |
| >19.7 | 329 | 23 (–49, 94) | –21 (–91, 49) |

(continued)

**Table 8.28 (continued)**

| $CHBrCl_2$ Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| $CHBrCl_2$ ingested amount (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0] | 354 | 0 | 0 |
| (0, 1.7] | 343 | –31 (–100, 38) | 11 (–56, 79) |
| (1.7, 7] | 330 | –15 (–85, 55) | 19 (–49, 87) |
| (7, 22.8] | 352 | 47 (–22, 116) | 31 (–36, 98) |
| >22.8 | 356 | 51 (–18, 120) | 48 (–20, 115) |
| Weeks 13 to 26 | | | |
| [0.0, 0.6] | 346 | 0 | 0 |
| (0.6, 2.2] | 344 | –44 (–114, 26) | 10 (–58, 77) |
| (2.2, 9.1] | 332 | –41 (–111, 29) | –7 (–75, 61) |
| (9.1, 25.1] | 355 | 28 (–41, 97) | 43 (–24, 110) |
| >25.1 | 358 | –1 (–70, 68) | 4 (–64, 72) |
| Week 27 until birth | | | |
| [0.0, 0.3] | 336 | 0 | 0 |
| (0.3, 2.2] | 331 | –58 (–130, 13) | –8 (–77, 60) |
| (2.2, 8.7] | 338 | –59 (–129, 12) | –34 (–102, 35) |
| (8.7, 25.5] | 345 | 11 (–59, 82) | 56 (–13, 124) |
| >25.5 | 342 | –7 (–78, 63) | –6 (–75, 63) |
| $CHBrCl_2$ total integrated exposure (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0] | 341 | 0 | 0 |
| (0, 0.1] | 341 | –119 (–189, –49) | –23 (–91, 45) |
| (0.1, 0.3] | 359 | 31 (–38, 100) | 3 (–62, 69) |
| (0.3, 0.5] | 359 | 0 (–69, 69) | –29 (–95, 37) |
| >0.5 | 331 | –88 (–158, –18) | –21 (–92, 49) |
| Weeks 13 to 26 | | | |
| [0.0, 0] | 347 | 0 | 0 |
| (0, 0.1] | 336 | –149 (–219, –80) | –57 (–125, 11) |
| (0.1, 0.3] | 357 | 45 (–24, 113) | 15 (–50, 80) |
| (0.3, 0.5] | 354 | –27 (–95, 42) | –33 (–99, 32) |
| >0.5 | 337 | –113 (–182, –43) | –49 (–120, 21) |
| Week 27 until birth | | | |
| [0.0, 0] | 328 | 0 | 0 |
| (0, 0.1] | 333 | –57 (–128, 14) | –27 (–95, 41) |
| (0.1, 0.3] | 349 | 96 (26, 166) | 20 (–48, 87) |
| (0.3, 0.4] | 349 | 22 (–49, 92) | –20 (–88, 47) |
| >0.4 | 333 | –19 (–91, 52) | –20 (–89, 50) |

(continued)

**Table 8.28 (continued)**

| $CHBrCl_2$ Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| $CHBrCl_2$ shower/bath (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0] | 342 | 0 | 0 |
| (0, 0.1] | 344 | –109 (–179, –40) | –28 (–95, 39) |
| (0.1, 0.3] | 357 | 54 (–15, 122) | 23 (–43, 88) |
| (0.3, 0.5] | 360 | 0 (–68, 69) | –26 (–92, 40) |
| >0.5 | 331 | –79 (–150, –9) | –19 (–90, 51) |
| Weeks 13 to 26 | | | |
| [0.0, 0] | 349 | 0 | 0 |
| (0, 0.1] | 333 | –140 (–210, –70) | –57 (–126, 11) |
| (0.1, 0.3] | 362 | 46 (–22, 114) | 16 (–49, 81) |
| (0.3, 0.5] | 352 | –36 (–105, 32) | –42 (–107, 24) |
| >0.5 | 338 | –108 (–177, –39) | –53 (–123, 17) |
| Week 27 until birth | | | |
| [0.0, 0] | 329 | 0 | 0 |
| (0, 0.1] | 329 | –41 (–113, 30) | –20 (–88, 49) |
| (0.1, 0.2] | 351 | 76 (5, 146) | –2 (–69, 66) |
| (0.2, 0.4] | 350 | 43 (–27, 114) | –5 (–72, 63) |
| >0.4 | 333 | –18 (–89, 53) | –21 (–90, 49) |

*Adjusted for maternal caffeine intake, race, education, income, smoking, body mass index (BMI), employment, diabetes status, live birth history, gestational age and gestational age$^2$.

**Table 8.29**
**Association between HAA9 exposure and term birth weight, all RFTS sites**

| HAA9 Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| HAA9 water concentration (µg/L) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 1.9] | 346 | 0 | 0 |
| (1.9, 30.1] | 339 | 40 (–30, 110) | 4 (–63, 70) |
| (30.1, 43.8] | 352 | 34 (–35, 104) | –47 (–114, 19) |
| (43.8, 51.7] | 344 | 45 (–25, 114) | 5 (–63, 73) |
| >51.7 | 357 | 118 (49, 187) | 43 (–23, 109) |
| Weeks 13 to 26 | | | |
| [0.0, 1.8] | 350 | 0 | 0 |
| (1.8, 29.3] | 332 | 35 (–35, 105) | 33 (–33, 99) |
| (29.3, 44.9] | 345 | 80 (11, 150) | 31 (–36, 97) |
| (44.9, 51.7] | 344 | 36 (–34, 105) | 11 (–57, 78) |
| >51.7 | 367 | 80 (12, 149) | 22 (–43, 88) |
| Week 27 until birth | | | |
| [0.0, 1.1] | 335 | 0 | 0 |
| (1.1, 28.5] | 330 | –16 (–87, 55) | 35 (–33, 102) |
| (28.5, 44.7] | 340 | 62 (–9, 132) | 13 (–55, 81) |
| (44.7, 52.3] | 330 | 5 (–66, 76) | 8 (–60, 76) |
| >52.3 | 357 | 72 (2, 142) | 31 (–36, 98) |
| HAA9 ingested amount (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0.1] | 346 | 0 | 0 |
| (0.1, 5.6] | 342 | 18 (–52, 88) | 42 (–25, 110) |
| (5.6, 36.4] | 342 | 25 (–44, 95) | 5 (–62, 72) |
| (36.4, 81.7] | 352 | 101 (31, 170) | 50 (–18, 117) |
| >81.7 | 353 | 98 (29, 167) | 53 (–15, 121) |
| Weeks 13 to 26 | | | |
| [0.0, 0.2] | 349 | 0 | 0 |
| (0.2, 7.1] | 334 | –18 (–88, 52) | 14 (–53, 81) |
| (7.1, 42.3] | 338 | 35 (–35, 104) | 6 (–61, 73) |
| (42.3, 88.4] | 357 | 52 (–17, 121) | 29 (–37, 95) |
| >88.4 | 357 | 86 (17, 155) | 36 (–31, 103) |
| Week 27 until birth | | | |
| [0.0, 0] | 442 | 0 | 0 |
| (0, 6] | 220 | –31 (–107, 45) | 18 (–54, 91) |
| (6, 42] | 333 | –3 (–69, 64) | –13 (–77, 50) |
| (42, 92.7] | 347 | 50 (–16, 116) | 35 (–28, 98) |
| >92.7 | 350 | 68 (2, 133) | 33 (–30, 97) |

*Adjusted for maternal caffeine intake, race, education, income, smoking, body mass index (BMI), employment, diabetes status, live birth history, gestational age and gestational age$^2$.

**Table 8.30**
**Association between HAA9 exposure and term birth weight, RFTS Sites 1 and 3 only**

| HAA9 Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| HAA9 water concentration µg/L) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 39.3] | 226 | 0 | 0 |
| (39.3, 44.2] | 226 | –41 (–128, 46) | –7 (–92, 77) |
| (44.2, 50] | 212 | –16 (–105, 72) | 52 (–35, 138) |
| (50, 54] | 229 | 39 (–48, 126) | 71 (–12, 154) |
| >54 | 231 | 82 (–4, 169) | 80 (–2, 162) |
| Weeks 13 to 26 | | | |
| [0.0, 39.6] | 223 | 0 | 0 |
| (39.6, 45.5] | 220 | –53 (–141, 35) | 18 (–68, 104) |
| (45.5, 50.7] | 218 | –79 (–167, 10) | 0 (–87, 88) |
| (50.7, 53.5] | 226 | 4 (–84, 91) | 35 (–49, 119) |
| >53.5 | 237 | –12 (–99, 74) | 12 (–71, 95) |
| Week 27 until birth | | | |
| [0.0, 38.7] | 222 | 0 | 0 |
| (38.7, 45.1] | 218 | –98 (–187, –10) | –90 (–178, –3) |
| (45.1, 50.4] | 204 | –63 (–153, 28) | –27 (–115, 61) |
| (50.4, 54.6] | 230 | –68 (–155, 20) | –46 (–129, 37) |
| >54.6 | 225 | –9 (–97, 79) | –15 (–98, 69) |
| HAA9 ingested amount µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 12.1] | 221 | 0 | 0 |
| (12.1, 40] | 223 | 29 (–59, 117) | 27 (–58, 113) |
| (40, 67.1] | 229 | 55 (–33, 142) | 28 (–58, 114) |
| (67.1, 102.7] | 224 | 102 (14, 190) | 95 (9, 180) |
| >102.7 | 227 | 100 (13, 188) | 75 (–11, 162) |
| Weeks 13 to 26 | | | |
| [0.0, 18.3] | 219 | 0 | 0 |
| (18.3, 45.6] | 221 | 0 (–88, 88) | –6 (–92, 80) |
| (45.6, 73.3] | 226 | 67 (–21, 155) | 70 (–16, 155) |
| (73.3, 114] | 229 | 20 (–68, 107) | 12 (–74, 99) |
| >114 | 229 | 91 (3, 178) | 57 (–28, 143) |
| Week 27 until birth | | | |
| [0.0, 18.1] | 213 | 0 | 0 |
| (18.1, 43.8] | 216 | 37 (–53, 127) | 38 (–49, 124) |
| (43.8, 75.6] | 221 | 48 (–42, 137) | 75 (–12, 161) |
| (75.6, 116.7] | 224 | 35 (–55, 124) | 9 (–77, 94) |
| >116.7 | 225 | 78 (–11, 167) | 66 (–20, 153) |

*Adjusted for maternal caffeine intake, race, education, income, smoking, body mass index (BMI), employment, diabetes status, live birth history, gestational age and gestational age$^2$.

**Table 8.31**
**Association between HAA9 exposure and term birth weight, RFTS Sites 1 only**

| HAA9 Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| HAA9 water concentration (µg/L) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 1.9] | 166 | 0 | 0 |
| (1.9, 30.1] | 176 | 5 (–95, 105) | 40 (–57, 138) |
| (30.1, 43.8] | 164 | 89 (–13, 191) | 101 (3, 199) |
| (43.8, 51.7] | 178 | 71 (–28, 171) | 101 (4, 198) |
| >51.7 | 168 | 74 (–27, 175) | 87 (–11, 184) |
| Weeks 13 to 26 | | | |
| [0.0, 1.8] | 159 | 0 | 0 |
| (1.8, 29.3] | 177 | –56 (–158, 45) | 0 (–98, 98) |
| (29.3, 44.9] | 169 | 1 (–101, 104) | 55 (–45, 154) |
| (44.9, 51.7] | 172 | –58 (–160, 44) | –3 (–101, 95) |
| >51.7 | 175 | –29 (–130, 73) | 1 (–96, 99) |
| Week 27 until birth | | | |
| [0.0, 1.1] | 170 | 0 | 0 |
| (1.1, 28.5] | 158 | 38 (–65, 141) | –15 (–114, 83) |
| (28.5, 44.7] | 165 | –35 (–137, 67) | –17 (–114, 81) |
| (44.7, 52.3] | 175 | –20 (–120, 80) | –16 (–113, 82) |
| >52.3 | 166 | 16 (–86, 117) | –8 (–105, 90) |
| HAA9 ingested amount (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0.1] | 169 | 0 | 0 |
| (0.1, 5.6] | 170 | 112 (11, 212) | 70 (–30, 169) |
| (5.6, 36.4] | 170 | 43 (–58, 143) | 12 (–87, 111) |
| (36.4, 81.7] | 173 | 115 (16, 215) | 111 (13, 208) |
| >81.7 | 170 | 134 (34, 234) | 113 (13, 213) |
| Weeks 13 to 26 | | | |
| [0.0, 0.2] | 166 | 0 | 0 |
| (0.2, 7.1] | 171 | 48 (–53, 148) | 57 (–40, 154) |
| (7.1, 42.3] | 169 | 108 (7, 209) | 111 (13, 208) |
| (42.3, 88.4] | 174 | 42 (–59, 142) | 55 (–44, 154) |
| >88.4 | 172 | 99 (–2, 199) | 90 (–9, 190) |
| Week 27 until birth | | | |
| [0.0, 0] | 163 | 0 | 0 |
| (0, 6] | 167 | –22 (–124, 80) | –9 (–107, 89) |
| (6, 42] | 166 | 55 (–47, 158) | 91 (–8, 191) |
| (42, 92.7] | 169 | 32 (–70, 134) | 21 (–79, 121) |
| >92.7 | 169 | 44 (–58, 146) | 45 (–55, 146) |

*Adjusted for maternal caffeine intake, race, education, income, smoking, body mass index (BMI), employment, diabetes status, live birth history, gestational age and gestational age$^2$.

**Table 8.32**
**Association between $CHCl_3$ exposure and term birth weight, all RFTS sites**

| $CHCl_3$ Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| CHCl3 water concentration (µg/L) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0.1] | 336 | 0 | 0 |
| (0.1, 9.7] | 345 | –66 (–136, 4) | –59 (–125, 8) |
| (9.7, 32.8] | 335 | 3 (–67, 74) | –38 (–107, 31) |
| (32.8, 48.6] | 355 | 41 (–29, 110) | –7 (–73, 60) |
| >48.6 | 367 | 86 (18, 155) | 20 (–47, 86) |
| Weeks 13 to 26 | | | |
| [0.0, 0.1] | 351 | 0 | 0 |
| (0.1, 12.2] | 324 | –35 (–105, 36) | 8 (–59, 75) |
| (12.2, 30.7] | 338 | –17 (–87, 53) | –43 (–110, 24) |
| (30.7, 48.7] | 365 | 87 (19, 155) | 29 (–37, 94) |
| >48.7 | 360 | 51 (–18, 119) | 20 (–46, 85) |
| Week 27 until birth | | | |
| [0.0, 0.1] | 331 | 0 | 0 |
| (0.1, 10.9] | 329 | –10 (–81, 61) | –18 (–86, 51) |
| (10.9, 30.4] | 336 | 9 (–62, 80) | –6 (–75, 62) |
| (30.4, 48.2] | 349 | 97 (27, 167) | 12 (–56, 80) |
| >48.2 | 347 | 84 (14, 155) | 28 (–39, 96) |
| CHCl3 ingested amount (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0] | 382 | 0 | 0 |
| (0, 0.2] | 304 | –5 (–75, 65) | 26 (–42, 93) |
| (0.2, 12.5] | 339 | –49 (–117, 19) | –10 (–76, 56) |
| (12.5, 53.5] | 347 | 44 (–23, 112) | 37 (–29, 103) |
| >53.5 | 363 | 77 (10, 144) | 56 (–10, 121) |
| Weeks 13 to 26 | | | |
| [0.0, 0] | 342 | 0 | 0 |
| (0, 0.1] | 347 | –47 (–116, 23) | 25 (–43, 92) |
| (0.1, 4.6] | 334 | –79 (–150, –9) | –4 (–73, 64) |
| (4.6, 17.8] | 351 | –6 (–76, 63) | 19 (–49, 87) |
| >17.8 | 361 | 20 (–49, 89) | 35 (–33, 103) |
| Week 27 until birth | | | |
| [0.0, 0] | 384 | 0 | 0 |
| (0, 0.3] | 281 | –21 (–93, 52) | 0 (–68, 69) |
| (0.3, 15.8] | 331 | –56 (–125, 12) | –30 (–96, 37) |
| (15.8, 57.5] | 346 | 5 (–64, 73) | 15 (–51, 80) |
| >57.5 | 350 | 55 (–13, 123) | 29 (–37, 96) |

(continued)

**Table 8.32 (continued)**

| $CHCl_3$ Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| CHCl3 total integrated exposure (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0] | 333 | 0 | 0 |
| (0, 0.3] | 345 | –81 (–151, –11) | –43 (–110, 24) |
| (0.3, 0.8] | 350 | 29 (–41, 98) | –19 (–87, 48) |
| (0.8, 1.4] | 354 | 64 (–5, 134) | 14 (–52, 81) |
| >1.4 | 349 | 6 (–64, 76) | –8 (–76, 59) |
| Weeks 13 to 26 | | | |
| [0.0, 0] | 348 | 0 | 0 |
| (0, 0] | 329 | –93 (–163, –23) | –32 (–99, 34) |
| (0, 0.2] | 360 | 15 (–54, 84) | –16 (–81, 49) |
| (0.2, 0.5] | 345 | 27 (–42, 97) | –3 (–68, 63) |
| >0.5 | 349 | –25 (–94, 45) | –20 (–88, 47) |
| Week 27 until birth | | | |
| [0.0, 0] | 329 | 0 | 0 |
| (0, 0.2] | 325 | 11 (–60, 83) | 10 (–58, 78) |
| (0.2, 0.8] | 349 | 62 (–8, 133) | –4 (–72, 63) |
| (0.8, 1.3] | 345 | 119 (48, 190) | 37 (–31, 105) |
| >1.3 | 344 | 72 (1, 143) | 32 (–36, 100) |
| | | | |
| CHCl3 shower/bath (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0] | 335 | 0 | 0 |
| (0, 0.2] | 343 | –57 (–127, 13) | –12 (–80, 55) |
| (0.2, 0.7] | 354 | 46 (–24, 116) | 4 (–63, 71) |
| (0.7, 1.1] | 353 | 87 (17, 156) | 26 (–41, 92) |
| >1.1 | 349 | 8 (–62, 78) | 8 (–59, 76) |
| Weeks 13 to 26 | | | |
| [0.0, 0] | 347 | 0 | 0 |
| (0, 0] | 331 | –85 (–156, –15) | –36 (–103, 30) |
| (0, 0.2] | 360 | –19 (–88, 50) | –43 (–108, 22) |
| (0.2, 0.4] | 352 | 24 (–46, 93) | –1 (–66, 65) |
| >0.4 | 344 | –23 (–93, 46) | –22 (–90, 45) |
| Week 27 until birth | | | |
| [0.0, 0] | 324 | 0 | 0 |
| (0, 0.2] | 327 | 23 (–49, 95) | –1 (–69, 68) |
| (0.2, 0.6] | 349 | 60 (–11, 131) | –7 (–74, 61) |
| (0.6, 1] | 348 | 105 (34, 175) | –8 (–76, 61) |
| >1 | 344 | 78 (7, 149) | 32 (–36, 100) |

*Adjusted for maternal caffeine intake, race, education, income, smoking, body mass index (BMI), employment, diabetes status, live birth history, gestational age and gestational age$^2$.

**Table 8.33**
**Association between THM-Br exposure and term birth weight, all RFTS sites**

| THM-Br Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| THM-Br water concentration (µg/L) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 3.1] | 341 | 0 | 0 |
| (3.1, 12.8] | 343 | –9 (–79, 61) | –30 (–97, 36) |
| (12.8, 17.9] | 356 | 95 (25, 164) | 14 (–53, 81) |
| (17.9, 31.6] | 361 | 49 (–20, 118) | –19 (–85, 48) |
| >31.6 | 337 | –18 (–88, 52) | –44 (–112, 25) |
| Weeks 13 to 26 | | | |
| [0.0, 3.2] | 349 | 0 | 0 |
| (3.2, 12.7] | 331 | –1 (–71, 69) | 9 (–57, 75) |
| (12.7, 17.6] | 363 | 104 (35, 172) | 46 (–20, 111) |
| (17.6, 32.7] | 359 | 69 (0, 137) | 11 (–55, 77) |
| >32.7 | 336 | –31 (–101, 38) | –46 (–116, 23) |
| Week 27 until birth | | | |
| [0.0, 3.4] | 326 | 0 | 0 |
| (3.4, 12.7] | 338 | 44 (–27, 115) | 12 (–55, 79) |
| (12.7, 17.1] | 355 | 129 (59, 199) | 51 (–17, 119) |
| (17.1, 32.5] | 350 | 108 (37, 178) | 29 (–40, 97) |
| >32.5 | 323 | –16 (–88, 56) | –54 (–126, 17) |
| THM-Br ingested amount (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0] | 354 | 0 | 0 |
| (0, 4.6] | 344 | –26 (–95, 43) | 10 (–58, 78) |
| (4.6, 11.4] | 335 | 2 (–68, 72) | 28 (–39, 96) |
| (11.4, 31.7] | 350 | 26 (–43, 95) | 22 (–45, 89) |
| >31.7 | 352 | 52 (–17, 121) | 49 (–19, 116) |
| Weeks 13 to 26 | | | |
| [0.0, 1.9] | 346 | 0 | 0 |
| (1.9, 5.8] | 341 | –31 (–101, 39) | 9 (–58, 77) |
| (5.8, 13.8] | 339 | –4 (–74, 66) | 3 (–65, 70) |
| (13.8, 36] | 356 | 6 (–63, 75) | 24 (–43, 91) |
| >36 | 353 | 5 (–64, 74) | 5 (–63, 74) |
| Week 27 until birth | | | |
| [0.0, 1.2] | 336 | 0 | 0 |
| (1.2, 5.8] | 335 | –68 (–139, 3) | –22 (–91, 47) |
| (5.8, 13.7] | 334 | –35 (–106, 36) | –6 (–75, 62) |
| (13.7, 36.4] | 347 | 3 (–68, 73) | 39 (–29, 107) |
| >36.4 | 340 | –23 (–93, 48) | –11 (–81, 58) |

(continued)

**Table 8.33 (continued)**

| THM-Br Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| THM-Br total integrated exposure (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0.1] | 341 | 0 | 0 |
| (0.1, 0.2] | 345 | –60 (–130, 9) | –14 (–80, 52) |
| (0.2, 0.4] | 363 | 33 (–36, 102) | 20 (–45, 86) |
| (0.4, 0.8] | 348 | –35 (–105, 34) | –42 (–108, 25) |
| >0.8 | 334 | –103 (–173, –32) | –41 (–112, 30) |
| Weeks 13 to 26 | | | |
| [0.0, 0.1] | 345 | 0 | 0 |
| (0.1, 0.2] | 343 | –54 (–123, 16) | –11 (–77, 55) |
| (0.2, 0.4] | 356 | 32 (–38, 101) | 8 (–57, 73) |
| (0.4, 0.8] | 351 | –30 (–99, 39) | –38 (–104, 29) |
| >0.8 | 336 | –82 (–152, –12) | –25 (–95, 45) |
| Week 27 until birth | | | |
| [0.0, 0.1] | 329 | 0 | 0 |
| (0.1, 0.2] | 337 | –26 (–97, 46) | –20 (–87, 47) |
| (0.2, 0.3] | 348 | 58 (–12, 129) | –4 (–72, 63) |
| (0.3, 0.7] | 345 | 5 (–66, 75) | –31 (–99, 37) |
| >0.7 | 333 | –37 (–108, 35) | –31 (–101, 39) |
| THM-Br shower/bath (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0.1] | 341 | 0 | 0 |
| (0.1, 0.2] | 346 | –24 (–93, 46) | 18 (–49, 84) |
| (0.2, 0.4] | 364 | 23 (–46, 92) | 15 (–50, 80) |
| (0.4, 0.8] | 349 | –20 (–89, 50) | –19 (–85, 48) |
| >0.8 | 334 | –95 (–166, –25) | –36 (–106, 35) |
| Weeks 13 to 26 | | | |
| [0.0, 0.1] | 344 | 0 | 0 |
| (0.1, 0.2] | 344 | –46 (–116, 23) | –7 (–73, 59) |
| (0.2, 0.3] | 362 | 39 (–30, 108) | 27 (–38, 92) |
| (0.3, 0.7] | 346 | –32 (–102, 37) | –39 (–106, 27) |
| >0.7 | 338 | –85 (–155, –15) | –26 (–96, 44) |
| Week 27 until birth | | | |
| [0.0, 0.1] | 329 | 0 | 0 |
| (0.1, 0.2] | 338 | –17 (–88, 54) | –13 (–81, 54) |
| (0.2, 0.3] | 349 | 57 (–13, 128) | –2 (–70, 65) |
| (0.3, 0.7] | 343 | 11 (–60, 82) | –25 (–94, 43) |
| >0.7 | 333 | –32 (–104, 39) | –26 (–97, 44) |

*Adjusted for maternal caffeine intake, race, education, income, smoking, body mass index (BMI), employment, diabetes status, live birth history, gestational age and gestational age$^2$

**Table 8.34**
**Association between HAA5 exposure and term birth weight, all RFTS sites**

| HAA-5 Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| HAA5 water concentration (µg/L)** | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0] | 353 | 0 | 0 |
| (0, 19.1] | 328 | –57 (–127, 13) | –62 (–128, 5) |
| (19.1, 26.2] | 338 | 6 (–63, 76) | –34 (–101, 34) |
| (26.2, 38] | 358 | 61 (–7, 130) | –2 (–68, 64) |
| >38 | 361 | 90 (22, 158) | 17 (–48, 83) |
| Weeks 13 to 26 | | | |
| [0.0, 0] | 367 | 0 | 0 |
| (0, 19.1] | 310 | –37 (–108, 33) | 13 (–55, 80) |
| (19.1, 26.1] | 335 | 3 (–66, 72) | –30 (–98, 37) |
| (26.1, 38.4] | 360 | 62 (–6, 130) | 18 (–47, 83) |
| >38.4 | 366 | 82 (15, 150) | 35 (–30, 99) |
| Week 27 until birth | | | |
| [0.0, 0] | 483 | 0 | 0 |
| (0, 18.6] | 173 | –26 (–107, 55) | 8 (–71, 86) |
| (18.6, 24.6] | 338 | 5 (–60, 70) | –14 (–77, 49) |
| (24.6, 40] | 345 | 73 (8, 137) | 15 (–47, 78) |
| >40 | 353 | 91 (26, 155) | 39 (–22, 101) |
| HAA5 ingested amount (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0] | 535 | 0 | 0 |
| (0, 0.5] | 154 | –12 (–95, 72) | –21 (–100, 58) |
| (0.5, 25.5] | 335 | 4 (–60, 67) | –9 (–70, 52) |
| (25.5, 58.8] | 353 | 58 (–5, 120) | –12 (–73, 49) |
| >58.8 | 358 | 112 (50, 175) | 54 (–6, 115) |
| Weeks 13 to 26 | | | |
| [0.0, 0] | 473 | 0 | 0 |
| (0, 0.7] | 207 | –41 (–117, 35) | 5 (–68, 79) |
| (0.7, 31.5] | 339 | 6 (–59, 71) | –5 (–68, 58) |
| (31.5, 63.1] | 352 | 54 (–10, 119) | 11 (–50, 73) |
| >63.1 | 364 | 96 (33, 160) | 48 (–14, 109) |
| Week 27 until birth | | | |
| [0.0, 0] | 629 | 0 | 0 |
| (0, 0.2] | 27 | 87 (–93, 267) | 106 (–64, 277) |
| (0.2, 30] | 340 | 3 (–59, 65) | –8 (–67, 51) |
| (30, 65.1] | 343 | 42 (–20, 103) | 25 (–34, 84) |
| >65.1 | 353 | 103 (42, 164) | 39 (–20, 99) |

*Adjusted for maternal caffeine intake, race, education, income, smoking, body mass index (BMI), employment, diabetes status, live birth history, gestational age and gestational age$^2$
** No RFTS study subjects exposed above regulatory cutpoint (>= 60 µg/L)

**Table 8.35**
**Association between HAA-Br exposure and term birth weight, all RFTS sites**

| HAA-Br Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| HAA-Br water concentration (µg/L) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 1.9] | 348 | 0 | 0 |
| (1.9, 8.3] | 333 | 78 (8, 148) | 37 (–30, 104) |
| (8.3, 11.3] | 356 | 88 (19, 157) | 6 (–60, 73) |
| (11.3, 17.1] | 364 | 141 (72, 209) | 60 (–6, 127) |
| >17.1 | 337 | 28 (–42, 98) | –14 (–83, 56) |
| Weeks 13 to 26 | | | |
| [0.0, 1.8] | 352 | 0 | 0 |
| (1.8, 8.1] | 331 | 50 (–20, 120) | 36 (–30, 102) |
| (8.1, 11.1] | 355 | 132 (63, 201) | 66 (0, 131) |
| (11.1, 17.1] | 365 | 82 (14, 150) | 22 (–44, 88) |
| >17.1 | 335 | –3 (–73, 67) | –23 (–92, 46) |
| Week 27 until birth | | | |
| [0.0, 1.1] | 335 | 0 | 0 |
| (1.1, 7.9] | 332 | –16 (–87, 55) | 31 (–37, 98) |
| (7.9, 11] | 350 | 106 (36, 176) | 55 (–12, 122) |
| (11, 16.9] | 352 | 66 (–4, 135) | 31 (–35, 98) |
| >16.9 | 323 | –37 (–108, 35) | –37 (–107, 34) |
| HAA-Br ingested amount (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 0.1] | 346 | 0 | 0 |
| (0.1, 3.6] | 349 | 17 (–53, 86) | 33 (–34, 101) |
| (3.6, 10] | 339 | 81 (11, 151) | 40 (–28, 107) |
| (10, 21.2] | 359 | 74 (5, 142) | 27 (–39, 93) |
| >21.2 | 342 | 79 (9, 149) | 52 (–16, 120) |
| Weeks 13 to 26 | | | |
| [0.0, 0.1] | 348 | 0 | 0 |
| (0.1, 4.5] | 340 | 14 (–56, 84) | 33 (–33, 100) |
| (4.5, 11.1] | 343 | 31 (–39, 100) | –5 (–72, 62) |
| (11.1, 23.1] | 352 | 72 (3, 142) | 44 (–23, 111) |
| >23.1 | 352 | 34 (–35, 104) | 13 (–54, 80) |
| Week 27 until birth | | | |
| [0.0, 0] | 442 | 0 | 0 |
| (0, 3.7] | 224 | –6 (–82, 69) | 8 (–64, 79) |
| (3.7, 11.1] | 341 | 29 (–37, 96) | 10 (–54, 73) |
| (11.1, 24.1] | 345 | 57 (–9, 123) | 50 (–14, 113) |
| >24.1 | 340 | 16 (–51, 82) | 2 (–62, 67) |

*Adjusted for maternal caffeine intake, race, education, income, smoking, body mass index (BMI), employment, diabetes status, live birth history, gestational age and gestational age$^2$.

**Table 8.36**
**Association between TOX exposure and term birth weight, all RFTS sites**

| TOX Exposure | n | Crude mean change in birth weight (grams) | Adjusted* mean change in birth weight (grams) |
|---|---|---|---|
| TOX water concentration (µg/L) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 16.9] | 331 | 0 | 0 |
| (16.9, 150.7] | 352 | 58 (–12, 128) | 25 (–42, 91) |
| (150.7, 172] | 347 | 103 (33, 173) | 25 (–43, 92) |
| (172, 181.8] | 355 | 90 (20, 160) | 16 (–52, 84) |
| >181.8 | 353 | 54 (–16, 124) | 20 (–48, 87) |
| Weeks 13 to 26 | | | |
| [0.0, 17.7] | 349 | 0 | 0 |
| (17.7, 149.1] | 331 | 52 (–19, 122) | 51 (–16, 117) |
| (149.1, 173.6] | 355 | 102 (33, 171) | 39 (–27, 106) |
| (173.6, 186.5] | 363 | 45 (–24, 113) | 1 (–64, 67) |
| >186.5 | 340 | 58 (–11, 128) | 27 (–41, 95) |
| Week 27 until birth | | | |
| [0.0, 18.7] | 326 | 0 | 0 |
| (18.7, 146] | 338 | 12 (–60, 83) | –12 (–79, 56) |
| (146, 173.9] | 353 | 97 (26, 168) | 7 (–61, 76) |
| (173.9, 188.1] | 345 | 54 (–17, 125) | –8 (–77, 60) |
| >188.1 | 330 | 24 (–47, 96) | –20 (–89, 49) |
| TOX ingested amount (µg/day) | | | |
| Weeks 0 to 12 | | | |
| [0.0, 14.9] | 348 | 0 | 0 |
| (14.9, 41.7] | 343 | 10 (–59, 80) | –1 (–69, 66) |
| (41.7, 116.9] | 339 | 30 (–39, 100) | 3 (–64, 70) |
| (116.9, 279.1] | 353 | 87 (18, 156) | 25 (–42, 92) |
| >279.1 | 352 | 77 (8, 147) | 27 (–40, 95) |
| Weeks 13 to 26 | | | |
| [0.0, 21.2] | 339 | 0 | 0 |
| (21.2, 51.7] | 344 | 28 (–43, 98) | 20 (–47, 87) |
| (51.7, 141.4] | 340 | 31 (–39, 102) | –7 (–74, 61) |
| (141.4, 315.8] | 357 | 55 (–15, 124) | 28 (–39, 95) |
| >315.8 | 355 | 84 (14, 153) | 27 (–41, 95) |
| Week 27 until birth | | | |
| [0.0, 19.8] | 325 | 0 | 0 |
| (19.8, 50.7] | 340 | 24 (–48, 95) | 22 (–46, 90) |
| (50.7, 145.7] | 334 | 22 (–50, 93) | –25 (–94, 44) |
| (145.7, 329.3] | 347 | 56 (–15, 127) | 46 (–23, 115) |
| >329.3 | 346 | 75 (3, 146) | 20 (–50, 89) |

*Adjusted for maternal caffeine intake, race, education, income, smoking, body mass index (BMI), employment, diabetes status, live birth history, gestational age and gestational age$^2$.

## INTERPRETATION

### Summary of Results

This pattern of results for preterm birth is not readily interpretable, with a high degree of consistency in the finding of an inverse association between especially concentration and ingested amount of DBP and risk of preterm birth. While the stronger inverse association associated with ingested amount may somehow be a reflection of the uncontrolled influence of water consumption or availability of home filters, water use would not affect the association of water concentration and outcome. It is difficult to propose some mechanism by which elevated levels of DBPs would causally reduce risk of preterm birth, other than by invoking some selective loss that leaves a heartier group of fetal survivals who are less prone to be adversely affected by chemical exposures. Nonetheless, it is difficult to dismiss the fairly consistent indications of an inverse association as a product of random error.

The pattern for SGA is quite different than for preterm birth, for which associations were largely inverse. The evidence for a possible influence of THM4 and BDCM on SGA births is difficult to dismiss as random error or an artifact of study design. The concentration of effect in later pregnancy (second and third trimesters) is consistent with the more rapid fetal growth in later pregnancy, making that the most likely period for exogenous influences to exert an effect However, there was not a clear downward shift in birth weight associated with higher levels of any of the DBPs, contradicting to some extent the results from the SGA analysis. It should be noted that the analysis of birth weight excluded preterm births (N = 196) that were included in the analysis of SGA but this is unlikely to have a major impact on the overall pattern.

Inherent in this study, the examination of multiple agents, exposure indices, time periods, and outcomes creates abundant opportunity for spurious associations to arise through random processes. Furthermore, the strong association of study site with DBP exposure levels introduces the potential for confounding that may be intractable despite our best efforts to control individual-level influences on pregnancy outcome.

### Comparison with Previous Studies

In contrast to the inverse association between preterm birth and THM exposure found this study, previous studies of this issue have generally indicated no association, with estimated relative risks (RRs) for preterm birth ranging between 0.7–1.2 and showing no notable dose-response trends (Savitz et al. 1995; Gallagher et al. 1998; Dodds et al. 1999; Wright et al. 2003). To date, only two studies have examined the association between BDCM and preterm birth (Wright et al. 2003; Kramer et al. 1992). Kramer et al. reported an OR for preterm birth of 1.1 (95% CI: 0.6–1.5) when comparing women with exposure to residential levels of BDCM > 10 μg/L to women with non-detectable residential BDCM levels, suggesting no effect. However, Wright et al. found a weak inverse effect of residential BDCM exposure on risk of preterm birth. We also found a weak inverse association between BDCM residential water concentrations and preterm birth, especially for first trimester exposure; however, results were largely null for other measures of exposure (i.e. showering/bathing, integrated exposure). Considering both previous studies and our study collectively, there appears to be little evidence to support an association between THMs and preterm birth.

Similar to our study, previous studies of the reproductive health effects of DBPs seem to provide greater support for increased risk of SGA associated with higher THM exposure. 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 (Dodds et al. 1999; Wright et al. 2003; Bove et al. 1995; Infante-Rivard 2004) and 1.1–1.7 for BDCM (Wright et al. 2003; Kramer et al. 1992), with the exception of a more recent study by Infante-Rivard which reported an inverse association (OR = 0.84; 95% CI: 0.5, 1.43 comparing residential BDCM > 6.3 μg/L to ≤ 6.3 μg/L). Of note, we found the strongest association between SGA and THM4 for exposure through showering/bathing alone and integrated exposure through water consumption plus showering/bathing. To date, there are no other studies of SGA that have used an exposure index modified for water consumption and use with which we can compare our study results.

While several studies of the impact of TTHM exposure on birth weight have been published, the majority of these studies have only provide results for risk of low birth weight (birth weight < 2,500 grams) and very low birth weight (birth weight < 1,500 grams) (Savitz et al. 1995; Gallagher et al. 1998; Dodds et al. 1999; Toledano et al. 2005). Only two studies have examined the association between term birth weight in grams (Wright et al. 2003; Bove et al. 1995) and both studies seem to suggest an decrease in birth weight associated with higher residential THM levels. In particular, Bove et al. reported a change in mean birth weight of –70.4 grams (99% CI: –23.8 grams, –117.0 grams) when comparing women exposed to residential levels of TTHMs > 100 μg/L to women exposed to levels between 0–20 μg/L TTHM. On the contrary, we did not find an association between term birth weight and THM exposure in our study.

Only one previous study by Wright et al. (2003) has examined the association between HAA exposure and measures of reduced fetal growth. They found a mean change in birth weight of 7 grams (95% CI: –25 grams, 39 grams), OR for SGA of 0.97 (95% CI: 0.77, 1.23) and OR for preterm birth of 1.03 (95% CI: 0.77, 1.39) when comparing women exposed to residential HAA5 levels between 49–58 μg/L to women with a residential HAA5 level between 4–30 μg/L, which is consistent with our findings of no association between HAA exposure and fetal growth restriction.

# CHAPTER 9
# BLOOD BIOMARKER STUDY

## INTRODUCTION

The blood biomarker study was conducted in order to determine whether exposure to trihalomethanes (THMs) of project participants differs as a function of the site in which they live. The study was not designed to examine the impact of differing water use activities (e.g., ingestion, bathing) on THMs in the blood but rather to identify a representative baseline level of blood THMs and to determine whether that baseline level varied as a result of the different concentrations of tap water THMs across the three project sites. It was anticipated that there would be relatively elevated levels of chlorinated THMs in the blood of Site 1 participants, low levels of all THMs in Site 2 participants, and elevated levels of brominated THMs in Site 3 participants. Because there was a clear seasonal variation in DBP levels in Site 1 tap water, we sought to collect blood from a subset of women in the summer and winter seasons. We attempted to collect blood samples from the same individual women in both seasons in order to determine whether the magnitude of variation in tap water THM levels by season would lead to a parallel variation in blood THM levels.

## FIELD METHODS

Recruitment: Right from the Start participants were eligible to take part in the blood biomarker study if they met the following enrollment criteria:

- at least 30 days postpartum.
- not pregnant at the time of screening and enrollment.
- still resident within the study areas.
- household served by city water.

A RFTS staff person called participants who were expected to be at least 30 days past their date of delivery to assess their willingness to participate in the study. The target enrollment for Site 1 was 50 women who would ideally provide water and blood samples twice and 50 women each for Sites 2 and 3. In Site 1, 104 women were screened and 71 women were judged to be eligible and agreed to participate in the study; not all of them provided specimens in both summer and winter. Ninety-one women were screened in Site 2 and 58 women participated in the study. For Site 3, 61 women were screened for the study and 50 women were eligible and agreed to participate. At the time of screening, staff reviewed with participants the overall study objectives, methods of collecting blood and water samples, and provided information on the monetary incentive at the time of screening. If a woman agreed to enroll in the blood biomarker study, a morning home visit appointment was scheduled for the collection of blood and water samples.

For Site 1, blood and tap water samples were collected from study participants once in the summer and once in the winter. In Sites 2 and 3, samples were collected from each study participant at only one point in time.

Portamedic, subcontractor of Hooper Holmes, was responsible for the sampling of water and blood during each home visit for Sites 1, 2, and 3. Portamedic examiners, hired for the blood biomarker study, were trained on the study protocol and ethical conduct in human subjects research. In addition to the collection of blood and water samples, examiners collected signed consent forms and 24-hour water activity diaries from participants on the morning of each home visit. They were also responsible for sending samples directly to the Centers for Disease Control and Prevention (CDC) laboratory via overnight carrier and pertinent study documents back to RFTS. CDC collaborators conducted the laboratory analyses of blood and water samples.

RFTS staff mailed a copy of the consent form, HIPAA authorization form, and 24-hour water activity diary to each study participant within 24 hours of enrollment in the blood biomarker study. RFTS also notified Hooper Holmes of each home visit appointment within 24 hours of subject screening and enrollment.

Participants were asked to complete the water activity diary 24-hours prior to the home visit. RFTS staff called participants 48-hours prior to the scheduled blood draw to discuss any questions they may have had pertaining to the study. At the time of the reminder call, RFTS staff provided instructions for filling out the water activity diary and reminded participants not to have any contact with water at least four hours preceding their home visit appointments. All participants in the blood biomarker study were asked to sign a consent form and HIPAA authorization on the morning of the home visit. The Portamedic examiner, a trained phlebotomist, obtained the signed consent form prior to collecting blood and water samples. All study participants received a copy of the signed consent and HIPAA authorization forms. Portamedic examiners also collected the 24-hour water activity diary during the home visits.

Portamedic examiners asked the study participant what the time of her last contact with water was, and recorded this information on the tracking form. If the participant had showered, bathed, or bathed anyone else within one hour of the home visit then blood was not drawn. Once the consent form was signed, the examiner collected a 10 mL blood sample from the participant via venipuncture into gray-top glass tubes (Vacutainer®, Becton Dickinson, Franklin Lakes, NJ) that were specially treated before use to remove background THM contamination (Cardinali et al. 1995). The blood samples were mixed thoroughly to dissolve the anticoagulant immediately after the blood draw. A 12mL water sample was also collected during the same home visit from a non-aerated, cold water tap. All water samples were collected into headspace-free 12-mL glass vials with screw-caps. Residual chlorine was quenched with sodium thiosulfate. No identifying information was included with the blood and water samples.

All blood and water samples were kept in coolers until they were shipped to the CDC. Portamedic examiners sent the blood and water samples to the CDC via overnight carrier weekly (Sites 1 and 2) and daily (Site 3). The examiners also sent the 24-hour water activity diaries, tracking forms, and consent and HIPAA authorization forms via overnight carrier to RFTS weekly. A monetary incentive of $25 was mailed to the study participants upon completion of the 24-hour water activity diary and collection of blood and water samples.

## LABORATORY METHODS

### Blood Samples

THM concentrations in whole blood were quantified using solid phase microextraction gas chromatography/isotope dilution mass spectroscopy (Bonin et al. 2005). Stable isotopically-

labeled analogs of the compounds of interest were added to 3 g of blood and this entire sample sealed in a 10-ml headspace vial. The sample was heated (30°C) and agitated (500 rpm) using a CTC CombiPal SPME autosampler (LEAP Technology, Carrboro, NC) to facilitate extraction of volatiles from the sample headspace onto a SPME fiber (Carboxen/PDMS, Supelco, Bellefonte, PA). Once the 6-min extraction cycle was complete, the fiber was inserted into hot GC inlet to desorb all volatile compounds. As the compounds were desorbed, they were trapped at the head of a DB-624 capillary column by a liquid nitrogen cryotrap at –150°C. Subsequently, the cryotrap was ballistically heated to 200°C to volatilize trapped compounds. The temperature of the gas chromatograph oven increased more slowly to chromatographically resolve the volatile components from the sample. Compounds eluting from the capillary column entered a magnetic sector mass spectrometer (Thermo MAT95, San Jose, CA) tuned for 10000 resolution and operated in selected ion reporting mode. Quantification was accomplished from specific ion responses relative to those of the corresponding labeled analogs. The responses of analytes and analogs were corrected for contributions from each other through the use of an isotope dilution calculation (Ashley et al. 1992). Final quantification was based on daily seven-point calibration curves and the concentrations were normalized according to sample weight.

**Water Samples**

THM concentrations in water were quantified using solid phase microextraction gas chromatography/isotope dilution mass spectroscopy (Cardinali et al. 2004). Stable isotopically-labeled analogs of the compounds of interest were added to 5 mL of water and this entire sample sealed in a 10-ml headspace vial. The sample was heated (50°C) and agitated (500 rpm) using a CTC CombiPal SPME autosampler (LEAP Technology, Carrboro, NC) to facilitate extraction of volatiles from the sample headspace onto a SPME fiber (Carboxen/PDMS, Supelco, Bellefonte, PA). Once the 8-min extraction cycle was complete, the fiber was inserted into the hot GC inlet to desorb all volatile compounds. As the compounds were desorbed, they were trapped at the head of a DB-VRX capillary column by a liquid nitrogen cryotrap at –150°C. Subsequently, the cryotrap was ballistically heated to 200°C. The temperature of the gas chromatograph oven increased more slowly to chromatographically resolve the volatile components in the sample. Compounds eluting from the capillary column entered the quadrupole mass spectrometer (Thermo TraceMS, San Jose, CA) and were detected in selected ion monitoring mode. Quantification was accomplished from specific ion responses relative to those of the corresponding labeled analogs. The responses of analytes and analogs were corrected for contributions from each other through the use of an isotope dilution calculation (Ashley et al. 1992). Final quantification was based on daily seven-point calibration curves and the concentrations were normalized according to sample weight.

**Statistical Methods**

Data for the blood and tap water samples were provided in two separate MS Excel files by the CDC. The Excel files were imported and merged in SAS version 8.0 for all data analysis.

Total THM4 concentration for blood and tap water samples were calculated by summing across all THM components ($CHCl_3$, $CHBrCl_2$, $CHBr_2Cl$, and $CHBr_3$). Any THM species with levels less than the minimum detection limit were reported as the detection limit, but these entries were assigned a value of “zero” in calculating THM4. Descriptive statistics were

generated to examine the mean, median, minimum, and maximum for each individual THM species and total THM4 in the blood and tap water samples. T-tests were used to compare blood THM levels across study sites and in the seasonal comparison of THM levels within Site 1. Estimates with p-values that were less than 0.05 were considered to be statistically significant. Scatterplots were created in MS Excel to provide visual comparisons between the blood and tap water concentrations for each individual THM species.

## RESULTS

### Recruitment

The final number of RFTS participants recruited into the blood biomarker study and the number of women who provided blood and water samples are shown in Table 9.1. Despite intensive efforts, we fell short of our goal of enrolling 50 women in three of the four cells, notably for Site 3. Nonetheless, these numbers are sufficient to generate reasonably stable estimates for comparisons across study sites, but less so for analyses within each study site.

**Table 9.1**
**Blood biomarker study recruitment and enrollment**

| Study Site | Number Recruited | Number Providing Samples |
|---|---|---|
| Site 1*, Winter | 55 | 51 |
| Site 1*, Summer | 54 | 49 |
| Site 2 | 58 | 49 |
| Site 3 | 50 | 32 |
| Total | 217 | 181 |

*Of those who were eligible and agreed to participate in Site 1: 32 women participated in both summer and winter collections; 22 women participated in summer collection only; and 23 women participated in winter collection only.

### Descriptive Analysis and Comparison of THM Levels

Mean, median, minimum, and maximum THM concentrations in the blood (ng/L) and tap water (μg/L) of the enrolled participants are shown in Tables 9.2 and 9.3, respectively.

**Table 9.2**
**THM levels in blood samples by study site and season**

| Study Site | N | Mean concentration (ng/L) | Median concentration (ng/L) | Maximum concentration (ng/L) | Minimum concentration (ng/L) | MRL* (ng/L) |
|---|---|---|---|---|---|---|
| **Site 1 Summer** | | | | | | |
| $CHBrCl_2$ | 42 | 5.0 | 4.0 | 17.0 | 0.9 | 0.6 |
| $CHBr_3$ | 49 | 0.3 | 0 | 2.4 | BMRL† | 1.0 |
| $CHCl_3$ | 49 | 21.7 | 18.0 | 61.0 | 5.3 | 2.1 |
| $CHBr_2Cl$ | 49 | 2.2 | 1.9 | 8.6 | BMRL | 0.6 |
| THM4 | 42 | 28.4 | 22.6 | 82.2 | 7.0 | |
| **Site 1 Winter** | | | | | | |
| $CHBrCl_2$ | 51 | 2.8 | 1.9 | 13.0 | BMRL | 0.6 |
| $CHBr_3$ | 52 | 0.1 | 0 | 1.2 | BMRL | 1.0 |
| $CHCl_3$ | 51 | 16.5 | 12.0 | 81.0 | BMRL | 2.1 |
| $CHBr_2Cl$ | 52 | 0.7 | 0.7 | 4.3 | BMRL | 0.6 |
| THM4 | 51 | 20.0 | 14.8 | 89.1 | BMRL | |
| **Site 2** | | | | | | |
| $CHBrCl_2$ | 50 | 1.3 | 1.1 | 7.4 | BMRL | 0.6 |
| $CHBr_3$ | 50 | 1.8 | 1.3 | 18.0 | BMRL | 1.0 |
| $CHCl_3$ | 50 | 15.0 | 6.1 | 130.0 | BMRL | 2.1 |
| $CHBr_2Cl$ | 50 | 1.4 | 1.3 | 10.0 | BMRL | 0.6 |
| THM4 | 50 | 19.5 | 10.4 | 132.8 | BMRL | |
| **Site 3** | | | | | | |
| $CHBrCl_2$ | 33 | 7.3 | 5.5 | 30.0 | 1.3 | 0.6 |
| $CHBr_3$ | 33 | 2.4 | 1.8 | 7.8 | BMRL | 1.0 |
| $CHCl_3$ | 33 | 11.4 | 8.6 | 47.0 | BMRL | 2.1 |
| $CHBr_2Cl$ | 33 | 7.2 | 6.3 | 27.0 | 1.5 | 0.6 |
| THM4 | 33 | 28.3 | 22.1 | 107.8 | 4.6 | |

*MRL: Minimum reporting level.
†BMRL: Below minimum reporting level. In calculating the concentrations for group parameters, the concentrations of individual species that were below the minimum reporting level were assigned a value of zero.

**Table 9.3**
**THM levels in tap water samples by study site and season**

| Study Site | N | Mean concentration (µg/L) | Median concentration (µg/L) | Maximum concentration (µg/L) | Minimum concentration (µg/L) | MRL (µg/L) |
|---|---|---|---|---|---|---|
| **Site 1, Summer** | | | | | | |
| $CHBrCl_2$ | 47 | 13.9 | 15.0 | 17.0 | 0.2 | 0.1 |
| $CHBr_3$ | 47 | 0.4 | 0.5 | 0.8 | BMRL* | 0.1 |
| $CHCl_3$ | 47 | 32.4 | 34.0 | 48.0 | 0.3 | 0.1 |
| $CHBr_2Cl$ | 47 | 5.9 | 6.4 | 7.1 | 0.2 | 0.1 |
| THM4 | 47 | 52.7 | 55.5 | 72.4 | 0.7 | |
| **Site 1, Winter** | | | | | | |
| $CHBrCl_2$ | 50 | 8.2 | 8.8 | 17.0 | 0.1 | 0.1 |
| $CHBr_3$ | 50 | 0.1 | 0 | 0.2 | BMRL | 0.1 |
| $CHCl_3$ | 50 | 24.2 | 23.5 | 65.0 | 0.2 | 0.1 |
| $CHBr_2Cl$ | 50 | 2.3 | 2.5 | 4.0 | BMRL | 0.1 |
| THM4 | 50 | 34.8 | 34.7 | 86.1 | 0.2 | |
| **Site 2** | | | | | | |
| $CHBrCl_2$ | 49 | 1.6 | 1.4 | 5.2 | BMRL | 0.1 |
| $CHBr_3$ | 49 | 1.0 | 0.6 | 8.0 | BMRL | 0.1 |
| $CHCl_3$ | 49 | 1.2 | 0.9 | 4.4 | BMRL | 0.1 |
| $CHBr_2Cl$ | 49 | 1.9 | 1.6 | 7.0 | BMRL | 0.1 |
| THM4 | 49 | 5.7 | 4.9 | 19.5 | BMRL | |
| **Site 3** | | | | | | |
| $CHBrCl_2$ | 29 | 20.5 | 18.0 | 66.0 | BMRL | 0.1 |
| $CHBr_3$ | 29 | 4.0 | 4.1 | 9.5 | BMRL | 0.1 |
| $CHCl_3$ | 29 | 19.2 | 9.6 | 85.0 | BMRL | 0.1 |
| $CHBr_2Cl$ | 29 | 18.5 | 19.0 | 41.0 | BMRL | 0.1 |
| THM4 | 29 | 62.2 | 52.7 | 197.0 | BMRL | |

*MRL: Minimum reporting level.
†BMRL: Below minimum reporting level. In calculating the concentrations for group parameters, the concentrations of individual species that were below the minimum reporting level were assigned a value of zero.

The blood levels of THMs varied by location and season in the expected direction (Table 9.2), with higher mean and median concentrations in the summer than in winter for Site 1, but with mean and median THM levels in Site 2 that were only moderately lower than those for Site 1 in winter. Site 1 summer and Site 3 mean and median concentrations were quite similar. As expected, brominated species in the blood were more prominent in Site 3 than in the other sites. The mean and median tap water levels (Table 9.3) exhibited a much more pronounced variation across study sites and between the two seasons at Site 1 than did the blood levels. Site 2 had the lowest THM levels by a large margin, Site 1 in winter had intermediate levels, and Site 1 in summer and Site 3 had the highest THM concentrations, consistent with the discussion in Chapter 3. Rather dramatic differences in tap water THM concentrations are in contrast to muted differences in blood THM levels.

**Comparison of Blood THM Levels Across Study Sites**

Mean blood THM concentrations (ng/L) across study sites are shown in Table 9.4. We compared blood THMs levels in Site 1 Summer and Site 1 Winter with Site 2, Site 1 Summer and Site 1 Winter with Site 3, and Site 2 with Site 3, for $CHBrCl_2$, $CHBr_3$, $CHCl_3$, $CHBr_2Cl$, and total THM4 (Table 9.5). Except for chloroform, Site 1 summer was clearly higher than Site 2, but Site 1 winter was found to be similar to Site 2 overall. Site 3 was modestly higher than Site 2. Even where total THMs were similar, the mix across sites and seasons tended to differ.

**Table 9.4**
**Comparison of THM levels in blood samples by site and season**

| Component | Site 1, Summer: Mean blood concentration (ng/L) | Site 1, Winter: Mean blood concentration (ng/L) | Site 2: Mean blood concentration (ng/L) | Site 3: Mean blood concentration (ng/L) |
|---|---|---|---|---|
| $CHBrCl_2$ | 5.0 | 2.8 | 1.3 | 7.3 |
| $CHBr_3$ | 0.3 | 0.1 | 1.8 | 2.4 |
| $CHCl_3$ | 21.7 | 16.5 | 15.0 | 11.4 |
| $CHBr_2Cl$ | 2.2 | 0.7 | 1.4 | 7.2 |
| THM4 | 28.4 | 20.0 | 19.5 | 28.3 |

**Table 9.5**
**Comparison of individual THM4s and total THM4 in blood samples**

| Component | Site 1 Summer versus Site 2: Test (p-value) | Site 1 Summer versus Site 3: Test (p-value) | Site 1 Winter versus Site 2: Test (p-value) | Site 1 Winter versus Site 3: Test (p-value) | Site 2 versus Site 3: Test (p-value) |
|---|---|---|---|---|---|
| $CHBrCl_2$ | Site 1 > Site 2 T=-7.14, df=90 (p<0.0001) | Site 3 > Site 1 T=1.95, df=73 (p=0.055) | Site 1 > Site 2 T=-3.56, df=99 (p=0.001) | Site 3 > Site 1 T=4.38, df=82 (p<0.0001) | Site 3 > Site 2 T=6.26, df=81 (p<0.0001) |
| $CHBr_3$ | Site 2 > Site 1 T=3.02, df=97 (p=0.003) | Site 3 > Site 1 T=7.79, df=80 (p<0.0001) | Site 2 > Site 1 T=3.73, df=100 (p=0.0003) | Site 3 > Site 1 T=9.76, df=83 (p<0.0001) | Site 3 > Site 2 T=0.98, df=81 (p=0.332) |
| $CHCl_3$ | Site 1 > Site 2 T=-1.71, df=97 (p=0.091) | Site 1 > Site 3 T=-3.71, df=80 (p=0.0004) | Site 1 = Site 2 T=-0.37, df=99 (p=0.711) | Site 1 > Site 3 T=-1.69, df=82 (p=0.096) | Site 2 > Site 3 T=-0.83, df=81 (p=0.410) |
| $CHBr_2Cl$ | Site 1 > Site 2 T=-2.47, df=90 (p=0.016) | Site 3 > Site 1 T=5.36, df=73 (p<0.0001) | Site 2 > Site 1 T=2.75, df=100 (p=0.007) | Site 3 > Site 1 T=7.93, df=83 (p<0.0001) | Site 3 > Site 2 T=6.69, df=81 (p<0.0001) |
| THM4 | Site 1 > Site 2 T=-1.97, df=90 (p=0.051) | Site 3 = Site 1 T=-0.01, df=73 (p=0.989) | Site 1 = Site 2 T=-0.13, df=99 (p=0.893) | Site 3 > Site 1 T=1.90, df=82 (p=0.061) | Site 3 > Site 2 T=1.71, df=81 (p=0.092) |

**Seasonal Comparison of THM Levels in Site 1**

Because water and blood samples were collected once in the summer and once in the winter from study participants in Site 1, we performed statistical analyses to examine whether there were statistically significant seasonal variations in THM levels. Both blood (Table 9.6) and tap water (Table 9.7) showed substantial seasonal variation, with higher levels in summer.

**Table 9.6**
**Blood samples: comparison of THM species by season in Site 1**

| Compound | Season | Mean blood concentration (ng/L) | Test (p-value) |
|---|---|---|---|
| $CHBrCl_2$ | Summer | 5.0 | T=3.57, df =91 |
| | Winter | 2.8 | (p=0.001) |
| $CHBr_3$ | Summer | 0.30 | T=2.82, df =99 |
| | Winter | 0.10 | (p=0.006) |
| $CHCl_3$ | Summer | 21.7 | T=1.77, df =98 |
| | Winter | 16.5 | (p=0.080) |
| $CHBr_2Cl$ | Summer | 2.2 | T=6.03, df =92 (p<0.0001) |
| | Winter | 0.7 | |
| THM4 | Summer | 28.4 | T=2.22, df =91 |
| | Winter | 20.0 | (p=0.029) |

**Table 9.7**
**Tap water samples: comparison of THM species by season in Site 1**

| Compound | Season | Mean water concentration (µg/L) | Test (p-value) |
|---|---|---|---|
| $CHBrCl_2$ | Summer | 13.9 | T=8.64, df =95 |
| | Winter | 8.2 | (p<0.0001) |
| $CHBr_3$ | Summer | 0.4 | T=18.9, df =95 |
| | Winter | 0.1 | (p<0.0001) |
| $CHCl_3$ | Summer | 32.4 | T=3.42, df =95 |
| | Winter | 24.2 | (p=0.0009) |
| $CHBr_2Cl$ | Summer | 5.9 | T=15.21, df =95 (p<0.0001) |
| | Winter | 2.3 | |
| THM4 | Summer | 52.7 | T=5.66, df =95 |
| | Winter | 34.8 | (p<0.0001) |

## Comparison of Blood and Water THM Concentrations Among All Subjects

We compared the levels of individual THM species in the blood of each of the subjects with the species concentrations in her tap water at the time the blood sample was taken. Figures 9.1 and 9.2 show that no simple linear relationship was apparent between these paired blood and water measurements for chloroform or bromodichloromethane, respectively, across all three study sites

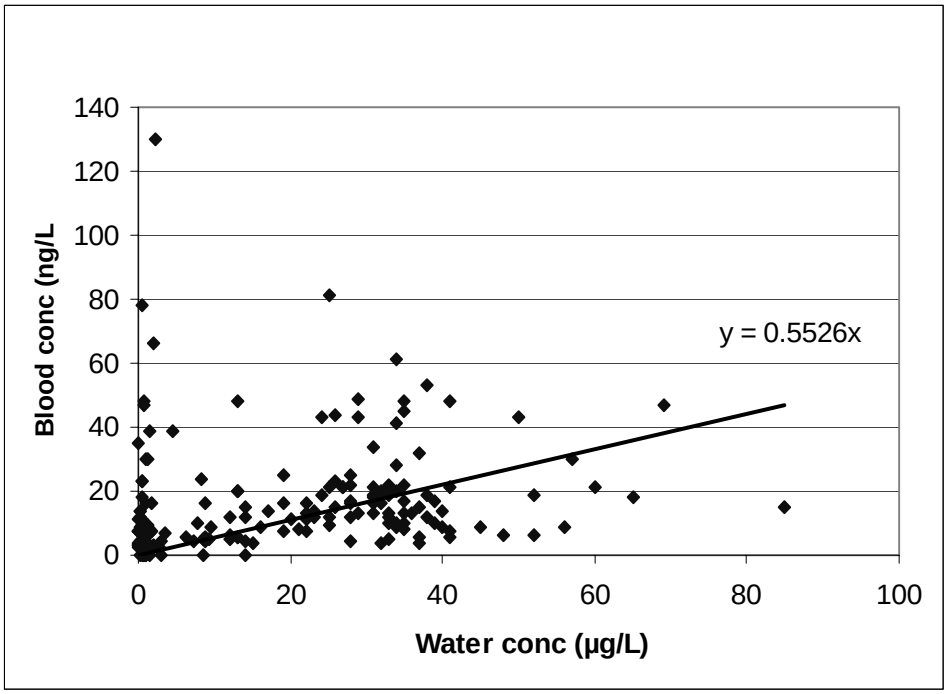



**Figure 9.1 $CHCl_3$ concentration in water and blood samples, all sites**

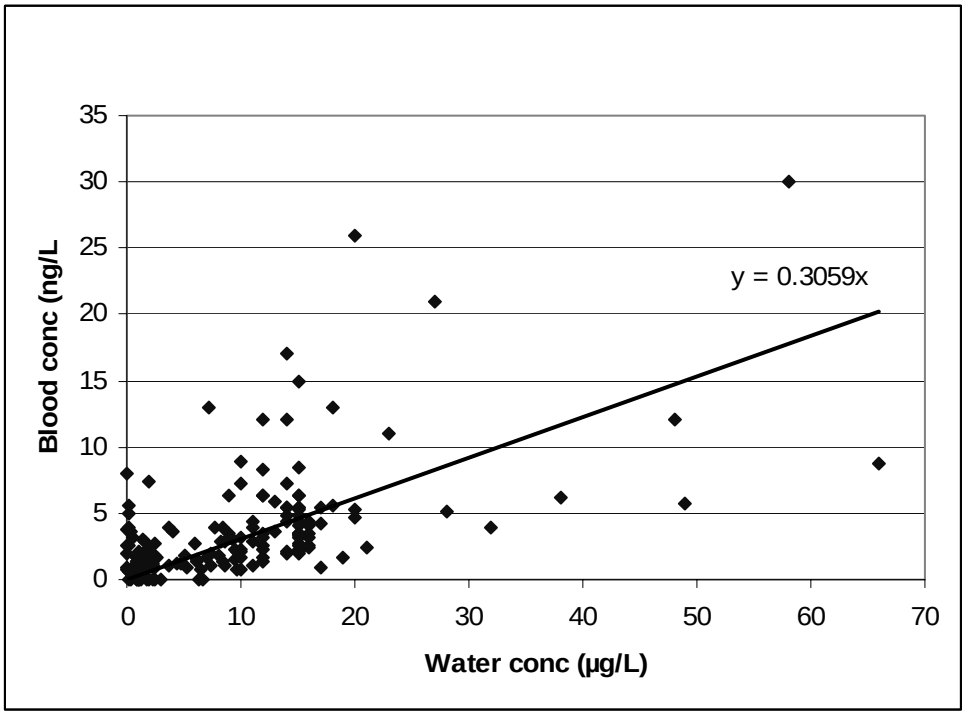



**Figure 9.2 $CHBrCl_2$ concentration in water and blood samples, all sites**

Likewise, no simple linear relationship was apparent for dibromochloromethane or bromoform (not shown). Even when the paired blood and water species concentrations were compared for all subjects within a given study site, no linear relationship could be discerned (see, for example, the bromodichloromethane results for Site 3 in Figure 9.3).

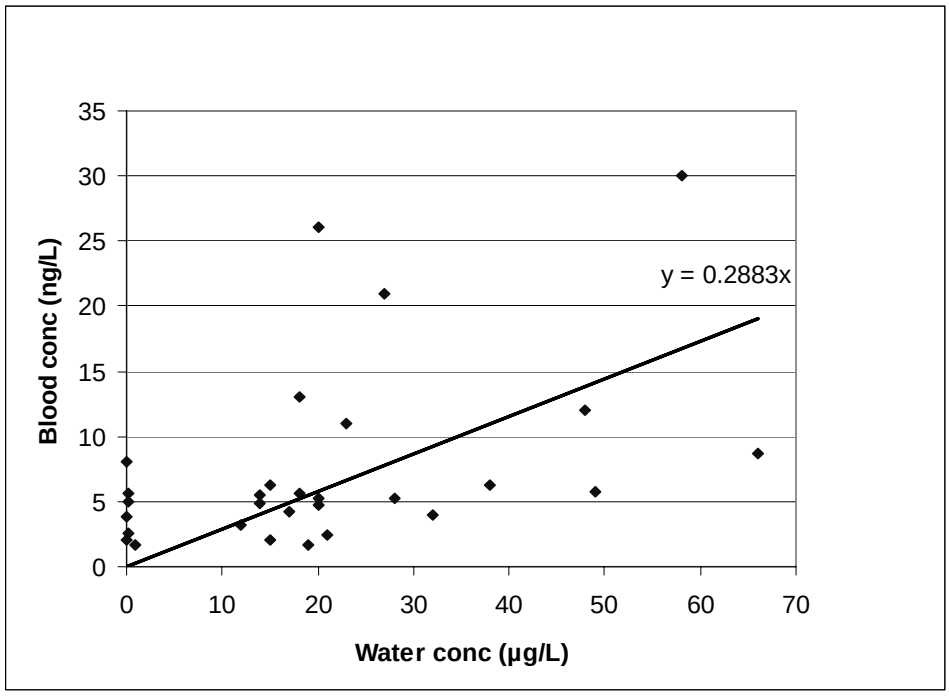



**Figure 9.3 $CHBrCl_2$ concentration in water and blood samples at Site 3**

## DISCUSSION

In the blood biomarker substudy, we examined whether exposures to THMs in tap water are associated with THM levels in the blood of our study participants. More specifically, we examined whether exposure to individual THMs using blood THM levels as a biomarker of exposure differed by study site. Study participants were asked not to shower, bathe, or have other contact with water for several hours prior to the blood draw so that a representative baseline level of blood THMs could be established. Samples of blood and tap water were collected concurrently at each home visit; thus each sample pair represents a snapshot measure of household and blood THM levels. Although data from water activities were not incorporated into the analysis, nonetheless, we utilized data from the tap water samples and the corresponding blood samples to examine any association between blood and water THM levels and to examine expected variations across study sites.

Because we recognize that there are differences in the THM levels in the tap water across study sites, we examined whether such differences would also be reflected in blood THM levels by area of residence. The differences in blood THM levels across the different study sites were relatively small compared to the relative differences in tap water concentrations. In particular, Site 2, with exceptionally low tap water THM concentrations, nonetheless showed surprisingly high blood levels of $CHCl_3$. The other THMs were generally low in the blood samples in Site 2, as expected, but were still not as markedly divergent from the Site 1 and Site 3 blood levels as anticipated based on the large differences in tap water concentrations. Brominated compounds were generally elevated in the Site 3 blood samples, as expected.

Because a pronounced seasonal variation in tap water THM levels was observed in Site 1, water and blood samples were collected at two time points—once during the summer months and once during winter. As expected, the mean concentration of $CHCl_3$, $CHBrCl_2$, $CHBr_2Cl$, and $CHBr_3$ measured in the blood of Site 1 participants were higher in the summer months compared to the winter months. Moreover, seasonal variation was found to be statistically significant in $CHBrCl_2$, $CHBr_2Cl$, and $CHBr_3$ blood samples, and seasonal differences were also statistically significant in all tap water THM levels. Our results from the blood and tap water samples were consistent with the expected seasonal variation across individual THM species, although the seasonal difference in the mean and median blood concentrations were not as great as the seasonal difference in tap water concentrations.

Despite a small sample size for each study site, tap water and blood samples collected from the study participants were sufficient to produce estimates for comparisons across study sites; however, a larger sample size is needed in order to generate more stable comparisons within study sites. In the comparison of paired tap water concentration and blood levels of each THM species, a simple linear correlation between the two measures was not apparent, regardless of the study site. Although we had instructed the participants to refrain from any contact with water for several hours prior to their home visit appointments, we cannot be certain that these instructions were adhered to prior to the blood draws. Furthermore, there may have been other sources of chloroform exposure that were not accounted for.

The overall pattern provides some support for the contention that baseline THM levels in the blood differ across sites, but not nearly to the extent expected. The variation in water use behavior, home ventilation, and other details of exposure may have tended to blur distinctions based solely on tap water concentrations. The contrast in Site 1 summer blood and water concentrations versus winter concentrations helps to validate the analyses that were conducted within Site 1, as reported in earlier chapters. These data provide a reminder of how the many subtle influences on exposure make it difficult to assign DBP exposures with a high level of certainty.

# APPENDIX

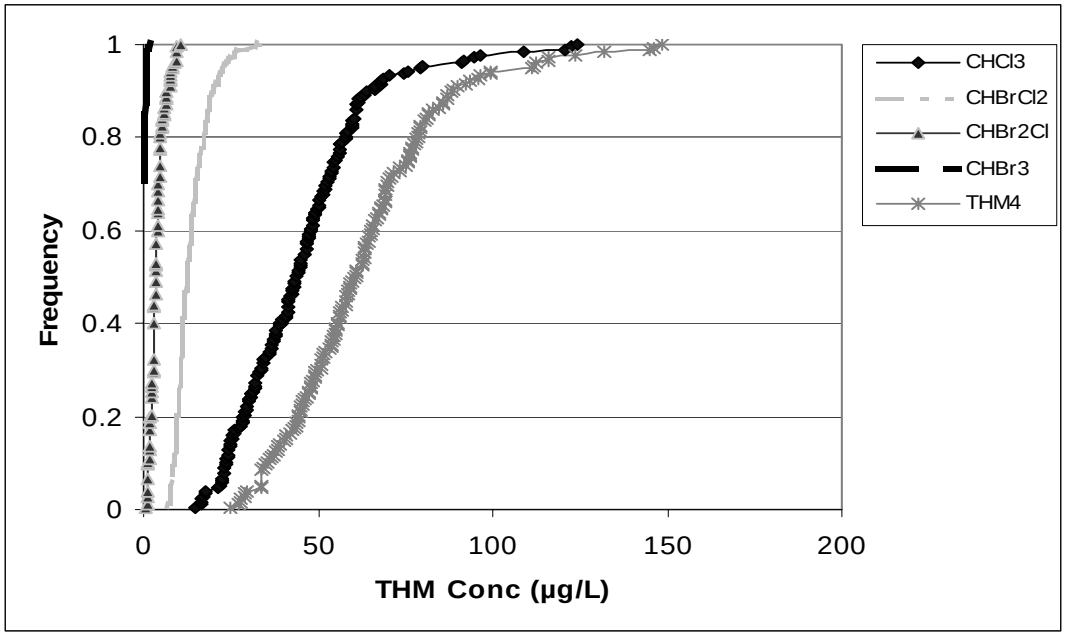



**Figure A: Cumulative frequency distribution of THM species concentrations at site 1.**

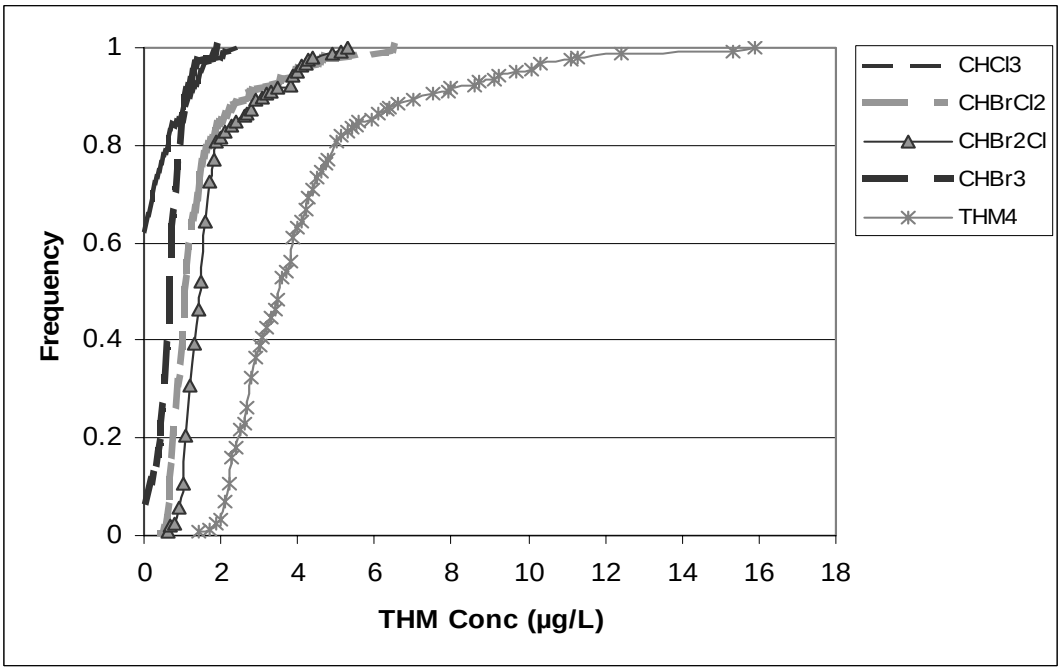



**Figure B: Cumulative frequency distribution of THM species concentrations at site 2.**

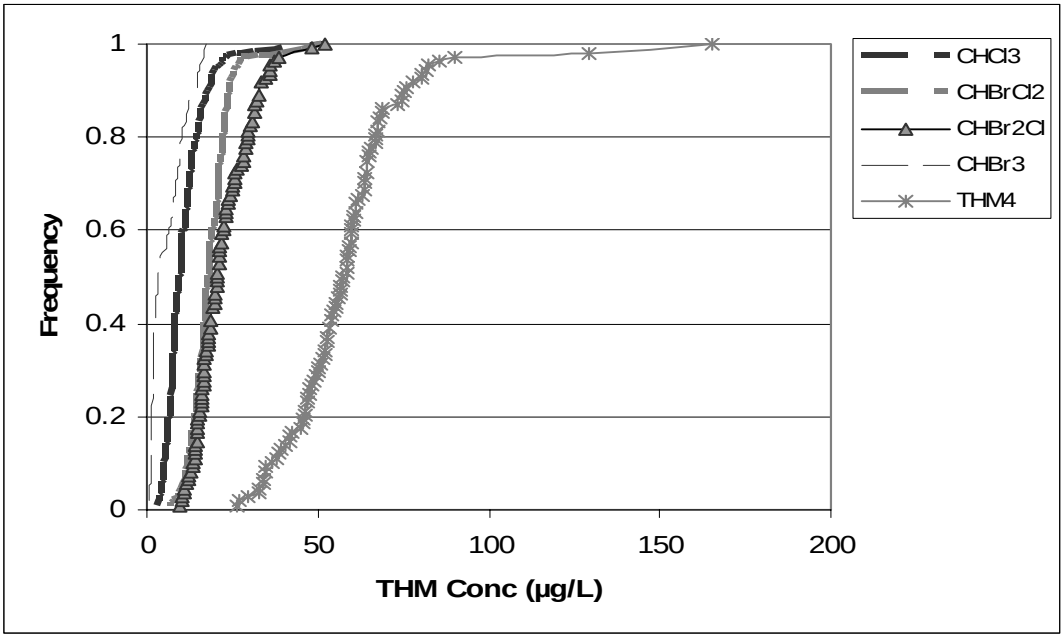



**Figure C: Cumulative frequency distribution of THM species concentrations at site 3.**

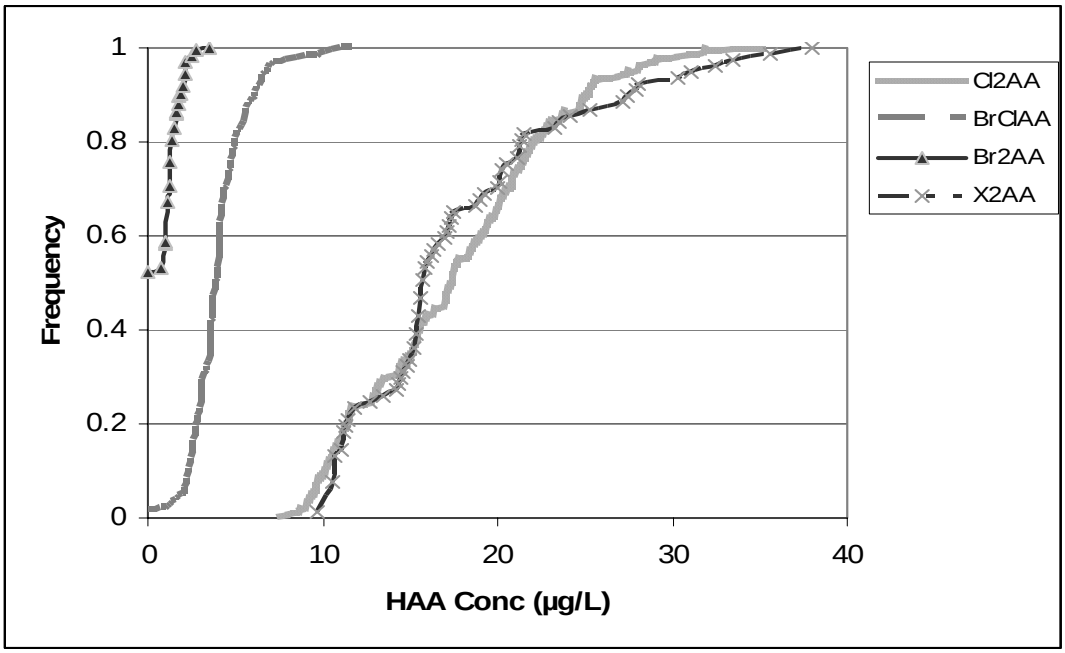



**Figure D: Cumulative frequency distribution of dihaloacetic acid species concentrations at site 1.**

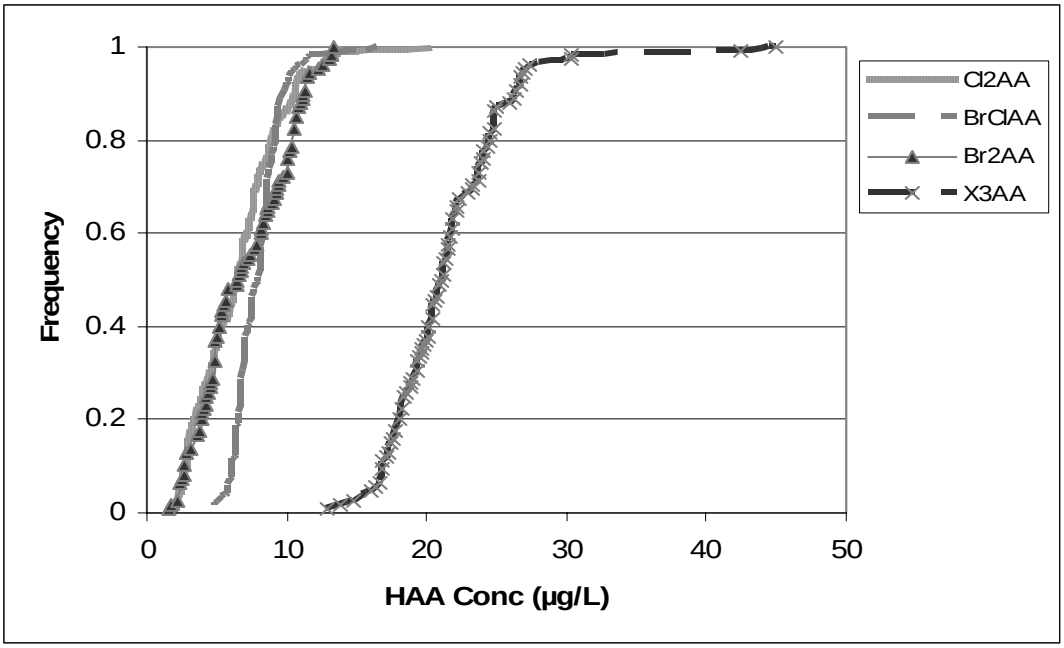



**Figure E: Cumulative frequency distribution of dihaloacetic acid species concentrations at site 3.**

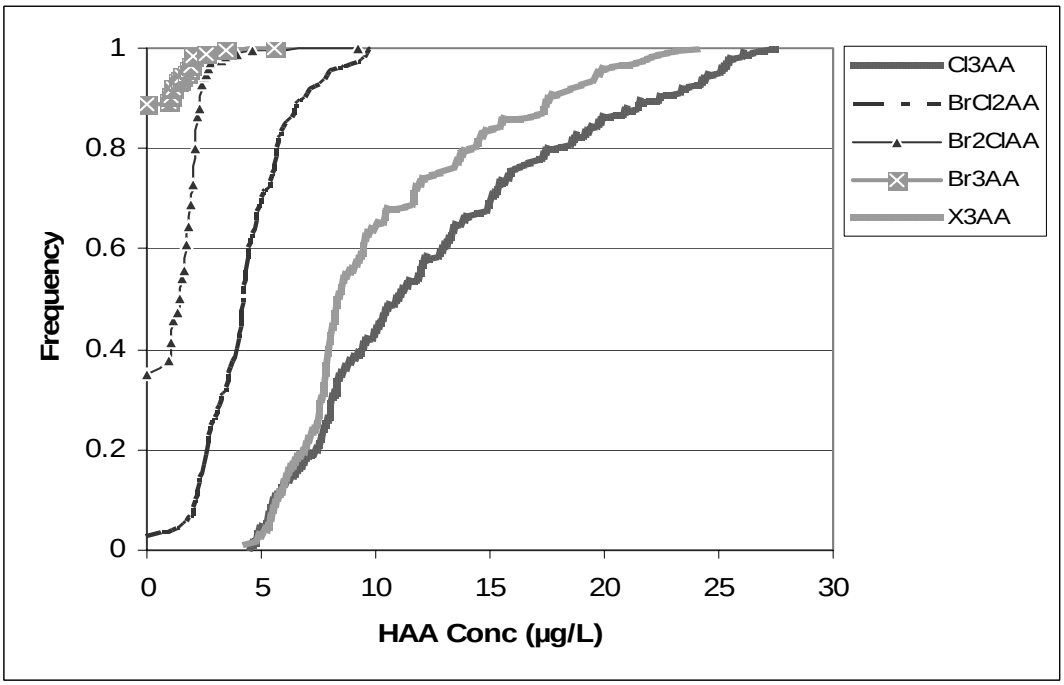



**Figure F: Cumulative frequency distribution of trihaloacetic acid species concentrations at site 1.**

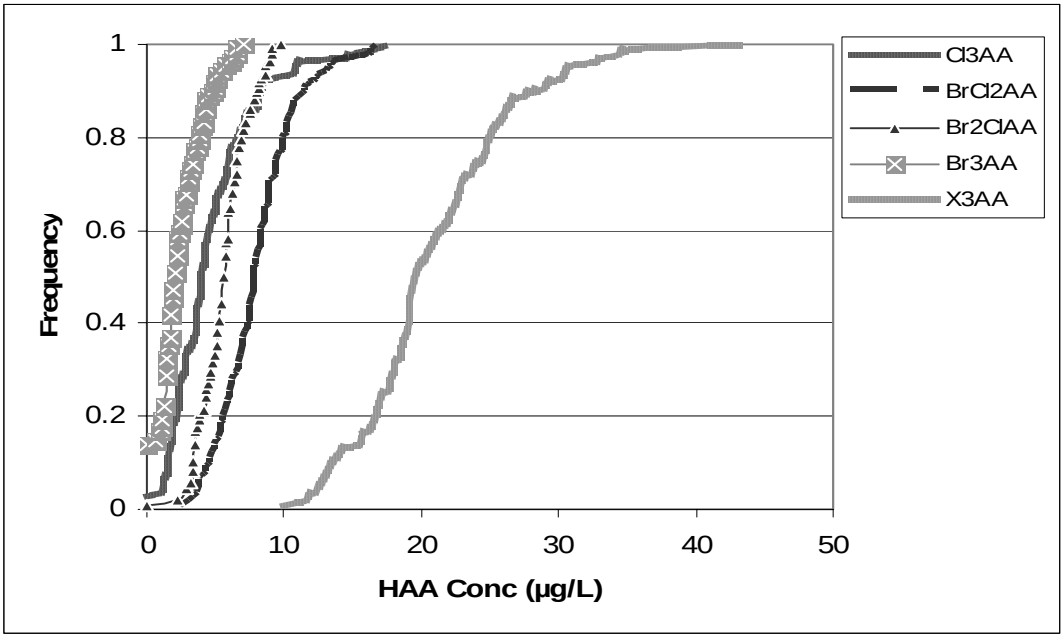



**Figure G: Cumulative frequency distribution of trihaloacetic acid species concentrations at site 3.**

# REFERENCES


American Public Health Association. 1998. Method 6251B. Disinfection By-Products: Haloacetic Acids and Trichlorophenol. In *Standard Methods for the Examination of Water and Wastewater*. Washington, D.C.: American Water Works Association and Water Environment Federation.

Aschengrau, A., S. Zierler, and A. Cohen. 1989. Quality of Community Drinking Water and the Occurrence of Spontaneous Abortion. *Arch. Environmental Health* 44:283–290.

Ashley, D.L., Bonin, M.A., Cardinali, F.L., McCraw, J.M., Holler, J.S., Needham, L.L., and Patterson, D.G. Jr. 1992. Determining Volatile Organic Compounds in Human Blood from a Large Sample Population by Using Purge and Trap Gas Chromatography/Mass Spectrometry. *Anal. Chem.* 64:1021–1029.

Bellar, T.A., J.J. Lichtenberg, and R.C. Kroner. 1974. The Occurrence of Organohalides in Chlorinated Drinking Waters. *Jour. AWWA* 66(12):703.

Bonin, M.A., L.K. Silva, M.M. Smith, D.L. Ashley, and B.C. Blount. 2005. Measurement of Trihalomethanes and Methyl Tert-Butyl Ether in Whole Blood Using Gas Chromatography with High Resolution Mass Spectrometry. *Jour. Anal. Toxicol.* 29(2):81–89.

Boorman, G.A., V. Dellarco, J.K. Dunnick, R.E. Chapen, S. Hunter, F. Hauchman, H. Gardner, M. Cox, and R.C. Sills. 1999. Drinking Water Disinfection By-Products: Review and Approach to Toxicity Evaluation. *Environmental Health Perspectives* 107 (Supplement 1):207–217.

Bove, F.J., M.C. Fulcomer, J.B. Klotz, J. Esmart, E.M. Dufficy, and J.E. Savrin. 1995. Public Drinking Water Contamination and Birth Outcomes. *American Jour. Epidemiol.* 141(9):850–862.

Brett, R.W., and R.A. Calverley. 1979. One-Year Survey of Trihalomethane Concentration Changes Within a Distribution System. *Jour. AWWA* 71:515–520.

Brophy, K.S., H.S. Weinberg, and P.C. Singer. 2000. Quantification of Nine Haloacetic Acids Using Gas Chromatography with Electron Capture Detection. ACS Symposium Series 761 (Natural Organic Matter and Disinfection By-Products), pp. 343–355.

Bull, R.J. 1985. Carcinogenic and mutagenic properties of chemicals in drinking water. *Science of the Total Environment*; 47:385-413.

Cardinali, F.L., D.L. Ashley, J.C. Morrow, D.M. Moll, and B.C. Blount. 2004. Measurement of Trihalomethanes and Methyl Tertiary-Butyl Ether in Tap Water Using Solid-Phase Microextraction GC/MS. *Jour. Chrom. Sci.* 42:200–206.

Cardinali, F.L., J.M. McCraw, D.L. Ashley, M.A. Bonin, and J.V. Wooten. 1995. Treatment of Vacutainers for the Analysis of Volatile Organic Compounds in Human Blood at the Low Parts-per-Trillion Level. *Jour. Chrom. Sci.* 33:557–560.

Chen, W.J., and C.P. Weisel. 1998. Concentraton Changes of Halogenated Disinfection By-Products in a Drinking Water Distribution System. *Jour. AWWA* 90:151-63.

Cox, D.R. 1972. Regression Models and Life Tables. *Jour. Royal Statistical Society* 34:187–202.

Deane, M., S.H. Swan, J.A. Harris, D.M. Epstein, and R.R. Neutra. 1992. Adverse Pregnancy Outcomes in Relation to Water Consumption: A Re-Analysis of Data from the Original Santa Clara County Sudy, California, 1980–1981. *Epidemiology* 3:94–97.

Dodds, L., W. King, C. Woolcott, and J. Pole. 1999. Trihalomethanes in public water supplies and adverse birth outcomes. *Epidemiology* 10(3): 233–237.

Fenster, L., A.E. Hubbard, S.H. Swan, G.C. Windham, K. Waller, R.A. Hiatt, and N. Benowitz. 1997. Caffeinated Beverages, Decaffeinated Coffee, and Spontaneous Abortion. *Epidemiology* 85(5):515–523.

Gallagher, M.D., J.R. Nuckols, L. Stallones, and D.A. Savitz. 1989. Exposure to Trihalomethanes and Adverse Pregnancy Outcomes. *Epidemiology* 10(3):484–489.

Hertz-Picciotto, I., S.H. Swan, R.R. Neutra, and S.J. Samuels. 1989. Spontaneous Abortions in Relation to Consumption of Tap Water: An Application of Methods from Survival Analysis to a Pregnancy Follow-Up Study. *American Jour. Epidemiology* 130:79–93.

Infante-Rivard, C. 2004. Drinking Water Contaminants, Gene Polymorphisms, and Fetal Growth. *Environ. Health Perspectives* 112(11):1213–1216.

Kramer, M.D., C.F. Lynch, P. Isacson, and J.W. Hanson. 1992. The Association of Waterborne Chloroform with Intrauterine Growth Retardation. *Epidemiology* 3(5):407–413.

Krasner, S. W., M. J. McGuire, J. G. Jacangelo, N. L. Patania, K. M. Reagan and E. M. Aieta. .1989. "The occurrence of disinfection by-products in US drinking water," *Journ. Amer. Wat. Works Assoc.* 81:8:41

Narotsky, M.G., R.A. Pegram, and R.J. Kavlock. 1997. Effect of Dosing Vehicle on the Development Toxicity of Bromochloromethane and Carbon Tetrachloride in Rats. *Fundam. Applied Toxicol.* 40:30–36.

Neutra, R.R., S.H. Swan, I. Hertz-Picciotto, G.C. Windham, M. Wrensch, G.M. Shaw, L. Fenster, and M. Deane. 1992. Potential Sources of Bias and Confounding in Environmental Epidemiologic Studies of Pregnancy Outcomes. *Epidemiology* 3:134–142.

Nieuwenhuijsen, M.J., M.B. Toledano, N.E. Eaton, J. Fawell, and P. Elliott. 2000. Chlorination Disinfection By-Products in Water and Their Association with Adverse Reproductive Outcomes: A Review. *Occupational Environ. Medicine* 57:73–85.

Orme-Zavaleta, J., and F. Hauchman. 1999. Epidemiology and Toxicology of Disinfection By-Products. In *Formation and Control of Disinfection By-Products in Drinking Water*. Edited by P.C. Singer. Denver, Colo.: American Water Works Association.

Pereira, V.J., H.S. Weinberg, and P.C. Singer, 2004. "Temporal and Spatial Variability of Disinfection By-Products in a Chloraminated Distribution System," *Journ. Amer. Wat. Works Assoc*., 96, 11, 91.

Prentice, R.L., and L.A. Gloeckler. 1978. Regression Analysis of Grouped Survival Data with Application to Breast Cancer Data. *Biometrics* 34:57–67.

Rook, J.J. (1974) "Formation of haloforms during chlorination of natural waters," *Wat Treat* Exam 23:234

Ruddick J.V., D.C. Villeneuve, and I. Chu. 1983. A teratological assessment of four trihalomethanes in the rat. *Journal of Environmental Science and Health*; B18:333-49.

Savitz, D.A., K.W. Andrews, and L.M. Pastore. 1995. Drinking Water and Pregnancy Outcome in Central North Carolina: Source, Amount, and Trihalomethane Levels. *Environmental Health Perspectives* 103:592–596.

Savitz, D.A., K.M. Brett, L.E. Evans, and W. Bowes. 1994. Medically Treated Miscarriage Among Black and White Women in Alamance County, North Carolina, 1988–1991. *American Jour. Epidemiology* 139:1100–1106.

Shimokura, G.H., D.A. Savitz, and E. Symanski. 1998. Assessment of Water Use for Estimating Exposure to Tap Water Contaminants. *Environmental Health Perspectives* 106:55–59.

Singer, J.D., and J.B. Willett. 2003. *Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence.* Oxford: Oxford University Press.

Singer, P.C. 1994. Control of Disinfection By-Products in Drinking Water. *Jour. Environmental Engineering* 120:727–744.

Singer, P.C., 2001. "Variability and Assessment of Disinfection By-Product Concentrations in Water Distribution Systems," p. 211-223 in *Microbial Pathogens and Disinfection By-Products in Drinking Water: Health Effects and Management of Risks*, G.F. Craun, F.S. Hauchman, and D.E. Robinson, eds., International Life Sciences Inst., Washington D.C.

Speitel, G.E. 1999. Control of Disinfection By-Product Formation Using Combined Chlorine. In *Formation and Control of Disinfection By-Products in Drinking Water.* Edited by P.C. Singer. Denver, Colo.: AWWA.

Swan, S.H., R.R. Neutra, M. Wrensch, I. Hertz-Picciotto, G.C. Windham, L. Fenster, D.M. Epstein, and M. Deane. 1992. Is Drinking Water Related to Spontaneous Abortion? Reviewing the Evidence from the California Department of Health Services Studies. *Epidemiology* 3:83–93.

Swan, S.H., K. Waller, B. Hopkins, G. Windham, L. Fenster, C. Schaefer, and R.R. Neutra. 1998. A Prospective Study of Spontaneous Abortion: Relation to Amount and Source of Drinking Water Consumed in Early Pregnancy. *Epidemiology* 9:126–133.

Thompson, D.J., S.D. Warner, and V.B. Robinson. 1974. Teratology studies on orally administered chloroform in the rat and rabbit. *Toxicology and Applied Pharmacology*; 29:348-57.

Toledano, M.B., M.J. Nieuwenhuijsen, N. Best, H. Whitaker, P. Hambly, C. de Hoogh, et al. 2005. Relation of Trihalomethane Concentrations in Public Water Supplies to Stillbirth and Birth Weight in Three Water Regions in England. *Environ. Health Perspectives* 113(2):225–232.

U.S. Environmental Protection Agency. 1995a. Method 551.1. *Determination of Chlorination Disinfection By Products, Chlorination Solvents, and Halogenated Pesticides in Drinking Water by Liquid-Liquid Extraction and Gas Chromatography with Electron-Capture Detection*. Cincinnati, Ohio: National Exposure Research Laboratory, Office of Research and Development.

U.S. Environmental Protection Agency. 1995b. Method 552. *Determination of Haloacetic Acids and Dalapon in Drinking Water by Liquid-Liquid Extraction, Derivatization and Gas Chromatography with Electron-Capture Detection*. Cincinnati, Ohio: National Exposure Research Laboratory, Office of Research and Development.

Waller, K., S.H. Swan, G. DeLorenze, and B. Hopkins. 1998. Trihalomethanes in Drinking Water and Spontaneous Abortion. *Epidemiology* 9:134–140.

Waller, K., S.H. Swan, G.C. Windham, and L. Fenster. 2001. Influence of Exposure Assessment Mmethods on Risk Estimates in an Epidemiologic Study of Total Trihalomethane Exposure and Spontaneous Abortion. *Jour. Exposure and Analytical Environmental Epidemiology* 11:522–531.

Wrensch, M., S.H. Swan, J. Lipscomb, D.M. Epstein, R.R. Neutra, and L. Fenster. 1992. Spontaneous Abortions and Birth Defects Related to Tap and Bottled Water Use, San Jose, California, 1980–1985. *Epidemiology* 3:98–103.

Wright, J.M., J. Schwartz, and D.W. Dockery. 2003. Effect of Trihalomethane Exposure on Fetal Development. *Occupational Environ. Medicine* 60(3):173–180.

Zhang J. and W.A. Bowes Jr. 1995. Birth-weight-for-gestational-age patterns by race, sex, and parity in the United States population. *Obstet Gynecol*. 86:200-208.

# ABBREVIATIONS

| | |
|---|---|
| AA | acetic acid |
| BMRL | below minimum reporting level |
| BMI | body mass index |
| %CV | coefficient of variation |
| DBP | disinfection by-product |
| ECD | electron capture detector |
| EGA | estimated gestational age |
| EPA | Environmental Protection Agency |
| g/L | grams per liter |
| gal | gallons |
| GC | gas chromatograph |
| HAA | haloacetic acids |
| HRT | hydraulic retention time |
| LGW | laboratory grade water |
| LMP | last menstrual period |
| mg | milligram |
| mg/L | milligram per liter |
| mg/mL | milligram per milliliter |
| mL | milliliter |
| mL/min | milliliters per minute |
| MtBE | methyl *tert*-butyl ether |
| µg/L | micrograms per liter |
| µL | microliter |
| ng | nanogram |
| ng/L | nanograms per liter |
| OB/GYN | Obstetric and Gynecology |
| POE | point of entry |
| POU | point of use |
| RFTS | Right from the Start |
| RPD | relative percent difference |
| THM | trihalomethane |

| | |
|---|---|
| TOBr | total organic bromine |
| TOX | total organic halide |
| UNC | University of North Carolina |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