Evaluation of subchronic chemical exposure and risks related to regulated disinfection by-products in drinking water distribution systems

by

Anne Carabin

B.Sc., Université Laval, 2012,
M.Sc., Institut national de la recherche scientifique, 2015

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We acknowledge and respect the lək̓ʷəŋən peoples on whose traditional territory the university stands and the Songhees, Esquimalt and W̱SÁNEĆ peoples whose historical relationships with the land continue to this day.

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Abstract

The practice of disinfecting potable water is widely accepted as a way of reducing the risk of waterborne infections. This practice, however, may also result in the formation of numerous compounds known as disinfection by-products (DBPs). Among the DBPs produced by chlorination of organic matter, trihalomethanes (THM_4) and haloacetic acids (HAA_5) are the most prevalent families in terms of occurrence and concentration. Toxicological and epidemiological studies, reviews and meta-analysis have investigated associations between those DBPs levels/exposure and carcinogenic effects and adverse reproductive effects with different findings. The occurrence of THM_4 and HAA_5 is determined based on regulatory quarterly sampling for many utilities where DBPs levels fluctuate along the year and more specifically during warmer months. Hence, there is a need to investigate how this variability during warmer months can impact DBPs subchronic exposure and the associated risks. To answer to this knowledge gap, this dissertation aims to highlight the importance of taking higher seasonal concentrations into account in regulatory frameworks. It also seeks to investigate subchronic exposure and risks, as well as evaluating alternative techniques for preventing the emergence of such peaks in the warm summer months.

The dissertation begins with a literature overview of DBPs health effects and a perspective paper that recommends re-examining some critical aspects of DBP risk assessment mostly related to subchronic exposure. Secondly, using an extensive dataset covering those warmer months of high variability, spatial and temporal variability of regulated DBPs were investigated in a middle-sized municipality. In order to assist stakeholders in limiting concentration peaks in the network, a model as well as an alternative technique, known as incremental differential UV-VIS, were evaluated for the first time throughout a distribution network. Furthermore, investigations were conducted to determine how this variability would affect exposure estimates and TCM subchronic risks when sampling is performed on a weekly or monthly basis. Disinfecting water is an essential public health measure, and since many people are exposed to DBPs, there is a strong need for the intra-seasonally spatial and temporal variability to be incorporated into DBP risk assessments, even if some relative health risks are small.

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Glossary

BDCM: Bromodichloromethane

CalEPA: California Environmental Protection Agency

CH: chloral hydrate

CHO: Chinese ovary hamster

CPK: Chloropicrin

DBAA: Dibromoacetic acid

DBAN: Dibromoacetonitrile

DBCM: Dibromochloromethane

DBPs: disinfection by-products

DCAA: Dichloroacetic acid

DOC: Dissolved organic carbon

DUVλ: incremental differential UV-VIS absorbances for a specific wavelength

HAA_5: Sum of the 5 regulated haloacetic acids or HAAs (monitored compounds)

HAA_6: Sum of the 5 regulated haloacetic acids, plus bromochloroacetic acid (analyzed compounds)

HAN: Haloacetonitriles

HBVs: Health-based values

HK: Haloketones

HRT: Hydraulic residence time

IARC: International Agency for Research on Cancer

MAC: Maximum allowable concentration

MBAA: Monobromoacetic acid

MCAA: Monochloroacetic acid

MCL: Maximum contaminant level (CMA in Canada)

MCLG: Maximum contaminant level goal

MDH: Minnestoa Department of Health

MOA: Mode of action

NDMA: Nitrosodimethylamine

NOM: Natural organic matter

PTD: preterm delivery

RfD: Reference dose

SGA: small for gestational age

SUVA: Specific UV absorbance at a wavelength of 254 nm

TBM: Tribromomethane, or bromoform

TCAA: Trichloroacetic acid

TCM: Trichloromethane, or chloroform

Term LBW: term low birth weight,

THM_4: Sum of the four chlorinated and brominated trihalomethanes (or THMs or total THM or TTHM)

TOC: Total organic carbon

UKWIR: UK water industry research

US EPA: U.S. Environmental Protection Agency

UV254nm: UV absorbance at a wavelength of 254 nm

WHO: World Heath Organization

Dedication

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1 Introduction

1.1 Background and knowledge gaps

The chlorination of water started in the late 1800s in Europe, particularly in Germany, Belgium, and England; however, widespread chlorination began in the early 1900s (McGuire 2013). In the 1970s, it was discovered that chlorine could react with naturally-occurring organic molecules to form halogenated organic compounds in drinking water (Bellar 1974, Rook 1974). Later on, an investigation conducted by the US Environmental Protection Agency (US EPA) in 1975 revealed that drinking water in 80 American cities contained halogenated compounds (Craun 1993). In 1974, the United States Congress passed the Safe Drinking Water Act where a few years later the US EPA defined Maximum Contaminant level goals (MCLGs) and Maximum Contaminant Level (MCL) for total trihalomethanes (THM_4,THMs or TTHM). Among the objectives of the interim standard, developed in 1979, was to strike a balance between the need to disinfect water continuously in order to prevent the spread of pathogens and the need to minimize exposure to animal carcinogens, such as chloroform (United States Environmental Protection Agency 2016). Hence, until the 1970s, the scientific community was unaware of the existence of these disinfection by-products (DBPs). Following their recognition, however, the scientific community and policymakers became interested in the potential outcomes of these DBPs (Craun 1993).

In Canada and United States, trihalomethanes (THM_4) and haloacetic acids (HAA_5) are currently monitored using an annual locational quarterly average (LRAA) where each plant must report quarterly concentrations (Health Canada 2006, Health Canada 2009, United States Environmental Protection Agency 2009). As THM_4 and HAA_5 concentrations evolve spatially in the network, the term locational refers to the choice of monitoring locations that must represent the highest formation potential for both families. Hence, identifying the most appropriate monitoring sites requires each utility to evaluate the potentially relevant locations throughout the distribution system. In terms of compliance monitoring, the number of samples per trimester varies according to the size (Canada, United States), type of the water system (United States), the method of treatment (United

States), and the disinfectant used in the system (Canada, United States) (Health Canada 2006, Health Canada 2009, United States Environmental Protection Agency 2010). Water systems are considered in violation when the mean LRAA of all samples over a four-quarter period exceeds the maximum contaminant level (MCL) or maximum acceptable concentration (MAC) for the United States and Canada, respectively.

In Canada, Health Canada provides guidelines for THM_4 and HAA_5, but each province is responsible for the monitoring and for adopting the guidelines and/or selecting a lower standard if desired. As an example, le *Règlement sur la qualité de l'eau potable* (RQEP) defined by the Province of Quebec requires the following minimum number of samples for each quarter beginning on January, April, July, and October for THM_4, according to the population supplied by the network: *i*) ≥ 21 and ≤ 5 000 inhabitants: 1 sample, *ii*) ≥ 5 001 and ≤ 100 000 inhabitants: 4 samples and *iii*) ≥ 100 001 inhabitants: 8 samples (Direction de l'eau potable et des eaux souterraines 2019). Moreover, the Canadian guidelines recommend that "utilities should make every effort to maintain concentrations as low as reasonably achievable (ALARA) without compromising the effectiveness of disinfection". The term ALARA was included because THM_4 and HAA_5 are considered surrogates for other non-regulated DBPs, so minimizing their formation should also reduce the formation of other by-products. Health Canada also recommends that the frequency of sampling may need to be increased during peak times when by-product formation occurs in surface water sources (Health Canada 2006).

According to previous researches, DBPs fluctuate along the year in temperate climates such as Southern Canada, with higher concentrations observed during the warmer months of the year (Rodriguez, Vinette et al. 2003, Rodriguez, Sérodes et al. 2004, Parvez, Rivera-Núñez et al. 2011, Parvez 2019). For instance, Parvez et al. (2011) studied temporal variability in 201 public systems in Massachusetts over 10 year and showed that higher concentrations happen during this period with a permanent baseline. Moreover, it was also demonstrated by Rodriguez et al. (2004) that variations are important on a seasonal basis. As such, better characterization of temporality and spatial variation of DBPs concentrations remains a fundamental need to adequately construct valid exposure estimates during those months. This is particularly essential because there is uncertainty regarding what

concentrations of THM_4/HAA_5 could constitute exposure causing adverse health outcomes. In addition, there is uncertainty regarding how much variation in estimated concentrations can be tolerated regarding those suspected health effects (Richter 2009).

A robust toxicological and epidemiological body of evidence have been generated regarding THMs and HAAs potential health effects over the decades. This body of evidence may provide guidance for better regulations in respect to potential health effects and guide to move towards technology able to reduce population exposure to DBPs. In the following section of this dissertation, the body of evidence is discussed in greater detail. Although some epidemiological studies/meta-analyses generally showed small associations, it remains compelling to investigate the health effects of DBPs as a large proportion of the population is exposed to a mixture of DBPs (Savitz 2011). Having a better understanding of possible health effects requires an assessment of exposure, which has been a limiting factor in epidemiological studies on DBPs in drinking water (Parvez, Rivera-Núñez et al. 2011).

However, there is a possibility of misclassification of exposure assessments due to poor spatial and temporal resolution of monitoring data (e.g., the use of quarterly samples) as well as physiological differences between and within individuals as to how DBPs are absorbed, distributed, metabolized, and excreted (Grellier, Rushton et al. 2015). Physicochemical properties of source water, treatment and distribution systems, and climate affect the concentrations/speciation of DBPs both locally and spatially. Certainly, this is true in temperate climates, where changes in temperature and organic matter content may cause DBP concentrations to fluctuate throughout the year. This makes characterizing general population exposures for population health impact assessments extremely difficult leading to exposure misclassification.

In many epidemiological studies, monitoring data available through regulatory compliance (trimester-specific averages derived from quarterly monitoring data) are used to estimate exposures for adverse reproductive outcomes or increased cancer risks, which can compromise the accuracy and precision of the results (Legay, Rodriguez et al. 2010, Parvez, Rivera-Núñez et al. 2011). Only a few studies employed a higher frequency sampling such as weekly DBP concentration to evaluate exposure (Lewis, Suffet et al.

2006, Savitz, Singer et al. 2006). In addition, as an attempt to reduce exposure misclassification, usually during months where higher exposure tends to occur, a few authors have investigated methods of interpolating quarterly THM_4 levels (e.g. linear interpolation and spline fit) (Richter 2009) or weighted averages (Infante-Rivard 2004). As an interpolation technique, Hinckley et al. (2005) also used a cubic spline fitted to sample data to estimate DBP levels between samples.

The terminologies short-term, subacute, and subchronic exposures are defined differently by public health/environmental organizations. The US EPA defines acute exposure as less than 24 hours, subacute exposure as more than 24 hours and up to 30 days while subchronic exposure is described as repeated exposure for more than 30 days, up to approximately 10% of the life span of humans. Chronic exposure refers to a period of time greater than approximately 10% of the life span of humans (~7 years) (United States Environmental Protection Agency 2002). On the other hand, the Institut National de Santé Publique du Québec (INSPQ) recommends that the development of subchronic health-based values (HBVs) should not exceed an exposure duration of one year (Institut national de santé publique du Québec 2015). The term subchronic exposure is used in this dissertation to refer to exposures lasting less than a year during months of increased exposure, particularly during the summer months and when DBPs are at their highest concentrations.

The vast majority of studies, however, still rely on averages for each trimester in order to estimate exposures for adverse outcomes, and the knowledge regarding the actual exposure to regulated DBPs during months with higher concentrations remains limited. By using average concentrations, this assumes that concentrations are monotonic and thus fails to take into consideration peak exposure during summer. Since peak exposure metrics are not developed or used consistently, they may be overlooked in epidemiological studies where average exposure metrics are used instead, potentially causing bias in exposure-response estimates. However, there does not appear to be a consistent and clear definition of the term "peak" in the literature. Peak exposure may simply be defined as a measurement that exceeds a threshold over time (Kriebel, Checkoway et al. 2007, Checkoway, Lees et al. 2019). In terms of risk assessment, this definition has very important limitations, since it does not consider the duration of exceeding, the magnitude of exceeding, the frequency of

peaks over longer periods, time interval between peaks, or aggregate peak values (Kriebel, Checkoway et al. 2007). In this dissertation and for simplification, the term peak will refer to higher concentrations exceeding the regulations from the Province of Quebec (80 µg/L for THM_4 and 60 µg/L for HAA_5).

A better control of THM_4 and HAA_5 concentration peaks is also needed in order to limit population exposure during this critical period. Water utilities still face challenges to limit DBP formation despite implementing control strategies such as using chlorination downstream from clarification and/or filtration and using enhanced coagulation and alternative oxidants and primary disinfectants (Singer 2006). In addition to a few engineering and complex technical challenges, there is the variability of dissolved organic matter, precursors of regulated DBPs, and a complex mixture of hydrophobic and hydrophilic organic compounds that increase the demand for coagulants. Furthermore, implementing, and operating DBPs control strategies can be demanding for municipalities, especially for smaller and medium-sized municipalities with limited financial, technological, and human resources. Hence, there is a strong need for the development of alternative and practical approaches to help municipalities in anticipating and better controlling those regulated DBPs peaks during periods of high formation potential.

Overall, the motivation for this dissertation is to bring more attention to subchronic exposure to regulated DBPs, both from a regulatory perspective and from our current viewpoint regarding the risk assessment of these substances that focuses primarily on chronic exposure. Since many utilities obtain information about DBP occurrence only through regulatory sampling, there is a need to unveil some knowledge gaps on short-term temporal and spatial variability during the warmer months to provide a better estimate of exposure and risks to regulated DBPs. Furthermore, this dissertation aims to use alternative techniques to help municipalities face this recurrent issue.

1.2 Questions, hypothesis, and objectives

The main objective of this dissertation is to investigate subchronic exposure and risk to regulated DBPs throughout a whole distribution system and to suggest a possible solution through a modeling approach to prevent the emergence of those peaks in summer season.

The research questions, hypothesises and specific objectives for each chapter are defined below:

Chapter 1:

- *Research question*: Does the monitoring of THM_4 as the sum of four halogenated compounds provide sufficient consideration of short-term variability?
- *Hypothesis*:
    - The current regulations don't cover the temporal variability of regulated DBPs in distribution networks
    - Current regulations should consider the individual concentrations of THM_4 rather than the sum of the four compounds
    - When brominated trihalomethanes formation is prevalent, subchronic exposure may be important to consider given the variability in the summer period and the higher toxicity of brominated compounds
- *Objective*: Revisit some of the aspects of THM_4 regulations with a subchronic perspective

Chapter 2:

- *Research question*: Can models help in predicting higher concentrations of regulated DBPs throughout distribution systems?
- *Hypothesis*: A model can be developed based on the extensive generated dataset that can help operators to limit concentrations above regulations
- *Objective*: Develop a statistical model to help prevent peaks of concentrations in networks

Chapter 3:

- *Research questions*:
    - Can we consider spatial and temporal variability during the assessment of our exposure and evaluation of subchronic risks?
    - Is the population exposed differently to regulated DBPs throughout the network?
- *Hypothesis*:

- Because of the spatial and temporal variability in warmer months of THM_4 and HAA_6 in drinking water and the non availability of an extensive DBPs datasets in municipality, the real exposure is higher than those calculated with quarterly means.
- Population supplied by a distribution network may be exposed differently depending on their locations.

- *Objective*:
  - Investigate subchronic exposure to DBP throughout the network and subchronic risks and how spatial variability impact population exposure throughout the network

1.3 Connection between chapters and dissertation structure

This dissertation is presented in the form of a manuscript-based doctoral thesis divided into three manuscripts/chapters that starts with a literature overview of DBPs health effects. As health effects are discussed in the manuscripts, this overview of health effects provides the reader with some background on DBPs health effects. Following these three manuscripts/chapters, a discussion section summarising the different results and interpretations, limitations, and future research perspectives is presented.

This first chapter provides a portrait and reflection on the monitoring of DBP using THM_4 as an example, in light of the increasing research on the development of subacute and subchronic HBVs. This chapter aims to provide special attention to a subject that has been largely overlooked in the scientific literature and to emphasize the importance of considering short-term fluctuations of DBP in the current framework used in North America. As well, the chapter provides the relevant toxicological background and rationale for this reflection, as well as for the research investigations conducted in the subsequent manuscripts. The second chapter examines the spatial and temporal variation of THM_4 and HAA_6 at the plant and in the network, providing essential information to support our reflection on the need to recalculate exposure/risks estimates that consider spatial and temporal variability. The third chapter examines how previously described variability impacts the misclassification of exposure in light of the regulation (by simulating quarterly means as specified in the Manuscript 1). Throughout the summer, subchronic exposure

should be examined more closely with regard to the toxicological aspects detailed in Chapter 1 and in light of this temporal and spatial variability (Chapter 2).

Manuscript 1 covers the specific aspects of THM monitoring and why individual compounds rather than the sum of each compound should be monitored. It also brings some evidence on why subchronic exposure need to be more addressed regarding health risks in the global monitoring and how monitoring based on quarterly averages cannot represent accurately the variability of DBPs and the true exposure to THM_4 and HAA_5. Moreover, the current regulation is defined based on chloroform health effects based on the rationale that it is the compound the most encountered in drinking water. However, the case is bit different when brominated THM_4 are more present than TCM when raw water quality is characterised with higher levels of bromide ions.

Manuscript 2 aimed at developing a statistic model to help prevent peaks of exposure using the probability of exceedances for different thresholds using the comprehensive dataset capturing the spatial and temporal variability of regulated DBPs. In order to help plant operators control threshold exceedances that may occur in the network, this model was constructed based on water quality data at the finished water just before distribution. The use of differential UV spectrophotometry was also assessed to predict differential THM concentrations for specific locations.

Manuscript 3 provides insights on the non representativity of quarterly means in terms of temporal variations in a network of middle-sized municipality. Monte Carlo simulations were performed in order to assess the spatial variation of exposure for trihalomethanes and haloacetic acids during those three months within the network. A comparison was made between those previous results and the exposure estimates calculated using only the quarterly means and monthly means for each location in order to determine to what extent these latest results tend to underestimate exposure to subchronic chemicals. Chemical risks for chloroform were then calculated using subchronic reference doses with both calculation approaches.

In the final section of this dissertation, the overall results are reviewed and discussed within the context of the overall research question and hypothesis. Limitations and perspectives for future research are also examined.

2 Occurrence of disinfection by-products and their suspected related health effects

2.1 General background

The US EPA defined the four main categories of drinking water contaminants as physical, chemical, biological, and radiological. The first relates to contaminants that affect the physical characteristics of water, such as sediments or organic matter, whereas the second refers to chemical elements or compounds found in water. The third and fourth categories concern organisms and chemical elements with an unbalanced number of protons and neutrons (cesium or uranium) (US Environmental protection agency 2022).

Water supplies may however contain inorganic and organic chemicals that could pose various health risks, if populations are exposed to a certain dose for a specific and prolonged period of time (Villanueva, Kogevinas et al. 2014). Some of these contaminants are naturally occurring in drinking water such as arsenic and fluoride while some are only present due to anthropogenic activities and contaminations (e.g. pesticides, hydrocarbons, volatile organic carbons) (Prüss-Ustün, Vickers et al. 2011). Due to important analytical progresses and developments over the recent decades, chemists can now detect and measure trace contaminants at parts per billion and trillion. Therefore, although scientists and the public have become more aware of the potential health risks associated with chemical exposure in drinking water, those risks appear to be greater given that contamination levels can now be measured more accurately within much narrower tolerances.

One of the key aspects of maintaining public health remains the safety of water supplies where the most common cause of waterborne diseases worldwide is related to the presence of pathogens in water (Ashbolt 2004, Villanueva, Kogevinas et al. 2014). One of the ten greatest achievements in public health during the 20th century has been the implementation of disinfection methods, including chlorine, which has been used for more than a century in Canada (Centers for Disease Control and Prevention 2012, Indigenous Services Canada 2019). Waterborne diseases such as typhoid fever, cholera, dysentery, and other

gastrointestinal diseases have almost entirely been eliminated with the introduction of chlorine to treat drinking water (Indigenous Services Canada 2019).

The issue of eliminating waterborne pathogens through disinfection can, however, present a delicate balance as unnecessary high disinfectant doses can reduce the acute risk posed by pathogens, but may also generate organic and inorganic disinfection by-products. Alternatively, failing to add sufficient chlorine needed for disinfecting for fear of not generating disinfection byproducts can result in adverse effects. Therefore, maintaining this inevitable risk assessment trade-off between acute microbial and chemical risks remains a challenge for water utilities. Previous authors explored and quantified the risks and benefits of disinfection and this complex balance using disability adjusted life-years (DALYs) as a metric (Havelaar, De Hollander et al. 2000). The potential health effects related to the occurrence of the protozoan parasite *Cryptosporidium parvum* (gastroenteritis) and the exposure of bromate linked to renal cancer have been investigated. According to the estimates, *Cryptosporidium parvum* reduction appears to be more beneficial than bromate formation, where the net benefit is approximately one DALY for every million person-years annually (Havelaar, De Hollander et al. 2000). Although the advantages of disinfection are undeniable, there is a crucial need to investigate health effects and chemical risks linked to the numerous detected DBPs in drinking water.

2.2 DBPs in drinking water are a complex issue due to their diversity

Two foundational publications reported on the formation of DBPs such as chloroform in disinfected drinking water and permanently transformed the viewpoint that water safety through disinfection was solely a matter of preventing diseases (Bellar 1974, Rook 1974, Hrudey 2009). Since the discovery that chloroform could be generated by chlorine through the reaction with organic matter, more than 700 halogenated compounds have been identified in disinfected water (Richardson and Plewa 2020). Those numerous compounds can be generated through different disinfection techniques such as chlorine, chloramine, chlorine dioxide and ozone and may promote distinct classes of DBPs depending upon the method of disinfection. Table 1 shows generated organic, inorganic by-products and nonhalogenated by-products that may be formed using chloramination, ozone, chlorine, chlorine dioxide.

Table 1: Organic and inorganic DBPs generated through the use of different disinfectants (modified from (Mazhar, Khan et al. 2020) (Richardson, Plewa et al. 2007). Writing in blue indicates compounds incorporated in the Canadian Guidelines (Health Canada 2020)

Disinfectant	Organic by-products	Inorganic by-products	Nonhalogenated by-products
Chlorine	**Trihalomethanes (THM_4), Haloacetic acids (HAA_5)**, haloacetonitriles (HANs), chloral hydrate (CH), chloropicrin, chlorophenols, N-chloramines, halofuranones, bromohydrins	**Chlorate** (with hypochlorite)	Aldehydes, cyanoalkanoic acids, alkanoic acids, **benzene**, carboxylic acids
Chlorine dioxide		**Chlorite, chlorate**	Unknown
Chloramine	HANs, cyanogen chloride, organic chloramines, chloramino -acids, chloral hydrate, haloketones (HK)	**Nitrate**, **nitrite**, **chlorate**, hydrazine	Aldehydes, ketones, Nitrosodimethylamine (NDMA)
Ozone	Bromoform, MBA, DBA, DBAC, cyanogen bromide	**Chlorate**, iodate, bromate, hydrogen peroxide, hypobromous acid, epoxides, ozonates	Aldehydes, ketoacids, ketones, carboxylic acids

Halogenated compounds however seem to represent only a fraction of total organic halogen (TOX) (Krasner, Weinberg et al. 2006). Based on a study of twelve U.S. full-scale treatment plants conducted in 2000-2002, where each plant was sampled four or five times throughout the year; THM_4, HAA_5, and haloacetaldehydes accounted for 14 %, 12 %, and 2% of the TOX, respectively. For all sampled plants, the sum of the halogenated DBPs (halo-DBPs) constituted ~30% of the TOX; implying that ~70% of the TOX remains unknown in disinfected water (Krasner, Weinberg et al. 2006). It is likely that disinfected water contains more than 1,000 DBPs due to the wide variety of precursors and disinfection techniques, emphasizing how difficult and critical it remains to investigate the unknown

TOX (Li and Mitch 2018). Studies attempting to characterize the missing fraction of DBPs have found that it is mostly composed of non-volatile and polar compounds having high molecular weights (>500 g/mol) such as bromoamine, polyamines, polycarboxylic acids, nitrosamines and organic peroxides (Diana, Felipe-Sotelo et al. 2019).

A growing body of scientific evidence on the toxicity of DBPs has been published since the 1970s. However, the exhaustive picture of the wide spectrum of DBPs is still incomplete as *in vivo* and *in vitro* toxicological studies have only been conducted on 80 of the ~700 individual DBPs (Diana, Felipe-Sotelo et al. 2019). Richardson et al. (2007) published a comprehensive review on regulated and emerging DBPs in drinking water detailing and linking occurrence, genotoxicity and carcinogenicity for each class and compounds (Richardson, Plewa et al. 2007). Interestingly, some compounds more ubiquitous and present at higher concentrations did not represent the most toxic in toxicological studies. For instance, there is evidence that nitrogen-based haloacetaldehydes and haloacetonitriles, haloacetamides, and halonitromethanes exhibit orders of magnitude greater cytotoxicity and genotoxicity than the regulated trihalomethanes (THM_4) and haloacetic acids (HAA_5), present at higher concentrations (Li and Mitch 2018).

The identification of plausible carcinogens formed during chlorination of drinking water in concentrations sufficient to account for the risk observed in epidemiological studies remains a challenge (Diana, Felipe-Sotelo et al. 2019). Since the putative causal agent or combination of agents of adverse health effects in the DBP mixture is currently unknown, the regulated THM_4 and HAA_5 may serve as a surrogate of this agent or combination of compounds in disinfected water although this assumption is now challenged (Li and Mitch 2018, Furst, Coyte et al. 2019, Richardson and Plewa 2020).

Because of the vast array of DBPs having distinct adverse toxicological effects, mammalian cell assays have become an interesting tool to compare and prioritize concentrations of DBPs weighted by metrics of toxic potency in terms of cytotoxicity, clastogenic, genotoxic (Wagner and Plewa 2017). A high number of DBPs and related compounds have been evaluated systematically for chronic cytotoxicity and acute genotoxicity based on Chinese hamster ovary (CHO) cell assays. This relatively new approach called ‘TIC-Tox’ has revealed important groups of toxicity drivers and enables a

comparison between different treated water in terms cytotoxicity or genotoxicity (Richardson and Plewa 2020). For instance, a difference was observed in the cytotoxic and genotoxic potency of specific DBP analogues based on their halogen species (I, Br, and Cl) where iodine-based compounds were more cytotoxic and genotoxic than brominated DBPs which were far more toxic than chlorinated DBPs (Plewa and Wagner 2011). Figure 1 shows the comparison between mammalian cell cytotoxicity and genotoxicity for different classes of DBPs.

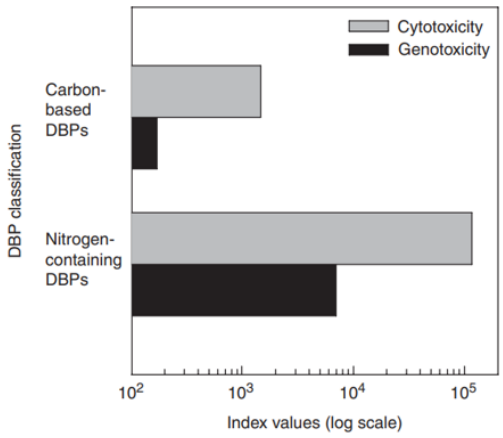


Figure 3 Mammalian cell cytotoxicity and genotoxicity index values of carbon-based and nitrogen-containing DBPs (log scale).

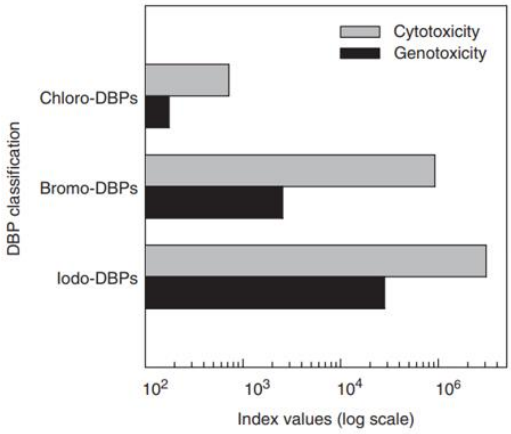


Figure 4 Mammalian cell cytotoxicity or genotoxicity index values of chloro-, bromo-, and iodo-DBPs (log scale).

Figure 1: Comparisons between mammalian cell cytotoxicity and genotoxicity between carbon-based DBPs and nitrogen-containing DBPs and between chloro-DBPs, bromo-DBPs and iodo-DBPs. The calculated DBP concentration that induced a CHO cell density that was 50% of the negative control were used to calculate the cytotoxicity index for all individual members within a single class of DBP (Plewa and Wagner 2011).

As a result of increased source water contamination (e.g. from bromide or iodine entry) or change in disinfection practices from chlorination to a combination of alternative primary disinfectants and chloramination as a secondary disinfectant, this issue of emerging DBPs may become more complex. These potentially toxic substances may raise concerns from a public health perspective.

2.3 Potential health effects related to exposure to regulated DBPs

The following sections focus on the two families of regulated DBPs: trihalomethanes (THM_4) and haloacetic acids (HAA_5). The first section will address the potential carcinogenic effects reported in the literature and the second section will describe evidence on noncarcinogenic effects for these two classes of regulated DBPs.

2.3.1 Potential carcinogenic effects

Throughout the years, the International Agency for Research on Cancer (IARC) has published toxicological evaluations for both individual THM_4 and HAA_5 compounds (Table 2). THM_4 were evaluated in 1991 and 1999 while toxicity of HAA_5 was assessed more recently in 2014. The compounds chloroform/trichloromethane (TCM), bromodichloromethane (BDCM), dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), dibromoacetic acid (DBAA) and bromochloroacetic acid (BCAA) were categorized as "Possibly carcinogenic to humans" which is an agent that has some evidence of cancer in humans or strong animal evidence or strong mechanistic evidence (Ward, Schulte et al. 2010).

Table 2: Carcinogenic evaluations for each THM_4 and HAA_5 compounds by The International Agency for Research on Cancer (IARC)

Family of DBPs	Compounds	Cancer group		IARC monography, Year	References
Trihalomethanes	TCM	2B	"Possibly carcinogenic to humans"	73 1999	(International Agency for Research on Cancer 1999)
	BDCM	2B	"Possibly carcinogenic to humans"	52 1991	(International Agency for Research on Cancer 1991)
	DBCM	3	"Unclassifiable as to carcinogenicity in humans"	52 1991	(International Agency for Research on Cancer 1991)
	TBM	3	"Unclassifiable as to carcinogenicity in humans"	52 1991	(International Agency for Research on Cancer 1991)
Haloacetic acids	MCAA	-			
	DCAA	2B	"Possibly carcinogenic to humans"	106 2014	(International Agency for Research on Cancer 2014)
	TCAA	2B	"Possibly carcinogenic to humans"	106 2014	(International Agency for Research on Cancer 2014)

	DBAA	2B	"Possibly carcinogenic to humans"	106 2014	(International Agency for Research on Cancer 2014)
	BCAA	2B	"Possibly carcinogenic to humans"	106 2014	(International Agency for Research on Cancer 2014)

Among the outcomes studied for their associations with DBPs concentrations, specifically THM_4, bladder cancer is the one that has the greatest relevance, as evidence for other cancers are weaker (e.g. colorectal, liver, and kidney cancer) (Nieuwenhuijsen, Grellier et al. 2009). A number of epidemiological studies have shown an association between exposure to tap chlorinated drinking water and bladder cancer in different cohort studies and in various regions in the world (King and Marrett 1996, Cantor, Lynch et al. 1998, Villanueva, Fernandez et al. 2003, Villanueva, Cantor et al. 2004, Villanueva, Cantor et al. 2007, Nieuwenhuijsen, Smith et al. 2009, Beane Freeman, Cantor et al. 2017, Evlampidou, Font-Ribera et al. 2020, Beane Freeman, Kogevinas et al. 2022). An important meta-analysis by Villanueva et al. (2004) found that DBP intake was associated with bladder cancer in men but not in women compared to the non exposed group (Villanueva, Cantor et al. 2004). The results from the meta-analysis are summarized in Table 3 and are presented in terms total THM exposure levels (mg) for both males and females. The physiological explanation for this difference between males and females may involve sex hormones modulating enzymes responsible for metabolizing chlorination by-products into reactive compounds (Villanueva, Cantor et al. 2004). Furthermore, another meta-analysis including case-control studies in Europe and in North-America also showed that as exposure levels in chlorinated water rose above 25 µg/l with a period of exposure over 30 years of exposure, risks increased significantly (N=4351 cases and N=7055 controls) (Costet, Villanueva et al. 2011). A number of epidemiological studies have found that the risk of bladder cancer generally increases with the level and duration of exposure to THM_4 (Regli, Chen et al. 2015).

Table 3: Pooled analysis of OR bladder cancer and total THM exposure (modified from (Villanueva, Cantor et al. 2004))(Nieuwenhuijsen, Grellier et al. 2009)

Total THM exposure level (mg) (concentration × consumption per day × years exposed)	**OR (95% CI)**	
	Male	**Female**
0-15	1.00	1.00
>15-50	1.22 (1.01–1.48)	0.92 (0.65–1.32)
>50 - 400	1.28 (1.08–1.51)	0.94 (0.70–1.27)
>400 - 1000	1.31 (1.09–1.58)	1.02 (0.74–1.41)
>1000	1.50 (1.22–1.85)	0.92 (0.65–1.30)

EPA used the estimates of bladder cancer cases avoided to quantify the benefits of the Stage 2 DBP regulation as the metric for calculating health effects under the new regulation, demonstrating the relevance of this outcome. Figure 2 shows the dose-response curve developed by Regli et al. (2015) for bladder cancer as an outcome to estimate the number of bladder cases that were attributable to THM_4 (Regli, Chen et al. 2015). Using the approach by Regli et al. (2015), Weisman et al. (2022) estimated that approximately 8,000 of the 79,000 annual bladder cancer cases in the United States were potentially attributed to THM_4 mostly for people served by large surface water systems rather than smaller supply networks (Weisman, Heinrich et al. 2022).

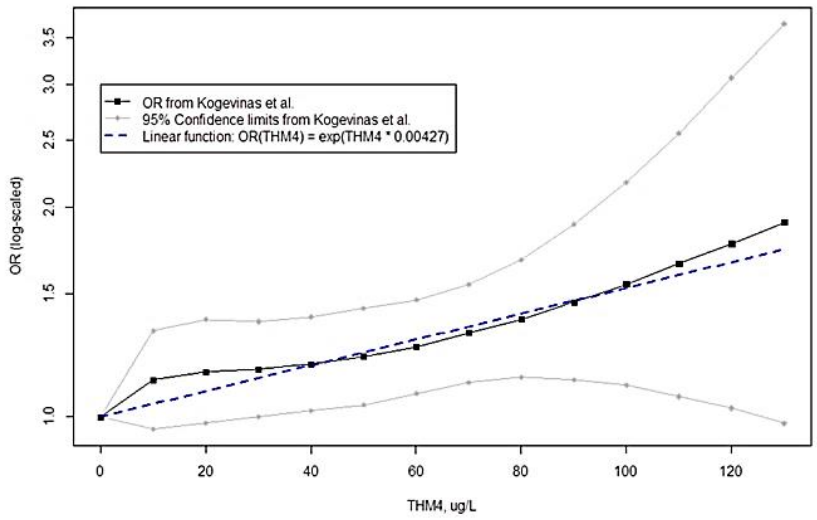


Figure 2: Pooled log OR of bladder cancer risk in function of THM exposure derived from six different studies. Data from personal communication from Villanueva and Kogevinas (Regli, Chen et al. 2015)

As mentioned previously, research suggested that exposure to brominated compounds may contribute to an increased cancer risk, and therefore the global THM_4 may not be the best indicator of the mutagenicity of chlorinated water (Costet, Villanueva et al. 2011) (Evans, Campbell et al. 2020). Indeed, brominated DBPs may pose greater health risks than chlorine-only species such as chloroform (Richardson, Fasano et al. 2008, Regli, Chen et al. 2015) which is particularly important in the climate change context where increasing bromide levels can be observed (Regli, Chen et al. 2015). In this regard, Regli et al. (2015) have investigated the potential increased excess lifetime bladder cancer risk as a function of increased source water bromide levels based on a pooled analysis of data obtained from six case-control studies (Figure 2). Interestingly, results based on data from 201 drinking water treatment plants indicated that a bromide increase of 50 μg/L could result in a potential increase of between 10^{-3} and 10^{-4} excess lifetime bladder cancer risk for populations served by roughly 90% of these plants (Regli, Chen et al. 2015).

2.3.1.1 Hypotheses on the mode of action for carcinogenic effects

Two families of enzymes CYP (cytochrome P450) and GST (glutathione S-transferase) appear to play key roles in the DBPs metabolization, the first one in the detoxification of THM_4 and the second one in the activation in mutagenic compounds by adding a conjugate (DeMarini 2020). GSTT1 and GSTZ1 are genes encoding enzymes involved in the biotransformation of two groups of DBPs, brominated THM_4 and α-haloacids. Indeed, glutathione S-transferase zeta-1 (GSTZ1) is the primary enzyme involved in the metabolization of di-HAA through the oxygenation of dichloro- and haloacids and may also be involved in brominated triHAA metabolism. It is believed that some GSTZ1 metabolites are carcinogenic in rodents. For brominated THM_4 such as DBCM, the GSTT1-mediated metabolism can produce reactive intermediates that covalently bind DNA and deoxyguanosine and thus act as a mutagenic carcinogen (Ross and Pegram 2004). Hence, brominated THM_4 may be activated into mutagens in subjects with the GSTT1-present genotype.

Moreover, an enzyme in the phase I metabolic pathway (first transformation by hepatic enzymes), CYP2E1, oxidizes many different organic compounds such as alkanes, alkenes, aromatic and halogenated hydrocarbons and is responsible for the first oxidation of THM_4

(Cantor Kenneth, Villanueva Cristina et al. 2010). Other cytochromes such as CYP1A2, CYP2A6 and CYP2D6 are also phase I xenobiotic-metabolizing enzymes involved in metabolic pathways of DBPs. Toxicological studies demonstrated that human isoenzymes CYP1A2 and CYP2A6 metabolize the bromodichloromethane (BDCM) (Bonou, Levallois et al. 2017). A gene, whether present or absent, unchanged or with one or a few mutations, may enhance, diminish, or maintain the production of certain enzymes, and thus may play a significant role in the development of cancer.

The U.S. Department of Health and Human Services (HHS) and the National Toxicology Program (NTP) recently evaluated thirteen HAAs in its 15th report on carcinogens published in 2021. They identified six HAAs as *reasonably anticipated carcinogens for humans*, including bromochloroacetic acid, bromodichloroacetic acid, chlorodibromoacetic acid, dibromoacetic acid, dichloroacetic acid, and tribromoacetic acid (National Toxicology Program 2021, Lunn, Mehta et al. 2022). As a result of NTP evaluation, all six compounds are found to be carcinogenic after experimentation on animals. However, the evidence of their carcinogenicity in humans yields different conclusions. Different conclusions were reached from mechanistic studies evaluating biological plausibility, and different results were observed from epidemiological studies demonstrating carcinogenicity (National Toxicology Program 2021). It has been demonstrated in various types of in vitro studies that all of the listed HAAs cause oxidative stress, which generates reactive oxygen species that can damage DNA and cause mutations (National Toxicology Program 2021). The strongest evidence is for brominated-HAA (National Toxicology Program 2021).

However, it is worth noting that no causal relationship has been established yet between bladder cancer and exposure to any particular DBP or class of DBPs (Weisman, Heinrich et al. 2022) (Regli, Chen et al. 2015). It is possible that additive or synergistic toxicological effects could contribute to the observed risk of bladder cancer. In addition, interactions between DBPs within a mixture could potentially affect the toxicity, the mechanism of action, and the target organ of each DBP. There is a need for further research concerning the toxicological effects of DBP mixtures (Diana, Felipe-Sotelo et al. 2019).

2.3.1.2 Findings on the role of human genetic polymorphisms (bladder cancer)

Cantor et al. (2010) found that people with the GSTT1(+) genotype were at significantly greater risk (odds ratio (OR) = 2.2; 95% confidence interval (CI): 1.1−4.3) for developing bladder cancer when exposed to the upper THM_4 exposure quartile (>49 µg/L) compared to GSTT1-null participants who had no increased risk at the same exposure level (Cantor Kenneth, Villanueva Cristina et al. 2010). In comparison, subjects with GSTT1 null, GSTZ1 CC, or CYP2E1 CT/TT genotypes did not exhibit any significant association with increasing THM quartiles, but subjects with GSTT1 present genotypes GSTZ1, GSTZ1 or CYP2E1 did exhibit significant positive trends associated with increasing THM exposure (Cantor Kenneth, Villanueva Cristina et al. 2010). In addition, individuals with GSTM1 null genotypes showed an increased risk of bladder cancer (García-Closas, Malats et al. 2005).

2.3.1.3 The importance of pathways of exposure for bladder cancer

Pathways of exposure have been shown to be important in terms of potential development of health effects. Indeed, it has been hypothesized that ingestion of THM_4 may result in their inactivation/elimination by first-pass metabolism in the liver and being detoxify by the enzyme CYPE1 before they can enter the systemic circulation (Richardson, Plewa et al. 2007, DeMarini 2020). In contrast, when dermal or inhalation exposure occurs, THM_4 would be directly absorbed into the bloodstream (by-passing the liver) and being distributed to organs throughout the body. Afterwards, they are activated into mutagens in the bladder that would covalently bind to DNA. The human bladder exhibits GSTT1 at greater levels than other tissues in human bodies which could make this organ more susceptible to THM (Figure 3) (DeMarini 2020). The findings of Villanueva et al. (2007) and Cantor et al. (2007) provided support for observations suggesting that disinfected water increases bladder cancer risk as a result of dermal/inhalation exposures from showering, bathing, and swimming due to exposure to volatile brominated THM (Villanueva, Cantor et al. 2007) (Cantor, Villanueva et al. 2006) (Richardson, Plewa et al. 2007). A schematic representation of the different metabolization processes according to exposure pathways is depicted in **Erreur ! Source du renvoi introuvable.**.

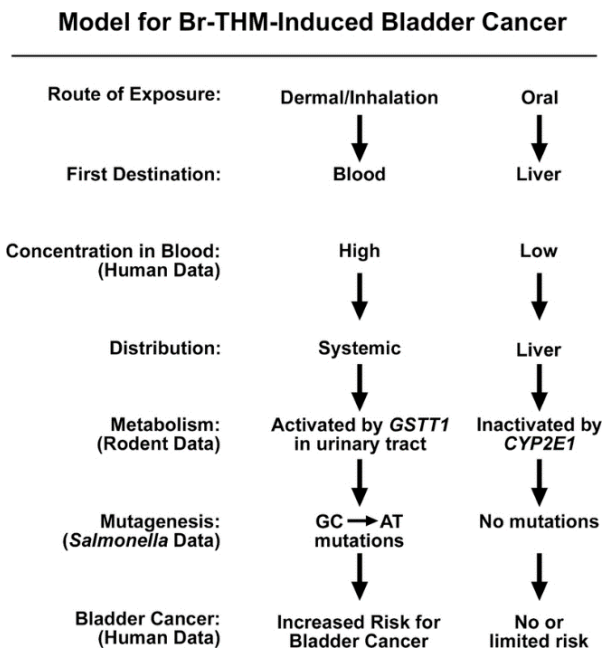


Figure 3: Schematic description on the impact of dermal/inhalation and oral exposure on the toxicity of Br-THM (DeMarini 2020)

2.3.2 Potential non carcinogenic effects

Congenital anomalies (e.g. neural tube defects), stillbirth, spontaneous abortion, low birth weight (LBW), small for gestational age (SGA), intrauterine growth retardation prematurity and semen quality have been the focus of epidemiological studies, meta-analyses, and reviews (Nieuwenhuijsen, Grellier et al. 2009, Zhang, Deng et al. 2023). Furthermore, there have been some small positive associations reported in literature for stillbirths (Nieuwenhuijsen, Grellier et al. 2010), preterm birth delivery (PTD) (Grellier, Bennett et al. 2010), small-for-gestational-age births studies (Graves, Matanoski et al. 2001, Wright, Schwartz et al. 2003, Lewis, Suffet et al. 2006, Nieuwenhuijsen, Martinez et al. 2009, Grellier, Bennett et al. 2010, Villanueva, Gracia-Lavedan et al. 2011, Costet, Garlantézec et al. 2012, Levallois, Gingras et al. 2012, Summerhayes, Morgan et al. 2012, Levallois, Giguère et al. 2016, Säve-Söderbergh, Toljander et al. 2020), low birth weight (Hinckley, Bachand et al. 2005, Danileviciute, Grazuleviciene et al. 2012), congenital anomalies (Nieuwenhuijsen, Martinez et al. 2009, Säve-Söderbergh, Toljander et al. 2021) and male reproductive health (Zhang, Deng et al. 2023). Results from some meta-analysis

and epidemiological studies are presented in Table 4 and Table 5. Definitions of the different outcomes are provided below[1].

2.3.2.1 Adverse reproductive effects during pregnancy

A meta-analysis by Grellier et al. (2010) using a total of 15 studies found an association of THM_4 exposure with SGA (n=8) but not with LBW (n=6) or PTD (n=8) for the third trimester for THM_4 (Table 4)). The data Q-statistics is a measure for heterogeneity/homogeneity between studies which in this case showed no heterogeneity (Viechtbauer 2007). Through a random-effects meta-analysis, authors found little to no evidence for associations between THM_4 concentrations and LBW, PTD and SGA. Grellier et al. (2010) highlighted that many studies used THM_4 concentrations, hence the sum of the four concentrations of TCM, BDCM, DBCM, and TBM as a proxy for exposure to unknown toxicity drivers at the mother's residence. Those studies focused primarily on ingestion, which may reduce the strength of associations when other pathways of exposure are not considered (Grellier, Bennett et al. 2010).

However, Grellier et al. (2010) also found that there was a slightly stronger association with exposure during the third trimester (OR=1.00–1.02), which is reasonable considering that weight gain occurs primarily during the third trimester (Grellier, Bennett et al. 2010). SGA is expected to have a greater power to detect small risks associated with retarded fetal

[1] A condition called intrauterine growth restriction/restriction or small for gestational age (SGA) is generally defined as a birth weight below the 10th percentile of weight for gestational age after adjustment for covariates (e.g. gender and race). The usual definition of low birth weight (LBW) being less than 2500 g, very low birth weight is typically less than 1500 g and term low birth weight is less than 2500 g at 37 weeks gestation. Stillbirth is a progression from spontaneous abortion whereby a fetus that has developed beyond 20 weeks gestation dies during birth or late stages of pregnancy. Preterm delivery (also known as premature birth) is birth before the standard duration of pregnancy (i.e. sooner than 37 weeks after the start of the last menstrual period). Various measures of low birth weight have been evaluated, with the usual definition of low birth weight being less than 2500 g, very low birth weight is typically less than 1500 g and term low birth weight is less than 2500 g at 37 weeks gestation.

Colman, J., G. E. Rice, J. M. Wright, E. S. Hunter, III, L. K. Teuschler, J. C. Lipscomb, R. C. Hertzberg, J. E. Simmons, M. Fransen, M. Osier and M. G. Narotsky (2011). "Identification of developmentally toxic drinking water disinfection byproducts and evaluation of data relevant to mode of action." Special Issue: TRAC 2008/2009 meeting **254**(2): 100-126. Hrudey, S. E. (2008). Chlorination Disinfection By-products (DBPs) in Drinking Water and Public Health in Canada: A Primer for Public Health Practitioners Reviewing Evidence from Over 30 Years of Research: a Knowledge Translation Review for the National Collaborating Centre [for] Environmental Health, National Collaborating Centre for Environmental Health.

growth since it takes into account the gestational age of the foetus (Grellier, Bennett et al. 2010). This period appears to be critical for this outcome in various studies, as associations between blood and urinary biomarkers and/or with DBP concentrations in drinking water tend to be higher during this trimester. For instance, according to Cao et al. (2016), elevated blood levels of brominated THMs (Br-THMs) and THM_4 indicated a dose-response relationship with an increased incidence of SGA (N=1,184 participants) (Cao, Zeng et al. 2016). Indeed, it was found that SGA was significantly associated with THM_4 in the second and third tertiles (44.2 – 74.4 µg/L) and also with Br-THM in the second and third tertiles (3.3 µg/L – 7.5 µg/L and > 7.5 µg/L). As for THMs, OR was 2.91 (CI: 1.32 – 6.42), and 2.25 (CI: 1.01; 5.03), respectively, while for BrTHM, OR was 1.48 (0.71, 3.04) and 1.92 (0.98, 3.79) (Cao, Zeng et al. 2016).

Other studies have investigated the association between DBPs concentrations in blood or urine and reproductive outcomes where those biomarkers tend to reflect the internal dose caused by multiple routes and pathways of exposure (Yang, Cao et al. 2019, Sun, Wang et al. 2020). The development of exposure biomarkers therefore has great prospects for improving exposure assessment, which is a limiting factor in the quality and conclusiveness of epidemiological studies (Savitz 2011).

Table 4: Summary table of results of meta-analyses for all health outcomes, including results of subset analyses for exposure agent and exposure timing. Health outcomes: low birth weight (LBW), term low birth weight (term LBW), small for gestational age (SGA) and preterm delivery (PTD). Modified from (Grellier, Bennett et al. 2010)

Exposure Agent	Exposure Timing	Health Outcome	No. Studies Included	OR Slope per 10 µg/L	95% CI	Q-Statistic
Only THM	Third trimester	LBW	4	0.9999	(0.9735–1.0270)	2.244
		Term LBW	4	1.0337	(0.9272–1.1525)	3.987
		PTD	6	0.9896	(0.9781–1.0013)	1.840
		SGA	6	1.0100	(1.0006–1.0194)	3.569
		LBW	5	1.0013	(0.974681–1.0286)	2.495

	Any exposure timing	Term LBW	5	1.0228	(0.9456–1.1063)	4.008
		PTD	8	0.9894	(0.9777–1.0007)	4.124
		SGA	8	1.0096	(1.0009–1.0184)	4.641
	Entire pregnancy	SGA	4	1.0105	(0.9712–1.0514)	4.659
THM and TCM	Any exposure timing	LBW	5	1.0001	(0.9737–1.0272)	2.495
		PTD	9	0.9894	(0.9777–1.0007)	4.125
	Entire pregnancy	PTD	4	0.9696	(0.9139–1.0286)	1.441

Even though Grellier et al. (2010) found no evidence for an association among selected studies between LBW and THM_4, a prospective cohort study in 2013 (N=4,161), has observed dose-response relationships for THM and chloroform internal doses for low birth weight and birth weight reduction risk (Grazuleviciene, Kapustinskiene et al. 2013). Authors found that an increase of the internal dose of chloroform of 0.1 grams per day was associated with an increased risk of LBW (OR 1.10, 95% CI 1.01-1.19) for the whole pregnancy. For second and third tertiles, respectively, the odds ratios for LBW were 1.77, 95% CI 0.95-3.30, and 2.13, 95% CI 1.17-3.87, compared to the first tertile for total THM. LBW adjusted odds ratio was 2.17, 95% CI 1.19-3.98 for third tertile chloroform internal dose vs. first tertile chloroform internal dose for the entire pregnancy.

Other studies investigated other DBPs and their associations to reproductive outcomes. Wright et al. (2004) conducted a study examining associations with SGA with THM_4, TCM, BDCM, total HAAs and TCAA for 109 communities in Massachusetts. Interestingly, authors found risk estimate below 1 (no risk) for total HAA and TCAA while the highest OR were estimated for BDCM (Table 4). Wright et al. (2004) detected a monotonic increase in risk for SGA for chloroform concentrations higher than 20 µg/L, for THM_4 concentrations higher than 40 µg/L and for BDCM (>5 µg/L). In a previous

publication, Wright et al. (2003) found a higher frequency of SGA birth for mothers exposed to concentrations higher than 80 µg/L during the pregnancy compared to the reference group (OR: 1.14, 95% CI 1.02 to 1.26).

Table 5: Association between SGA and various DBPs (µg l−1) (modified from (Wright, Schwartz et al. 2004, Nieuwenhuijsen, Grellier et al. 2009)(N= 196,000)

Exposure	Concentrations (µg/L)	SGA	Preterm delivery
		OR (95% CI)	OR (95% CI)
THM_4	>74–163 versus 0–33	1.13 (1.07–1.20)	0.88 (0.81 to 0.94)
TCM	>63–135 versus 0–26	1.11 (1.04–1.17)	0.90 (0.84 to 0.97)
BDCM	>13–46 versus 0–5	1.15 (1.08–1.22)	0.92 (0.85 to 0.99)
Total HAAs	>49–58 versus 4–30	0.97 (0.77–1.23)	1.03 (0.77 to 1.39)
DCAA	>22–24 versus 2-15	0.90 (0.75 to 1.09)	0.99 (0.79 to 1.23)
TCAA	>27–37 versus 0–18	0.95 (0.76–1.19)	1.07 (0.81 to 1.42)

A previous study found that the third quintile of exposure to MCAA was associated with intrauterine growth retardation (OR= 1.27, 95% CI = 1.00–1.61) and the second quintile of exposure to dichloroacetic acid was associated with intrauterine growth retardation (OR=1.29, 95% CI =1.02–1.64) while no consistent association was encountered for the two class of DBP, HAAs and THMs for all pregnancy (Porter, Putnam et al. 2005). According to Porter et al. (2005), the conclusions regarding the associated risks associated with exposure to DCAA and to THM_4 differ from those of Wright et al. (2003) and Wright et al. (2004) (Wright, Schwartz et al. 2003, Wright, Schwartz et al. 2004, Porter, Putnam et al. 2005). However, intrauterine growth retardation and small for gestational age are not the same outcome and communicates different aspects of growth which may explain these differences for the effects of individual HAAs and THM_4.

2.3.3 Reported male reproductive effects

Several articles covered the association with male reproductive health and concentration of THM_4 and HAA_5 in drinking water (tap and pool) or in biological fluids (e.g. blood, urine) (Xie, Li et al. 2011, Zeng, Zhou et al. 2016). A recent review which included 15 epidemiological studies concluded that there is sufficient toxicological evidence to support the hypothesis that HAA_5 are male reproductive toxicants and may contribute to a reduction

in epididymal weight, a decrease in semen parameters, a decrease in sperm protein 22, and a decline in testosterone levels. An interesting finding from Zheng et al. (2016) showed that blood Br-THMs and TCAA may have synergistic effects on below-reference sperm counts. Indeed, compared to men with low Br-THMs (lower than the median) and TCAA levels, men with high Br-THMs (higher than the median) and TCAA levels were 3.31 times more likely to have below-reference sperm counts (Zeng, Zhou et al. 2016). However, in spite of the fact that some studies demonstrated that blood and urine DBP biomarkers are associated with decreased semen quality, in their review, Zhang et al. (2023) concluded that epidemiological evidence is inconsistent and does not support a correlation between DBP exposures and adverse male reproductive outcomes in all studies (Zhang, Deng et al. 2023). It is likely that the inconsistency of the results is related to differences in exposure assessment methods (e.g., external exposure surrogates vs. internal biomarkers) (Zhang, Deng et al. 2023).

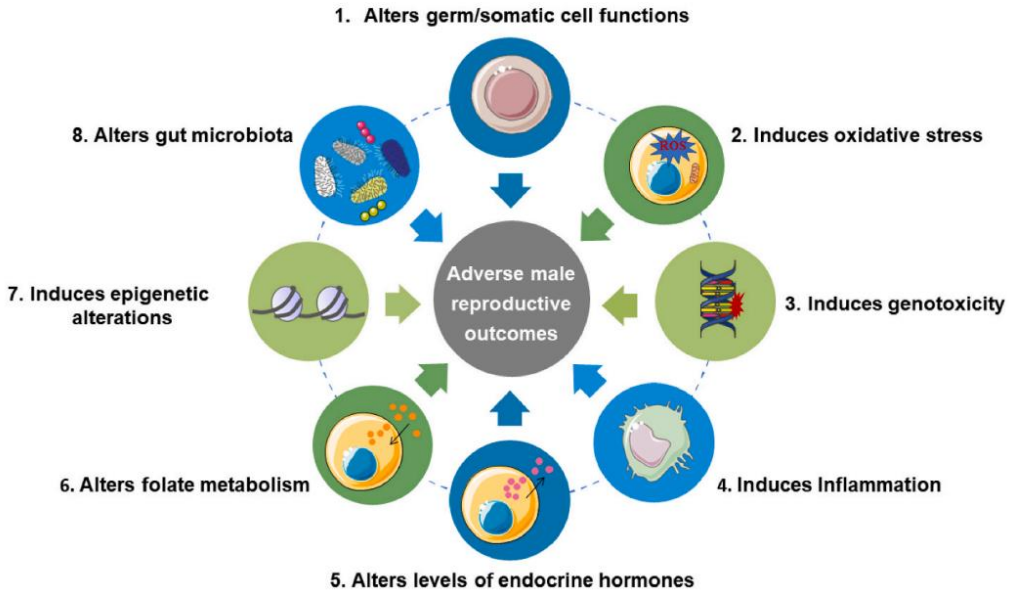


Figure 4: The possible mechanisms responsible for DBPs-induced adverse male reproductive outcomes(Zhang, Deng et al. 2023)

2.3.4 Hypotheses on the mode of action

Considering that epidemiological associations do not necessarily imply causality, toxicological studies are also required to investigate DBP potential mode of action (MOA) (Colman, Rice et al. 2011). Several toxicological studies have demonstrated that DBPs

molecules are capable of passing through the placenta, resulting in decreased conception rates, pregnancy losses, birth weight reductions, and dysmorphogenetic in rodents (Sun, Wang et al. 2020).

The adverse effects on reproductive health have been studied in literature primarily with rodents, and several modes of action have been identified. These modes of action remain to be investigated in further detail. The effects of total THM on intrauterine growth retardation are likely to result from intermediates resulting from increased metabolic activation of trihalomethanes in genetically sensitive fetuses (Agency for Toxic Substances and Disease Registry (ATSDR) 2011, Agency for Toxic Substances and Disease Registry (ATSDR) 2011). Furthermore, it is possible that DBPs may affect foetal growth through an oxidative stress mechanism. Indeed, evidence suggests that maternal oxidative stress during pregnancy contributes to adverse developmental outcomes for the fetus. In particular, increased concentrations of oxidative stress biomarkers (8-OH-dG and MDA) found in urine of pregnant women have been linked to decreased birth weight (Kim, Hong et al. 2005). The evidence has also shown that TCM and TCAA can lead to deficiencies in folate and folic acid (forms of vitamin B), which are required to construct, repair, and function DNA, as well as to support a rapidly developing fetus (Nieuwenhuijsen, Grellier et al. 2009).

In addition, in terms of pregnancy loss, BDCM has been examined the most extensively and its MOA for full-litter resorption in animals is well characterized (Colman, Rice et al. 2011). Findings suggest that BDCM disrupts pregnancy in F344 rats via a disruption of luteinizing hormone secretion, one of the main hormones that control the reproductive system, resulting in a decrease in progesterone levels (Colman, Rice et al. 2011, United States Environmental Protection Agency 2016). While many hypotheses have been proposed over the last few decades, modes of action have yet to be defined for cardiovascular defects, neural tube defects, low birth weight, and small for gestational age outcomes, for which there is insufficient evidence (Colman, Rice et al. 2011).

For adverse male reproductive outcomes, there is limited understanding and no consensus on the mechanisms associated with DBP exposure. Zhang et al. (2023) summarized the different mechanisms that may be play a role such as germ/somatic cell dysfunction,

oxidative stress, genotoxicity, inflammation, endocrine hormones, folate metabolism, epigenetic alterations, and gut microbiota disruption (Figure 4).

2.3.5 Findings on the role of human genetic polymorphisms (adverse reproductive effects)

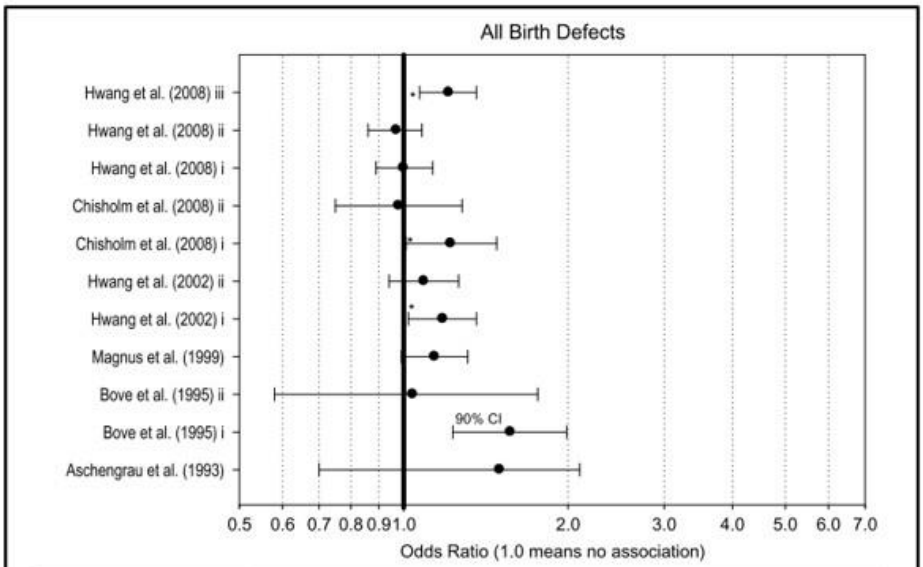
Few studies investigated the genetic susceptibility and polymorphisms for genes (cytochrome P450 - CYP2E1 and Glutathione S-Transferase - GST) encoding for enzymes responsible for the biotransformation of THMs and HAA_5 (Infante-Rivard 2004, Yamada, Sata et al. 2004, Danileviciute, Grazuleviciene et al. 2012, Levallois, Giguère et al. 2016, United States Environmental Protection Agency 2016, Bonou, Levallois et al. 2017). Different versions of genes-encoding metabolic enzymes seem to be associated differently with different outcomes.

In these previous studies, associations with different alleles of those genes were studied for association with adverse reproductive outcomes such as SGA. A significant association with CYP2E1 rs117618383 was reported by Bonou et al. (2017) with one or two allele variations compared to wild type for THM_4 above the 3rd quartile (p-value: 0.03, OR = 4.6 (1.2;17.6)) (Levallois, Giguère et al. 2016). However, no positive interactions were found with CYP2E1 rs3813867 and GSTT1 deletion with THM exposure (Levallois, Giguère et al. 2016). In a subsequent study, Bonou et al. (2017), did not find significant interactions between genetic variants in CYP1A2, CYP2A6, CYP2D6 and CYP17A1 genes and exposure to THMs or HAAs on and SGA. Danileviciute et al. (2012) investigated the association between THM internal doses and LBW and SGA. Interaction between internal doses and GST genes polymorphism showed that effect of THM_4 and individual THM on SGA and more greatly for LBW is amplified when women appear to have the GSTM1–0 genotype (Danileviciute, Grazuleviciene et al. 2012). If these data are corroborated, people carrying the CYP2E1 variant could have considerably greater risk of SGA than reported for pooled populations (Grellier, Bennett et al. 2010)

2.3.6 Disparities among studies and discussion

Due to disparities between studies and meta-analyses, different results have been presented in order to capture the diverse conclusions that have been drawn in the literature throughout

the last decades. It is generally thought that there is a small, positive association between concentrations of trihalomethanes/chloroform in drinking water and adverse birth outcomes associated with fetal growth restriction specifically small for gestational age, however, evidence does not always converge, and this hypothesis may not be supported by all data (Figure 5 and Figure 6 as examples).



Reference	Exposure Comparison	Adjusted OR (95% CI)
Hwang et al. (2008) iii	Low TTHM (5 – 9 µg/L) vs. Lowest (0 - 4 µg/L)	1.21 (1.07 – 1.36)*
Hwang et al. (2008) ii	Medium TTHM (10 - 19 µg/L) vs. Lowest (0 - 4 µg/L)	0.97 (0.86 – 1.08)
Hwang et al. (2008) i	High TTHM ≥20 µg/L) vs. Lowest (0 - 4 µg/L)	1.00 (0.89 – 1.13)
Chisholm et al. (2008) ii	Medium TTHM (avg 109 µg/L) vs. Low (avg 54 µg/L)	0.98 (0.75 – 1.48)
Chisholm et al. (2008) i	High TTHM (avg 137 µg/L) vs. Low (avg 54 µg/L)	1.22 (1.01 – 1.48)*
Hwang et al. (2002) ii	Chlorination- high color vs. no chlorination-low color	1.09 (0.94 – 1.26)
Hwang et al. (2002) i	No chlorination-high color vs. no chlorination – low color	1.18 (1.02 – 1.36)*
Magnus et al. 1999	Chlorinated water, high color vs. no chlorination	1.14 (0.99 – 1.31)
Bove et al. (1995) ii	TTHM >80 µg/L vs. < 20 µg/L	1.04 (0.58 – 1.76)[a]
Bove et al. (1995) i	TTHM >80 µg/L vs. < 20 µg/L	1.57 (1.23 - 1.99)[a]
Aschengrau et al. (1993)	Major malformations: chlorination vs. chloramination, surface water only	1.05 (0.7 – 2.1)

[a] 90% confidence interval
*significant with respect to 95% confidence interval

Figure 5: Summary of some epidemiological evidences on all birth defects and exposure to chlorination (Hrudey 2009)

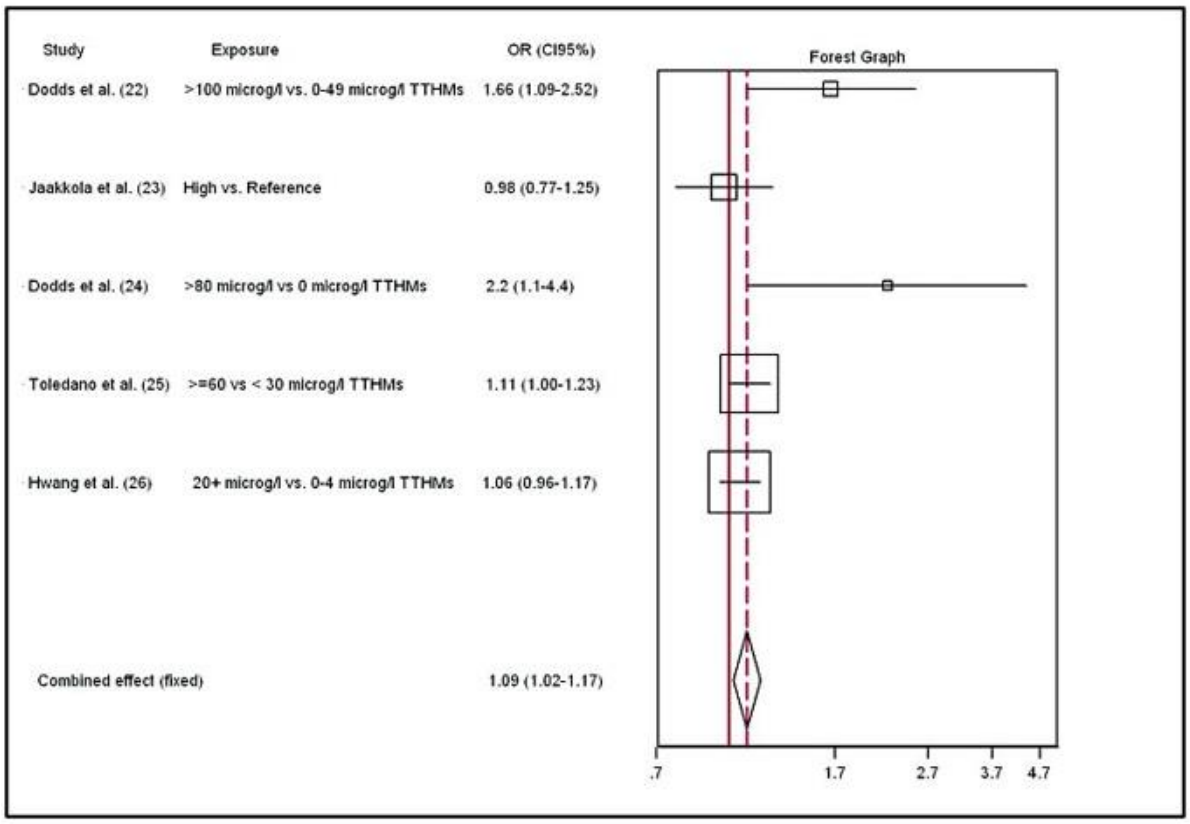


Figure 6: Summary of some epidemiological evidences on all birth defects and exposure to chlorination (Nieuwenhuijsen, Grellier et al. 2010)

Figure 5 and Figure 6 compares evidences from two reviews from different meta-analyses (Hrudrey et al. (2009) and Nieuwenhuijsen et al. (2010)) where associations for THM_4 and birth defects were compiled from different studies. According to Figure 5, comparing the highest and lowest exposure groups in the studies, Nieuwenhuijsen et al. (2010) concluded that stillbirth was associated with a small excess risk with the combined effect of OR = 1.09 (1.02-1.17). According to Hrudrey (2009) (Figure 5), epidemiological studies for birth defects do not support the assumption that THM_4 may be causally related to birth defects. In spite of this, it is important to note that neither of the authors used the same studies, aside from Hwang et al. (2008), nor did they use the same methodology to compute the combined OR, which may have influenced the conclusions of their meta-analyses. For SGA, only a few studies found no association between this outcome and THM_4 (Nieuwenhuijsen, Martinez et al. 2009, Villanueva, Gracia-Lavedan et al. 2011).

Different exposure metrics have used distinct proxies of exposure to THM_4 or HAA_5 that may influence the results from epidemiological studies. The concentrations of contaminants in the area surrounding a mother's place of residence have been used as a metric of exposure in most of the studies, often only through ingestion. The total THM concentration was the most common exposure agent in epidemiological studies although the ratios of Br-THMs/THM_4 are not always known or may differ between studies. Chloroform is more commonly encountered in epidemiological investigations than Br-THM_4, whose levels in drinking water are lower despite the fact that ORs for different outcomes can be as high as for TCM. In addition, THM_4 or HAA_5 levels and exposure categories differed among studies where some studies showed higher levels for high exposure category (>80 µg/L) (Wright, Schwartz et al. 2004, Savitz, Singer et al. 2006, Cao, Zeng et al. 2016) whereas papers showed lower levels for the same high exposure category (≥10 µg/L) (Kramer, Lynch et al. 1992). In a few cases, DBP modeling in network was also performed to assign specific exposures to mothers, whereas in the majority of studies, routine monitoring data were used. Biomarkers exposure were also used to evaluate associations with reproductive outcomes where positive associations were usually found compared to other exposure proxies (DBP concentrations in drinking water) (Costet, Garlantezec et al. 2012, Zhou, Xu et al. 2012, Cao, Zeng et al. 2016, Sun, Wang et al. 2020).

As other by-products may be present in the DBPs mixture, it would be useful to also assess the associations with others compounds such as emerging DBPs because co-exposure to other DBPs is believed to happen (Simmons, Richardson et al. 2008). Hence, the relationship between non-THM_4 and non-HAA_5 compounds and reproductive outcomes would also need to be investigated in order to identify if other DBPs may be responsible for the associations observed and to establish if THMs or HAAs are representative of other toxicity drivers (Nieuwenhuijsen, Grellier et al. 2009). According to these findings, data limitations in exposure assessment and other limitations in the study likely contributed to the lower statistical power, which hindered the ability to detect small risks and estimate dose-response relationships (Colman, Rice et al. 2011).

In conclusion, THM_4 and HAA_5, both as classes and as individual compounds, have been shown to be associated with reproductive effects in many studies, and epidemiologic studies demonstrated fairly consistent findings, particularly for THM_4 and intrauterine growth retardation. Some of the conclusions from epidemiological studies, however, are not statistically significant and most of them are small in magnitude (Colman, Rice et al. 2011). In spite of the modest relative risks observed, the attributable risk could be substantial, given the large potential population affected and the continuous nature of the exposure.

3 Is it time to revisit trihalomethanes monitoring and risk assessment to improve regulatory frameworks in North America?

Manuscript Title:

Making waves: Is it time to revisit trihalomethanes monitoring and risk assessment to improve regulatory frameworks in North America?

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AC designed and wrote the paper under DP, MR, and CD supervision. SG, ID provided valuable feedbacks on the manuscript.

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Highlights

- Quarterly monitoring is unlikely to provide an accurate estimate of THM_4 exposure due to intra-seasonal variability.
- Speciation of THM_4 should be considered when exceeding standards and assessing subchronic exposure.
- THM_4 risk assessment should be revaluated to consider repeated short-term high-level exposure over the course of a lifetime.

Abstract

Regarding the complex and challenging issues raised by disinfection by-products (DBPs) in drinking water, trihalomethanes (THM_4) are recurrent contaminants that need monitoring and control, especially during warmer months when regulatory exceedances are often observed. This work describes some critical aspects of THM monitoring and risk assessment in temperate climates characterized by strong seasonal temperature variations that induce DBPs spatiotemporal variations within a network along the year. During warmer months, peak concentrations (e.g. exceedance of a threshold) occurring more frequently may constitute an important component of cumulative exposure to DBPs that should be considered in the risk assessment approach. Additionally, differences in individual THM toxicities suggest that their monitoring should be conducted individually since differential speciation of THM_4 could lean towards the predominance of more toxic brominated compounds in specific conditions (ex. high bromide levels in raw water). Hence, under specific conditions, it could lead to higher brominated THM_4 concentrations in warmer months This perspective stresses that current monitoring of THM_4 using quarterly measurements may underestimate exposure and health risk as it does not account for THM speciation, differential toxicity, or short-term exposures to high concentrations. Therefore, efforts should be made to consider these parameters when revising regulatory frameworks as current regulations do not address them.

3.1 Introduction

Reactions between chlorine and natural organic matter generate multiple disinfection by-products (DBPs) in treated water. Among them, trihalomethanes (THMs) and haloacetic acids (HAAs) are the most investigated and regulated compounds on a global scale. In the United States, Canada, and the European Union, regulatory frameworks to control DBPs in drinking water address inorganic compounds such as chlorate, chlorite, bromate and THM and HAA, based on specific indicators for these broad classes of chemicals. For THM, regulations refer to THM_4 concentrations as the sum of chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (TBM) concentrations. Regulations are mostly based on chronic exposure and compliance is based on yearly averages of quarterly measurements that must remain lower than the threshold defined by regulatory agencies (Health Canada 2006, United States Environmental Protection Agency 2010). US EPA defines a maximum contaminant level (MCL) of 80 µg/L for total THM and a guideline of 100 µg/L is recommended by Health Canada for the sum of the four compounds (United States Environmental Protection Agency 2010). The rationale underlying this regulatory approach is that controlling these specific agents will also reduce exposure to other DBPs. One major limitation of this approach is that it focuses on annual averages of quarterly measurements, sums of individual THM and chronic toxicity, without considering the different toxicities of individual compounds and the variability of their relative concentrations throughout the year and throughout distribution networks.

Comprehensive research studies focusing on evaluating THM_4 annual intra-seasonal variability often report exceedances well beyond regulatory requirements (Singer, III et al. 1981, Serodes, Rodriguez et al. 2003, Symanski, Savitz et al. 2004, Guilherme and Rodriguez 2014, Dyck, Cool et al. 2015, Monti, David et al. 2019). Fluctuations in raw water quality (e.g., precipitation increases organic matter levels and summer increases in temperatures) caused by weather variations in temperate climates are the main factors explaining intra-seasonal variations of THM (Delpla and Rodriguez 2017). Moreover, THM_4 concentrations mostly encountered in the ppb levels vary according to many other factors such as pH, type/quantity of dissolved organic matter, disinfectants doses and

hydraulic characteristics of the network and treatments (Wang, Mao et al. 2015). It is also likely that water networks with long residence times, reservoirs, and rechlorination stations may influence the formation of THM_4, especially in the summer months. THM_4 exposure through drinking water follows recurrent seasonal variations, decreasing between fall and winter and increasing to ultimately peak in late summer (LeBel, Benoit et al. 1997, Symanski, Savitz et al. 2004, Guilherme and Rodriguez 2014, Valdivia-Garcia, Weir et al. 2019). As noted by US EPA and in Brett et al (1979) and Chen and Weisel (1998), there is also a temporal variability associated with Br-THM_4 mainly due to the fluctuations of precursors (Chen and Weisel 1998, United States Environmental Protection Agency (EPA) 2005).

The four THM compounds used in the above-mentioned regulatory frameworks are all rodent carcinogens. The International Agency for Research on Cancer (IARC) categorizes compounds or physical factors into four groups according to the existing scientific evidence of carcinogenicity: Group A "Carcinogenic to humans", Group 2A "Probably carcinogenic to humans", Group 2B "Possibly carcinogenic to humans", Group 3 "Unclassifiable as to carcinogenicity in humans", and Group 4 "Probably not carcinogenic to humans". IARC classified TCM and BDCM as possible human carcinogens (2B), whereas TBM and DBCM are not classifiable (3) (International Agency for Research on Cancer 1991, Richardson, Plewa et al. 2007). The Canadian and American guidelines are based on estimated cancer risk levels considered essentially negligible for lifetime exposure (70 years) (Health Canada 2006). Epidemiological studies have investigated the associations between THM_4 exposure and bladder, colon and rectal cancers, where the strongest evidence was shown for bladder cancer in men (King and Marrett 1996, Koivusalo, Pukkala et al. 1997, Villanueva, Fernandez et al. 2003, Villanueva, Cantor et al. 2007, Costet, Villanueva et al. 2011, Jeong, Wagner et al. 2012, Villanueva, Cordier et al. 2015, Villanueva, Gracia-Lavedan et al. 2017, Weisman, Heinrich et al. 2022). Researchers at the US EPA developed a dose-response function, based on bladder cancer as a health effect metric, in order to estimate the benefits of the current American regulations.(Regli, Chen et al. 2015, Weisman, Heinrich et al. 2022). Although causality and mode of action have not yet been clearly established, evidence has grown over the past decades (Richardson Susan 2022). THM_4 have also been largely investigated for their

developmental and reproductive effects where one of the largest recent nationwide prospective studies, based on more than 500,000 births, have shown that exposure was associated with an increased risk of small for gestational age (SGA) (OR=1.20, 95% CI: 1.08, 1.33, p-trend < 0.001, highest TTHM exposed group > 15 µg/L and the non exposed). After an examination of the associations between malformations and TTHM, the same authors found different impacts with respect to nervous system effects (OR=1.82, 95% confidence interval: 1.07, 3.12), urinary system effects (OR=2.06; 95% confidence interval: 1.53, 2.78), genital system effects (OR=1.77; 95% confidence interval: 1.38, 2.26), and limb effects (OR=1.34; 95% confidence interval: 1.10, 1.64) (Poleneni 2020, Säve-Söderbergh, Toljander et al. 2021). However, a few studies and reviews/meta-analysis led to different conclusions on the link between reproductive outcomes and the exposure to TTHM concentrations in drinking water (Hrudey 2009, Nieuwenhuijsen, Martinez et al. 2009, Villanueva, Gracia-Lavedan et al. 2011).

This perspective article underlines some aspects of the current THM_4 monitoring and regulations and how they could be addressed in future regulatory iterations. The main issue raised here is the impact on risk assessment brought by short-term exposures to higher concentrations of THM_4, and their differential speciation and respective toxicities of individual compounds. Unlike HAA_5 and emerging DBPs, some health-based short-term values (HBVs) have been developed by environmental and public health agencies for THM_4, and therefore guided our critical analysis (Richardson and Plewa 2020). Finally, even though emerging disinfection by-products such as nitrogenous disinfection by-products or iodoacetic acids are important toxicity drivers, the toxicity of these compounds is not well characterised by regulated THM_4 (Richardson, Plewa et al. 2007, Richardson and Plewa 2020, Richardson Susan 2022). Our focus is on rethinking some elements of the current THM_4 monitoring, and extending this assessment to other classes of DBPs is beyond the scope of this article. However, this perspective raises methodological issues that could be applicable to other classes of DBPs, mainly regarding the choice of adequate proxies to assess the risk attributable to a complex class of compound, and how this can be translated into regulatory frameworks that are more precise, adapted to specific contexts of DBPs variations, and hence more protective for public health.

3.2 On the importance of examining THM_4 individually

3.2.1 Formation of brominated THM_4

Current regulatory thresholds for THM_4 in drinking water are concentrations associated with estimated exposure levels that are deemed acceptable throughout life (70 years) (Health Canada 2006). The latter are based on hepatotoxicity as a precursor to carcinogenic effects resulting from TCM chronic exposure in animal studies (Heywood, Sortwell et al. 1979, Health Canada 2006, United States Environmental Protection Agency 2010, Direction de l'eau potable et des eaux souterraines 2019). This approach proposed by Health Canada in 2006, uses TCM as a model compound for THM_4, because of its comprehensive toxicological characterization compared to other THM_4, and it is primarily supported by the assumption that TCM is the most prevalent THM_4 in drinking water (Health Canada 2006).

However, growing evidence is now challenging this assumption and suggests that THM_4 speciation may favor brominated THM_4 (BDCM, DBCM and TBM) over TCM in certain circumstances. Upon reaction with bromide ions, chlorine produces HOBr, which reacts faster than HOCl with organic matter ($k= 0.7\text{-}5\ M^{-1}s^{-1}$ vs $k=15\text{-}167\ M^{-1}s^{-1}$) and tends to increase molar mass of DBPs (Sharma, Zboril et al. 2014). Numerous studies have shown that TCM may not be the most prevalent compound generated from naturally bromide-rich raw water (e.g. soils with high bromide content or affected by seawater intrusion) or from water impacted by anthropogenic activities (e.g. ballasts discharge into surface water, desalination plants, gas produced water discharges, disinfection of wastewater, curing companies) (Health Canada 2006, States, Cyprych et al. 2013, McTigue, Cornwell et al. 2014, Parker, Zeng et al. 2014, Landis, Kamal et al. 2016, Grote, Boudenne et al. 2022). For sea water intrusion, this issue is particularly important in the context of climate change where, as shown in the IPCC Synthesis Report (AR6), sea levels are expected to rise along nearly every coast in the coming decades potentially leading to seawater intrusion in the coming years (Zhongming, Linong et al. 2022), with droughts being a potential aggravating factor. Literature has shown that the composition of THM_4 (often expressed as the ratio of TCM/THM_4) in finished water may vary significantly according to bromine content on raw water. For example, a study from 2005 to 2017 examined THM_4 speciation across 207

utilities in 23 states (United States) and determined that TCM/THM_4 ratios ranged from 0.52 to 0.66, with an arithmetic mean of 0.59 (Samson, Seidel et al. 2017). Furthermore, researchers examined the geographic distribution of THM_4 speciation and the influence of bromine on higher levels of THM_4 and HAA_5 in 113 North Carolina water systems serving 10,000 or more residents. With decreasing TCM-to-THM_4 ratios from the mountains to the coastal plains and with TCM made up 70-80% of the THM_4 in most of the state, a few counties showed TCM/THM_4 ratios as low as 6% and 12% in coastal areas (Health Canada 2006, Shoaf and Singer 2007, Grote, Boudenne et al. 2022)

Taken into consideration THM_4 speciation and its known annual variability with potentially higher brominated THM_4 concentrations during warmer months are of great importance, as the formation of brominated DBPs, such as BDCM will significantly impact cytotoxicity and genotoxicity (Richardson, Plewa et al. 2007, Richardson, Fasano et al. 2008, Regli, Chen et al. 2015, Liu, Ling et al. 2022). From a public health standpoint, both the concentration and toxicity of each THM should be considered to determine the potential contributions of TCM, DBCM, BDCM, TBM to the overall toxicity of THM_4. This calls for a reconsideration of the common use of TCM as a model compound for THM_4.

3.2.2 Developments of health-based values support the relevance of refining exposure windows and considering individual THM_4 compounds in a public health perspective

A few organizations have developed individual guidelines/health-based goals for subchronic (e.g. EPA, Minnesota Department of Health - MDH, UK Water Industry Research - UKWIR)(Goeden 2018, Leusch, Khan et al. 2020, Minnesota Department of Health (MDH) 2020) and chronic exposures for non cancer and cancer effects (e.g. California Environmental Protection Agency - CalEPA, World Health Organization - WHO) (California Environmental Protection Agency 2004, California Environmental Protection Agency 2020). The wide span of proposed values is explained by the different parameters used to determine health-based values (HBVs) by each organisation, (targeted population, critical effect/reference dose, body weight adjusted water consumption, relative source contributions). Exposure can be classified differently based on exposure duration, such as: 1) short-term (lasting more than 24 hours up to 30 days), 2) subchronic

(lasting more than 30 days for approximately 10% of a lifetime) and chronic (lasting more than 10% of a lifetime) (United states Environmental Protection Agency 2002).

Table 6 : Subchronic and chronic health-based values for oral exposure to individual THM_4, as defined by public health and environmental organizations

		Health-advisories (10d) (Donohue and Lipscomb 2002)	**Health-based values (Goeden 2018)**	**UKWIR short-term no adverse response levels (SNARL) (Leusch, Khan et al. 2020)**	**Maximum Contaminant Level Goal (United States Environmental Protection Agency 2023)**	**Public Health Goal: Cancer effects (cancer risk level of 10^{-6}, 70 years)(California Environmental Protection Agency 2020)**	**Public Health Goal: Non-Cancer effects (California Environmental Protection Agency 2020)**	**Guidelines values (World Health Organization 2017)**
Exposure duration		Subacute/ subchronic (10 days)	Subacute/ subchronic (Up to 10% of a lifetime)	Subacute (7 d)	Chronic'	Chronic	Chronic	Chronic
Targeted population		Child (approximatively 1-year-old)	Infant (1 to <3 months)	Adults		-	-	Adults
Daily water intake		0.1 L/kg*d (1 L/d, 10 kg)	95th percentile of the water intake distribution:0.285 L/kg*d)	0.033 L/kg-d (2 L/d; 60 kg)		TCM: 0.180 L_{eq}/kg-d (life)[1] BDCM: 0.181 L_{eq}/kg-d (life)[1] DBCM: 0.185 L_{eq}/kg-d (life)[1] TBM: 0.182 L_{eq}/kg-d (life)[1]	TCM: 0.080 L_{eq}/kg-d[2-3] BDCM: 0.083 L_{eq}/kg-d[2-3] DBCM: 0.083 L_{eq}/kg-d[2-3] TBM: 0.081 L_{eq}/kg-d[2-3]	0.033 L/kg-d (2 L/d; 60 kg)
Organization		US EPA	MDH	UKWIR	US EPA	CalEPA	CalEPA	WHO
HBV (µg/L)	**TCM**	4000	20	450	70	0.4	170	300
	BDCM	600	30	180	0	0.06	110	60
	DBCM	600	N/A	6000	60	0.1	13	100
	TBM	200	N/A	540	0	0.5	430	100

[1]: During a lifetime, drinking water intake is weighted based on the time spent in a life stage (dd), the age sensitivity factor during that life stage, and the amount of water consumed in that life stage per day. 2: An equivalent amount of tap water to account for exposure through oral, inhalation, and dermal routes to a chemical.3: Water ingestion rates for a 70-year lifetime are usually calculated using the time-weighted average. PHG calculations will, however, use the 95th percentile estimates of age-specific water ingestion rate for the subgroup rather than the time-weighted average if a particularly sensitive age group exists (California Environmental Protection Agency 2020).

A very small number of organizations around the world developed guidance based solely on individual HBVs, or on the sum of a limited number of THM_4 (Table 6). It is important to note that all of these HBVs developed by these organizations have their own methodologies relating to: 1) selecting the appropriate population, 2) choosing the appropriate daily water intake, 3) selecting the reference dose, and 4) determining the source contribution and 4) selecting weights that contributed to those differences in HBV values. The World Health Organization (WHO) has developed an additive approach by summing up the ratios of each THM_4 measured concentrations on its corresponding

guidelines values (World Health Organization 2017). TBM, TCM and DBCM guidance were derived using hepatoxicity as an endpoint, and for BDCM, on the incidence of kidney tumours in mice. Initially, WHO recommended a guideline of 21 µg/L for BDCM, but mainly because BDCM concentrations below 50 µg/L were hard to achieve with current technology, the value of 60 µg/L has been preferred over the most protective value of 21 µg/L. MDH also derived HBVs (Table 6) using an exposure scenario for infants, considering their vulnerability attributable to their high water intake rates per body weight by using the 95th percentile for water intake that reflects the consumption of formula fed-infants, a vulnerable population (Goeden 2018, Minnesota Department of Health (MDH) 2020). For many utilities, especially small ones, those HBVs of 20 µg/L and 30 µg/L are often exceeded during summer and are more susceptible to be exceeded for utilities using high-bromine raw water (Rodriguez, Vinette et al. 2003, Rodriguez, Sérodes et al. 2004, Dyck, Cool et al. 2015, Samson, Seidel et al. 2017). Furthermore, US. EPA Health Advisories are derived with a 10 kg-child water intake of 1 L/d (0.1 L/kg-d) without the use of relative source contributions which usually leads to higher HBVs (Donohue and Lipscomb 2002, Goeden 2018). UKWIR' HBV were derived for adults with a relative source contribution of 50% leading also to higher HBVs values (Table 6).

For reproductive health effects, BDCM has been the most extensively examined DBP for pregnancy loss and its mode of action for full-litter resorption in animals is reasonably well characterized (Colman, Rice et al. 2011). In the past, the maximum acceptable concentration (MAC) for BDCM in Canada was set at 16 µg/L. This guideline was defined to be protective against both cancer and non-cancer health effects and calculated based on the estimated lifetime cancer risk, treatment methods in drinking water treatment plants and analytical method (Health Canada 2006). A reassessment by Health Canada in 2008 based on the findings and recommendations of the Expert Panel recommended that BDCM be rescinded as a separate guideline following the addition of new information about BDCM considering potential reproductive effects (increased risk for spontaneous abortion or stillbirth) (Health Canada 2006) It is important to note, however, that the weight of evidence has grown since 2008 and a re-evaluation of epidemiological and toxicological evidence may be needed.

The US EPA has also developed Provisional Peer-Reviewed Toxicity Values (PPRTV) for BDCM for use in the Superfund Program (United States Environmental Protection Agency 2009). Specifically, a benchmarked dose ($BMDL_{05}$) of 0.76 mg/kg-day was calculated using the induced full litter resorption as a critical effect with a subchronic reference dose of 8×10^{-3} mg*kg/d derived for oral ingestion (United States Environmental Protection Agency 2009). Even though the US EPA IRIS database has not developed subchronic reference doses based on reproductive effects, the development of PPRTV by the same organization tends to emphasize the importance of keeping reproductive health effects in mind when investigating THM_4 potential health effects. A subchronic RfD of 3×10^{-2} mg/kg-d was also developed for TBM based on hepatic effects.

3.3 Differences in toxicokinetic and toxicodynamic for TCM and brominated THM_4

Traditional risk assessment paradigms typically consider measures of external exposure; however consideration should also be given to toxicokinetic and toxicodynamic and how chemicals are metabolized in relation to external exposure. In addition to confirming the existence of an exposure, the direct measurement of a biomarker of exposure (THM_4 concentrations in urine or blood) also provides information regarding the intensity of that exposure (Blount, Silva et al. 2011). Aside from the variability of THM_4 concentrations in water in several studies, authors have also found that seasonality can influence levels of total THM in urine and blood, with higher levels during the summer months (Rivera-Núñez, Wright et al. 2012, Andrianou, Charisiadis et al. 2014, Wang, Liu et al. 2019).

Aside from their different toxicological effects, the four THM_4 also have different toxicokinetic and toxicodynamic characteristics in addition to physico-chemical characteristics that differ between the four compounds. These differences need be considered, as they may affect metabolization and therefore internal concentrations of the compounds (Table 7). Considering that internal exposure is responsible for the toxic effect, those different characteristics play a significant role in assessing potential health effects specially with regards to potential accumulation and reaching a critical concentration at the target site (Klaassen and Watkins , Geraets, Nijkamp et al. 2016).

For instance, using a PBTK model, authors found that brominated THM_4 are absorbed more readily than TCM by inhalation and dermal absorption due to differences in its

lipophilic characters (e.g. K_{ow} values in Table 7) (Haddad, Tardif et al. 2006). Furthermore, a higher amount is metabolized for brominated THM_4 at the same concentrations (Haddad, Tardif et al. 2006). Meanwhile, volatilization defined in the Henry's constant (Table 7) shows the capacity of a compound to be volatized and which dictates the concentration present in the air and thus the dose potentially absorbed. For instance, TCM and BDCM demonstrate higher volatilization that DBCM and TBM. In addition, Cantor et al. (2010) indicated that Br-THM_4 could be involved in the development of bladder cancer in particular among people having the enzyme glutathione S-transferase theta-1 (GSTT1(+)) genotype, where brominated THMs may be activated to mutagens in the bladder, increasing the risk of cancer (Cantor Kenneth, Villanueva Cristina et al. 2010, Regli, Chen et al. 2015).

Furthermore, the elimination half-life parameter provides valuable information regarding the rate of elimination and the potential extent of accumulation when the exposure fluctuates over time (Geraets, Nijkamp et al. 2016). Four to five times the elimination half-life is usually used as a cut-off point for evaluating the potency of an accumulation of a specific chemical (Geraets, Nijkamp et al. 2016). Chemicals with log K_{ow} values of 3 or less are unlikely to accumulate with the repeated intermittent exposure patterns but may accumulate if exposures are continuous (Geraets, Nijkamp et al. 2016, European Chemicals Agency 2022)). Elimination half-life should be regarded considering 1) the duration of an intake or exposure above a health-based limit value and 2) the time interval without exposure or the time interval with exposure though below a health-based limit value. A minimum of 32h to a maximum of 40h without exposure would be necessary to theoretically eliminate potential for accumulation if an interval of four to five times the elimination half-life is taken into consideration. As a result, although brominated THM_4 with a half-life 10 times higher than TCM are less present in water, they have a greater potential for accumulation, thereby causing higher cumulative doses during periods of higher exposure.

Table 7: Physico-chemical characteristics, toxicokinetics and toxicodynamics THM_4 characteristics (according to [68])

	TCM	**BDCM**	**DBCM**	**TBM**
Elimination half-life (h)	2.50	28.4	37.6	54.3
Days to Steady State (days)	N/A	2.00	3.00	5.00
Volume of distribution (L/kg)	1.72	1.86	2.13	2.39
Log Kow	1.85	2.05	2.20	2.54
Henry's law (atm-m^3/mole)	3.67×10^{-3}	2.12×10^{-3}	7.83×10^{-4}	5.35×10^{-4}

3.4 Importance of redefining temporal THM_4 pattern of exposure

Exposure assessment for chemical contaminants in drinking water remains a critical part due to low exposure levels, mixture of chemicals, long-term exposure windows, multiple exposure routes and spatiotemporal variability (Villanueva, Kogevinas et al. 2014). Since THM_4 concentrations have a unique temporal pattern with a slightly changing baseline that ultimately peaks late in the summer, hypotheses can be formulated about recurrences during an individual's lifetime based on the continuous DBP exposure experienced (LeBel, Benoit et al. 1997, Symanski, Savitz et al. 2004, Guilherme and Rodriguez 2014, Valdivia-Garcia, Weir et al. 2019).

In light of this, one aspect of THM_4 risk assessment that has received little attention is its recurrence, i.e., THM_4 peak periods may occur periodically throughout a person's life for a few months each year. The result would be a lifelong, repetitive, and higher exposure over a short period of time, equivalent to approximately a quarter to a third of a lifetime (less-than-lifetime exposure). Hence, recurrent exceedance during summer raises two major concerns: 1) exceeding chronic values for a few months over the course of a lifetime, and 2) exposing oneself to months of subchronic exposure sometimes far beyond short-term health-based values and regulations (The Minnesota Department of Health (MDH) 2020).

While authors have studied the association between cancer and adverse health effects and exposure to THM_4 with different conclusions, long-term epidemiological studies have not yet investigated the contribution of those repetitive higher concentrations exceeding

subchronic and chronic health-based values (Hwang, Jaakkola et al. 2008, Nieuwenhuijsen, Martinez et al. 2009, Danileviciute, Grazuleviciene et al. 2012, Grazuleviciene, Kapustinskiene et al. 2013, Grellier, Rushton et al. 2015, Kogevinas, Bustamante et al. 2016, European Chemicals Agency 2017, Mashau, Ncube et al. 2018, Säve-Söderbergh, Toljander et al. 2020, Lewis, McKeon et al. 2021). Averaging quarterly measurements, as they are at the basis of THM_4 regulations, may not provide an accurate picture of population exposure to THM_4 because they do not capture temporal variability per trimester specially within months or weeks. It is important to recognize, however, that limited resources, high sampling costs, and logistical restrictions may hinder a comprehensive monitoring particularly for small networks.

As described by previous authors, average concentrations and exposure is described by using arithmetic or geometric means of past exposures for slowly or partially reversible effects while cumulative exposure is the product of intensity and duration and tend to be representative of cumulative or irreversible effects as for instance reproductive effects (Kriebel, Checkoway et al. 2007). With the presence of some higher peaks and because reproductive effects have a certain window of susceptibility, averaging doses for developmental toxicity endpoints would be not recommended and might be only appropriate when variations in exposure occur within a narrow range (Haber, Sandhu et al. 2016). Developmental effects can occur following short-term exposure if this happens to coincide with the critical formative stages of embryonic and foetal development which seems to be particularly crucial for THM_4 during the third trimester (Sun, Wang et al. 2020). For instance, authors demonstrated that there was a slightly stronger association between THM_4 and SGA and low birth weight, with exposure during the third trimester (Grellier, Bennett et al. 2010, Danileviciute, Grazuleviciene et al. 2012, Grazuleviciene, Kapustinskiene et al. 2013). This period appears to be critical for this outcome in various studies as associations between blood and urinary biomarkers and/or with DBP concentrations in drinking water tend to be higher during this trimester (Cao, Zeng et al. 2016, Sun, Wang et al. 2020).

Moreover, vulnerable populations such as infants and children are likely to be at risk groups due to biological reasons. For instance, tissues in children are in stages of development

during which they exhibit a high level of proliferation while showing differences in the capacity to metabolize chemicals making them particularly vulnerable to carcinogens. (Bos, Baars et al. 2004, Hughes, Naile et al. 2019). Assessment that incorporates intra-seasonal and annual variability will be particularly helpful for improving estimates of population exposure to THM_4. In addition, if technical issues prevent plants from meeting current regulations, a refined assessment would be needed that can assist in determining what the long-term health effects are of being exposed to higher concentrations.

3.5 Final thoughts

Public health benefits associated with disinfection are accompanied by omnipresent contamination of DBPs at ppb range in drinking water. As well described by the literature, THM_4 as a group of regulated DBPs compounds peak during warmer months, causing higher exposure that could raise some health issues for vulnerable populations.

A knowledge gap needs to be addressed regarding how higher concentrations of DBPs in warmer months may lead to overexposure of the population for a quarter or a third of an individual's life. Repeated overexposure during summer raises two major concerns: 1) exceeding chronic values over a lifetime, and 2) exposing individuals to months of subchronic exposure that can exceed short-term health-based values. As also addressed in this perspective piece, monitoring, and risk assessment of THM_4 in this context of subchronic exposure, cannot be limited to TCM, given that bromine-containing water (e.g. freshwater affected by seawater intrusion) may contain more brominated compounds far more toxic. Because BDCM, DBCM and TBM concentrations may peak during warmer months under favorable conditions, risk assessment should take individual compound variability into account rather than on a group indicator. Even though disinfection must never be compromised, it is imperative to raise awareness on the subject, as some plants and networks have reported above-regulation concentrations during specific timeframes for decades.

4 Alternative tools to track and limit short-term DBPs exceedances in networks

Manuscript Title:
Alternative tools to track and limit short-term DBPs exceedances in networks

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ID contributed to the design and conceptualized of the methods (choice of sampling points, parameters, and methods), AC collected the data and performed the analysis under CD and MR guidances, AC performed the statistical analysis with CD and MR supervision, and AC wrote the paper under MR, SG, ID, and CD supervision. All authors will revise and comment the manuscript, prepared by AC.

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Abstract

Located running annual averages of at least four quarterly samples are used in the Canadian Guidelines and regulations for monitoring THM_4 and HAA_5. However, previous findings from the literature have demonstrated those compounds vary annually and within a season where recurrent high concentrations are more likely to occur in months with higher water temperatures and organic matter content increase. Limiting concentration peaks during warmer months can represent a challenge for distribution networks as they can vary depending on, for instance, weather. Based on a comprehensive dataset, spatial and temporal variability in a Canadian middle-sized municipality during this critical period was investigated. Alternative and indirect techniques such as a logistic model and incremental UV-VIS spectrophotometry were examined afterwards to help operators and stakeholders track and limit those higher concentrations, developed on the finished water quality.

Highlights:

- THM_4 and HAA_6 concentrations vary spatially and temporally among the network from June to October with highest concentrations of HAA_6 were found in June and THM_4 in August
- A logic model was developed to help water operators to estimate peaks of concentrations of THM_4
- ΔDUV254nm, ΔDUV272nm, ΔDUV350nm, ΔDUV400nm were found to be the best predictors for ΔTHM_4 (for the entire network)

4.1 Introduction

A key advancement in public health during the 20th century has been the control of waterborne diseases through the disinfection of public drinking water supplies (Tugulea, Aranda-Rodriguez et al. 2015). With chlorine or chloramine, water is disinfected before entering the distribution system to prevent microbiological recontamination and limit biofilm growth. Since disinfection cannot be compromised, disinfection by-products (DBPs) are an undesirable side effect of controlling waterborne illnesses. Indeed, reactions between chlorine, iodide, bromide and natural organic matter and other precursors can give

rise to DBPs where trihalomethanes (THM_4) and haloacetic acids (HAA_5) have been by far, the most investigated and regulated compounds (Richardson and Postigo 2015). As more than 700 DBPs have been detected in disinfected water, those classes of halogenated compounds have been used as a proxy for population exposure to overall DBPs and for more toxic ones and toxicity drivers (e.g. haloacetonitrile, iodinated DBPs) (Richardson 2011, Regli, Chen et al. 2015, Li and Mitch 2018, Mian, Hu et al. 2018). Recent studies have challenged this assumption because of the lack of correlation explained by the diversity of precursors and the different conditions under which the precursors are formed (Li and Mitch 2018, Furst, Coyte et al. 2019, Furst, Bolorinos et al. 2021).

Main precursors for THM_4 and HAA_5 are known to be aquatic and hydrophilic/hydrophobic natural organic materials (NOM), such as humic substances, which are subject to seasonal variations, (Liang and Singer 2003). Because THMs and HAA_5 formation depend on different parameters, from the NOM/physicochemical characteristics of water intake to the nature of treatment, distribution systems, network characteristics, residence time of water and climate, their concentrations vary temporally and geographically (Rodriguez, Sérodes et al. 2004, Legay, Rodriguez et al. 2010). The result is changes within networks, from the water treatment plant to the distribution extremities where population is exposed to varying levels of THM_4 and HAA_5. As a result, certain areas are more likely to have higher THM4 levels within the same supply chain, such as extremities of networks (Rodriguez, Sérodes et al. 2004). Due to spatial and also temporal variability, higher concentrations may be observed during warmer months in temperate climates regardless of whether utilities are in compliance with regulations (in terms of annual running averages) (Rodriguez, Vinette et al. 2003, Rodriguez, Sérodes et al. 2004, Symanski, Savitz et al. 2004, Adams, Timmons et al. 2005, Seidel, Samson et al. 2017). Because temporal variability is observed, annual means may not reflect short-term and higher concentrations where some plants exhibit greater seasonal levels of DBPs, as shown in a few studies in United States and in Canada (Williams, LeBel et al. 1997, Rodriguez, Sérodes et al. 2004, Adams, Timmons et al. 2005, Parvez, Rivera-Núñez et al. 2011, Seidel, Samson et al. 2017). Using an extensive dataset, authors reported that use of monthly averages concentrations may be more appropriate for some systems than quarterly average for utilities reporting higher variability (Parvez, Rivera-Núñez et al. 2011). This

may reinforce the importance of collecting data during critical periods to obtain a more accurate picture of the population exposure to DBPs and minimize exposure misclassification.

Health effects due to exposure to THMs have been investigated in the literature for carcinogenic effect but also for developmental and reproductive outcomes (Kavcar, Odabasi et al. 2006, Kogevinas 2011, Legay, Rodriguez et al. 2011, Pan, An et al. 2014, Villanueva, Cordier et al. 2015, Zhang, Chang et al. 2018, Wang, Zhu et al. 2019). According to a nationwide prospective study based on 500,000 births, exposure to THMs over 15 µg/L (with hypochlorite) increased the risk of small for gestational age (SGA) in comparison to populations not exposed to THMs (OR = 1.20 ; 95% CI: 1.08;1.33) (Poleneni 2020). The SGA effect-window in the case at hand is deemed to exist during the third trimester of exposure, which is a relatively short exposure of a few months (Lewis, Suffet et al. 2007, Säve-Söderbergh, Toljander et al. 2020). Because of its associations with infant morbidity and mortality, fetal growth is a major health issue (Levallois, Gingras et al. 2012). Even though some studies have revealed some inconclusive results, several epidemiologic studies and meta-analyses have demonstrated an association between THMs and/or HAAs exposures and a few reproductive and developmental outcomes (birth anomalies, abnormal fetal growth, and short gestation periods) at concentrations below regulatory levels (Hoffman, Mendola et al. 2008, Levallois, Gingras et al. 2010, Nieuwenhuijsen, Grellier et al. 2010, Villanueva, Gracia et al. 2011, Costet, Garlantezec et al. 2012, Levallois, Gingras et al. 2012, Kogevinas, Bustamante et al. 2016, Parvez, Frost et al. 2017). Furthermore, epidemiological studies have also investigated the link between exposure to DBP and cancers such as bladder, colon, and rectal cancers. Bladder cancer has been the most frequently studied cancer with studies finding positive associations with consumption of chlorinated drinking water (Villanueva, Cantor et al. 2004, Costet, Villanueva et al. 2011, Jeong, Wagner et al. 2012, Regli, Chen et al. 2015, Weisman, Heinrich et al. 2022).

Chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (TBM) are the four individual THM_4 regulated in Canada and the United States, while HAA_5 under regulations include monochloroacetic acid (MCAA),

dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), monobromoacetic acid (MBAA), and dibromoacetic acid (DBAA) (Health Canada 2006, United States Environmental Protection Agency 2010). Even though adverse reproductive effects are suspected, current American and Canadian regulations are defined in terms of chronic exposure and are based on yearly averages of quarterly measurements with maximum concentration levels or maximum acceptable concentration (MCLs or MACs). Existing compliance requires aggregated levels for THM_4 and HAA_5, rather than individual levels of these DBPs. In the Final Stage 2 D/DBPR, the US EPA specifies that MCLs for THM_4 and HAA_5 are of 80 µg/L and 60 µg/L (United States Environmental Protection Agency 2010). In most parts of Canada, the Canadian guidelines serve as regulatory thresholds with a maximum concentration of THM_4 of 100 µg/L and a threshold of 80 µg/L for HAA_6. The Province of Quebec, however, has established lower THMs and HAAs thresholds than the rest of the country of 80 µg/L and 60 µg/L, respectively (Health Canada 2006, Direction de l'eau potable et des eaux souterraines 2019). In developing the THM guideline, considerations have been given to the health effects for exposure level that is acceptable throughout life (70 years). The recommendation also stipulates that even though individual measurements exceed the guideline value, this will only become a concern if it causes the quarter-over-quarter average to exceed the guideline value (Health Canada 2006).

Current regulations, which consider maximum concentrations of THM_4 and HAA_5 in terms of long-term toxicity, fail to consider the intra-spatial and seasonal variability throughout a year or a season, that may lead to exceeding concentrations, especially during summer. Although some organizations have defined short-term health-based values to guide water stakeholders such as operators or managers, there are no current regulations that require local governments to perform THM_4 and HAA_5 exhaustive monitoring or define short-term levels during peak seasons (Donohue and Lipscomb 2002, Goeden 2018). The *Minnesota Department of Health* has developed short-term and subchronic health-based values of 20 and 30 µg/L for TCM and BDCM because chronic assessments may not be protective of short-term exposures in highly exposed populations such as formula-fed infants (Goeden 2018). Therefore, the health risks management strategies must also consider shorter exposure, as adverse reproductive effects are suspected and to protect vulnerable populations such as pregnant women, infants, and children.

During the warmer months, monitoring strategies covering variability of THM_4 and HAA_5 throughout the network require high frequency sampling which is a resource-intensive process, demanding both human resources and cost-intensive laboratory analysis. In this context, statistical models may be a useful tool to assist in tracking DBP concentrations. Such models may help utilities to act when exceedances are presumed and guide appropriate interventions to limit short term population exposure to DBPs. Over the recent decades, several studies have focused on predicting THM_4 and HAA_5 concentrations in distribution networks and developed statistical empirical and mechanistic models (Rodriguez, Serodes et al. 2000, Serodes, Rodriguez et al. 2003, Rodriguez, Sérodes et al. 2004, Legay, Rodriguez et al. 2010, Legay, Rodriguez et al. 2011, Azeem, Burham et al. 2014, Guilherme and Rodriguez 2014, Guilherme and Rodriguez 2015, Scheili, Rodriguez et al. 2015, Samson, Seidel et al. 2017, Seidel, Samson et al. 2017, Park, Lee et al. 2018, Hong, Zhang et al. 2020, Ike, Karanfil et al. 2020).

As an additional classification introduced by Ike et al. (2020), models were also divided into static-variable or dynamic variable, where the term dynamic variable refers to certain changes/differentials in water quality triggered by the disinfection process (Ike, Karanfil et al. 2020). In this case, it is only the chlor(am)ination-induced changes that are considered variables in dynamic variable models. Recent research has proposed the use of dynamic variables such as differential UV absorbance (Δ_λ) which has been shown to be a promising predictor for DBPs at bench scale and in full scale plant with the forms of linear, curvilinear or log-linear correlations (Korshin, Benjamin et al. 1999, Korshin, Wu et al. 2002, Korshin, Benjamin et al. 2007, Roccaro, Chang et al. 2008, Yan, Korshin et al. 2014, Beauchamp, Dorea et al. 2018, Beauchamp, Dorea et al. 2019, Beauchamp, Bouchard et al. 2020, Guilherme and Dorea 2020).

Although empirical/mechanistic and static/dynamic models are essential to understanding the behavior of these regulated compounds, effort is needed to better predict DBPs during months where reported concentrations are higher than MACs or MCLs. An important consideration for this would be to protect vulnerable populations from health-based value exceedances that are frequently reported in utilities (20 µg/L for TCM and 30 µg/L for

BDCM) (Meyer, Parvez et al. 2011, Parvez, Rivera-Núñez et al. 2011, Parvez, Frost et al. 2017, Seidel, Samson et al. 2017, Minnesota Department of Health (MDH) 2020).

This article aims to provide a comprehensive portrait of the spatial and intra-seasonal variability of THM_4 and HAA_5 at the municipal scale during months where higher concentrations are expected. Linear and logistic regression models were developed and tested based on the disinfected water quality parameters to predict and limit exceedances. Using sensitivity analysis to assess how each input parameter impacts probability of exceeding, stakeholders may be able to identify operational strategies at the plant to control future THM peaks. This paper also evaluates, for the first time, differential absorbance as an alternative and dynamic modelling technique to estimate THM_4 levels in a full-scale municipal distribution network. As this methodology is fairly simple that requires only a spectrophotometer, it may assist utilities in evaluating and responding quickly during conditions where peaks of concentrations may be observed.

4.2 Materials and methods

4.2.1 Water sample collection

To characterize the intra-seasonal variability of THM_4 and HAA_6, a high frequency campaign was conducted during the warmest months in a municipal water supply system supplying about 40,000 people in a Canadian municipality of approximatively 150,000 inhabitants located in the Province of Quebec, Canada (Statistics Canada 2021). In the system under study, raw surface water is treated through coagulation/flocculation/sedimentation, pre-chlorination, filtration, ozonation, and final chlorination before reaching the distribution network. A total of 324 samples were collected from June to November, every week. For week-to-week comparisons, samples were collected at the same time and on the same day each week. Samples were collected in the drinking water treatment plant from raw surface water to finished water (n=5/week) and in public places in the network (n=12/week) as presented in Figure 7. Estimated hydraulic residence times of water in the distribution system were provided by the municipality and are detailed in Figure 77. Hydraulic residence time is a term used to describe the amount of time water spends between the treatment plant (finished water) and the end user (Tinker, Moe et al. 2010). For each campaign, we estimated sampling times

based on daily raw water flow and hydraulic residence times for each point to be consistent with water path from the inlet to the outlet (1-raw water, 2-after coagulation/flocculation/settling, 3-after pre-chlorination and filtration, 4-after ozonation and 5-finished water). Because hydraulic residence time is an important parameter impacting DBP formation, the sampling points were chosen at locations with different hydraulic residence times (Figure 77) to provide a comprehensive assessment of water quality throughout the network. Sampling was conducted considering the water path along the distribution network from the treatment plant to the network extremities. Samples of finished water (plant) and tap water were collected at the faucet after letting cold water run for approximately five minutes to get water from the network as performed in previous studies (Legay, Rodriguez et al. 2011, Legay, Rodriguez et al. 2011).

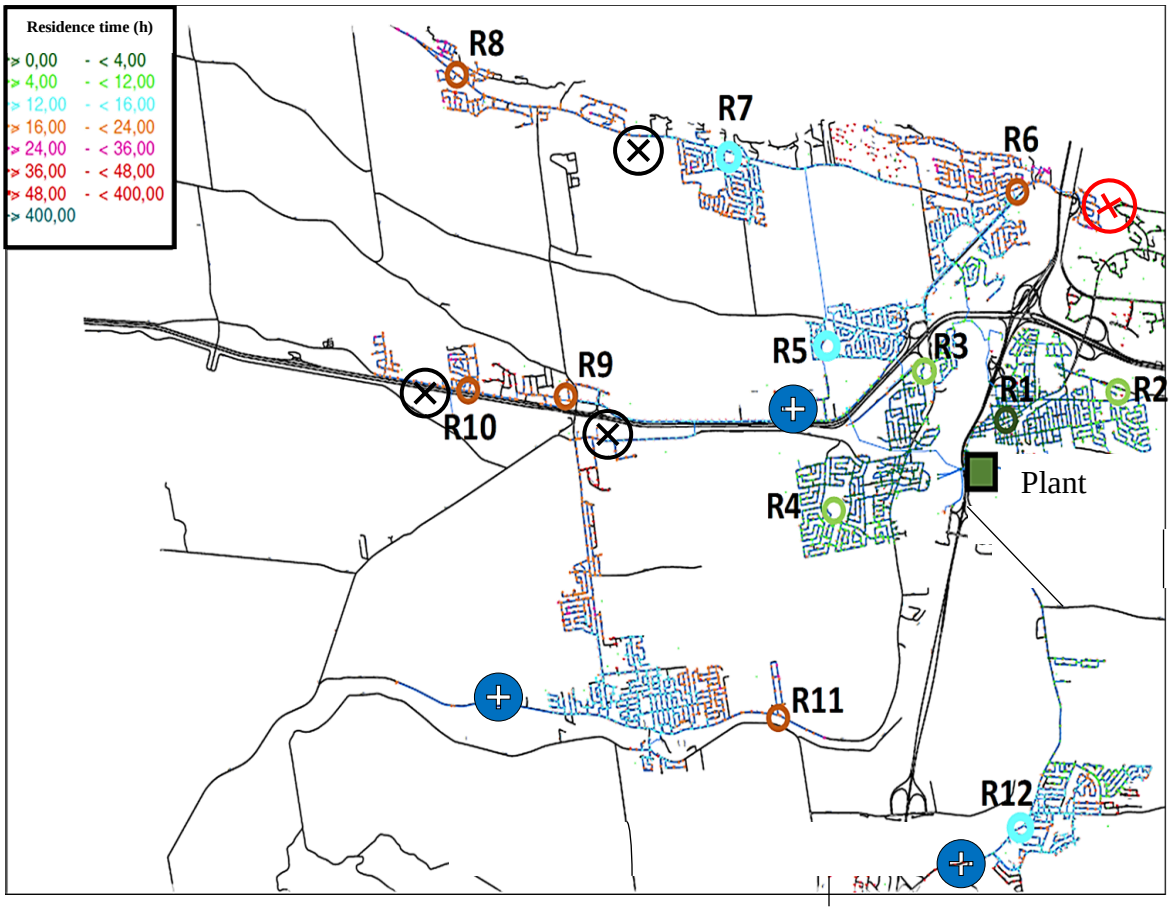

Figure 7 : Overview of the 12 sampling points in the distribution network (R1 to R12) and ⊕ reservoirs + rechlorination stations, ⊗ booster stations + rechlorination stations, ⊗ rechlorination station. Figure provided by the Municipality.

Physicochemical parameters such as pH, temperature, free and total chlorine were analyzed *on-site* at the time of sampling whereas supplementary samples were collected for further analysis. Sodium sulphite was used as a quenching agent to remove residual chlorine in samples as described elsewhere (Beauchamp, Laflamme et al. 2018). For collecting THM_4 and HAA_6 samples, three samples per class of compounds were collected in amber glass vials of 40 mL and each was gently poured until it reached the edge, and the screw cap was put on. Chloroform is a volatile compound, samples were checked for the presence of air bubbles and, if any were found, samples were discarded (National Center for Biotechnology Information 2022).

4.2.2 Analytical procedures

Within 24h after collection, samples were filtered using a vacuum pump set-up on 0.7 µm glass microfiber filters, pre-carbonized at 550 °C for 2 h. Ultraviolet-visible (UV-VIS) absorbances analysis were performed on filtered samples between wavelengths of 200 and 400 nm were obtained using a 10 cm quartz cells and a double-beam Agilent Cary 100 UV-Vis spectrophotometer with a wavelengths path of 1 nm and with a calculated detection limit of 0.002 a.u (absorbance unit). Blanks and baseline samples consisted of MilliQ water. Free chlorine residuals were measured using the DPD colorimetric method with a Hach DR-900 colorimeter (low range, 0.00 -2.00 ± 0.02 mg/L) and pH was measured using a Thermo Scientific Orion 8157BNUMD Ross pH meter (Hach Company/Hach Lange GmbH 2014). Individual concentrations of TCM, BDCM, DBCM and TBM, were determined for all chlorinated samples. THM_4 were extracted using solid-phase microextraction (SPME) fibres and analysed with gas chromatography with ion-trap mass spectrometry (GC-MS). Detection limits were respectively of 0.8 µg/L, 1.7 µg/L, 1.5 µg/L and 1.9 µg/L for TCM, BDCM, DBCM and TBM. The investigated HAAs (HAA_6) were MCAA, DCAA, TCAA, MBAA, DBAA, BCAA. HAAs were extracted using liquid-liquid extraction in MTBE and were analysed using gas chromatography with electron capture detection (GC-ECD) (Beauchamp, Laflamme et al. 2018). Bromochloracetic acid (BCAA) was included in the analysis, whereas the regulations include five different compounds (MCAA, DCAA, TCAA, MBAA, DBAA), so the appellation in this study refers to HAA_6.

4.2.3 Statistical analysis, development of regression models and sensitivity analysis

4.2.3.1 Statistical analysis

The dependent variable called "THM_4" was calculated by adding the concentrations of TCM, BDCM, DBCM, and TBM at each sampling point, and the individual concentrations of each HAA were likewise added together to obtain the total of the six compounds HAA_6. Measurements below detection limits for each compound were replaced by detection limit values divided by two, one of the commonly used methods for data treatment below detection limits (Croghan 2003). Normality tests were at first conducted using the Kolmogorov-Smirnov Z and maximum likelihood estimation was performed to test the goodness-of-fit to the normal distribution. The one-sample Wilcoxon signed rank test was used to determine if THM_4 and HAA_6 concentrations for each sampling points were significantly different from the regulations (THM_4<80 µg/L and HAA_6<60 µg/L). Kruskal-Wallis, a nonparametric alternative test, was conducted for physico-chemical parameters (UV254nm, SUVA, dissolved organic carbon, TCM, HAA, TCM and THM_4) at different sampling points for determining if samples were drawn from the same population (Sijtsma and Emons 2010). Each of these tests was carried out using the statistical significance level of 0.05 (p-value<0.05). P-values were determined by an asymptotic method with the law of K approximated by a Chi^2 rule with (k-1) degrees of freedom (Addinsoft 2022).

A differential absorbance spectrum is produced by the reaction between NOM and oxidants which results in the NOM exhibiting a lower absorbance after chlorination (Korshin, Wu et al. 2002). For the testing of differential UV-VIS absorbances technique, the variable "ΔTHM_4" referred as the difference between THM_4 concentrations at the sampling points in the network minus the THM_4 concentrations at the finished water (plant). "ΔA_λ" is the absorbance difference, for the wavelength λ, between the final chlorination point at the plant and one sampling point in the distribution system as generally defined by (Beauchamp, Dorea et al. 2018). Korshin et al. (2007) brought the notion of incremental differential spectra which is the difference between two times defined after chlorination as $\Delta_{A\lambda}$ (t_1, t_2) = A_λ (t_2) - A_λ (t_1) rather than difference in absorbances before and after chlorination (Korshin, Benjamin et al. 2007). Hence, as the two definitions show some slight differences, current investigations refer as incremental differential UV-VIS because

they explore the use of $\Delta_{A\lambda}$ within the network after secondary chlorination between the absorbances at specific points and the absorbances at finished water. To explore different types of regression, logistic, linear, LASSO, SVM were investigated between $\Delta_{A\lambda}$ and ΔTHM_4. All statistical analyses were performed using XLSTAT 2021.3.1.

4.2.3.2 Development of empirical multiple linear/log linear regression models

A number of water quality and operational parameters have been shown to influence the formation of DBPs in drinking water (Sadiq, Rodriguez et al. 2019). Hydraulic residence times, water temperature, organic matter indicator (UV254nm), pH, chlorine residuals, and differential UV absorbances were examined as they are known to be important variables to consider (Sadiq, Rodriguez et al. 2019). To assist operators in better controlling peak of DBPs, this model was built using parameters that could be easily adjusted at the plant. By focusing on relevant operational parameters, this model may help to limit high DBP formation in the municipal network. The first step of the study was to perform a non-parametric Spearman's correlation analysis on the relation and correlation between each independent variable (X) and the dependent variable (Y). Multicollinearity for all explanatory variables were also evaluated. Development of linear regression models was performed afterwards using a multivariate stepwise regression procedure. Binary logit regression was also tested to model the probability of occurrence in this case, the probability of exceedance (0= no exceedance, 1= exceedance). The technique has showed good prediction performance in the literature for DBPs (Cool, Lebel et al. 2015, Guilherme and Rodriguez 2017, Deng, Zhou et al. 2021). Models for estimating probability of exceedance were developed based on information regarding the different explanatory variables (qualitative or quantitative) that may contribute to the formation of THM_4. The probability of exceedance has been calculated for different values: 40, 60, 80 and 100 µg/L that refers to different thresholds, respectively 1) Half of the USEPA and Quebec threshold, 2) intermediate value between the half of the regulation and the regulation, 3) USEPA and Quebec thresholds and 4) Maximum acceptable concentration (MAC) according to Health Canada.

Akaike's Information Criterion (AIC) was used to compare models whereas the determination coefficient (R^2) to measure how well the models were adjusted. Chi^2 values

and p-values (Pr> Chi^2) were used to evaluate if variables provided a significant amount of information to explain the response variable's variability and for evaluating the contribution of each variable X to Y.

4.2.4 Sensitivity analysis

Sensitivity analyse were conducted to understand how input parameters impact probability of exceedances and to identify seasonal-based strategies and developing priorities for risk mitigation. For the investigated parameter, coefficient was assumed to be normally distributed and coefficient value and its standard deviations were used to generate a random dataset of 500 values based on a normal distribution. Using the model equation, outputs were recalculated using the 500 coefficients values by varying the minimum, 1st quartile, median and 3rd quartile and maximum for the parameter of interest and by keeping median values for the other parameters in the equation (Frey and Patil 2002).

4.3 Results and discussion

4.3.1 Physicochemical parameters and DBPs levels at the plant

Physicochemical parameters at the plant are presented in Table 8. Temperature remained stable from the inlet to the outlet and pH dropped in the settled water (after coagulation) that may be due to pH decrease caused by the coagulation process. Natural organic matter indicators such as UV254nm, total organic carbon, dissolved organic carbon decreased after coagulation-flocculation-settling with removals of 75.6% (UV254nm), 63.4% (DOC), 58.4% (TOC). UV254, DOC, and TOC were reduced by 16.9%, 2.3%, and 18.4%, respectively, through the filtration process. During coagulation-flocculation-settling, hydrophobic NOM appears to be removed, with a decrease in SUVA from 4.21 to 2.06 (Health Canada 2019).

According to Table 8, there is evidence that THM_4 and HAA_6 are detected from the filtration step since a pre-chlorination step occurs between settled water and filtered water. Those levels increased mostly following secondary chlorination (beginning of the reservoir), with a 55.0% rise before water enters the reservoir after two hours (finished water). This also may indicate that some THM_4 and HAA_5 precursors were not completely removed after coagulation and filtration and/or degraded by ozonation. Indeed, fulvic acids

represent a complex mixture of low molecular weight compounds that are more hydrophilic than humic acids and which a higher proportion are non-coagulable at any pH or coagulant dose. Fulvic acids are important precursors of THM_4 (Health Canada 2019). To evaluate the contribution of ozonation to the degradation/formation of DBPs, Mann-Whitney test (α=0.05) was conducted to evaluate statistical differences between TCM, THM_4 and HAA_5 levels between filtered water and ozonated water (Supplementary information). THM_4 levels showed no statistically significant difference between treatment groups (p-value: 0.06), whereas TCM levels showed a slight significant difference (p-value: 0.05) and HAA_5 levels showed a significant difference (p-value: 0.003), suggesting that HAA_5 increased between filtration and ozonation (21.7 % mean difference). As for SUVA and UV254nm, statistical differences were also observed between filtrated and ozonated water (p-values of <0.0001 for SUVA and p-value of 0.01 for UV254m), but no difference were observed regarding DOC. The ozonation process is believed to affect UV254nm and SUVA as ozone reacts with double bonds, activated aromatic systems, and non-protonated amines (von Gunten 2003).

4.3.2 Physicochemical parameters and DBPs levels in the distribution network

Free residual chlorine was low for R6, R8 and R11 with mean levels below 0.03 mg/L. Those points are at the extremities of the distribution network, far away from a rechlorination station. Meanwhile, R5, R10 and R12 showed the highest levels with means ± SD of 0.71 ± 0.29 mg/L, 0.60 ± 0.52 mg/L, and 0.34 ± 0.23 mg/L and with maximums of 0.90 mg/L, 1.87 mg/L and 0.73 mg/L. pH was constant within the network with values from 7.6 ± 0.2 and 7.7 ± 0.1 and recorded temperatures were higher at the beginning of the distribution network (R1, R2, R3). Kruskal-Wallis tests were conducted to test statistical differences between UV absorbances at 254 nm between each location. UV absorbances at R5, R9 and R12 (points with hydraulic residence times from 12h to 16h) were shown to be different from UV absorbances at R6, R8 and R11 (points with hydraulic residence times of 16 to 24h) for the whole dataset with p-values lower than 0.05 (α=0.05).

TCM was always encountered in all samples, with chloroform constituting the majority of THM_4. DBCM and TBM were never detected above the detection limit (1 µg/L) whereas BDCM was encountered at low levels with a mean level of 5.7 µg/L and with a minimum

concentration of 2.0 µg/L and a maximum of 13.5 µg/L. Highest levels of THM_4 were encountered during August and at the end of the distribution network (R_6, R_8, R_{11}) where estimated hydraulic residence time were between 18h and 24h. R_{10} exhibited different characteristics due to its location downstream of a reservoir and a rechlorination station.

Over the course of the summer, recurrent and significant deviations from the maximum permissible concentrations of THM were observed (100 µg/L in Canada and 80 µg/L in Quebec). One-sample Wilcoxon signed rank test was performed to determine whether the median of the THM_4 concentrations for the sampling period was equal to the threshold value of 80 µg/L Table 18 – Annexe 1). P-values below 0.05 indicate that medians of THM_4 concentrations were statistically different from the regulations.

Table 19 (Supplementary information – Annexe 1) exhibits the same statistical analysis for the HAA_6 concentrations for the 12 different sampling points (for a threshold value of 60 µg/L). Among HAA_6, only DCAA and TCAA were identified, and other compounds were below detection limits. HAA_6 medians were statistically significant below the regulation of 60 µg/L for each sampling locations with a maximum value of 87.6 µg/L. HAA_6 concentrations for the sampling period rarely exceeded the regulatory value (Quebec regulations and Canadian Guidelines) with a frequency of exceedance of 11 % (for the full data set). In addition, those results showed that HAA_6 formation diminish along the network and that a degradation is noticeable from R1 onwards. Broadly speaking, HAA_6 are formed at the beginning and are expected to decrease through distribution, while THM_4 are also formed in networks and are expected to increase through distribution (Rodriguez, Sérodes et al. 2004). Therefore, one can assume that HAA_6 decay rates were greater than the rate at which they were formed after chlorination due to diverse degradation pathways. Previous works have shown that HAA_5 was prone to biological degradation in networks (Zhang, LaPara et al. 2009, Pluchon, Sérodes et al. 2013, Berthiaume, Gilbert et al. 2014). Moreover, this degradation may also be initiated from chemical transformation where authors suggested that HAA_5 can be transformed into THM_4 and thus may constitute a complementary pathway for the formation of THMs in distribution networks (Zhang and Minear 2002).

Figure 8 shows HAA_6 and THM_4 and concentrations for all 12 sampling points summarizing temporal and spatial variability for the whole network. The different colors (data label) refer to specific hydraulic residence times from the shortest to the longest (≥0 to <4h, ≥4 to 12h; ≥12h to <16h; ≥16h to 24h). Temporal variability varies from locations to locations that seemed to be higher for longest hydraulic residence times and for THM_4. Further information of temporal variability can be found in Appendices

Appendix A: Supplementary information (Manuscript 2) where 1st quartile, median, 3rd quartile, standard deviation and variance for each point are presented.

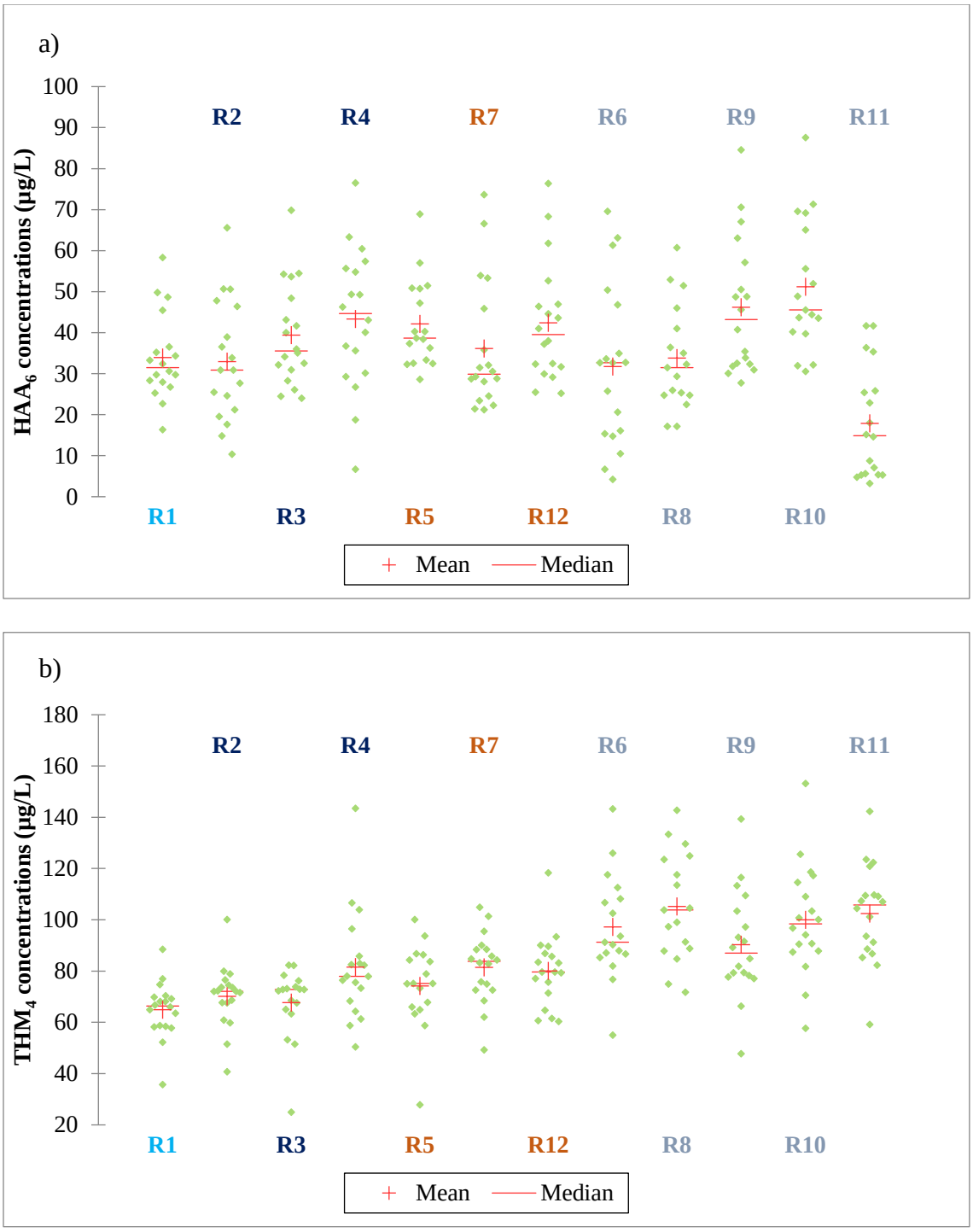

Figure 8: HAA_6 and THM_4 scatter plots (a) HAA_6 and b) THM_4 describing spatial and temporal variabilities for each location. Blue label: ≥0 to <4h, dark blue label: , ≥4 to 12h; dark orange label: ≥12h to <16h and grey label: ≥16h to 24h

Table 8 : Physicochemical parameters from the inlet to the outlet (n =18 for each location). Results are presented in terms of means and standard deviations (temporal variability)

		Raw water	Settled water	Filtered water	Ozonated water	Post-secondary chlorination	Finished water
UV254	Min	0.2258	0.0426	0.0369	0.0175	0.0178	0.0185
(cm^{-1})	Mean ± SD	1.887 ± 1.591	0.4607 ± 0.3058	0.3830 ± 0.2549	0.2024 ± 0.1400	0.1680 ± 0.1123	0.1670 ± 0.1115
	Max	4.716	0.8278	0.7519	0.4137	0.3345	0.3368
Free residual chlorine	Min	-	-	< 0.02	< 0.02	1.21	0.84
(mg/L)	Mean ± SD	-	-	0.03 ± 0.02	0.06 ± 0.03	1.50 ± 0.15	1.14 ± 0.14
	Max	-	-	0.06	0.15	1.74	1.40
Total residual	Min	-	-	0.09	0.15	1.53	1.05
chlorine	Mean ± SD	-	-	0.18 ± 0.05	0.26 ± 0.07	1.80 ± 0.14	1.36 ± 0.11
(mg/L)	Max	-	-	0.27	0.36	1.98	1.52
Temperature (°C)	Min	9.0	8.0	8.0	10.0	9.5	10.0
	Mean ± SD	16.7 ± 4.4	16.5 ± 4.7	16.8 ± 4.7	17.5 ± 4.6	17.7 ± 4.5	17.7 ± 4.5
	Max	26.0	26.0	26.0	27.0	26.5	27.0
pH	Min	7.5	6.1	6.1	6.1	6.4	6.5
	Mean ± SD	7.8 ± 0.1	6.5 ± 0.2	6.6 ± 0.3	6.6 ± 0.3	6.8 ± 0.3	7.6 ± 0.5
	Max	8.0	6.9	6.9	7.0	7.3	8.6
Total organic	Min	3.8	2.30	1.80	1.78	1.73	1.56
carbon	Mean ± SD	8.3± 2.5	3.47 ± 0.90	2.83 ± 0.99	2.89 ± 0.68	2.67 ± 0.95	3.19 ± 2.33
(mg C/L)	Max	12.5	5.10	4.20	4.10	4.50	12.00
Dissolved organic	Min	4.0	1.90	1.90	2.00	1.90	1.80
carbon	Mean ± SD	8.1 ± 2.5	2.96 ± 0.64	2.89 ± 0.62	2.87 ± 0.58	2.75 ± 0.68	3.15 ± 2.33
(mg C/L)	Max	13.0	3.90	3.90	4.00	4.50	12.00 ± 2.27
SUVA	Min	2.05	1.42	1.22	0.46	0.43	0.28
(L/mg*m)	Mean ± SD	4.21 ± 1.86	2.06 ± 0.24	1.78 ± 0.27	0.95 ± 0.19	0.86 ± 0.18	0.84 ± 0.24
	Max	11.25	2.46	2.33	1.22	1.15	1.17
THM_4	Min	-	-	3.90	1.00	12.70	25.10
(µg/L)	Mean ± SD	-	-	12.89 ± 4.6	9.91 ± 4.07	20.26 ± 4.43	45.02 ± 9.63
	Max	-	-	24.40	16.86	30.60	68.30
HAA_6	Min	-	-	5.38	9.58	19.54	21.70
(µg/L)	Mean ± SD	-	-	12.60 ± 4.0	16.08 ± 3.18	26.53 ± 4.26	33.88 ± 5.97
	Max	-	-	20.94	21.06	34.14	46.60

Table 9: Physicochemical parameters for the 12 locations in the network (n=18 for each location). Results are presented in terms of means and standard deviations (temporal variability)

		R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12
Estimated hydraulic residence times (h)		0- <4	≥ 4 - <12	≥ 4 - <12	≥ 4 - <12	≥ 12 - <16	≥ 16 - <24	≥ 12 - <16	≥ 16 - <24	≥ 16 - <24	≥ 16 - <24	≥ 16 - <24	≥ 12 - <16
UV254 (cm^{-1})	Min	0.0122	0.0121	0.0130	0.0108	0.0110	0.0137	0.012	0.0162	0.0112	0.0123	0.0154	0.0129
	Mean ± SD	0.0288 ± .0084	0.0280 ± 0.0081	0.0292 ± 0.0084	0.0268 ± 0.0087	0.0241 ± 0.0072	0.0343 ± 0.0077	0.0292 ± 0.0086	0.0350 ± 0.0087	0.0249 ± 0.0073	0.0262± 0.0079	0.0328 ± 0.0079	0.0257 ± 0.0069
	Max	0.0440	0.0433	0.0445	0.0415	0.0365	0.0455	0.0422	0.0513	0.0393	0.0437	0.0452	0.0398
Free residual chlorine (mg/L)	Min	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	0.05	<0.02	0.01
	Mean ± SD	0.28 ± 0.20	0.17 ± 0.18	0.18 ± 0.18	0.19 ± 0.26	0.71 ± 0.29	0.03 ± 0.03	0.10 ± 0.14	0.03 ± 0.04	0.22± 0.20	0.60 ± 0.52	<0.02	0.34 ± 0.23
	Max	0.58	0.54	0.47	0.75	0.90	0.12	0.46	0.15	0.72	1.87	<0.02	0.73
Total residual chlorine (mg/L)	Min	0.19	0.11	0.07	0.05	0.09	<0.02	0.08	0.05	0.16	0.15	<0.02	0.10
	Mean ± SD	0.45 ± 0.21	0.33 ± 0.19	0.32 ± 0.22	0.32 ± 0.29	0.71 ± 0.29	0.02 ± 0.06	0.22 ± 0.14	0.14 ± 0.08	0.38 ± 0.22	0.77 ± 0.55	0.05 ± 0.05	0.50 ± 0.24
	Max	0.78	0.69	0.67	0.96	1.09	0.12	0.65	0.29	0.97	2.11	0.15	0.93
Temperature (°C)	Min	11.0	11.0	10.0	10.0	0.09	9.0	8.0	10	12.5	9.0	7.0	9.0
	Mean ± SD	16.9 ± 3.1	16.6 ± 2.5	16.6 ± 3.2	15.1 ± 2.5	16.1 ± 3.3	15.0 ± 3.0	16.8 ± 3.1	15.3 ± 2.4	16.9 ±3.0	14.6 ± 2.9	13.8 ± 3.4	15.4 ± 3.1
	Max	23.0	22.0	22.5	18.0	20.0	18.0	20.5	18.5	24.0	18.0	18.0	20.0
pH	Min	6.8	6.8	6.8	7.0	7.3	7.0	6.9	7.5	6.7	7.0	7.0	6.9
	Mean ± SD	7.6 ± 0.2	7.6 ± 0.2	7.6 ± 0.2	7.6 ± 0.2	7.6 ± 0.2	7.6 ± 0.2	7.6 ±0.2	7.7 ± 0.1	7.7 ± 0.3	7.7 ± 0.3	7.6 ± 0.2	7.6 ± 0.2
	Max	8.2	7.8	7.8	7.9	7.9	7.9	7.9	7.9	8.1	8.1	7.9	7.9
THM_4 (µg/L)	Min	35.7	40.8	24.95	50.5	27.8	55.0	49.3	71.81	47.8	57.7	59.2	60.4
	Mean ± SD	64.9 ± 11.1	70.1 ±12.3	68.11 ± 13.61	81.6 ± 21.3	75.1 ± 16.4	96.0 ± 20.7	81.4 ± 13.7	105.7 ± 21.6	90.4 ± 20.9	96.9± 17.6	109.7± 19.0	80.1± 14.1
	Max	88.5	100.1	82.36	143.5	100.2	143.3	104.9	142.80	139.3	125.6	142.3	118.3
HAA_6 (µg/L)	Min	16.3	10.4	24.0	6.7	28.6	4.2	21.2	17.16	27.7	30.6	3.3	25.2
	Mean ± SD	34.0 ± 10.5	33.0 ± 14.7	39.4 ± 12.53	43.3± 17.2	42.2± 10.7	31.8 ± 19.8	36.1 ± 15.8	33.3 ± 13.1	46.2 ± 16.5	51.2 ± 16.2	17.9 ± 13.6	42.4 ± 14.6
	Max	58.3	65.6	69.85	76.5	68.9	69.6	73.6	60.71	84.5	87.6	41.6	76.4

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4.3.3 Development of an operational multivariate model for trihalomethanes exceedances

A linear regression, log regression, and logit regression were tested; however, the last one achieved better results in terms of AIC and R^2 (data not shown). The following table presents McFadden, Cox, and Snell and Nagelkerke R^2 and Chi^2 values and their associated p-values. Models were developed based on the entire dataset. The different proportions of the binary dependent variable (exceedance or no exceedance) according to the thresholds of 40 µg/L, 60 µg/L, 80 µg/L and 100 µg/L were also reported. In this work, the focus was on developing a model specifically for THM_4, while a model for HAA_6 was not built since there were no recurrent exceedances observed in the network.

Table 10 : Comparison of models for different THM_4 thresholds (40 µg/L, 60 µg/L, 80 µg/L and 100 µg/L), $\alpha = 0.05$, calibration set: n = 178, validation set: n = 35). Outputs for Model 1, 2, 3 and 4 are probabilities of exceedances if the thresholds are set to 40 µg/L, 60 µg/L, 80 µg/L and 100 µg/L.

Statistics		**Model 1 Threshold 40 µg/L**	**Model 2 Threshold 60 µg/L**	**Model 3 Threshold 80 µg/L**	**Model 4 Threshold 100 µg/L**
R^2 McFadden – Validation set		0.38	0.61	0.50	0.49
R^2 Cox and Snell – Validation set		0.05	0.32	0.50	0.41
R^2 Nagelkerke – Validation set		0.39	0.66	0.65	0.60
Chi^2 and Pr > Chi^2		8.2 0.016	64.1 <0.0001	114.0 <0.0001	86.3 <0.0001
Exceedance THM_4 calibration set (%)	No	1.2	9.6	48.2	65.7
	Yes	98.8	90.4	51.8	34.3

As shown in Table 10, the p-values obtained indicated that all the models were statistically significant. Nonetheless, the distribution of Yes/No for the dependent variable differed depending on the tested threshold, with THM_4 concentrations were generally above 40 and 60 µg/L, with a median of 82.2 µg/L. Consequently, models with threshold values of 40, 60, or 100 µg/L are expected to have an uneven distribution in the category Yes/No for the output variable (e.g., 1.2% of Yes, 98.8% for Model 1) and thus may have a detrimental effect on their capability of predicting probability of exceedance (as shown by the R^2 Cox and Snell and Chi^2 values). For instance, for a threshold of 40 µg/L despite that Pr > Chi^2 was below 0.05, this model's Chi^2 was lower (8.2) than those of other threshold models. Moreover, standard errors for each input variables were higher than the coefficients (data not shown), and each input parameter had a Pr > Chi^2 above 0.05 meaning that each variable was not providing enough information to the model.

Each input variable for the 80 µg/L threshold model had a Pr > Chi^2 below 0.05 except for the qualitative variable residence time between 0h and 4h, confirming that this variable did not contribute to the probability of exceedance. This is consistent with other papers indicating that THM_4 are formed through the network and their concentrations tend to increase when residence time increases. (Rodriguez, Sérodes et al. 2004). The highest Chi^2 value was obtained for the concentration of THM_4 at finished water (Chi^2 = 14.55, p-value = 0.0001). Since each input parameter demonstrated a higher Chi^2 value with significant p-values below 0.0001, and because this model demonstrated the highest R^2 and a relative equal distribution of observations for the dependent dichotomous variable (48.2% No/51.8% Yes), it was considered for further analysis in this paper. Furthermore, the threshold of 80 µg/L is already used in the current monitoring by the US. EPA and the Province of Quebec (RQEP) (United States Environmental Protection Agency 2010, Direction de l'eau potable et des eaux souterraines 2019). The equations of the selected model are presented below (Eq.1 model coefficient and Eq.2 standardized coefficient). In the case of Eq.2 using standardized coefficients, all coefficients are converted to a common unit of measurement regardless of the original unit of measurement.

$$Pr(Exceedance\ \ 〚THM〛\_4\ \geq\ 80\,\mu g/L\ =Yes)\ =\ 1\ /\ (1\ +\ exp(-(-27.947 \pm 7.913 + \mathbf{0.280} \pm 0.130 * Dissolved\ organic\ carbon + \mathbf{1.985} \pm 0.793 * pH + \mathbf{0.244} \pm 0.092 * Temperature\ + \mathbf{0.117} \pm 0.031 *\ 〚THM〛\_(4)\ finished\ water - \mathbf{1.479} \pm 1.172 *\ 〚Residence\ times〛\_(0 -< 4) +$$

$\mathbf{1.812} \pm 0.590 * \ 〚Residence\ times〛\_(\geq\ 12\ et\ <16) + \mathbf{4.802} \pm 0.793 * \ 〚Residence\ times〛\_(-\geq 16\ et\ <24))))$ *Eq. 1*

$Pr(Exceedance\ \ 〚THM〛\_4\ \geq\ 80\ \mu g/L\ = Yes)\ =\ 1\ /\ (1\ +\ exp(-(-27.947 \pm 7.913 + \mathbf{0.383} \pm \mathbf{0.178} * Dissolved\ organic\ carbon + \mathbf{0.471} \pm 0.188 * pH + \mathbf{0.545} \pm 0.206 * Temperature\ + \mathbf{0.634} \pm 0.166 * \ 〚THM〛\_(4\ )\ finished\ water - \mathbf{0.241}\ \pm 0.191 * \ 〚Residence\ times〛\_(0 -<\ 4) + \mathbf{0.441} \pm 0.144 * \ 〚Residence\ times〛\_(\geq\ 12\ et\ <16) + \mathbf{1.289} \pm 0.213 * \ 〚Residence\ times〛\_(-\geq 16\ et\ <24))))$ *Eq. 2*

According to the Eq.2 , hydraulic residence times between 16h and 24h was the most influential quantitative input parameter on the probability of exceedance with a coefficient value of 1.289 ± 0.213, followed by THM_4 concentrations in finished water (0.634 ± 0.166), temperature (0.545 ± 0.206), pH (0.471 ± 0.188), hydraulic residence times between 12h and 16h (0.441 ± 0.144) and, by organic carbon concentrations (0.383 ± 0.178). This study indicates that it may be possible to limit peak formation by reducing hydraulic residence times, as well as to better control THM_4 formation within the plant. Using specific measures such as enhanced coagulation in order to remove DBP precursors at the plant could be an appropriate alternative to reduce THM_4 concentrations in the finished water (Matilainen, Vepsäläinen et al. 2010, Beauchamp, Bouchard et al. 2020). Although THM_4 empirical models vary greatly among papers, temperature and pH greatly influences the formation of THM_4 and has been reported in many studies as an input variable in modelling THM_4 formation (Sadiq and Rodriguez 2004, Chowdhury, Champagne et al. 2009). Distribution systems do not typically monitor DOC on a daily basis, however, it can still be helpful to operators in identifying situations where an exceedance is possible and in acting, such as improving pH control or removing precursors.

It is worth noting that free and total chlorine residuals at finished water have not been included in the model as this parameter did not bring additional and useful information (Pr > Chi^2 above 0.05). As indicated in Figure 9, chlorine levels vary considerably between finished water and throughout the network due to the presence of reservoirs and rechlorination stations, among other factors. It is therefore difficult to correlate free chlorine residuals at the plant to THM_4 formation as the behavior of chlorine change widely among the network compared to the plant. Consequently, chlorine levels fluctuate from one location to another, making it more difficult to correlate THM_4 levels at the network

scale. Furthermore, as rechlorination stations are present along the network, predicting THM exceedance, according to chlorine levels at finished water may not completely representative of a location located downstream a reservoir/rechlorination station, bringing complexity into predicting THM_4 exceedance.

4.3.4 Evaluation of incremental differential UV-VIS absorbances as an alternative technique to predict peak of concentrations

Table 11 and Figure 9 present the different R^2 for prediction sets and validation sets for Δ_{254nm}, Δ_{272nm}, Δ_{350nm} and Δ_{400nm} as independent variables and THM_4 as the dependent variable. To the best of our knowledge, this is the first time that such evidence of correlation is reported at the scale of a municipal network. Correlations between THM_4 concentrations and other unique wavelengths (200-450 nm) have also been investigated, although 254 nm, 272 nm, 350 nm, and 400 nm have shown the most significant results with respect to R^2. To assess whether the use of multiple wavelengths would increase the accuracy of the models, multilinear types of linear regressions (linear, LASSO, SVM) were also tested. In this case, AIC hand R^2 were used as parameters to evaluate models. There was, however, a slight reduction in R^2 when using multiple wavelengths compared to using a single wavelength (data not shown). While the difference between unique and combined wavelengths is relatively small, this is inconsistent with previous research indicating that using multiple predictors may enhance accuracy, since multiple wavelengths can be used to quantify the contributions of different chromophores (Beauchamp, Dorea et al. 2019). The incremental differential UV-VIS analysis in a dynamic system such as a network, however, may differ from the bench scale analysis before and after chlorination. Indeed, networks are highly complex dynamic systems where DBPs are known to be formed and transformed influenced by precursors, pipe materials, rechlorination steps/reservoirs, biofilms, and deposits (Dong, Zhu et al. 2023. Such dynamic systems may complicate comparisons and interpretations compared to bench scale experiments. For instance, earlier research has shown that aromatic DBPs can be transformed into aliphatic DBPs in networks. (Jiang, Han et al. 2020).

Table 11 shows that prediction sets demonstrated similar R^2 for the four tested wavelengths while the highest R^2 reached for validation was observed for Δ_{400nm} followed by Δ_{254nm},

Δ_{270nm} and Δ_{350nm}. Previous works from Beauchamp et al. (2019) identified specific wavelengths and developed a LASSO multilinear regression models to predict THM_4, DCAA, TCAA and HAA_6 concentrations, and where Δ_{270nm} and Δ_{425nm} and absorbances at 270nm where used to predict THM_4 concentrations (Beauchamp, Dorea et al. 2019). Therefore, the present use of Δ_{270nm} is consistent with previous works (Beauchamp, Dorea et al. 2019). Chlorinated water initially exhibits a decrease in UV absorbance around 270 nm, which is likely related to the chlorination of phenolic and diketone moiety (Beauchamp 2019). Other authors have also studied different forms of phenolic substances for the generation of chloroform and identified monohydroxybenzenes as potential precursors responsible for the slow formation of THM during chlorination (Gallard and von Gunten 2002).

Additionally, the wavelengths of 350 nm and 400 nm were found to be important predictors of THM_4. As previously reported in literature, DBP formation is most closely related to the involvement of slow chromophores that can be characteristics of Δ_{350nm} and Δ_{400nm} (Korshin, Benjamin et al. 2007) (Yan, Korshin et al. 2014). Slow chromophores appear only after a important fraction of the fast chromophores have reacted with chlorine (Korshin, Benjamin et al. 2007). In accordance with previous research, absorbances at greater than 300 nm reflect the formation and hydrolysis of the active ketones associated with DBP formation and thus those absorbances have a higher correlation with DBP levels (Chen, Zhang et al. 2020). Considering that this technique is used in a network, it is consistent that those wavelengths appeared also as promising indicators for the estimation of THM_4. Despite being different from the wavelength of 400 nm used in this study, another wavelength in the visible range (λ=425 nm) was also identified by Beauchamp et al. (2019) as a significant predictor for all the DBPs studied. Additionally, it is important to note that this explanatory study used all data from the distribution network scale, combining locations with diverse characteristics (extremities, different hydraulic residence times) which makes it harder to attain a high R^2 for validation sets.

Table 11 : R^2 and R^2-adjusted for prediction set and validation set for each independent variable (Δ254nm, Δ272nm, Δ350nm, Δ400nm). Dependent variable is the differential THM_4 concentration between finished water and each sampling points.

	Δ254nm	Δ272nm	Δ350nm	Δ400nm
Prediction set - R^2	0.650	0.612	0.628	0.668
Prediction set - R^2 adjusted	0.646	0.608	0.624	0.664
Validation set - R^2	0.363	0.260	0.159	0.597

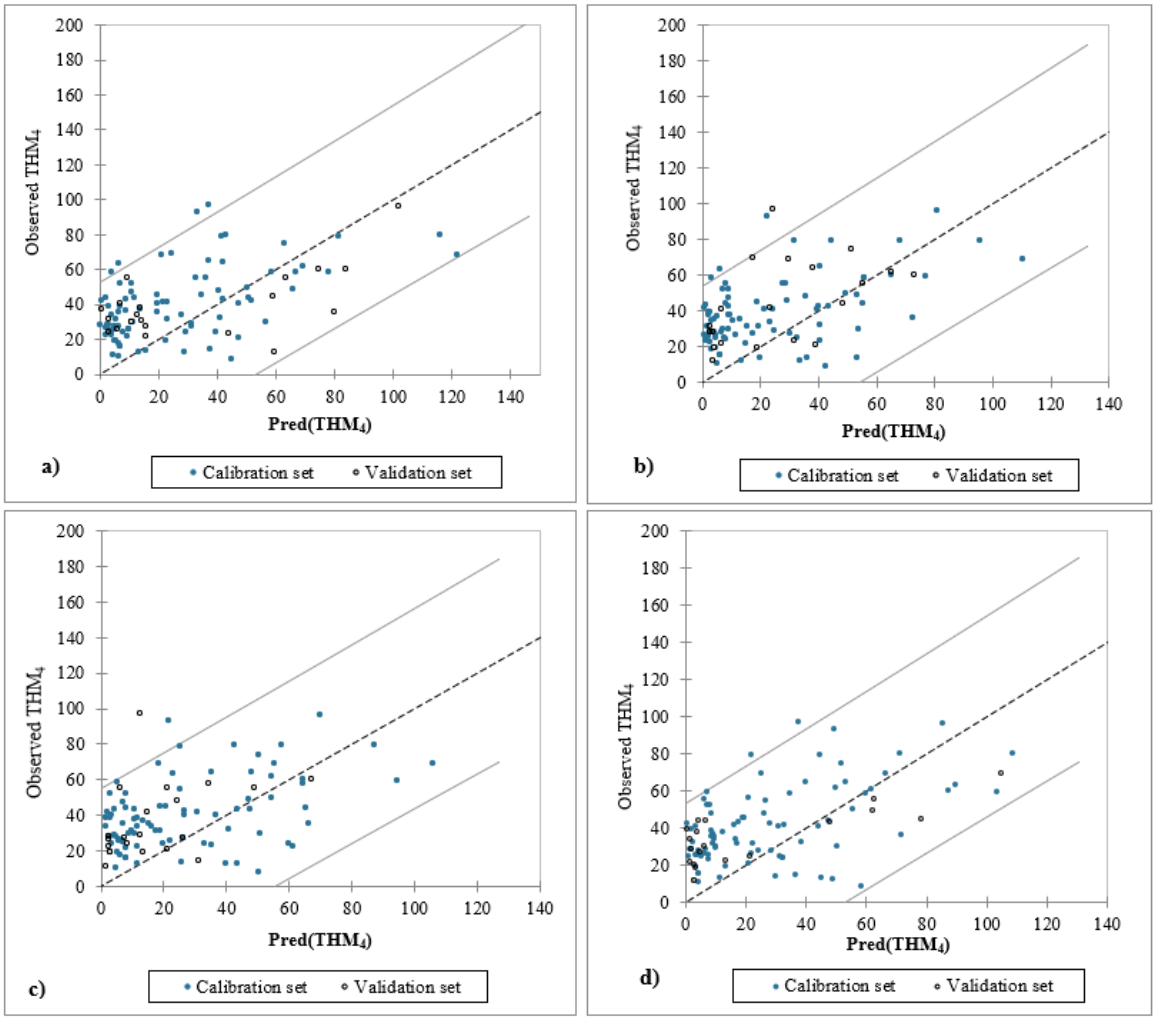

Figure 9 : Predicted values from linear models versus actual measurements with UV absorbance as independent variable and differential THM4 concentrations as dependent variable (a) Δ254nm, b) Δ272nm, c) Δ350nm and d) Δ400nm. Dataset included all sampling points expect those directly located downstream a rechlorination station.

4.3.5 Incorporation of incremental differential UV-VIS absorbances in the previous model

Δ254nm, Δ272nm, Δ350nm and Δ400nm were incorporated to assess if those variables would bring further information and accuracy into the previous developed logistic regression model. The incorporation was tested for each of the four inputs (Δ254nm, Δ272nm, Δ350nm and Δ400nm) and also tested for all input together. Models were evaluated in function of their respective AIC and R^2 (McFadden, Cox, and Snell, Nagelkerke). The model including only Δ254nm showed the highest AIC value of 157.97 with the respective values of R^2(McFadden) of 0.54, R^2(Cox and Snell) of 0.55 and R^2(Nagelkerke) of 0.67. It should be noted, however, that the AIC and R^2 values with the other models including the other inputs (Δ272nm, Δ350nm and Δ400nm) were very similar (data not shown). Equations of the logistic regression including the Δ254nm variable are presented below (Eq. 2, equation with non standardized coefficients and Eq.3, equation with standardized coefficients): Interestingly, Δ254nm regression coefficient was the second highest compared to the other standardized coefficients (Table 12), indicating that this variable has the greatest effect on the output (Siegel and Wagner 2022).

Table 12: Standardized coefficients of input parameters and Pr > Chi² (α = 0.05)

Input parameters	Value	Standard error	Wald Chi-Square	Pr > Chi²
Dissolved organic carbon	0.280	0.139	4.097	0.0430
pH	0.381	0.148	6.630	0.0100
Temperature	0.491	0.155	10.064	0.0015
THM_4 concentrations in finished water	0.580	0.154	14.244	0.0002
Δ254nm	0.524	0.238	4.836	0.0279
Residence times (h)-0 - < 4	-0.265	0.186	2.041	0.0153
Residence times (h)-≥ 12 et <16	0.321	0.130	6.074	0.0137
Residence times (h)-≥ 16 et <24	1.136	0.177	41.182	<0.0001

$$Pr\,(Exceedance\ THM) \geq 80\ \mu g/L = Yes) = 1 / (1 + exp\,(-(-24.552 + \mathbf{0.222} \pm \mathbf{0.109} * Dissolved\ organic\ carbon + \mathbf{1.626} \pm \mathbf{0.631} * pH + \mathbf{0.202} \pm \mathbf{0.063} * Temperature + \mathbf{0.118} \pm \mathbf{0.031} * [\![THM]\!]\_4\ finished\ water + \mathbf{80.324} \pm \mathbf{36.524} * DUV254nm - \mathbf{1.718} \pm \mathbf{1.202} * Residence\ times\ (h) - 0 - < 4 + \mathbf{1.347} \pm \mathbf{0.546} * Residence\ times\ (h) - \geq 12\ et\ < 16 + \mathbf{4.184} \pm \mathbf{0.652} * Residence\ times\ (h) - \geq 16\ et\ < 24)))$$ *Eq. 3*

$$Pr\,(Exceedance\,THM) \geq 80\,\mu g/L = Yes) = 1 / (1 + exp\,(-(-24.552 + \mathbf{0.280} \pm \mathbf{0.139} * Dissolved\,organic\,carbon + \mathbf{0.381} \pm \mathbf{0.148} * pH + \mathbf{0.491} \pm \mathbf{0.155} * Temperature + \mathbf{0.580} \pm \mathbf{0.154} * [\![THM]\!]\_4\ finished\,water + \mathbf{0.524} \pm \mathbf{0.238} * DUV254nm - \mathbf{0.265} \pm \mathbf{0.186} * Residence\,times\,(h) - 0 - < 4 + \mathbf{0.321} \pm \mathbf{0.130} * Residence\,times\,(h) - \geq 12\,et < 16 + \mathbf{1.136} \pm \mathbf{0.177} * Residence\,times\,(h) - \geq 16\,et < 24)))$$ *Eq. 4*

4.3.6 Model sensitivity analysis

An analysis of sensitivity was performed to illustrate the applicability of the previous model (Figure 9) in identifying strategies which are likely to minimize the probability of THM_4 exceedance in the network. To conduct this analysis, probabilities were calculated based on the model that includes incremental DUV (Figure 9) and by considering the standard error of the regression coefficient for the studied parameter (for pH: 1.626 ± 0.631). As a result, standard deviations are also provided for each scenario: 1) DOC, temperature, THM_4 concentrations at finished water and DUV254nm at their minimum values (1.8 mg/L, 10.0 °C, 25.1 µg/L, 0.0001 cm^{-1}), 2) DOC, temperature, THM_4 concentrations at finished water and DUV254nm at their 1st quartile values (2.2 mg/L, 15.0 °C, 41.0 µg/L, 0.001 cm^{-1}, 3) DOC, temperature, THM_4 concentrations at finished water and DUV254nm at their median values (2.7 mg/L, 18.0 °C, 45.6 µg/L, 0.003 cm^{-1}), 4) DOC, temperature, THM_4 concentrations at finished water and DUV254nm at their 3rd quartile (3.2 mg/L, 21.0 °C, 50.0 µg/L, 0.008 cm^{-1}) and 5) DOC, temperature, THM_4 concentrations at finished water and DUV254nm at their maximum values (12.0 mg/L, 27.0 °C, 68.3 µg/L, 0.147 cm^{-1}).

Figure 10 illustrates the results of the sensitivity analysis conducted to determine whether combinations of variables such as pH influence the likelihood of THM concentrations exceeding 80 µg/L in the network. For operators, pH would be a critical parameter to control as it can impact DBP formation (Hua and Reckhow 2008). For a slight increase in pH from 7.3 to 7.8, the probability of exceedance increases from 0.59 to 0.64 for a median concentration of DOC, temperature, THM_4 at finished water, and DUV254nm. The likelihood of exceeding in different settings (input values at the third quartile and at the maximum) increases with even a small change in pH. A few authors suggested different mechanisms with one more comprehensive described by Reckhow and Singer. In this mechanism, THM_4 and HAA_5 share the same precursor structure (R-CO-CX3), and the relative formation of these DBP species depends on the nature of the R group and pH.

Indeed, as pH increases base-catalyzed hydrolysis predominates leading to an increased THM formation (Liang and Singer 2003).

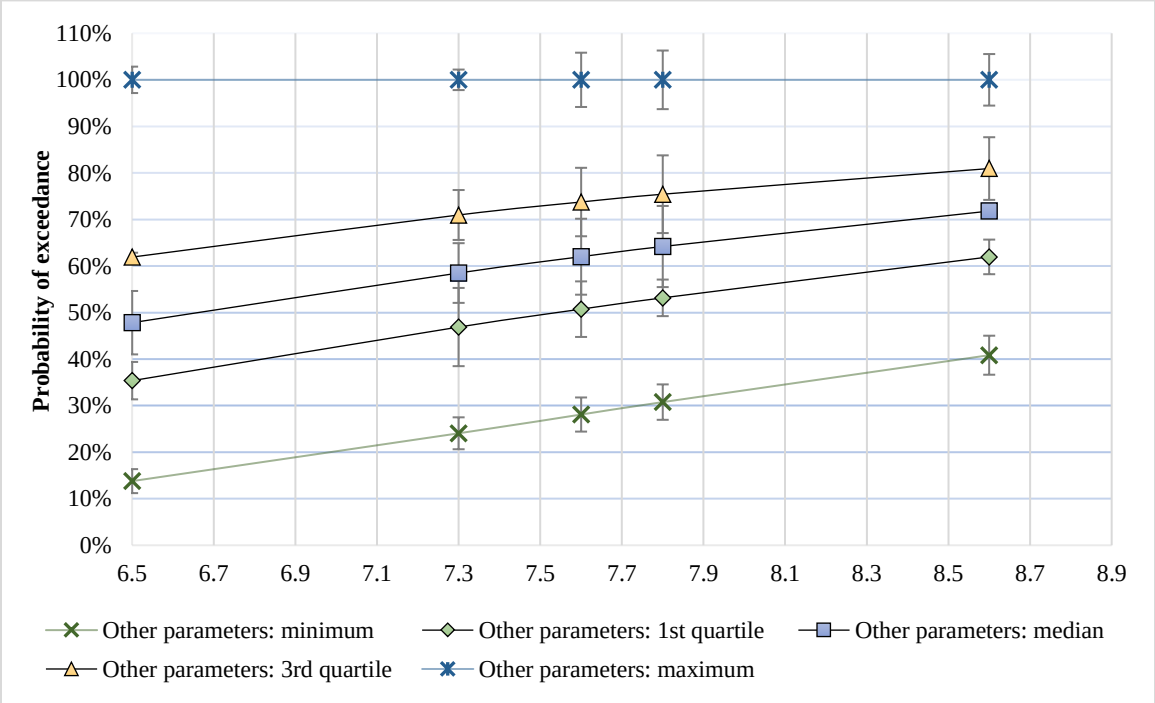

*Figure 10 Predicted probabilities of exceeding ≥ 80 µg/L according to pH: -**x**- Effect pH with other input parameters at their minimum values (dissolved organic carbon, temperature, THM_4 at finished water, DUV254nm); -◊- Effect pH with other input parameters at their 1st quartile values (dissolved organic carbon, temperature, THM_4 at finished water, DUV254nm) ; -□- Effect pH with other input parameters at their median values (dissolved organic carbon, temperature, THM_4 at finished water, DUV254nm); -Δ- Effect pH with other input parameters at their 3rd quartile values (dissolved organic carbon, temperature, THM_4 at finished water, DUV254nm); -**x**- Effect pH with other input parameters at their maximum values (dissolved organic carbon, temperature, THM_4 at finished water, DUV254nm);*

4.4 General Discussion

This study employed a high frequency campaign to examine THM_4 and HAA_6 behavior in a middle-sized network during months that are commonly associated with threshold exceedances. Recurrent and large deviations for THM_4 were observed from the maximum permissible concentrations (100 µg/L in Canada and 80 µg/L in Quebec). THM_4 levels exceeding the regulations/recommendations are more frequent in locations with longer residence times (R6, R8, R11) and downstream of reservoirs/rechlorination stations (R_{10}). In the meantime, HAA_6 concentrations were observed to decrease along the network with a frequency of exceedance of 11% (n= 212), mostly at the beginning of the network. In addition, those compounds were found to be statistically lower than the regulation of 60 µg/L (Quebec regulations and USEPA) for each location (Supplementary information).

Those THM_4 and HAA_6 behaviors described hereby are in accordance with previous works describing the behaviours of THM_4 and HAA_6 in distributed water for temperate climates (Rodriguez, Vinette et al. 2003, Rodriguez, Sérodes et al. 2004).

Furthermore, the developed logistic model and an application using sensitivity analysis provide utilities with an insight into how they may anticipate THM_4 peaks, when THM_4 exceedances are more likely to occur at the scale of drinking water systems. For example, operators could measure single DOC levels in periods in which higher concentrations are likely to occur in order to determine the probability of an exceedance occurring in the system. If the probability of those outcomes is high, treatment could be adjusted to achieve DOC concentrations that relate to less likely outcomes, such as adjusting the dose of coagulants.

As a second strategy technique for tracking THM in critical periods, incremental differential UV-VIS has shown promising results as a field technique to predict THM peak based solely on absorbance differences between finished water and the targeted sampling point (Δ254nm, Δ272nm, Δ350nm and Δ400). This may be particularly useful during times when THM_4 levels are suspected to exceed the threshold limit, thus allowing operators and stakeholders to confirm rapidly whether levels are high and whether measures need to be taken. More research works need to be done to confirm the use of those specific wavelengths for THM_4 prediction.

Since this model (Eq.2) relies on finished water quality, operators can predict exceedances from finished water quality without having to measure the concentrations of THM_4 in the network. However, despite efforts to maintain consistency with the water path, this was more difficult to achieve in the entire network due to logistical constraints (specifically for high residence times). Hence, it is possible that this was not the same "drop" that was collected at finished water (plant) and at locations with longer residence times (e.g. 16h and 24h) and consequently that the water collected at longer residence times represent the water quality that was not sampled the same morning at the plant. It is likely, however, that short residence times (0-4 hours; 4-12 hours) represent better quality samples obtained early in the morning at the plant. Although these limitations exist, results have shown good prediction capabilities; however, events that may substantially change water quality, such

as heavy rainfalls, may affect both water quality and THM_4 formation (Delpla, Bouchard et al. 2023).

As other empirical models that are derived from specific data sources and/or include parameters of source water quality and operations, this model is site-specific for the studied network (Rodriguez, Serodes et al. 2000). Because weather and watershed characteristics/activities, as well as treatment/operations, impact water quality, those logistic models are highly reliant on the input dataset. This methodology, however, can be applied and tested for any distribution system for which valid THM information is available. Furthermore, the quality of water is heavily affected by seasonality as well as temporality. This is particularly true for THM_4 formation, which can be observed at higher levels during warmer months in temperate climates (Rodriguez, Vinette et al. 2003, Rodriguez, Sérodes et al. 2004, Symanski, Savitz et al. 2004, Adams, Timmons et al. 2005, Seidel, Samson et al. 2017). Using this model in other seasons, such as winter, would require validation. Finally, whenever this model is used, the input parameters should remain within the minimum and maximum of the input parameters.

Globally speaking, several water quality parameters such as bromide concentrations, pH, SUVA, and DOC content may influence DBP speciation and concentrations. Several operational parameters, including chlorine doses and treatment and operations, may also affect DBP concentrations in finished water and in piping systems (Sadiq and Rodriguez 2004). For instance, the presence of halogens (I^-, Br^-) is known to influence the speciation of THM (Chowdhury, Champagne et al. 2010, Dong, Zhu et al. 2023). Due to the fact that chloroform constitutes the majority of THM_4, and that the intake is supplied by surface water, it is unlikely that high bromide concentrations are present. However, bromide concentrations have not been investigated. In water quality conditions where bromide concentrations exceed 0.2 mg/L, correlations between THM_4 and differential UV-VIS absorbances may be affected, so the use of this technique under those conditions may not be recommended (Beauchamp, Dorea et al. 2019).

Finally, it is necessary to conduct further research to confirm the potential of incremental UV-VIS in other contexts, to gain a better understanding of its biases, possible interferences, and limits, and to verify how far it can be applied to the estimation of lower

or upper concentrations. For instance, while some authors have demonstrated that differential UV-VIS is not affected by temperature at bench scale, this would need to be verified in a complex dynamic system, such as a network during other seasons characterized by different water quality (Roccaro, Chang et al. 2008).

4.5 Conclusion

Logistic regression was used to establish in terms of probability of exceedance the likelihood that drinking water utilities would exceed certain threshold levels of THM_4. An important feature of this site-specific empirical model (Probability of exceedance (THM_4 $\geq$ 80 µg/L)) is that it makes use of easily obtainable explanatory variables to help water stakeholders and operators to anticipate THM_4 peaks during warmer months. Despite the usefulness to develop a model to estimate probability of exceedance based on the 40 and 60 µg/L thresholds, the database used for the development of the models limits their applications at lower concentrations. As a second technique, incremental differential UV-VIS has demonstrated promising results with Δ254nm and Δ400nm showing the highest correlations for the validation sets. This technique would need to be further investigated at the scale of a network.

As this research has shown THM_4 recurrent exceeding concentrations for specific locations in the network, these alternative techniques would be useful to operators for limiting population exposure associated with short-term population exposure. THM_4 monitoring is currently conducted based on annual quarterly averages and thus current risk assessments fail to take short-term exposure into consideration. As chronic assessments of DBPs may not be protective of short-term exposures in highly exposed populations such as formula-fed infants (Goeden 2018) and because THM_4 analysis and monitoring are resourceful for municipalities, the use of these methods may be essential as part of a road map to protect vulnerable populations. A better estimate using alternative techniques would also assist public health practitioners in conducting epidemiological investigations and water operators, given the high spatiotemporal variability of HAA_6 and THM_4 and the difficulty of determining the true levels of population exposure during critical periods.

5 Subchronic exposure to THM_4 and HAA_6: do we need to refine our exposure assessment? A full-scale case study in a Canadian municipality

Manuscript Title:
Subchronic exposure to THM_4 and HAA_6: do we need to refine our exposure assessment? A full-scale case study in a Canadian municipality

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AC collected the data where sampling and analytical methods were planned by ID, AC performed the statistical and exposure and risk analysis under DP supervision, CD and MR guidances, AC wrote the paper under MR, SG, ID, and CD supervision. All authors will revise and comment the manuscript, prepared by AC.

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Abstract

Regulated disinfection by-products (e.g. trihalomethanes and haloacetic acids) are subject to high spatial and temporal variability throughout the year with increased concentrations during the summer months. Trihalomethanes and haloacetic acids monitoring is based on yearly averages of quarterly measurements with maximum acceptable concentrations where extensive monitoring of DBPs is not required during those warmer months. In this paper, the representativity of quarterly means was investigated along with the subchronic exposure to regulated DBPs. Secondly, Monte-Carlo simulations were conducted to understand how domestic exposure to trihalomethanes and haloacetic acids could vary throughout the network. Based on different scenarios, further investigations were conducted to determine the extent to which chloroform subchronic risks differed: 1) for quarterly means using all data, 2) for quarterly means calculated using the first week of June/July/August, the second week of June/July/August, the third week of June/July/August, and the fourth week of June/July/August, and 3) using all weekly concentrations. One significant finding relevant to epidemiological studies and health effect investigations is that subchronic exposure varies throughout the network, with the most exposed subpopulation located between the middle and extremities, with trihalomethanes and haloacetic acids contributing to the exposure.

Highlights:

- The quarterly means are not indicative of the monthly means
- Exposure to regulated DBPs vary spatially throughout the whole network
- TCM risk estimates are different if calculated through weekly concentrations, monthly means, and quarterly means

5.1 Introduction

The distribution system is a major component of the physical infrastructure of water distribution systems and serves as the last line of defense against contamination. The use of a disinfection process before distribution and within distribution networks prevent post-treatment microbial recontamination. Even though the benefits of chlorinating drinking

water are undeniable, some concerns have been raised about the health effects of disinfection-by-products (DBPs) in tap water. At present, there have been more than 700 compounds identified. These chemicals are estimated to account for more than half of the total amount of organic halogen in chlorinated water (Richardson and Plewa 2020). While some are still called "emerging", many are known as important toxicity drivers, such as haloacetonitrile. Trihalomethanes (THM_4) and haloacetic acids (HAA_5) are the two classes of regulated compounds and the most encountered ones in terms of molar concentrations proportions. However, recent perspectives highlighted the strong need for a discussion on the significance of the current use of THM_4 and HAA_6 as indicators of DBPs (Richardson and Plewa 2020, Richardson Susan 2022). As public water systems use disinfection strategies, a large proportion of the population are continually and ubiquitously exposed to DBPs at levels that are significantly higher than those of other emerging contaminants that are currently gaining public attention, such as perfluorinated alkyl substances (Richardson Susan 2022).

THM_4 and HAA_5 regulations were adopted in response to the evidence that chronic exposure to those classes of compounds is associated with an increased risk of cancer. Current American and Canadian guidelines are defined in terms of chronic exposure and are based on yearly averages of quarterly measurements with maximum acceptable concentration (Health Canada 2006, United States Environmental Protection Agency 2016, Direction de l'eau potable et des eaux souterraines 2019). The Canadian guidelines, defined by Health Canada, recommend a maximum of 100 µg/L for trihalomethanes (THMs) and 80 µg/L for haloacetic acids (HAAs), while in United Stated and in Quebec, those values are 80 µg/L for trihalomethanes (THMs) and 60 µg/L for haloacetic acids (HAA_5). The regulations refer to HAA_5 as the sum of MCAA, DCAA, TCAA, MBAA, DBAA. Those regulations are based on a locational running annual average of a minimum of quarterly samples. Health Canada used chloroform as a model THM to define the health-based target of 80 µg/L which was increased to 100 µg/L for feasibility reasons (Health Canada 2006).

In temperate climates, these compounds exhibit a unique pattern of variability, with a fluctuating baseline throughout the year and higher peaks during warmer months (Rodriguez, Vinette et al. 2003, Rodriguez, Sérodes et al. 2004, Richter 2009, Parvez,

Rivera-Núñez et al. 2011). In the absence of guidelines on exposure duration relevant to quarterly sample collection, the relevance of those exceedances for public health remains uncertain, and therefore their management is challenging for health authorities (Buteau and Valcke 2010).

Recent decades have seen an increasing body of evidence suggesting an association between DBP exposure and bladder cancer as well as adverse reproductive effects. Although conclusions differ between epidemiological studies and causality has not yet been established, some studies have reported associations between DBP exposure and increased risk of adverse developmental outcomes including term low birth weight or small for gestational age (Wright, Schwartz et al. 2003, Infante-Rivard 2004, Lewis, Suffet et al. 2006, Hoffman, Mendola et al. 2008, Säve-Söderbergh, Toljander et al. 2020), birth defects such as cardiovascular and neural tube defects/congenital malformations (Hwang, Magnus et al. 2002, Chisholm, Cook et al. 2008, Hwang, Jaakkola et al. 2008, Nieuwenhuijsen, Toledano et al. 2008, Säve-Söderbergh, Toljander et al. 2021), spontaneous abortion (Savitz, Singer et al. 2006), and stillbirths (Toledano, Nieuwenhuijsen et al. 2005). Other toxicological effects have been reported for animals such as hepatic effects (e.g. lesions, fatty cyst formation) that are points of departure for some health standards or guidelines, specifically for THM_4 (Toxic Substances and Disease Registry (ATSDR) 1997, Health Canada 2006, Agency for Toxic Substances and Disease Registry (ATSDR) 2011, Agency for Toxic Substances and Disease Registry (ATSDR) 2011). Furthermore, evidence shows that brominated THM_4 have been demonstrated to be mutagenic when activated by glutathione S-transferase theta1 (GSTT1), as opposed to chloroform, which does not become mutagenic when activated (Richardson, Plewa et al. 2007).

DBPs specific pattern of exposure is characterized by a constant baseline of exposure with a recurrent high spatial and temporal variability in summer. It is likely that certain populations will be more exposed than others due to higher concentrations of HAA_5 at the beginning of the network and higher concentrations of THM_4 at the extremities of the network (Rodriguez, Sérodes et al. 2004, Scheili, Rodriguez et al. 2015). In terms of individual levels of exposure, drinking tap water, showering, bathing, swimming, boiling water, and dishwashing are the main activities that can contribute to differences in terms

of exposure among population (Nieuwenhuijsen, Toledano et al. 2000, Whitaker, Nieuwenhuijsen et al. 2003). Exposure to volatile compounds such as THM_4 in drinking water occurs through those multiple routes and pathways (e.g. ingestion, inhalation, dermal absorption) and varies from person to person depending on the individual's water usage. By contrast, the major route of exposure appears to be ingestion for HAA_5 because those compounds are non volatile (Nieuwenhuijsen, Toledano et al. 2000).

Although evidence of adverse effects is growing, there is still a lack of information regarding short-term exposure to THM_4 and HAA_5 during periods of higher exposure (e.g. summer season). Because of the suspicion of adverse reproductive outcomes, it is essential to accurately capture the temporal variation in exposure over a shorter period covering the relevant time windows for pregnant women (Villanueva, Kogevinas et al. 2014). Moreover, we need to document how recurrent higher seasonal concentrations contribute to the overall exposure to THM_4 and HAA_5 and how vulnerable populations such as pregnant woman or infants can be overexposed during those times.

To address those gaps, our objectives were to explore the spatial and temporal variability for THM_4 and HAA_5 within a season for a network when peaks of concentration are frequently reported, based on a robust and intensive dataset. In order to evaluate the effect of the monitoring approach on TCM subchronic risk estimates, Monte-Carlo simulations (MCS) were conducted using all data (weekly concentrations, n=12), quarterly concentrations, and monthly samples assuming the plant would provide one sample per month (samples collected on every first week for June, July, and August, second week, third week, or fourth week). A subsequent objective was to estimate short-term exposure based on multiple pathways and estimate non cancer risks using short-term health reference values.

The information may assist public health authorities in evaluating whether and how peaks of exposure and DBP variability may influence exposure to DBPs and subchronic risks. Furthermore, this paper provides a case study in a Canadian municipality on how high frequency sampling are needed to avoid exposure underestimation.

5.2 Materials and methods

5.2.1 Case study, demography, and GIS analysis

The study was conducted in a Canadian municipality with a population of 149,685 inhabitants and a mean density per square meter of 334.1. With 73,535 males and 76,150 females, this population has a median age of 42.8 for males and 44.8 for females, and a total population of 1,305 under 1 year old and 8,685 under 5 year old (Statistics Canada 2021). Residents receive drinking water from two drinking water plants. The specific network under study is supplied by surface water and treated by coagulation/flocculation/sedimentation using ®Actiflo, pre-chlorination, filtration, ozonation, and final chlorination with sodium hypochlorite. Prior to distribution, water is stocked at the plant in a reservoir for approximatively seven hours, and several reservoirs are present in the network where water is rechlorinated before being redistributed.

The dissemination area was selected as a unit of analysis since they represent the smallest geographical area for which all census data are available. A unit of analysis consists of one or more adjoining dissemination blocks with an average population of 400 to 700 individuals (Statistics Canada 2016). For the area covered by the studied network, demographic data were extracted from the latest census (2021) and was comprised of 97 dissemination areas. Data from Statistics Canada, the latest census demographic data from 2021, and documents provided by the municipality were used to estimate that the plant under study supplies water to approximately 39 917 residents over an area of 292.8 km^2 (Statistics Canada 2021, Statistics Canada 2021). GIS analysis was performed using QGIS 3.12.0.

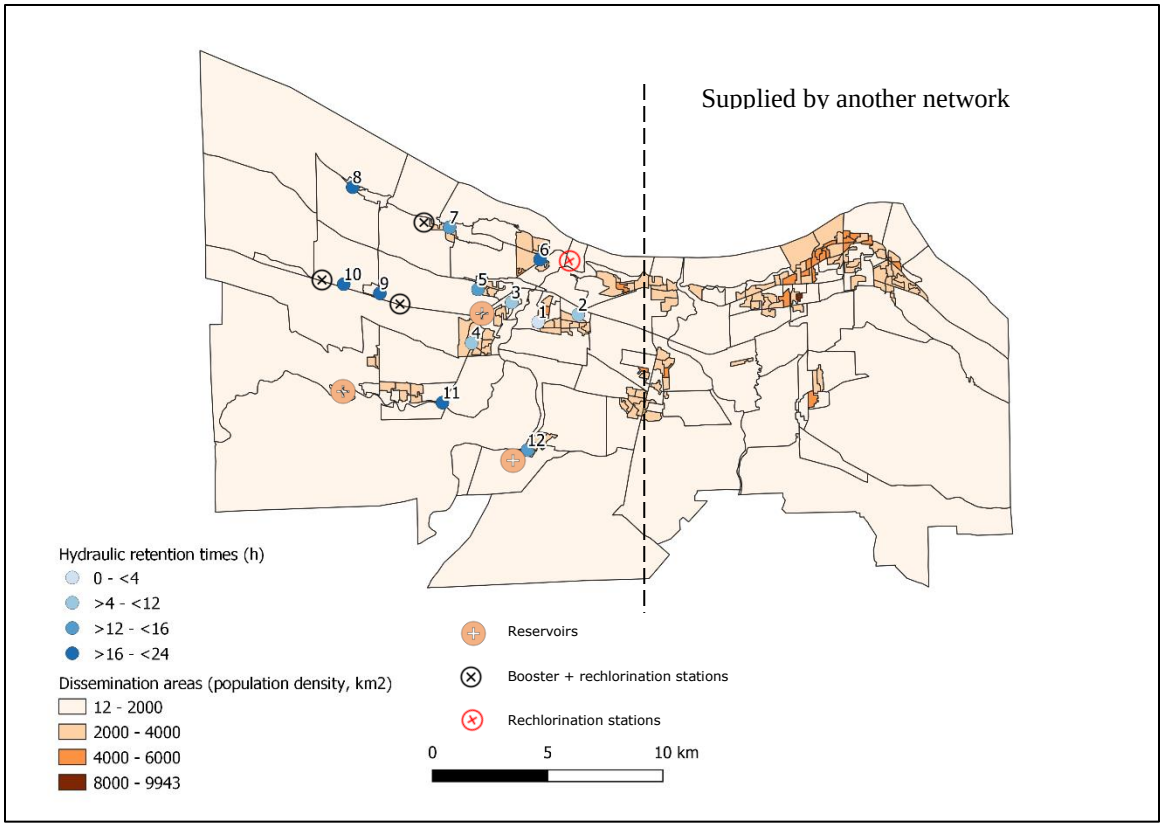


Figure 11 :Dissemination areas for the studied network (black line). Red circle: the plant, blue triangle (R1): locations with estimated residence times between ≥0 and <4h, yellow circle (R2, R3, R4): locations with estimated residence times between ≥4 and <12h, green diamond (R5, R7, R12): locations with estimated residence times between ≥12 and <16h, blue circle (R6, R8, R9, R10, R11): locations with estimated residence times between ≥16 and <24h.

5.2.2 Sampling procedure

Water samples were collected during the months of June, July, August, September, and October 2019 corresponding to the period where higher concentrations are frequent as previously reported in previous Canadian studies (Rodriguez, Sérodes et al. 2004, Buteau and Valcke 2010). Over an 18-week period, 216 samples were taken on a weekly basis on the same day weekly and time. Twelve public sites were selected (R1 to R12) differing in terms of estimated hydraulic residence times, and by the presence of upstream rechlorination stations or reservoirs to account for spatial variability. By identifying points having different hydraulic conditions, we ensured that some of the hydraulic factors that are known to influence DBPs concentrations in a network were considered (Idornigie, Templeton et al. 2010). Further, samples were collected after water was left running for approximately five minutes to ensure that the sampled water was representative of the water quality in the network and not stagnant water in the domestic pipes (Legay,

Rodriguez et al. 2011). The water was also sampled in accordance with the supposed path it takes along the distribution network (from the closest location to the plant to the extremities).

The THM_4 and HAA_6 samples collections were conducted in amber glass vials of 40 mL, in which three samples per class of compound were collected, and each was gently poured until it reached the edge, before being sealed with the screw cap (Beauchamp, Dorea et al. 2019). The presence of air bubbles was verified in the samples and were discarded if found. THM_4 and HAA_6 vials were stored at 4°C before analysis.

5.2.3 Analytical methods

THM_4 includes chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (TBM); individual regulated HAA_5 consists of monochloroacetic acid (MCAA), dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), monobromoacetic acid (MBAA), and dibromoacetic acid (DBAA). Solid-phase microextraction (SPME) fibres were used to extract THM_4 and gas chromatography with ion-trap mass spectrometry (GC-MS) was applied for analysis. Detection limits were respectively of 0.8 µg/L, 1.7 µg/L, 1.5 µg/L and 1.9 µg/L for TCM, BDCM, DBCM and TBM. The investigated HAAs (HAA_6) were MCAA, DCAA, TCAA, MBAA, DBAA, BCAA. MTBE was used as a solvent for the extraction of HAA_5, which were then analysed using gas chromatography with electron capture detection (GC-ECD). HAA_6 were extracted using liquid-liquid extraction in MTBE and were analysed using gas chromatography with electron capture detection (GC-ECD) (Beauchamp, Laflamme et al. 2018). Detection limits for MCAA, DCAA, TCAA, MBAA, DBAA, BCAA were of 1 µg/L for each compound.

5.2.4 Definition of multi-pathways exposure scenario

Exposure assessment is a critical step that has many limitations such as low exposure levels, chemicals occurring in mixture, time-space variability, long-term exposure windows, lack of monitoring data and multiple exposure routes (Villanueva, Kogevinas et al. 2014). Because considering all relevant pathways of exposure remains essential, an exposure assessment was conducted to evaluate the potential THM_4 and HAA_6 uptake via

oral ingestion, inhalation, and dermal absorption. The estimation of subchronic exposure was performed based on DBPs concentrations during the summer season (June, July, and August) as the objective was to compare with quarterly means, the basis of the current American and Canadian monitoring and regulations.

THM_4 are considered volatile compounds with Henry's Law constant of 3.67×10^{-3} and 2.12×10^{-3} for TCM and BDCM to moderately volatile for DBCM 7.83×10^{-4} and 5.35×10^{-4} for TBM (United States Environmental Protection Agency 2021, National Center for Biotechnology Information 2022). Exposure to volatile DBPs compounds may occur through ingestion, dermal absorption, and inhalation, as well as through any activity involving chlorinated water, such as drinking tap water or swimming in chlorinated water (Whitaker, Nieuwenhuijsen et al. 2003). For THM_4, several studies conducting multipathways risk assessment with physiological based pharmacokinetic modeling (PBPK) have shown that the dose received from other routes (dermal, inhalation) may contribute greatly to the internal dose and potentially have just as great an effect on health as the dose received from oral exposure (Krishnan and Carrier 2008, Basu, Gupta et al. 2011). Occupational exposure and activities such as swimming, were not taken into consideration as the objective was to estimate domestic exposure to DBPs from the supplied drinking water. In this study, for THM_4 exposure showering or bathing were assumed to be the major activity for inhalation and dermal contact [12]. Since HAA_6 are neither volatile nor lipophilic, non-ingestion exposure (dermal and inhalation) to these compounds is considered negligible (Xu and Weisel 2003). Indeed, the dermal dose of HAA_6 is also expected to be low because of their very low skin permeability ($1–3 \times 10^{–3}$ cm/h, pH 7) (Xu, Mariano et al. 2002). Hence, risk assessment should include the dermal pathway for THM_4 but not for HAA_5 (Xu, Mariano et al. 2002). Calculation of the absorbed dose by ingestion can be performed by using the following equation (Buteau and Valcke 2010):

$$Absorbed\ dose = {Ing \times Cw \times FA_{ing}}/{BW} \qquad Eq.\ 5$$

Where **Ing** : Volume of water ingested daily (L/d), $\mathbf{C_w}$: Concentration of DBPs in water (mg/L), **FAing**: the absorbed fraction by ingestion (unitless), **BW**: Body weight (kg)

5.2.5 Absorption through inhalation

US EPA recommends that the showering/bathing frequency should be estimated as one event per day (United States Environmental Protection Agency 2004). It is also assumed that the entire body surface is exposed to water during a shower (United States Environmental Protection Agency 2004). A time of 10 min of shower is recommended by Institut national de santé publique (Institut national de la santé publique du Québec 2010). Bathing was considered only for children for a duration of 1 hour and for 1 bath per day (EPA. 2004). As shower or bathroom's volumes will affect the concentrations of volatile THM_4 in the air, those parameters are considered in the calculation (Eq. 4 and Eq. 5). The bathroom and shower volumes were obtained from a previous study conducted in Quebec, which determined that the mean bathroom and shower volumes were of 12,800 x 6,200 L and 2,400 x 800 L, respectively. (Levesque, Ayotte et al. 2002). Furthermore, it is presumed that the vapors disperse uniformly throughout the bathroom (Institut national de la santé publique 2010). The following equations describe the calculation for the dose absorbed by inhalation by adding the uptake during showering and the uptake following showering (Institut national de la santé publique 2010):

$$C_{air\ shower} = \frac{Cw \times K \times F \times T/2}{V_{shower}} \qquad \textit{Eq. 6}$$

$$C_{air\ bathroom} = \frac{Cw \times K \times F \times T}{V_{bathroom}} \qquad \textit{Eq. 7}$$

$$D_{inh} = \frac{C_{air\ shower} \times \mathrm{FA_{inh}} \times Inhalation\ rate \times Ft_{\ shower}}{BW} + \frac{C_{air\ bathroom} \times \mathrm{FA_{inh}} \times Inhalation\ rate \times Ft_{\ bathroom}}{BW} \qquad \textit{Eq. 8}$$

Where $\mathbf{C_w}$: concentration of DBPs in water (mg/L), **K**: Contaminant transfer coefficient from water to air (unitless), **F**: Shower water flow (L/min), **T**: Water flow time (min), $\mathbf{V_{shower}}$: Volume of the shower (L), $\mathbf{V_{bathroom}}$: Volume of the bathroom (L), $\mathbf{D_{inh}}$: Dose absorbed by inhalation of vapors (mg/kg-day), $\mathbf{C_{air\ shower}}$: Concentration in the air of the shower (µg/L) $\mathbf{C_{air\ bathroom}}$: Concentration in the air of the bathroom (mg/L), $\mathbf{T_{inh}}$: Inhalation rate (L/d), $\mathbf{ft_{shower}}$: Fraction of time the individual is exposed to shower air daily (without unit), $\mathbf{ft_{bathroom}}$: Fraction of time the individual is exposed daily to shower air

bathroom immediately after shower (without unit), **FA_{inh}**: Fraction of the contaminant absorbed by inhalation (without unit), **BW**: Body weight (kg).

5.2.6 Absorption through skin

Eq.9 was used to calculate the total surface area of the body based on body weight and height, while Eq.10 was used to calculate the absorbed dose via dermal absorption following contact with organic compounds present in water (United States Environmental Protection Agency 2004, Institut national de la santé publique 2010). As reported by the US EPA, this latest equation can be applied if the duration of the event (shower duration) is inferior to the time to reach the steady state which is of 1.19h for TCM and 2.12h for BDCM. As part of the evaluation, a fraction absorbed term (FA) has been included in order to account for the loss of chemicals due to desquamation; however, only lipophilic chemicals with log K_{ow} > 3.5 would be affected (United States Environmental Protection Agency 2004). Consequently, because of their K_{ow} lower than 3.5, for TCM and BDCM, US EPA has recommended FA values of 100 % (Table 13).

$$SA = 0.0239 \times H^{0.417} \times BW^{0.517} \quad \textit{Eq. 9}$$

SA: Total body surface area (m^2), **H**: Height (cm), **BW**: Body weight (kg)

$$D_{dermal} = \frac{2 \times FA_{dermal} \times K_p \times C_w \times CF \times SA\sqrt{6\tau \times t/\pi}}{BW} \quad \textit{Eq. 10}$$

D_{dermal}: Dose absorbed by skin contact with water (mg/kg-day), **K_p**: Skin permeability coefficient in water (cm/h), **FA_{cut}**: Fraction of contaminant absorbed compared to the quantity having penetrated the skin (without unit), **C_w**: Concentration in water (mg/L), **CF**: Unit conversion factor (1L/1,000 cm^3), **SA**: Skin surface area exposed to water (cm^2), **t**: Exposure time per event (h/event), **τ**: Latency time per event (h/event), **BW**: Body weight (kg)

Table 13: Determinist and probabilistic input parameters for multipathways exposure assessment

Parameters	Units	Values	Type of distribution	References
Body weight (BW)	Kg	< 0.5 year: 6.7 ± 1.5	Log-normal	(Institut national de santé publique du Québec 2012)
		0.5 à <5 year: 14.9 ± 3.5	Log-normal	
		20+ year: 74.6 ± 17	Log-normal	

(males and females combined)				
Height (H) (males and females combined)	cm	< 0.5 year : 61.7 ± 0.5 0.5 à <5 : 91.6 ± 15.3 20+ : 165.9 ± 9.6	Log-normal Log-normal Log-normal	(Institut national de santé publique du Québec 2012)
Oral ingestion				
Concentration of DBPs in water (C_W)	mg/L	See Figure 12	-	This study
Fraction absorbed (FA_{ing})	Dimensionless	TCM : 100% BDCM : 100% HAA : 100%	-	(Institut national de la santé publique 2010)
Water ingestion rate (males and females combined)	L/d	< 0.5 year : 0.682 ± 0.241 0.5 à <5 : 0.728 ± 0.485 20+ : 1.528 ± 0.920	Log-normal Log-normal Log-normal	(Institut national de santé publique du Québec 2012)
Dermal absorption				
Volumetric conversion factor for water (CF)	L/cm^3	10^{-3}	-	(Buteau and Valcke 2010)
Exposure time per event (t) (showering)	(h/event)	0.17 (20 min)	-	(Institut national de la santé publique du Québec 2010)
Exposure time per event (t) (bathing)	(h/event)	1 (60 min)	-	(United States Environmental Protection Agency 2004)
Lag time per event (τ)	(h/event)	TCM: 0.5 BDCM: 0.88	-	(Institut national de la santé publique 2010)
Fraction absorbed (FA_{skin})	Dimensionless	TCM : 100% BDCM : 100%	-	(United States Environmental Protection Agency 2004, Institut national de la santé publique 2010)
Dermal permeability	cm/h	TCM: 0.015 ± 0.019 (25°C)	Normal	(Xu, Mariano et al. 2002, United States

coefficient of the compound (K_p)		BDCM: 0.015 ± 0.019 (25°C)		Environmental Protection Agency 2004, Xu and Weisel 2005, Institut national de la santé publique 2010)
Inhalation				
Estimated 24h inhalation rates (males and females combined)	L/d	< 0.5 year: 2.2 ± 0.6 0.5 à <5 year: 8.3 ± 2.2 20+ year: 16.6 ± 4.1	Log-normal Log-normal Log-normal	(Allan, Richardson et al. 2008, Institut national de la santé publique 2010)
Fraction absorbed (FA_{inh})	Dimensionless	TCM: 77%, BDCM: 100 %	-	(Institut national de la santé publique 2010)
Bathroom volumes	L	12,800 ± 6,200	Normal	(Lévesque, Ayotte et al. 2002)
Shower volumes	L	2,400 ± 800	Normal	(Lévesque, Ayotte et al. 2002)
Shower flow rate	L/min	10	-	(Krishnan and Carrier 2008)
Transfert coefficient water/air (K)	Dimensionless	TCM : 0.56 ± 0.11 BDCM : 0.17		(Xu and Weisel 2005)
F shower frequency	(shower/day)	1	-	(Institut national de la santé publique du Québec 2010)
t shower duration (adults)	(min/shower)	10	-	(Institut national de la santé publique du Québec 2010)
Bathing time **< 0.5 years** **0.5 – 5 years**	(min/bath)	 19 (mean) 24 (mean)		(United States Environmental Protection Agency 2009)
Bath volume	L	60		(Buteau and Valcke 2010)
Time spent in the bathroom after showring or bathing **< 0.5 years**[2]	(min)	 2 (mean)		(United States Environmental Protection Agency 2009)

0.5 – 5 years[1]	3.67 (calculated mean)	(United States Environmental Protection Agency 2009) (Institut national de la santé publique (INSPQ) 2006)
20+	3	

[1] Calculated mean from *Child-Specific Exposure Factors Handbook (2008)*: 1 to <2 (mean 3 min), 2 to < 3years (mean 4 min), 3 to <6 years (mean 4 min)

[2] Birth to <1: 2 min (mean)

5.2.7 Probabilistic approach

A probability assessment involves more complex modeling approaches that rely on probability distributions for inputs rather than point values for exposure parameters. In this manner, the distribution of possible exposure estimates is obtained and it is possible to determine the level of uncertainty and variability (United States Environmental Protection Agency 2022). Hence, to estimate exposure associated with THM_4 and HAA_6, we used Monte-Carlo simulations (1,000 iterations) and a random number sampling method (latin hypercube sampling) based on the data from our case study. Monte-Carlo inputs were both determinist and probabilistic data (Table 13). Probability distribution functions were calculated using Kolmogorov–Smirnov and Khi^2 tests for each sampling point and for TCM, THM_4 and HAA_6 weekly concentrations (expressed in µg/L). Exposure estimates (expressed in mg/kg*d) were calculated for all locations in the network and for three groups (infants, children, and adults) with genders combined. Probabilistic simulations and statistical analysis were obtained using Excel Stats 2022.5.1 (Addinsoft 2022). A comparison of TCM subchronic risks derived from monthly means (samples collected during the first, second, third and fourth week of each month) versus quarterly sampling was also carried out by calculating exposure estimates and cumulative density for infants. In this comparison, all other exposure inputs remained constant except TCM concentrations. Sensitivity analysis were also conducted to understand the source of uncertainty in the risk estimation (Frey and Patil 2002).

5.2.8 Multi-pathway risk assessment for chloroform

The risk quotients (RQi) for ingestion, inhalation, and dermal absorption were calculated using Eq.10 and summed up to obtain contributions from all pathways (Eq.11) (Institut

national de la santé publique 2010). The target is that the summation of all indices should be less than 1. Because the daily intake of chloroform may also be impacted by other sources of exposure (swimming activities, occupational exposure), an additional factor of 80% is added to Eq. 10 (Buteau and Valcke 2010).

$$RQ_{i,TCM} = \left({}^{D_i}/_{RfD_i} \right) * 80\ \% \quad \textit{Eq. 11}$$

$$RQ_{total,TCM} = RQ_{ing} + RQ_{inh} + RQ_{dermal} \quad \textit{Eq. 12}$$

where $\mathbf{D_i}$ is the dose for a pathway i, $\mathbf{RQ_{tot}}$ is the total risk quotient (unitless), $\mathbf{RQ_{inh}}$ the risk quotient for inhalation (unitless), $\mathbf{RQ_{ing}}$ the risk quotient for ingestion (unitless), $\mathbf{RQ_{der}}_{\mathrm{m}}$ the risk quotient for dermal contact (unitless), $\mathbf{RfD_i}$ is the reference dose for chloroform for ingestion, inhalation, and dermal absorption.

Public health and environmental databases and articles were screened to identify preferentially subchronic or "intermediate" reference doses for non-cancer assessment for the investigated compounds. The ATSDR Minimal Risk Levels (MRLs) are derived for intermediate exposure for a duration of >14 to 364 days while subchronic exposure is defined by the US. EPA as a repeated exposure for more than 30 days, up to 10 % of the life span in human (Agency for Toxic Substances and Disease Registry (ATSDR) 2018, United States Environmental Protection Agency 2022). A few TCM toxicological values were determined by different organizations using various points of departure, however there was a lack of toxicological values (non-cancer assessment) for haloacetic acids and brominated THM_4 specifically for pathways other than ingestion (Table 14). Considering that the objective was to assess non-cancer risks, oral slope factors were compiled for information only and were not incorporated into the calculations in Table 14. Data were collected from Comptox, Agency for Toxic Substances and Disease Registry (Minimal risk levels and IRIS database) (Agency for Toxic Substances and Disease Registry (ATSDR) 2018, United States Environmental Protection Agency 2020), Institut national de la santé publique (Institut national de la santé publique 2010), The Risk Assessment Information System (RAIS) (Risk Assessment Information System 2022), Health Canada (Health Canada 2006, Health Canada 2009), Peer-Reviewed Toxicity Values (PPRTV) defined by

the US EPA (through the Superfund program) (United States Environmental Protection Agency) and previous articles (Buteau and Valcke 2010).

Table 14: Toxicological values for carcinogenic and subchronic non carcinogenic risk assessment. RfD in blue color were the ones used in the calculation for risk assessment.

Compounds	RfD Oral (mg/kg-jour)	Critical point	Reference	RfD Inhalation (mg/kg-jour)	Critical point	Reference	RfD dermal (mg/kg-jour)	Critical point	Reference
TCM	**0.13** Intermediate MRL	Significant increased of serum glutamic pyruvic transaminase activity	(Toxic Substances and Disease Registry (ATSDR) 1997, Buteau and Valcke 2010)	**0.056** Calculated from ATSDR RfC (mg/m^3)	Hepatic effects	(Buteau and Valcke 2010)	**0.056** Calculated from ATSDR RfC (mg/m^3)	Hepatic effects	(Buteau and Valcke 2010)
BDCM	0.008 Subchronic PPRTV 0.062	Full litter resorption IRIS, oral slope factor	(United States Environmental Protection Agency 2009) (Health Canada 2009)	0.02 mg/m^3 Subchronic PPRTV	Histopathologic evidence of kidney degeneration	(United States Environmental Protection Agency 2009)	*not defined*	*not defined*	*not defined*
DBCM	0.07 Subchronic PPRTV 0.084	Hepatic lesions IRIS, oral slope factor	(United States Environmental Protection Agency 2009)	*not defined*	*not defined*	*not defined*	*not defined*	*not defined*	*not defined*
TBM	0.2 Subchronic RfD 0.0079	Slight increase in postnatal mortality IRIS, oral slope factor	(National toxicology program 1989, Institut national de la santé publique 2010)	*not defined*	*not defined*	*not defined*	*not defined*	*not defined*	*not defined*
MCAA	0.0117 Chronic	Changes in body, liver, kidney, and testes weights	(Health Canada 2009)	*not defined*	*not defined*	*not defined*	*not defined*	*not defined*	*not defined*
DCAA	0.004 Chronic	Lesions observed in the testes, cerebrum, cerebellum, and liver	(United States Environmental Protection Agency)	*not defined*	*not defined*	*not defined*	*not defined*	*not defined*	*not defined*

	0.005	Cancer, oral slope factor	(Health Canada 2009)						
TCAA	0.0325 Chronic	Decreased body weight, increased liver serum enzyme activity and liver histopathology compared with control animals	(Health Canada 2009)	*not defined*	*not defined*	*not defined*	*not defined*	*not defined*	*not defined*
	7.0×10^{-2}	IRIS, oral slope factor	(Health Canada 2009)						
BCAA	*not defined*	*not defined*	*not defined*	*not defined*	*not defined*	*not defined*	*not defined*	*not defined*	*not defined*

5.3 Results

5.3.1 Regulated DBPs concentration in the network

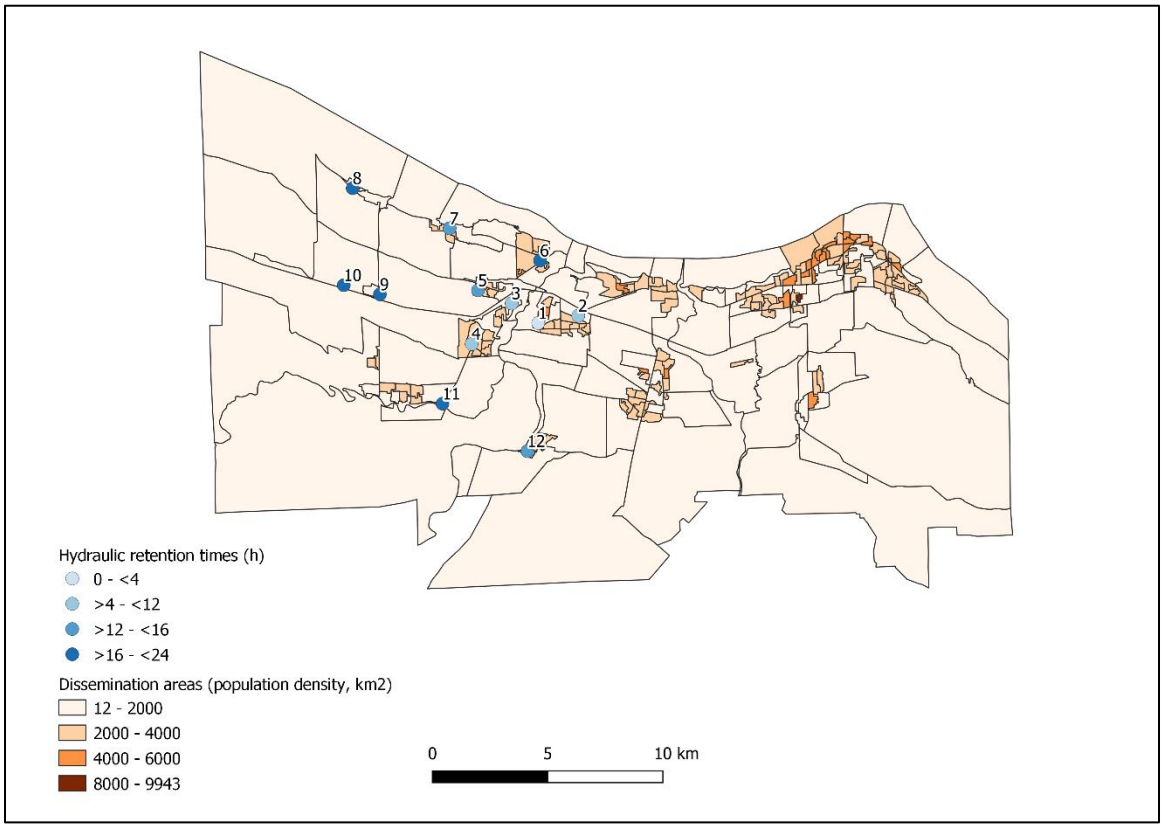


Figure 11Figure 12 shows the THM_4 and HAA_5 concentrations in the network for each sampling location in June, July, and August. Based on the concentrations detected, haloacetic levels exhibit lower levels than trihalomethanes in terms of mass concentrations. Lesser concentrations of THM_4 and HAA_5 are observed at the beginning of the network (≥0 and <4h), compared with the values obtained with increasing residence time (≥4 and <12h, ≥12 and <16h). During some weeks in July and August, THM_4 concentrations were twice as high at locations with hydraulic residence times of 16 hours to 24 hours. HAA_5 levels were smaller for R11 that is considered the very end of the network which also shows the highest medians of all sampling points of 106 µg/L for THM_4.

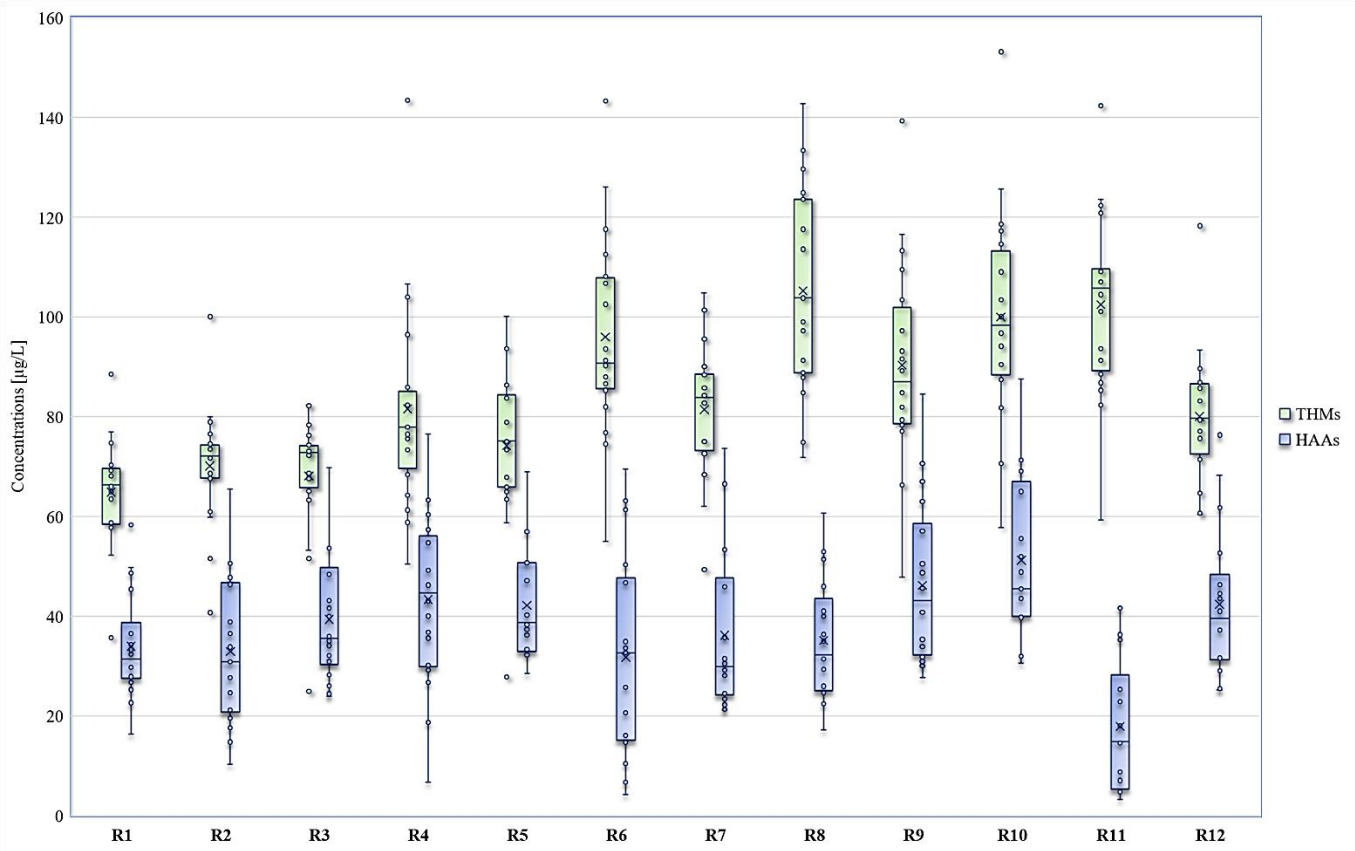


Figure 12 : THM4 and HAA5 concentrations in the network for locations with estimated residence times between ≥0 and <4h (R1), R2, R3, R4: locations with estimated residence times between ≥4 and <12h, R5, R7, R12: locations with estimated residence times between ≥12 and <16h, R6, R8, R9, R10, R11: locations with estimated residence times between ≥16 and <24h.

5.3.2 Comparison of quarterly means and monthly averages

Figure 13 compares the quarterly means for each site with the monthly means of June (N=4), July (N=5) and August (N=3). In comparison with sampling points located at the beginning of the network (R1, R2, R3), where the estimated hydraulic residence times are shorter (0-4 hours; 4 and 12 hours), changes between monthly and quarterly mean values are smaller than at other locations. In R1, R2, and R3, the weekly concentrations exceeding the health-based target of 80 µg/L were only 5.6%, 5.6%, and 11.1% respectively. As we go along the network (R_4 onward), exceedances are more frequently observed, and the corresponding quarterly means differs from monthly means. This is coherent with previous papers demonstrating that THM_4 concentrations increase through the network (Rodriguez, Vinette et al. 2003, Rodriguez, Sérodes et al. 2004). For instance, R6, R8, R10 and R11, means in August differed by 115%, 111%, 110% and 121% from the quarterly means. As

a result, quarterly means in those instances no longer represent higher peaks of concentration in the network. The highest concentration was found to be at R_{10} with a maximum of 153.2 µg/L during the first week of August. The maximum THM_4 values for each sampling point were of 143.5 µg/L, 100.2 µg/L, 143.3 µg/L, 104.9 µg/L for R4, R5, R6, and R7 respectively. For R8, R9, R10, R11 and R12, those concentrations were of 142.8 µg/L, 139.3 µg/L, 153.2 µg/L, 142.3 µg/L and 118.3 µg/L. The highest values for each point were recorded mostly for all point at the end of July and during the month of August.

On the opposite, as shown in Figure 14, locations with higher residence times (R6, R8, R10, R11) demonstrated lower concentrations of HAA_6 in terms of quarterly means and medians. There was no quarterly mean value that exceeded 60 µg/L (Regulations from the Province of Quebec) nor 80 µg/L (Health Canada Guidelines) during this period. In contrast to THM_4, where the month of August presented the largest difference between medians and monthly average concentrations, the month of June displayed the largest difference from the HAA_6 quarterly average. This dataset indicates that quarterly averages are not sufficiently representative of higher concentrations of these classes of compounds and underestimate peak concentrations in this network. Parvez et al. (2011) have also demonstrated that quarterly means are not representative of THM_4 and HAA_6 monthly trends for chloraminated surface water system and for chlorinated system supplied by surface and groundwater (Parvez, Rivera-Núñez et al. 2011).

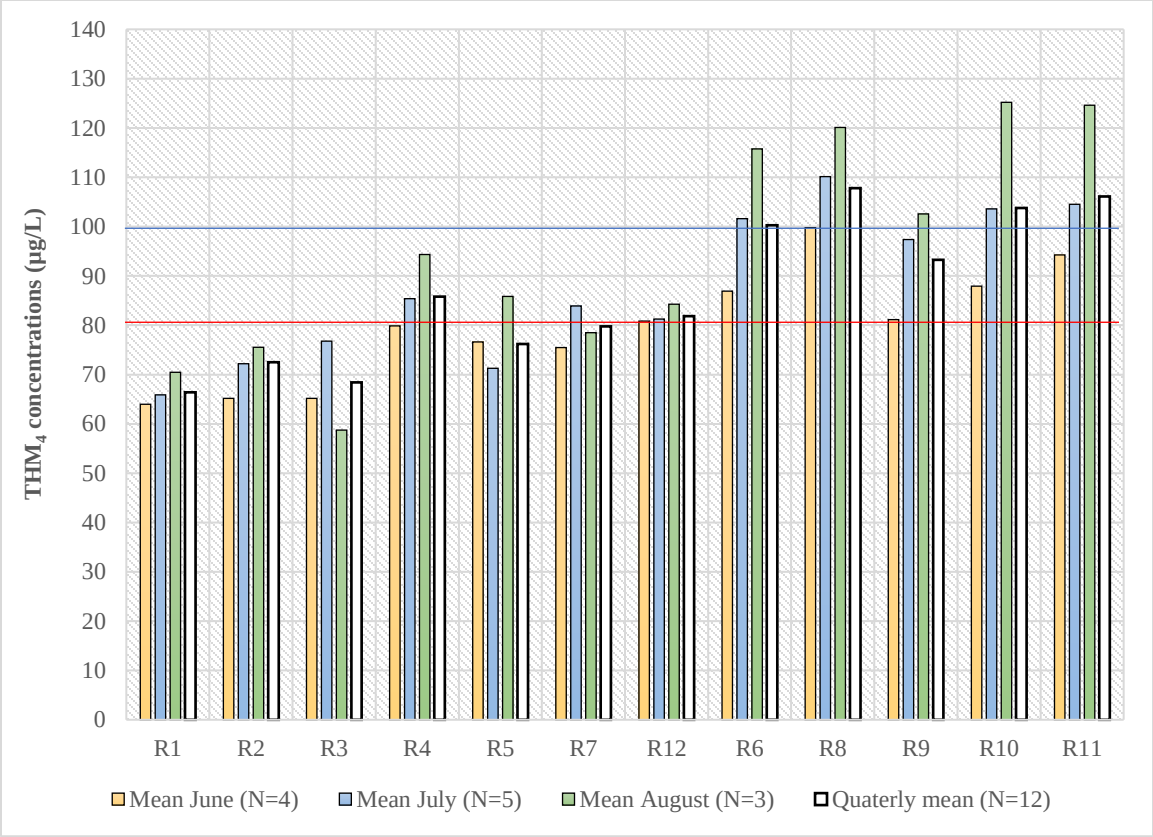


Figure 13: Comparison between quarterly THM_4 means and monthly means for each site (n=12). The blue line indicates the MAC defined by Health Canada and the red line refers to the standard for the Province of Quebec. Locations with estimated residence times(R_1) between ≥0 and <4h, R2, R3, R4: locations with estimated residence times between ≥4 and <12h, R5, R7, R12: locations with estimated residence times between ≥12 and <16h, R6, R8, R9, R_{10}, R11: locations with estimated residence times between ≥16 and <24h.

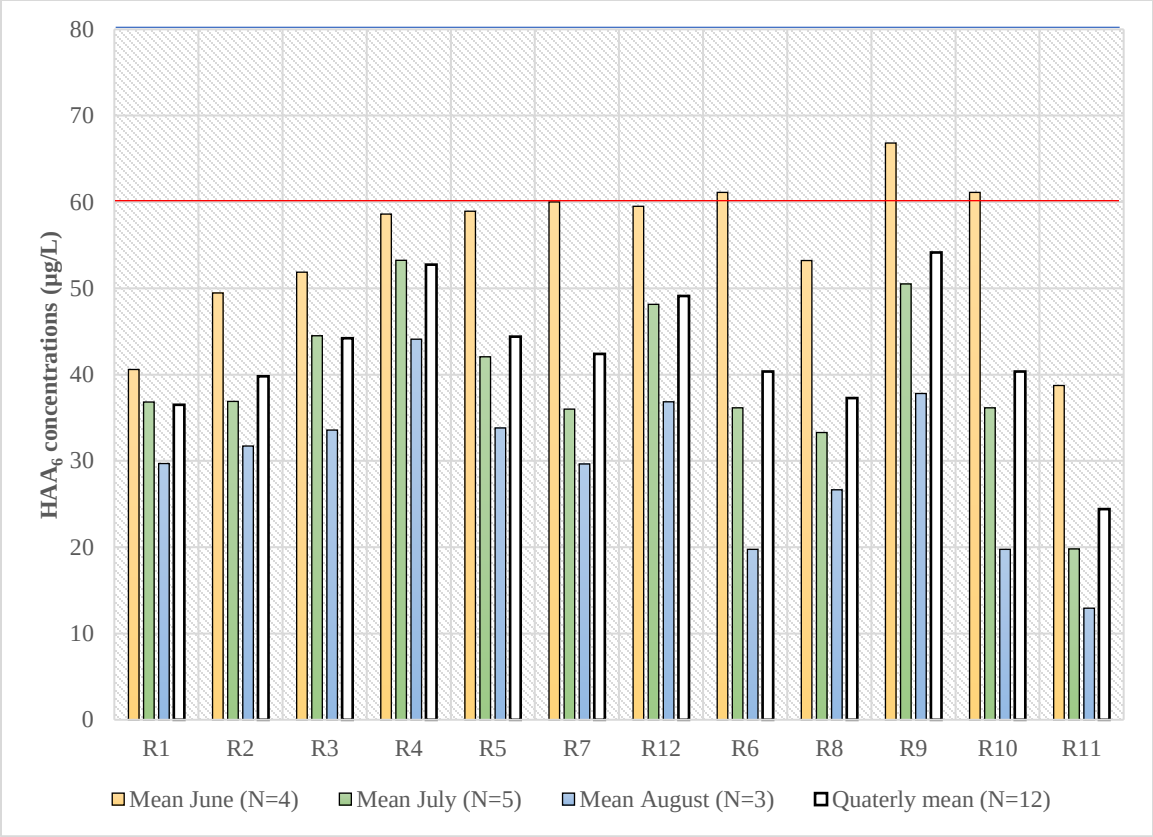


Figure 14 : Comparison between quarterly HAA_6 means and monthly means for each site (n=12). The blue line indicates the MAC defined by Health Canada and the red line refers to the standard in the Province of Quebec. Locations with estimated residence times(R1) between ≥0 and <4h, R2, R3, R4: locations with estimated residence times between ≥4 and <12h, R5, R7, R12: locations with estimated residence times between ≥12 and <16h, R6, R8, R9, R_{10}, R_{11}: locations with estimated residence times between ≥16 and <24h.

5.3.3 Spatial variations of subchronic exposure in the network (MCS using weekly sampling)

Table 15 presents the median total exposure estimates for total THM (TCM and BDCM) and total HAA (DCAA, TCAA and BCAA) for infants (<0.5 years), toddlers (≥0.5 years to 5 years) and adults (≥20 years). As only those previous compounds were detected in the studied network, calculations were performed for those specific DBPs. Exposure through ingestion was calculated for TCM, BDCM, DCAA, TCAA and BCAA whereas exposures through dermal absorption and inhalation were estimated for TCM and BDCM. Exposure estimates for each compound and for each pathway were calculated using MCS and all weekly concentrations for the months of June, July, and August (N=12). The total exposure for each group of DBPs is the sum of each exposure for the different pathways and for the different compounds. Results are detailed in the Supplementary information section

(Annexe 2 - Table 21 and Table 22) in terms of 25th, 50th and 75th percentiles to illustrate the ranges of values for each compound and pathway for the calculated exposures.

Ingestion, dermal absorption, and inhalation are the primary routes of exposure to THM_4 while oral intake is considered the major pathways of exposure to HAA_6. Ingestion is the main contributing pathway to the total absorbed dose for all groups, followed by inhalation and dermal absorption. These latest pathways of exposure are considered relevant only for THM_4 which tend to decrease exposure to non-volatile HAA_6 (Xu, Mariano et al. 2002, Xu and Weisel 2003). Results are in accordance with previous studies (Buteau and Valcke 2010).

Mean THM_4 total exposures for the entire population served by the network were of 9.52E-03 ± 1.61E-03 mg/kg*d for infants, 4.60E-03 ± 7.85E-04 mg/kg*d for toddlers, 1.92E-03 ± 3.23E-04 mg/kg*d. As presented in Table 15, R11 exhibited the highest total THM exposure (median) among infants, toddlers, and adults: 1.17E-02 (infants), 5.33E-03 (toddlers), 2.27E-03 mg/kg/d (adults). R8 also demonstrated similar results. For HAA_6, median total exposures were of 4.23E-03± 7.94E-04 mg/kg*d for infants, 1.91E-03 ± 3.57E-04 mg/kg*d for toddlers, 7.38E-04 ± 1.52E-04 mg/kg*d for adults. A maximum exposure level of 5.33E-03 was found for infants, 2.19E-03 for toddlers, and 9.40E-04 for adults for R9, located close to rechlorination station and having an estimated hydraulic residence time between 16h and 24h (Table 15). Infants showed the highest subchronic exposure, followed by toddlers and adults. Indeed, infants and toddlers have the highest water ingestion rate by weight (e.g. infants: 0.10 L/kg*d, toddlers: 0.04 L/kg*d, adults: 0.02 L/kg*d) compared to adults, leading to a higher exposure by weight. This is in accordance with previous works from Haddad et al. (2006) and from S. Buteau and M. Valcke. (2010) (Haddad, Tardif et al. 2006, Buteau and Valcke 2010).

*Table 15: Median subchronic exposure estimates for total THM (TCM and BDCM) and total HAA (DCAA, TCAA and BCAA) for infants, toddlers, and adults (mg*kg/d). Results in bold correspond to highest values.*

		Total exposure THM_4			**Total exposure HAA_6**		
	Estimated residence times (h)	<0.5 years	0.5 – <5 years	20+ years	<0.5 years	0.5 – < 5 years	20+ years
R1	0-<4	7.24E-03	3.33E-03	1.43E-03	3.43E-03	1.44E-03	6.16E-04
R2	≥4 - <12	7.88E-03	3.66E-03	1.54E-03	4.79E-03	2.00E-03	8.67E-04
R3	≥4 - <12	7.75E-03	3.65E-03	1.51E-03	4.28E-03	1.82E-03	7.73E-04
R4	≥4 - <12	9.07E-03	4.25E-03	1.77E-03	5.14E-03	2.13E-03	9.35E-04
R5	≥12 - <16	8.22E-03	3.88E-03	1.63E-03	4.30E-03	1.82E-03	7.92E-04
R7	≥12 - <16	8.65E-03	3.95E-03	1.67E-03	3.90E-03	1.66E-03	7.19E-04
R12	≥12 - <16	8.83E-03	4.04E-03	1.71E-03	4.53E-03	1.89E-03	8.26E-04
R6	≥16 - <24	1.08E-02	4.97E-03	2.10E-03	3.84E-03	1.62E-03	6.91E-04
R8	≥16 - <24	1.17E-02	5.28E-03	2.27E-03	3.39E-03	1.44E-03	6.24E-04
R9	≥16 - <24	1.01E-02	4.54E-03	1.95E-03	**5.33E-03**	**2.19E-03**	**9.40E-04**
R10	≥16 - <24	1.12E-02	5.16E-03	2.21E-03	3.96E-03	1.61E-03	6.99E-04
R11	≥16 - <24	**1.17E-02**	**5.33E-03**	**2.27E-03**	2.09E-03	9.02E-04	3.76E-04

In terms of total absorbed doses, TCM contributed the most to total exposure, primarily due to its presence at high levels and because it can be absorbed through ingestion, dermal absorption, and inhalation. The results of this study are comparable in terms of order of magnitude to previous results obtained in the Province of Quebec, where median absorbed doses for chloroform concentrations were estimated to be of 5.08E-03, 2.40E-03, and 1.14E-03 respectively for infants, toddlers, and adults (medians, scenario 1) (Buteau and Valcke 2010). This scenario is based on the THM_4 concentrations of all samples collected in Quebec during the month of July through October. Based on scenario 2 (MCS using only concentrations that exceeded 80 µg/l), Buteau and Valcke (2010) reported median values of 1.87E-02, 9.10E-03, and 4.29E-03 for infants, toddlers, and adults, respectively.

Figure 15 and Figure 16 present on how spatial variability impacts total exposure to THM_4 and HAA_6, for infants as an example. CDFs are represented for different areas in the distribution network (nearest point to the plant: R1, intermediate points between the plant and the extremities: R4, R7, R12, and the most remote points from the plant: R8, R10,

R11). Results for total THM showed a difference of 56% between the closest point to the plant and the end of the network (for a probability of 0.9), while results for total HAA indicated a difference of 69% between the extremity and the center (for a probability of 0.9). As additional information, Figure 24 and Figure 25 (presented in the Supplementary Information section) exhibit Kruskal-Wallis tests to evaluate statistical differences between different parts of the networks (closed point from the plant: R1, intermediate distance from the plant and furthest point in the network – R11) .

Due to lower concentrations of THM_4 at the beginning of the distribution network (R1), and lower levels of HAA_6 at the end of the distribution network (R11), there is a lower total absorbed doses at the beginning for THM_4 (R1) and at the end of the distribution network for HAA_6 (R11). Regardless of the sampled location, THM_4 exposure was always higher than HAA_6 exposure due to the contribution of other pathways of exposure such as inhalation and dermal absorption, in addition to the lower HAA_6 concentrations than THM_4 levels, for most samples.

Furthermore, the results of this study also revealed that total population exposure to both families is greater in the middle of the network/end of the network (R9, R10) where both the THM_4 and HAA_6 levels are higher, thus contributing to the total exposure. Those two locations are located downstream of rechlorination stations where DBP formation may increase depending on several environmental conditions (e.g. chlorine doses, pH, temperature) (Tian, Guo et al. 2017).

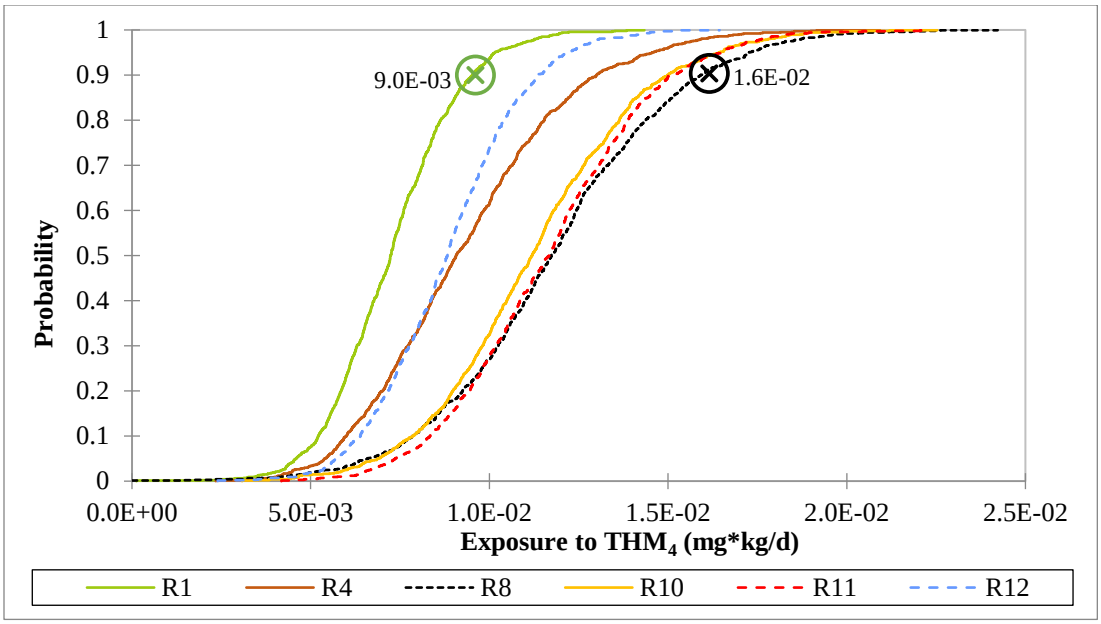


Figure 15 : Cumulative CDF exposure for total THM (BDCM+TCM) for the months of June, July, and August. R1: locations with estimated residence times between ≥0 and <4h, R4: locations with estimated residence times between ≥4 and <12h, R7, and R12: locations with estimated residence times between ≥12 and <16h, R8, R10, R11): locations with estimated residence times between ≥16 and <24h. Results are presented for infants.

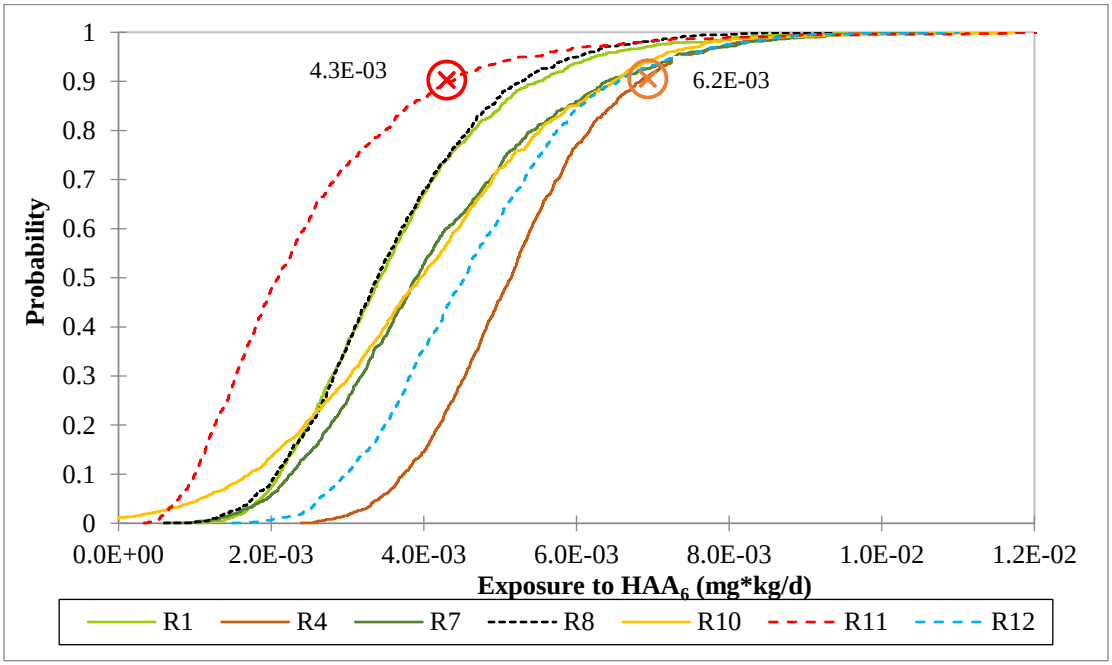


Figure 16: Cumulative CDF exposure (DCAA, TCAA, BCAA) for the months of June, July, and August. R1: locations with estimated residence times between ≥0 and <4h, R4: locations with estimated residence times between ≥4 and <12h, R7, and R12: locations with estimated residence times between ≥12 and <16h, R8, R10, R11): locations with estimated residence times between ≥16 and <24h. Results are presented for infants.

5.3.4 Comparison between subchronic non carcinogenic risk calculated using weekly sampling, quarterly means, and monthly sampling (1st week, 2nd week, 3rd week and 4th week).

Following spatial comparisons of total THM_4 and HAA_6 exposure, further calculations have been performed to evaluate the effect of the sampling method and temporality on estimated subchronic toxicological risk. In this comparison, we aimed to understand the differences in risk estimates resulting from sampling occurring only on a monthly basis as opposed to weekly sampling, and from calculations based on quarterly data. The monthly sampling tends to simulate if a water operator would sample on the same week (1^{st}, 2^{nd}, 3^{rd}, 4^{th}) for the month of June, July, and August based on our data.

For risk calculations, TCM has been taken as a model compound as subchronic RfD have been defined for each pathway of exposure (ingestion, inhalation, and dermal absorption). Public health and environmental organizations have not developed an RfD specifically for short-term exposure to HAA_6, and to the best of our knowledge, all available reference doses are intended for acute or chronic exposure. Risk assessment for subchronic exposure to a defined compound cannot be conducted using chronic or acute RfD because toxicological values representative of critical endpoints for the specific exposure duration are required (Table 14). Additionally, TCM remains the compound with the greatest contribution to THM and HAA exposure in terms of mass concentrations.As a means of illustrating the difference between these methods of estimating exposure and risk for TCM, we examined infant data, since this vulnerable group has demonstrated the greatest exposure to DBPs.

Using the weekly calculation approach, higher mean TCM risks for infants were found for R8, R10 and R11 with risk quotients of respectively 0.096, 0.095 and 0.095 and with maximum values of 0.213, 0.212 and 0.203. With median and maximum risk quotient values of 0.057 and 0.126, R1 (the location closest to the plant) had the lowest risk quotients. Therefore, infants living farther away from the plant are at a greater risk than those living closer.

In order to determine the likelihood of a random variable, both probability density functions (PDFs) and cumulative distribution functions (CDFs) can be used. For the

purpose of allowing adequate comparisons between the different approaches (1- weekly sampling, 2-quarterly means, and 3-monthly samplings), all input determinist and probabilistic data remained constant except TCM concentrations (expressed in µg/L). Figure 17, Figure 18, Figure 19, Figure 20 show cumulative density functions for all twelve locations grouped by hydraulic residence times. Probability density functions are also provided in this section. For all sampling points, CDFs generated indicate that the estimated risks differ depending on the method of calculation used.

There is no clear tendency for monthly sampling, where no specific week would underestimate or overestimate subchronic risks for every twelve points. In fact, monthly sampling performed every fourth week of June, July, and August tends to overestimate risk estimates in comparison with weekly sampling for R4, R7, R12, R6, R8, R9, R10, and R11. However, for the remaining points, it tends to be comparable or underestimated. When compared to the approach using weekly concentrations, it can be observed that monthly sampling performed during each first week along the summer season would underestimate subchronic risks (Figure 17 - R1, R2, R3, R4 and R7, R12 - Figure 18 and Figure 19 - R9). For instance, for R7, there is a probability of 80% of having TCM subchronic risks equal or below 0.09 (weekly sampling) while this risk is below or equal to ~0.07 (monthly sampling – 1st and 3rd week) and of 0.10 (monthly sampling - 4th week). As for R_4, there is a probability of 80% of obtaining risk estimates lower than or equal to 0.08 (2nd week), 0.11 (4th week), and 0.096 (weekly sampling). Specifically for this location, maximum values of subchronic risks are of 0.126, 0.117, 0.094, 0.118, 0.109 and of 0.105 respectively for weekly sampling, for quarterly mean, monthly sampling (1st week), monthly sampling (2nd week), monthly sampling (3rd week) and monthly sampling (4th week). Maximums for weekly sampling are higher than for other calculation approaches as it takes into to account the weekly variability of THM_4 and HAA_6 concentrations and thus considers all exposure derived from higher concentrations.

Figure 21 represents the percentage differences between means of TCM subchronic risks calculated using weekly sampling compared to quarterly means and monthly samplings (1st, 2nd, 3rd, and 4th week). There was the greatest underestimation (%) in R1 and R3 during the first and third weeks, meaning that higher concentrations were found at those locations

during those weeks. Interestingly, locations with higher hydraulic residence times such as R11, where TCM formation would tend to be higher along the season, did not exhibit the greatest differences from weekly sampling. Because higher TCM levels are frequently encountered thus it may not affect the difference with weekly sampling and the incorporation of peaks in the calculation method.

The previous results demonstrated that as TCM concentrations fluctuate from week to week depending on raw water quality and treatments/operations at the plant and throughout the network (e.g. rechlorination stations and reservoirs), the choice of sampling at week 1, week 2, week 3, or week 4 may influence the evaluation of subchronic risks. At specific locations and weeks, it can be seen that there is either an underestimation or an overestimation of subchronic risks. As a result, weekly sampling that better capture this variability would be the more suitable sampling method for conducting a proper short-term risk assessment. Furthermore, as also brought by Parvez et al. (2011), the use of quarterly means doesn't provide enough information for DBPs risk assessment considering this short-term variability (Parvez, Rivera-Núñez et al. 2011). The approach taking into consideration short-term spatial and temporal variability may be important to consider if higher concentrations have a greater effect than average levels in producing adverse health outcomes. The averaging of doses for developmental toxicity endpoints would not be recommended and may only be appropriate when variation in exposure occurs within a narrow range (Haber, Sandhu et al. 2016). Furthermore, when the substance is administered during the critical period during pregnancy, teratogenic effects can occur after a single exposure (Van Raaij, Janssen et al. 2003). This is particularly true for brominated THM_4 and HAA_5 having higher subchronic toxicity than TCM as described in Table 14: Toxicological values for carcinogenic and subchronic non carcinogenic risk assessment (BDCM, ingestion, RfD: 8×10^{-3} mg/kg-day, endpoint: significantly increased incidence of full litter resorption). However, due to the lack of subchronic RfDs for those compounds and respective pathways, risk assessment has not been performed.

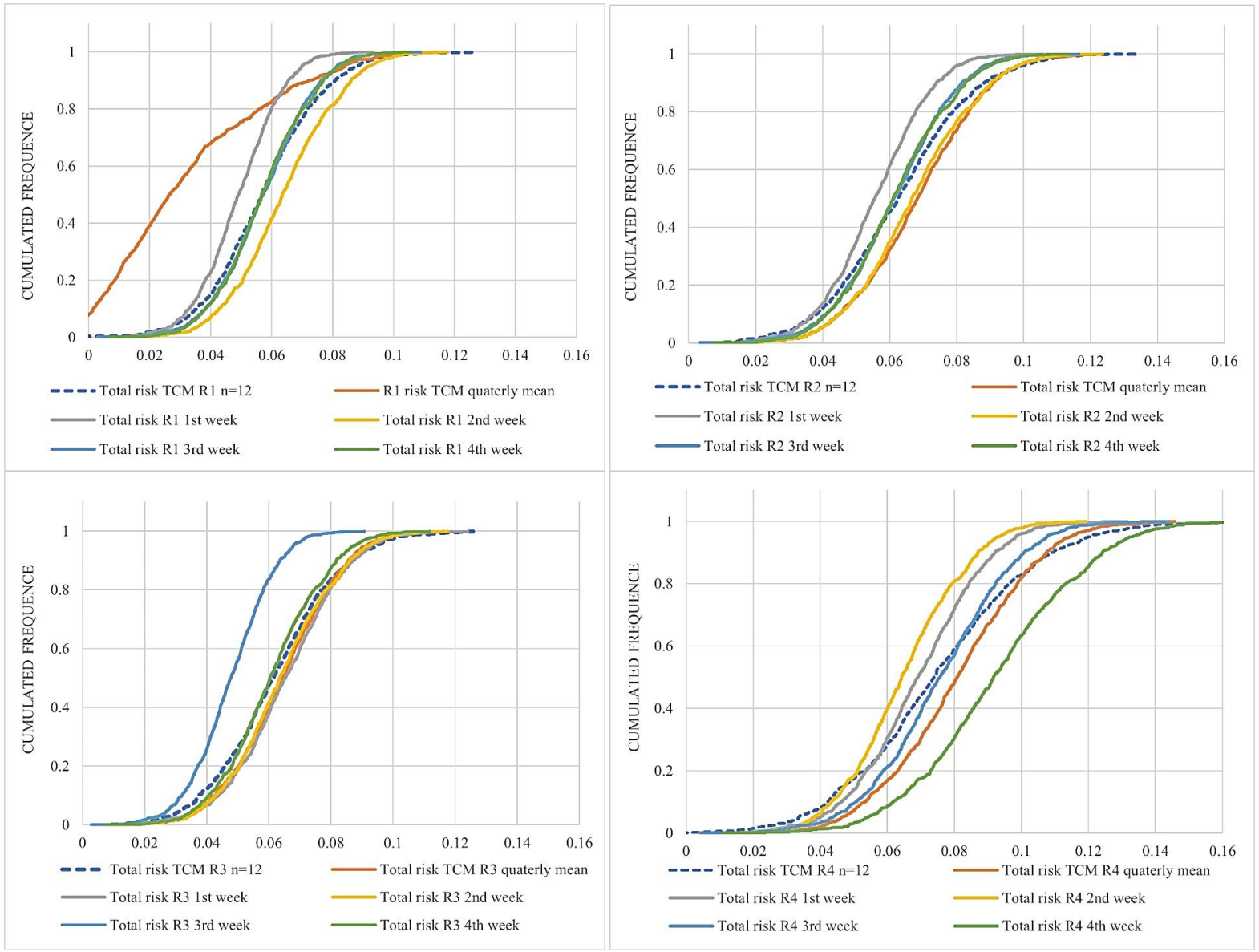


Figure 17 : Comparison of TCM estimated risks distribution for R1, R2, R3 and R4 (HRT: 0-4h; 4-12h). Cumulative probability functions were generated for the following scenarios: 1) using the whole dataset (n=12, weekly sampling), 2) using quarterly mean, 3) using the first week of each month (monthly sampling, n=3), 3) using the second week of each month (monthly sampling, n=3), 3) using the third week of each month (monthly sampling, n=3), 3) using the fourth week of each month (monthly sampling, n=3)

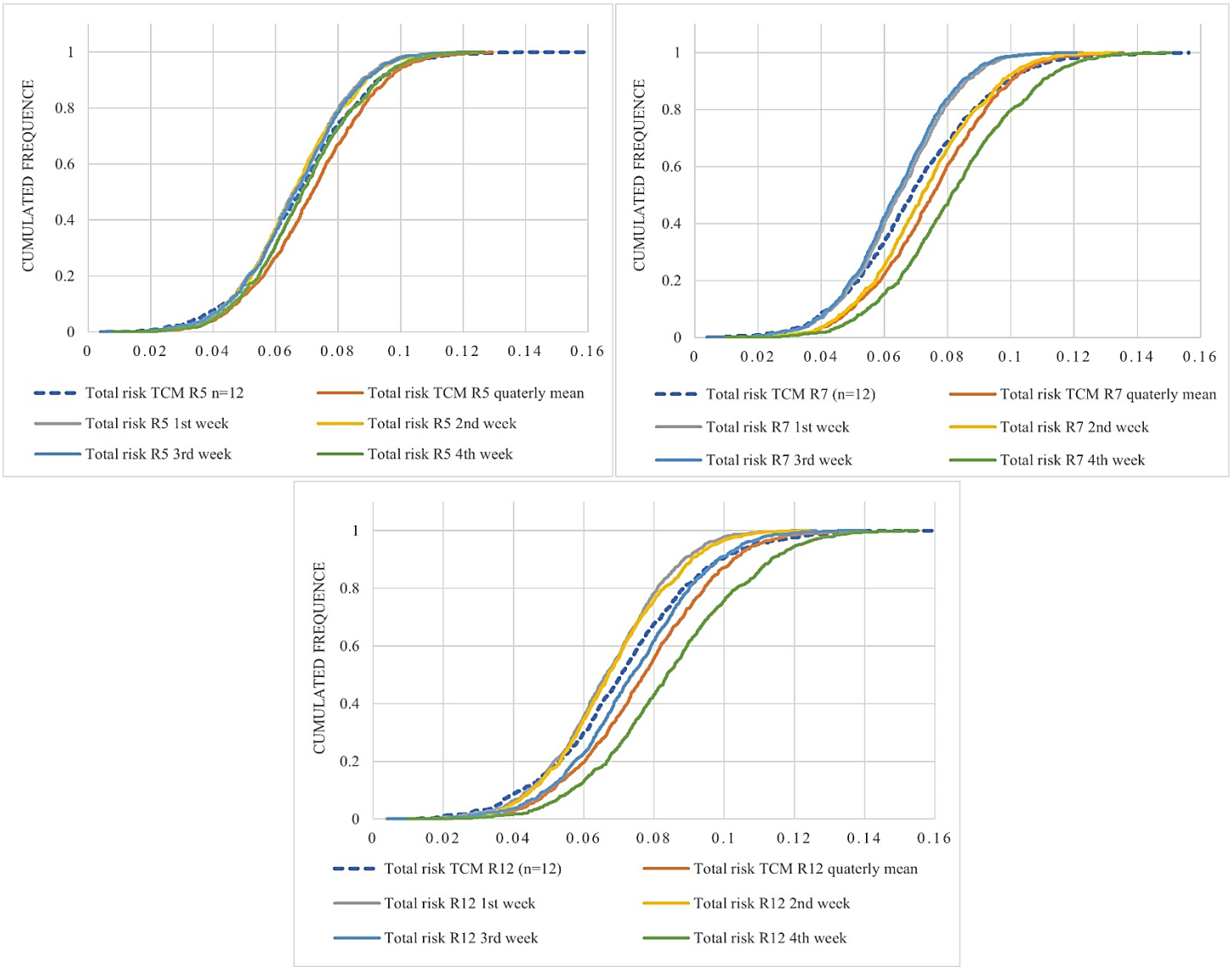


Figure 18 : Comparison of TCM estimated risks distribution for R5, R7, R12 (HRT: 12h-16h). Cumulative probability functions were generated for the following scenarios: 1) using the whole dataset (n=12, weekly sampling), 2) using quarterly mean, 3) using the first week of each month (monthly sampling, n=3), 3) using the second week of each month (monthly sampling, n=3), 3) using the third week of each month (monthly sampling, n=3), 3) using the fourth week of each month (monthly sampling, n=3)

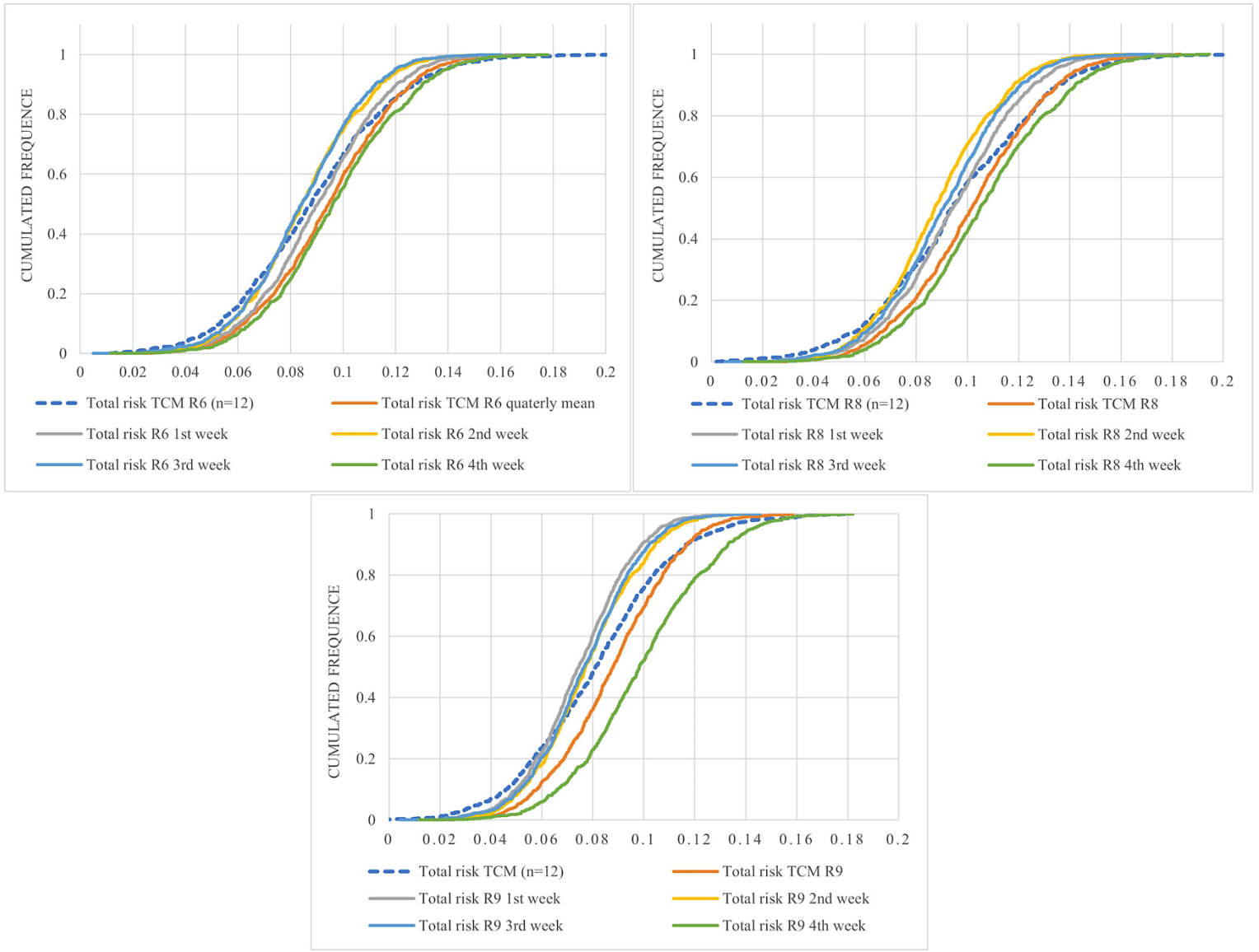


Figure 19 : Comparison of TCM estimated risks distribution for R6, R8, R9 (HRT: 16h-24h). Cumulative probability functions were generated for the following scenarios: 1) using the whole dataset (n=12, weekly sampling), 2) using quarterly mean, 3) using the first week of each month (monthly sampling, n=3), 3) using the second week of each month (monthly sampling, n=3), 3) using the third week of each month (monthly sampling, n=3), 3) using the fourth week of each month (monthly sampling, n=3)

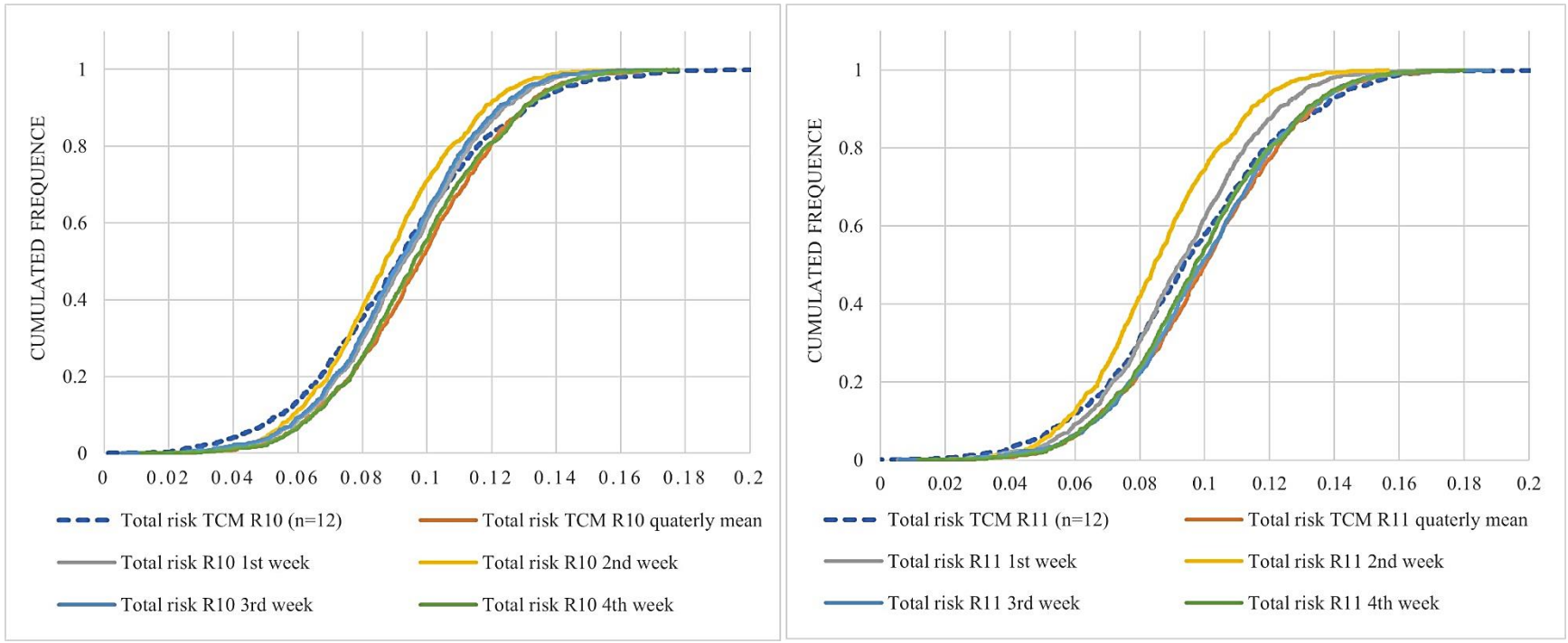
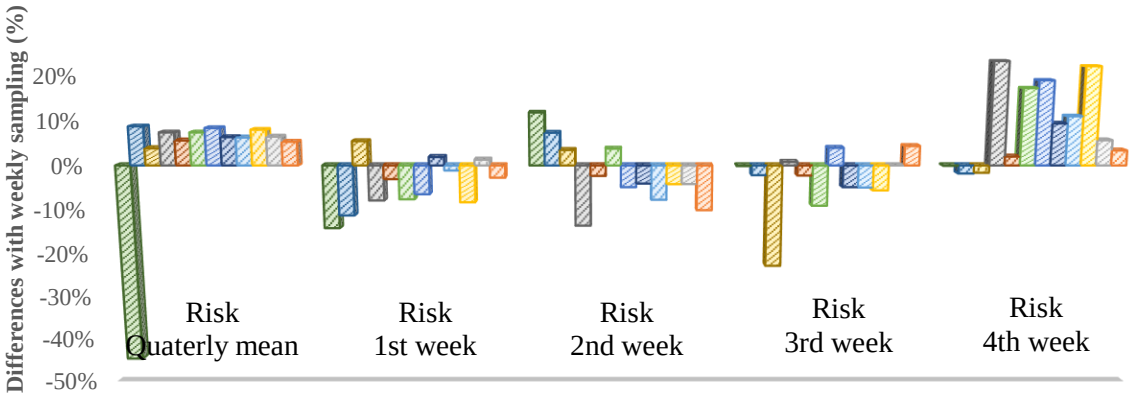


Figure 20: Comparison of TCM estimated risks distribution for R10 and R11 (HRT: 16h-24h). Cumulative probability functions were generated for the following scenarios: 1) using the whole dataset (n=12, weekly sampling), 2) using quarterly mean, 3) using the first week of each month (monthly sampling, n=3), 3) using the second week of each month (monthly sampling, n=3), 3) using the third week of each month (monthly sampling, n=3), 3) using the fourth week of each month (monthly sampling, n=3)



R1	-45%	-14%	12%	0%	0%
R2	9%	-11%	7%	-2%	-2%
R3	4%	5%	3%	-23%	-2%
R4	7%	-8%	-14%	1%	23%
R5	6%	-3%	-2%	-2%	2%
R7	7%	-8%	4%	-9%	17%
R12	8%	-6%	-5%	4%	19%
R6	6%	2%	-4%	-5%	9%
R8	6%	-1%	-8%	-5%	11%
R9	8%	-8%	-4%	-6%	22%
R10	6%	1%	-4%	0%	6%
R11	5%	-3%	-10%	4%	3%

R1 R2 R3 R4 R5 R7 R12 R6 R8 R9 R10 R11

Figure 21 : Percentage differences between means of TCM risks calculated using the whole dataset (weekly sampling) and using the other approaches: 1) using quarterly mean, 2) using the first week of each month (monthly sampling, n=3), 3) using the second week of each month (monthly sampling, n=3), 4) using the third week of each month (monthly sampling, n=3), 5) using the fourth week of each month (monthly sampling, n=3).

5.3.5 Sensitivity analysis

Sensitivity analyses were conducted to understand the impact of each input variable on the outcome (subchronic risk estimates) and therefore the uncertainty related to this estimation (Figure 22). Among the factors contributing to TCM subchronic risk, TCM concentration (36.5%) is ranked highest, followed by the dermal permeability coefficient "K_p" (12.7%). As expected, TCM concentrations play a crucial role in estimating the TCM risks for infants. There is substantial variation in the estimation of the K_p coefficient at 25°C, with values of 0.015-± 0.019 for TCM, which may explain its contribution to the outcome.

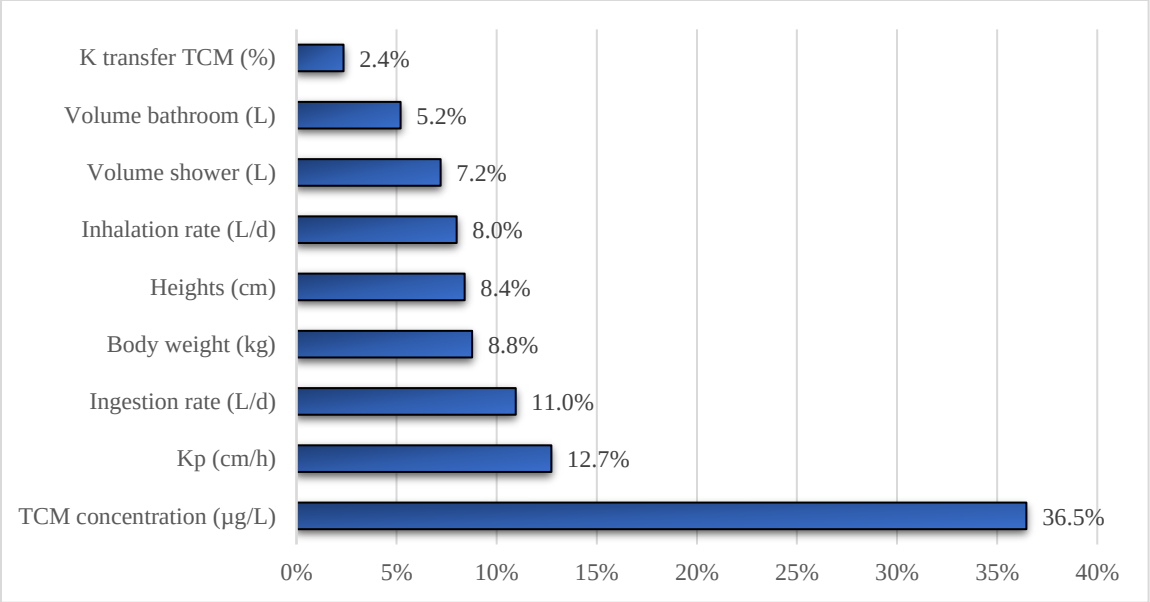


Figure 22: Contributions (absolute values, mean for all data points) of each input parameter in the Monte-Carlo simulations for the estimation of TCM risk (weekly concentrations).

5.4 General discussion

To the best of our knowledge, this is the first time that MCS were used to compare exposure estimated with quarterly means, monthly means to exposure calculated using weekly concentrations during months where temporal and spatial variability is known to occur. Moreover, a spatial assessment of exposure and risk has been conducted, and the results indicate that population exposure varies greatly among networks and is not uniform. There is a clear difference between exposure levels for regulated DBP in different locations, which is critical from an epidemiological point of view.

The main strength of this study is the high frequency sampling approach as it allows the evaluation of whether a dataset with higher sampling frequency can minimize exposure misclassification, as well as the extent to which exposure misclassification might occur. A valid assessment of exposure to DBP remains dependent on a comprehensive characterization of the temporal and spatial variability.

Subchronic risk assessment has been conducted for TCM as subchronic toxicological values were defined for the three different pathways. It is worth noting that all risk quotients were below one for infants, indicating that subchronic exposure to TCM are likely to be without appreciable risk of noncancer health effects. However, exposure and DBPs risk

assessment via chlorinated water remains complex as DBPs are present as a mixture with varying levels of brominated THM_4 and HAA_6 and emerging and unknown DPBs. To be complete, risk assessment would require subchronic toxicological values for all relevant pathways for the detected compounds. The development of subchronic RfD for short-term exposure is a crucial knowledge gap and a limitation for an improved DBPs risk management that incorporates peaks of exposure during summer.

One source of uncertainty in DBP risk assessment is the variability of DBP exposure metrics over time (Figure 22). As such, short-term temporal variability during the summer months may play a key role in studies that attempt to relate health outcomes where peaks of exposure are of primary importance (e.g., reproductive, and developmental effects). Results from this study in terms of seasonality are comparable to other studies that report higher concentrations during the summer and temporal and spatial fluctuations within networks (Rodriguez, Vinette et al. 2003, Chang, Tung et al. 2010, Parvez, Rivera-Núñez et al. 2011, Parvez, Frost et al. 2017). Furthermore, results from simulations may be less representative if the frequency of sampling does not enable to capture all fluctuations and higher concentrations. Indeed, as THM_4 and HAA_6 fluctuates over days and weeks, a high sampling frequency would also be needed for a risk assessor to have the most accurate exposure assessment as possible. This would particularly be relevant in contexts that favor the formation of brominated THM_4 and HAA_6, known to be more toxic than non brominated THM_4 and HAA_6 (Richardson, Plewa et al. 2007, McTigue, Cornwell et al. 2014) .

The study makes a few assumptions and hypotheses that may contribute to underestimation or overestimation of exposure. First, we calculated DBPs levels during the summer using a weekly sampling methodology, where concentrations are assumed to remain constant during the week and to reflect weekly levels. Even though this weekly sampling allows a better estimate of the population's exposure to DBPs, it cannot describe shorter variations (within-day) or variations between days that may be impacted by weather conditions. (Catto, Rodriguez et al. 2010, Kogevinas, Villanueva et al. 2010, Catto, Charest-Tardif et al. 2013, Delpla and Rodriguez 2017).

Furthermore, the concentrations of THM_4 were measured in cold water, after a 5 min flush, taken from the distribution system, however, this may underestimate the concentrations of THM_4 in hot water at home and the overall intake since temperature increase promotes the formation of THM_4 (Buteau and Valcke 2010). Several studies demonstrated differences between cold and hot water DBP levels for THM_4 and HAA_6 (Liu and Reckhow 2013, Liu and Reckhow 2015, Legay, Leduc et al. 2019). Previously conducted research has also demonstrated that the level of chlorinated DBPs in water may vary from the moment it enters the residence to the point of exposure, leading to differences or variations in the level of indoor exposure. Handling strategies such as tap water filtration, storage in uncovered pitcher and boiling water are examples of domestic practices that may lead to fluctuations of indoor exposures (ingestion) (Levesque, Rodriguez et al. 2006). Moreover, THM_4 and HAA_6 concentrations are known to increase when water stagnates in domestic pipes but also in hot water tanks where the latest may impact absorbed DBPs levels during shower or baths (Dion-Fortier, Rodriguez et al. 2009).

Water uses, quantities and activities (e.g. number of showers per day, outdoor activities, increased volumes of water ingested) may be impacted by seasonality and warmer temperatures. According to a survey conducted in Portland between 2001 and 2005, households consume 1,164 L/d during the summer, compared to 642 L/d in the winter (N=460) (Straus, Chang et al. 2016). Moreover, indoor, or outdoor swimming is known to be a route of exposure to DBPs that is not negligeable, and which contributes to increasing DBP daily uptake for individuals (Nieuwenhuijsen, Toledano et al. 2000, Whitaker, Nieuwenhuijsen et al. 2003, Villanueva, Cantor et al. 2007, Tardif, Catto et al. 2016, Font-Ribera, Marco et al. 2019). The exposure scenario only takes into consideration domestic exposure to DBPs which doesn't consider other activities or behaviors such as swimming or ingestion of other tap water (e.g. outside the house) or bottled or household treatments. However, our sampling mainly focused on assessing spatial and temporal variability of THM_4 and HAA_6 in a distribution network and assessing exposure from swimming was beyond the scope of this study. This difference in water uses in the summer season may have an impact on the estimation of subchronic exposure during the months of June, July, and August.

Calculations of exposure for infants were performed using the case of infants exclusively bottle-fed with formula as the most extreme case scenarios for water consumption in terms of body weight. Considering formula-fed infants is relevant as they are more exposed to water contaminants (on a body weight basis) on a greater scale than adults and are more sensitive to toxic chemicals commonly found in tap water (Levallois, Gingras et al. 2008). Ingestion rates for infants bottle-fed with milk formula (8 weeks) may be different from breastfed infants.

It is known that THM_4 are volatile compounds whose concentrations may not be constant over time. Therefore, the estimated dose of THM_4 absorbed through the skin may be overestimated since we assumed the concentrations of THM in bath water did not vary during the bathing period. Even though the showering and bathing durations were derived from a real dataset from environmental studies, these durations represent a major source of uncertainty since they may vary widely among individuals. Moreover, it is important to consider how tap water is consumed, as volatilization by heating leads to a reduction in chloroform levels. The concentration of chloroform in water can be reduced by 85% in hot beverages (Batterman, Huang et al. 2000, Whitaker, Nieuwenhuijsen et al. 2003).

5.5 Conclusion

As a result of the observed temporal variability in DBP exposure, it is imperative that more robust data collection and methods specific to DBPs be developed to increase the accuracy of exposure assessments where populations tend to be unevenly exposed to THM_4 and HAA_6 with varying levels. The subchronic exposure to those compounds varies also spatially where for instance, inhabitants at the end of the distribution network will demonstrate higher exposure compared to those at the beginning of the network. Developing epidemiological studies that investigate health outcomes resulting from short critical periods of exposure can be challenging (e.g. reproductive and developmental effects), as spatial and temporal variability can make it difficult to assess exposure in a complex system such as a supply network, which may cause the true exposure to be misclassified.

6 Discussion

As early as the 1970s, evidence began to accumulate that there may exist a trade-off between the elimination of pathogens and the protection of public health afforded by chlorination and the concomitant generation of DBPs. First reported by Rook in 1974, the first DBPs to be identified in chlorinated water were chloroform, bromodichloromethane, dibromochloromethane, and bromoform (Rook 1974). A few epidemiological studies in the 1950s and 1960s found that deaths due to cancer were more elevated in zones supplied by surface water than for areas served by groundwater. As surface water shows usually more organic matter content, these findings suggested that contaminants neither present nor generated in groundwater but present in surface water increased the risk of cancer (DeMarini 2020). Since those decades, DBP research has highly developed covering various topics including identification of DBPs precursors, development of analytical chromatographic methods, identification and occurrence of organic and inorganic DBPs, epidemiological and toxicological evidences, and technologies testing and development for DBP removal (Tang, Long et al. 2020).

The evidence of seasonal THM_4 and HAA_6 levels was reported in 1997 in Canadian supply systems where lower and higher levels were observed during the winter and summer seasons, respectively (Williams, LeBel et al. 1997). Ever since, numerous studies have confirmed the temporal and spatial variability of DBPs in temperate climates, however too few studies have investigated their intra-seasonality variability and their impact on exposure and risk assessment. Due to the low density of mandatory sampling in the Canadian and American regulatory frameworks, it is not possible to adequately characterize and assess subchronic exposure to THMs and HAAs. Indeed, utilities may conduct only one or a few samplings during the warmer months depending on the size/population of the supply system (Direction de l'eau potable et des eaux souterraines 2019). Regulatory sampling is the primary source of information regarding DBP occurrence for many utilities, especially those that serve small to medium-sized municipalities with relatively few financial, human, and technical resources. Considering this lack of information during summer and because risks may be higher due to this effect of seasonality, further knowledge was necessary.

6.1 Main findings of this dissertation

This dissertation provides insight on the spatial and temporal behavior of regulated DBPs over warmer months in a complex hydraulic system such as a distribution network. Based on the evidence presented in Chapter 2 and Chapter 3, THM_4 and HAA_6 exposure in drinking water varies significantly throughout the system, making risk assessment in such context highly challenging (Chapter 3). It is therefore essential to examine all network characteristics and possible areas that may lead to spatial variability. Also, it was found that temporal variability is more prevalent during warmer months, and that quarterly means cannot represent accurately the temporal variations of THM_4 and HAA_6. (Chapter 3). There follows a summary of the main findings and limitations of this dissertation, as well as some ideas of future research needs in the field of DBP.

Manuscript 1 raised two major concerns related to higher and repeated exposures: 1) what are the impacts of exceeding chronic values over a lifetime? and 2) what are the health effects of exposing individuals to months of subchronic exposure that can exceed short-term health-based values? Health Canada has set a chronic guidance for THMs based on a health-related target of 80 µg/L (based on chloroform health effects, increased to 100 µg/L for feasibility reasons in the guidance) (Health Canada 2006). Nonetheless, it is not certain whether repeated exceedances along the years with such DBP variability may still meet this annual standard each year. In addition, there is also a lack of subacute or subchronic health-based values developed by environmental and public health organizations. This is more critical for haloacetic acids where from the best of my knowledge, no short-term HBVs have been developed. Several HBVs have been established for THMs, but none covers all relevant pathways, and such guidances are available primarily for ingestion (Chapter 3 - Table 14: Toxicological values for carcinogenic and subchronic non carcinogenic risk assessment). Hence, this raises the question of how to interpret risk to human health when a chronic health-based limit is exceeded, as well as how to interpret short-term and higher concentrations of chemicals in chlorinated water (Chapter 1).

Moreover, this dissertation suggests that we should rethink our idea of repeated high exposure levels during warmer months. Those repetitive exposure could be regarded as less-than-a-lifetime exposure, where peaks may appear annually for the remainder of one's

life. A few papers detailed methodologies for less-than-a-lifetime exposures to carcinogens and non carcinogens (including short-term, peak and/or intermittent exposures) which could be applicable to some regulated DBPs and emerging DBPs (Felter, Conolly et al. 2011) (Geraets, Nijkamp et al. 2016) (Bos, Baars et al. 2004, Haber, Sandhu et al. 2016). Geraets et al. (2016) noted that because of their particular modes of action, where one exposure can trigger effects, compounds having genotoxic carcinogenic effects and developmental effects might require specific considerations (Geraets, Nijkamp et al. 2016). Developmental toxicity, for example, is considered an acute endpoint if any adverse effects on fetuses or offspring have resulted from exposure at any stage of development during the treatment (OECD 2008). Because of those suspected reproductive and developmental effects, DBPs peaks should be investigated and treated differently from the baseline exposure.

One key element in those methodologies is the notion of internal doses and potential accumulation which depends in particular on the elimination half-life. The elimination half-life should be regarded considering 1) the duration of an intake or exposure above a health-based limit value and 2) the time interval without exposure or the time interval with exposure though below a health-based limit value. When evaluating the potency of an accumulation of a particular chemical, four to five times its elimination half-life is typically used as a cut-off point (Geraets, Nijkamp et al. 2016). As mentioned in Chapter 1, the estimated elimination half-lives of TCM, BDCM, DBCM, and TBM are respectively of 2.5h, 28.4h, 37.6h, and 54.3h, which give little time for completing elimination specifically for brominated compounds. Depending on the mode of action and the compounds toxicokinetic and toxicodynamic, it may affect the dose at the target organ.

In addition to the topics discussed in Chapter 1, the definition of standards for THM_4 should not rely exclusively on TCM health effects. The rationale adopted by Health Canada is based on two points: 1) scientific evidence, since TCM is the THM_4 for which the most scientific data exist, and 2) its occurrence, because it is the predominant THM_4 in drinking water. Although those arguments are valid, the second argument is not applicable in all circumstances as speciation of THM_4 will be dependent on halogens content in raw water (e.g. bromine, iodine). For instance, bromine-containing water (e.g. some sources of

groundwater, freshwater affected by seawater intrusion, industrial activities) may form more toxic brominated compounds than TCM. Guidances should take individual compound toxicity and variability into consideration rather than relying on TCM since BDCM, DBCM, and TBM concentrations may also peak during warmer months under favorable conditions (Chapter 1). It is worth noting that US EPA has developed individual Maximum contaminant level goals (MCLGs) for TCM, BDCM, BDCM, TBM, MCAA, DCAA and TCAA that represent the level of a contaminant below which there is no known or expected chronic risk (non-enforceable). MCLGs recommend a 0 mg/L for BDCM, TBM, DCAA (United States Environmental Protection Agency 2018).

Hence, discussions can be held regarding the current DBPs regulations specifically for foetus, infants and children as developmental and reproductive effects are suspected (Introduction section). A substantial amount of evidence exists concerning early-life sensitivity to chemical exposures and how their physiology (absorption, distribution, metabolism, excretion) differs from that of adults (Felter, Daston et al. 2015). For the reasons brought in the previous paragraphs (e.g. occurrence of peaks of concentration, different speciation of DBPs, difference in toxicity and potential developmental and reproductive effects), the situation may be more critical for utilities having a predominance of brominated THM_4 and HAA_6 in their drinking water.

Manuscript 2 investigated spatial and temporal variability of trihalomethanes and haloacetic acids as well as how alternative techniques can help in preventing higher concentrations of THM_4 throughout the network. In some drinking water systems, there is a seasonal peak of THM_4 concentration during the summer months, but few studies have examined the seasonality of HAA_6 (Rodriguez, Vinette et al. 2003, Rodriguez, Sérodes et al. 2004, Parvez, Rivera-Núñez et al. 2011). In this study, both DBPs groups demonstrated weekly variability with an increase or a decrease of concentrations from week to week. Highest variances were encountered for points having a higher residence time between the middle and the extremities such as R6 (HAA_6, variance: 392.8) and for R10 (THM_4, variance: 426.0). Furthermore, it is more common to find THM_4 levels above regulations/recommendations in locations with longer residence times (R6, R8, R11) and downstream of reservoirs or rechlorination stations (R10). In the meantime, HAA_6

concentrations decreased along the network as previous findings examined the biological degradation of those compounds and transformation into other compounds along the distribution system (Zhang, LaPara et al. 2009, Pluchon, Sérodes et al. 2013, Berthiaume, Gilbert et al. 2014) (Zhang and Minear 2002).

Based on an extensive dataset, a logistic model was developed and presented in Chapter 2 (the probability of exceeding THM at and above 80 µg/L). In addition, a technique referred as incremental differential UV-VIS absorbances has shown promising results as a field technique to predict THM_4 peaks based solely on absorbance differences between finished water and the targeted sampling point (Δ254nm, Δ272nm, Δ350nm and Δ400nm). Best results were found for linear regression models with DUV254nm and DUV400nm as inputs (prediction and validation sets). To the best of my knowledge, it is the first time that such findings were obtained in distribution networks since it has only been successfully validated at benchmark scale (Korshin, Benjamin et al. 2007) (Yan, Korshin et al. 2014, Beauchamp, Laflamme et al. 2018, Beauchamp 2019, Beauchamp, Dorea et al. 2019, Beauchamp, Bouchard et al. 2020, Guilherme and Dorea 2020). There is a great deal of potential in this preliminary investigation that needs to be further investigated. In addition, the incorporation of the variable DUV400nm exhibited slightly better results that the first logit model with respective values of R^2 (McFadden) of 0.54, R^2 (Cox and Snell) of 0.55 and R^2 (Nagelkerke) of 0.67.

Those alternative techniques designed to help water operators have been developed on the whole water distribution network which shows a variety of hydraulic conditions (e.g. difference in hydraulic residence times, presence, or absence of a rechlorination station and a reservoir) and that covers an estimated surface of 292.8 km^2. Moreover, a notable advantage of those site-specific empirical models (logit regression model and incremental differential UV-VIS (Δλ)) is the fact that it makes use of easily accessible explanatory variables to assist stakeholders and operators in anticipating THM_4 peak events during the summer months.

Manuscript 3 examined how exposure to THM_4 and HAA_6 vary spatially throughout middle-sized municipality. Trihalomethanes can be absorbed through ingestion, inhalation, and dermal absorption whereas ingestion is the main pathway of exposure for haloacetic

acids. Infants showed the highest subchronic exposure, followed by toddlers and adults. Due to lower concentrations of THM_4 at the beginning of the distribution network (R1), and lower levels of HAA_6 at the end of the distribution network (R11), there are lower total absorbed doses at the beginning (R1) and at R11. The results from this chapter revealed that population exposure is greater in the middle of the network where both THM_4 and HAA_6 levels are higher, thus contributing to the total intake. As those classes of compounds may trigger different health effects (TCM: suspected hepatic effects, BDCM: reproductive effects or DCAA: carcinogenic effects), epidemiological studies could benefit from its findings regarding which populations should be targeted for specific health outcomes (Toxic Substances and Disease Registry (ATSDR) 1997, Agency for Toxic Substances and Disease Registry (ATSDR) 2011, Agency for Toxic Substances and Disease Registry (ATSDR) 2023).

This study also examined how sampling frequency can impact subchronic risk estimates, as well as the extent to which exposure misclassification might occur. I believe that Monte-Carlo simulations have never been used to compare exposure estimated by quarterly and monthly means to exposure calculated by weekly concentrations when spatial and temporal variability is known to occur. Considering that in Chapter 2 we demonstrated the temporal variability of THM_4 and HAA_6, the difference in risk estimates between monthly sampling and weekly sampling clarifies the importance of sampling time in determining risk estimates. TCM risks were mostly below 0.1 for most sampling points and for infants. Nonetheless, risk related to other regulated DBPs compounds have not been investigated due to a lack of subchronic RfD for all relevant pathways. With TCM accounting for more than 90% of total THM, it would be interesting to investigate whether the same tendency could be detected in other THMs, HAAs, or other emerging compounds that may also exhibit high variability.

6.2 Limitations of this dissertation

In addition to the limitations stated for each chapter, overall limitations related to the study area, methodology, analytical methods, and research process/literature review should be acknowledged. Although this research provides insights on exposure and risk, estimations are specific to our study case and cannot be extrapolated to other networks. Nonetheless,

certain conclusions and observations from this research can be used to refine methods for future studies and helps to define recommendations to adequately assess subchronic exposure to DBPs.

The findings of our case study indicate that trihalomethanes levels exceeded the chronic health-based value of 80 µg/L in this medium-sized Canadian municipality, while haloacetic acid levels did not exceed 60 µg/L. While our primary concern lies with the health of the vulnerable population that may be more impacted by the occurrence of DBPs (Chapter 1), from a strictly regulatory standpoint, it is possible that the Canadian or American/Quebec guidelines of 100 µg/L or 80 µg/L have still been met, since regulations are presented in terms of annual quarterly means. However, the study design did not provide a way to determine if the annual means were below or above regulatory limits. It should be noted, then, that even if the regulations are followed, repeated violations of the chronic regulations still occurred during the summer. There is an additional need to recognize that utilities can differ in many ways, including hydraulic characteristics, water quality, organic matter removal, efficiency of treatment and operations, etc. Therefore, concentrations during warmer months may vary between municipalities and/or may be adequately controlled by operators using mitigation strategies.

The empirical and logistic model described in Chapter 2 is highly reliant on input data and should be used within the limits of each input variable. Moreover, each application within the model's inputs ranges for other utilities should be tested first and validated, because other parameters not evaluated in this dissertation, may affect the accuracy and precision of the model (e.g. bromide ions). We can potentially infer from our research that the treated surface water contained low bromide concentrations since TCM comprised more than 90% of the total THM. However, the bromide concentration has not been determined and it would have been beneficial to validate the contribution of bromide concentrations as input to the model.

There are a few limitations associated with the use of the technique such as incremental UV-VIS absorbances. Due to the fact that this technique relies on spectrophotometry and absorbance changes, modifications in organic matter content or concentration could affect the accuracy of the method. Organic matter may change according to weather (e.g.

temperature, precipitations) and therefore can change the absorption spectrum (Beauchamp, Dorea et al. 2018) (Korshin, Wu et al. 2002). Despite the fact that this approach was calibrated and validated over 18 weeks using samples with different absorbances and weather conditions, it has not been tested for other seasons involving varying levels of DBPs precursors. Moreover, it is unlikely that input values outside the range of those used to calibrate the model would be reliable for predicting outcomes. It is also important to note that the effect of pH and temperature on incremental UV-VIS absorbances have not been tested in this full-scale preliminary investigation. Those parameters are known to affect the yield of DBPs and consequently may impact the relationship between ΔTHM_4 and DUV254nm, DUV272nm, DUV350nm and, DUV400nm (Beauchamp, Dorea et al. 2018).

As brought by Susan Felter & Michael Dourson (1998), *"risk assessment is not an exact science*" and relies on many hypotheses and calculations that could influence the conclusion of a study either related to exposure and to dose-response/toxicological data (Felter and Dourson 1998). Major limitations in exposure assessment, small sample sizes and potential biases may account for inconclusive and inconsistent results. The first limitation in this study is due to temporal variability of DBPs. Taking samples each week may not necessarily provide a complete representation of other peaks during the week or during the day. The levels of DBPs can fluctuate on a daily and weekly basis, as shown by Pereira et al. (2004). Indeed, an analysis of a 1-week sampling period during which samples were taken every six hours revealed a coefficient of variability as high as 31%, with differences between DBPs as well as locations (Pereira, Weinberg et al. 2004).

THM_4 and HAA_6 concentrations and their variability in domestic pipes, hot water tanks, and air were not considered in this dissertation, nor were water uses and water-related activities. Only the main water use activities were included such as drinking and bathing/showering. For this, dishwashing, cooking, and using a washing machine were not accounted for, but they are unlikely to have a significant impact on the total uptake (Whitaker, Nieuwenhuijsen et al. 2003). Although we chose relevant and representative data to assess exposure (e.g. distribution of water consumption among infants, toddlers, and adults), it remains complex to evaluate volatile DBPs, since most exposures result from

inhalation and dermal absorption, which is a function of bathing and showering that can vary from individual to individual. In addition, exposure can be affected by a wide range of subtleties (leaving the bathroom window/door open or closed, bathing children a couple of time per day, washing hands, flushing toilets, etc.).

For water-related activities, it is known that a certain portion of the population practices regular swimming which can greatly impact the overall uptake of DBPs (Chowdhury, Alhooshani et al. 2014). Although we focused on the investigation of domestic subchronic exposures through drinking water, the assessment of exposure from water related activities was beyond the objectives of chapter 3, which examined the contribution of spatial and temporal variability on subchronic exposure across a whole network. The activities carried out outside the house were not evaluated despite the fact that they contribute to the total exposure. It was also assumed that the sample taken at the public location represented households in the same sector as the sample taken at the public location.

Carcinogenic risks were not explored since fluctuations in DBPs levels during the summer could not serve as a representative example of annual exposure and other seasons such as winter. Thus, the design of the five-month sampling campaign (June to October) was inadequate for assessing adequate exposure for carcinogenic risk.

6.3 Research needs and future research perspectives in the DBPs science

The findings and limitations of this study may provide the basis for future research. First, a potential research need would be the validation of the relationship between concentration peaks and incremental differential absorbances for utilities having different raw water quality (e.g. influence of bromide or iodide), using other treatments and for networks with different hydraulic characteristics (e.g. longer residence times). For instance, evaluating this method in utilities with different treatment methods, such as chlorination or chloramination, and with different raw water quality (e.g. pH, organic matter) would be interesting, since both factors might influence the type of DBP that would be formed. Further, testing with other compounds, such as emerging compounds known to be toxic drivers (e.g. acetonitrile), would also be of interest. In order to prevent the occurrence of higher concentrations of DBPs, water utilities might benefit from investigating simple and relatively inexpensive such as incremental differential absorbances.

There would also be a need to generate datasets from other distribution networks to evaluate spatial-temporal variability and estimate subchronic exposure and risks. Comparing the previous results using utility-reported quarterly means would also be interesting to validate the outcomes from this dissertation demonstrating the risks are clearly underestimated. Thus, results could be validated and further documented in other distribution systems with a variety of characteristics (different types of treatment, water quality, hydraulic conditions, and network specificities) that could influence the formation of regulated DBPs. Understanding the factors contributing to subchronic risks will facilitate the identification of potential networks that demonstrate the same factors that could lead to increased population exposure in the future. The level of exposure at the individual level should also be investigated during those months when water is more readily consumed in volume and when exposure through water may be greater. For this, a questionnaire could be developed for a representative sample of the population served by the distribution network to collect specific information on water behaviors and activities in summer. Combining this latest approach with a broad set of data collected from their tap water several times per week, and sampling in both hot and cold water, would provide a more accurate assessment of exposure.

There has been growing evidence of non-cancer toxicity as well as carcinogenic effects for regulatory DBPs as well as emerging DBPs over the course of the past several decades. DBPs' genotoxic potencies in both bacterial and mammalian cells, for example, tend to rank in iodinated, brominated, or chlorinated order as recently found by some authors for HAAs or for non regulated DBPs (Lan, Rahman et al. 2018) (Pérez-Albaladejo, Pinteño et al. 2023) (Cortés and Marcos 2018). The presence of a specific dose for a certain duration of exposure is required for some carcinogens to produce tumors. In the absence of adequate exposure duration, a human cancer risk is unlikely to develop, except in the case of genotoxic compounds (Felter, Conolly et al. 2011). According to experimental animals and theoretical models, the excess cancer risk differs for long to short durations having the same cumulative dose. Therefore, the risk of cancer may be higher from a single and higher exposure to a carcinogen than from the same total dose administered little by little over an extended period of time (Bos, Baars et al. 2004, Geraets, Nijkamp et al. 2016). Considering that populations are exposed to different DBPs and theoretical toxicological models, the

following question can then be asked: what are the consequences of those peaks of exposure on the increased risk of cancer?

Apart from assessing exposure, risk assessment for DBPs remains also complex as various compounds may be present concomitantly which have distinct toxicological profiles with various potential effects and different levels of suspect carcinogenicity. Additionally, aside from the ones detected, most of the TOX remain unknown (Krasner, Weinberg et al. 2006). As a result of this wide variety of compounds that are potentially mutagenic and carcinogenic, the International Agency for Research on Cancer (IARC) placed "disinfected water" on its priority list for the period 2015-2019 (Straif, Loomis et al. 2014). There is a high degree of complexity in the DBP mixtures found in chlorinated water, as the composition of the mixture depends on the specificities of raw water and the treatments and applications (e.g. ozone, chlorine dioxide, chlorine hypochlorite, chloramination). The research work by Simmons et al. (2004) has provided a basis for developing component-based and whole-mixture methods, however, little is known about the toxicological effects of those mixtures and the interactions between substances which can have significant impact on the assessment of risk (Simmons, Teuschler et al. 2004).

7 Conclusion

In the process of disinfection, potentially adverse by-products are generated, known as disinfection by-products. Nonetheless, since water disinfection remains a necessary process, a delicate balance is required between eradicating harmful bacteria (acute risk) and preventing the formation of regulated DBPs (subchronic and chronic risk). Those compounds have a distinct pattern of concentrations in temperate climates, with a slightly fluctuating baseline over the year with higher concentrations in warmer months. Even though Health Canada encourages surface water utilities to increase sampling during when peak times, the majority of utilities in Canada lack the technical, financial, and human resources to conduct more than just the mandatory quarterly sampling.

This thesis was designed to investigate subchronic exposure and risk to regulated DBPs throughout an entire distribution system and to suggest possible solutions through a modeling approach to prevent the emergence of those peaks during summer. In the three chapters of this dissertation, the following contributions addressed the different research questions and objectives. In the first chapter, the reader is provided with a unique insight into DBP monitoring combining different toxicological and technical aspects, leading to reflect on the importance of considering exposures other than chronic exposures, which have undergone the majority of the research. Furthermore, the dissertation contributes to the understanding of short-term temporal and spatial variations of THM_4 and HAA_6, as well as the potential and further application of differential UV-VIS spectroscopy in the network, which is used here for the first time, to estimate peaks of exposure (Chapter 2). Although validation is required in other networks, this dissertation unveils the possibility of using this empirical approach to facilitate the rapid detection of high DBPs concentrations. Moreover, I believe that this is the first time that subchronic exposure/risks have been examined using an extensive dataset in a full-scale network that allows both temporal and spatial variability to be considered, thus refining our current exposure assessment. It also revealed that quarterly means are not good surrogate for representing this variability as subchronic risks are underestimated/overestimated using this monitoring approach (Chapter 3). The results of this study are expected to lead to a more realistic estimation of DBP subchronic exposure and the potential bias associated with it, as well as

documenting a better understanding of DBP complexity in a full-scale distribution network.

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Appendices

Appendix A: Supplementary information (Manuscript 2)

Table 16: 1st quartile, median, 3rd quartile, mean, variance and standard deviation for the 12 sampling points (THM_4)

Sampling points	1st Quartile (µg/L)	Median (µg/L)	3rd Quartile (µg/L)	Mean (µg/L)	Variance	Standard deviation (µg/L)
R1	62.3	67.4	71.1	66.4	147.0	12.7
R2	71.0	73.6	77.2	72.5	172.6	13.7
R3	68.4	72.9	75.0	68.4	230.4	15.9
R4	73.4	82.5	98.3	85.8	568.0	24.9
R5	67.4	75.1	84.9	76.2	122.6	11.6
R6	87.7	99.0	113.9	100.2	514.9	23.7
R7	71.6	83.0	88.8	79.7	212.3	15.2
R8	88.6	107.4	126.1	107.8	496.2	23.3
R9	79.1	93.3	110.5	93.3	522.0	23.9
R10	87.7	98.8	115.3	98.5	335.8	19.1
R11	93.0	108.2	121.3	106.1	422.3	21.5
R12	73.9	83.3	87.6	81.9	226.3	15.7

Table 17:1st quartile, median, 3rd quartile, mean, variance and standard deviation for the 12 sampling points (HAA_6)

Sampling points	1st Quartile (µg/L)	Median (µg/L)	3rd Quartile (µg/L)	Mean (µg/L)	Variance	Standard deviation (µg/L)
R1	28.0	31.5	36.2	34.0	110.8	10.5
R2	22.1	30.9	44.5	33.0	217.1	14.7
R3	31.2	35.6	47.1	39.4	157.1	12.5
R4	31.5	44.7	55.4	43.3	297.6	17.3
R5	33.4	38.7	50.8	42.2	114.6	10.7
R6	15.5	32.7	43.8	31.8	392.8	19.8
R7	25.4	29.9	43.3	36.2	250.4	15.8
R8	24.8	31.5	41.0	33.8	163.6	12.8
R9	32.4	43.2	55.5	46.2	273.6	16.5
R10	40.2	45.6	65.0	51.2	263.0	16.2
R11	5.4	14.9	25.7	17.9	185.0	13.6
R12	31.8	39.5	46.8	42.4	213.2	14.6

Table 18: Wilcoxon signed ranks test on THM_4 concentrations for all 12 sampling points

Sampling points	Wilcoxon Z value	p-value	Confidence interval - median	Statically different from 80 µg/L?	If yes, above, or below
R1	-3.57	0.000	]60.9; 69.8[	Yes	Below
R2	-3.049	0.002	]65.3; 74.6[	Yes	Below
R3	-3.484	0.000	]63.2; 74.6[	Yes	Below
R4	-0.174	0.862	]70.9; 90.0[	No	No difference
R5	-1.373	0.170	]67.0; 82.6[	No	No difference
R6	2.918	0.004	]86.0; 106.4[	Yes	Above
R7	0.566	0.571	]75.2; 88.4[	No	No difference
R8	3.314	0.001	]93.5; 116.7[	Yes	Above
R9	1.829	0.067	]79.5; 99.4[	No	No difference
R10	3.049	0.002	]89.3; 109.1[	Yes	Above
R11	3.397	0.001	]93.6; 112.4[	Yes	Above
R12	-0.131	0.896	]72.5; 86.3[	No	No difference

Table 19 : Wilcoxon signed ranks test on HAA_6 concentrations for all 12 sampling points

Sampling points	Wilcoxon Z value	p-value	Confidence interval - median	Statically different from 60 µg/L?	If yes. above or below
R1	-3.70	0.000	]28.7; 39.4[	Yes	Below
R2	-3.66	0,000	]24.7; 40.7[	Yes	Below
R3	-3.53	0,000	]32.3; 45.1[	Yes	Below
R4	-3.14	0,002	]34.7; 52.5[	Yes	Below
R5	-3,46	0,001	]35.6; 47.7[	Yes	Below
R6	-3.44	0,001	]20.1; 41.6[	Yes	Below
R7	-3.44	0,001	]26.7; 44.4[	Yes	Below
R8	-3.43	0,001	]27.0; 41.9[	Yes	Below
R9	-2.83	0,005	]36.6; 54.3[	Yes	Below
R10	-2,08	0,037	]41.9; 59.2[	Yes	Below
R11	-3,70	0,000	]10.0; 24.4[	Yes	Below
R12	-3,223	0,001	]34.6; 49.8[	Yes	Below

Table 20 :Results from the Mann-Whitney test (α=0.05) to test differences between UV254nm absorbances, concentrations of dissolved organic carbon, SUVA, THM_4 concentrations, chloroform concentrations and HAA_6 concentrations in filtrated water and ozonated water (N=18).

	UV254	Dissolved organic carbon	SUVA	THM_4	TCM	HAA_6
U	216	168	324	222	225	73
p-values	0.013	0.877	<0.0001	0.059	0.048	0.003

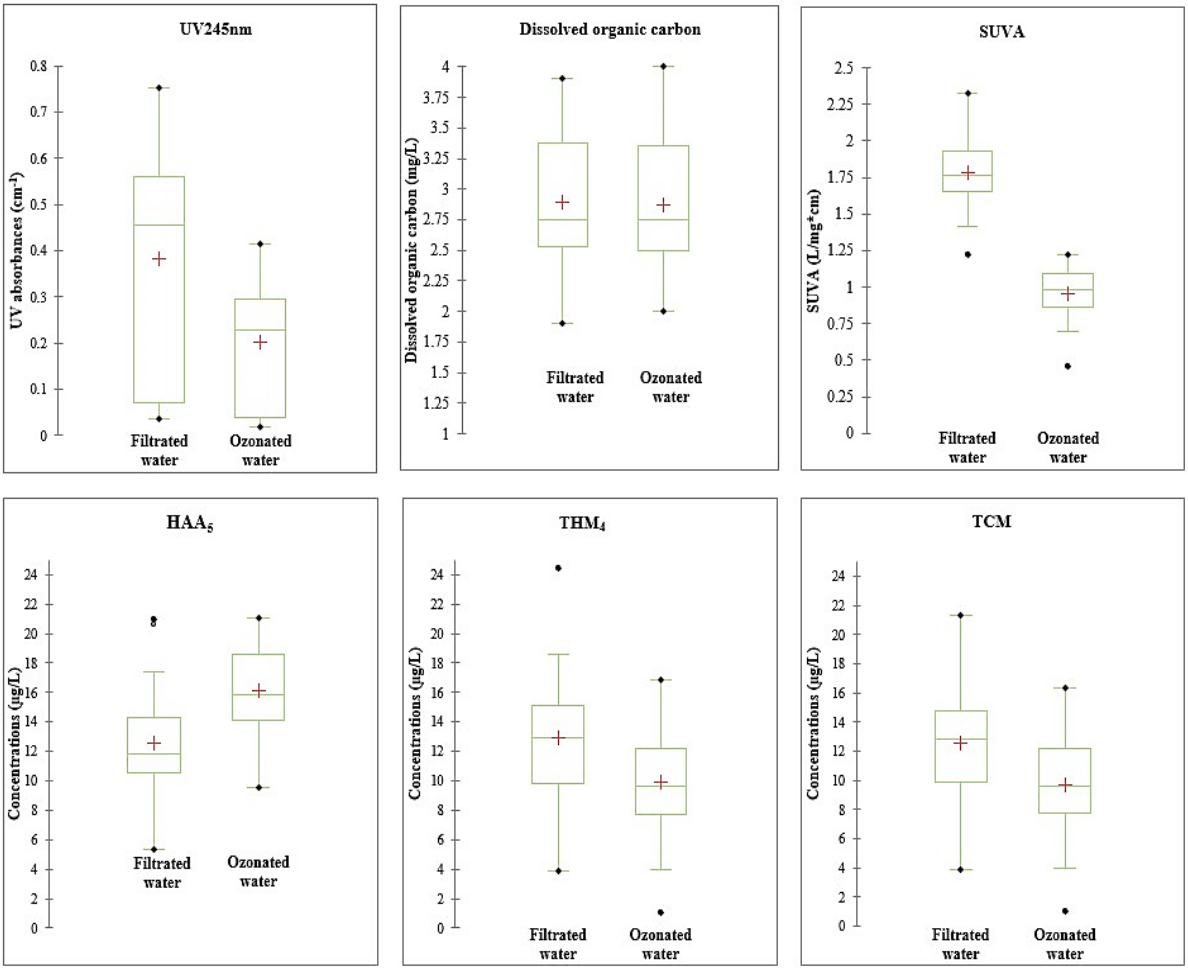

Figure 23 : Box plots comparing UV254nm, dissolved organic carbon, SUVA, HAA_6, THM_4 and TCM in filtrated water and in ozonated water (n=18)

Appendix B: Supplementary information (Manuscript 3)

Table 21: Exposure to TCM, BDCM, DCAA, TCAA, BCAA by ingestion for the different sampling points

		TCM ingestion			BDCM ingestion			DCAA ingestion			TCAA ingestion			BCAA ingestion		
		<0.5 years	**0.5 – < 5 years**	**20+ years**	**<0.5 years**	**0.5 – < 5 years**	**20+ years**	**<0.5 years**	**0.5 – < 5 years**	**20+ years**	**<0.5 years**	**0.5 – < 5 years**	**20+ years**	**<0.5 years**	**0.5 – < 5 years**	**20+ years**
R1	25th quartile	9.61E-04	3.91E-04	1.58E-04	3.84E-05	1.79E-05	7.01E-06	1.34E-04	5.55E-05	2.85E-05	1.90E-04	9.06E-05	3.75E-05	3.85E-05	1.52E-05	6.81E-06
	Median	1.18E-02	4.85E-03	2.17E-03	2.26E-03	1.03E-03	4.17E-04	4.37E-03	1.93E-03	8.21E-04	5.07E-03	2.22E-03	9.06E-04	1.06E-04	4.63E-05	1.95E-05
	75th quartile	4.69E-02	1.99E-02	8.36E-03	2.39E-02	1.01E-02	4.29E-03	3.05E-02	1.35E-02	5.57E-03	3.29E-02	1.35E-02	6.29E-03	2.27E-04	9.90E-05	4.09E-05
R2	25th quartile	1.07E-03	4.22E-04	1.84E-04	4.68E-05	1.64E-05	7.78E-06	1.36E-04	5.80E-05	2.39E-05	2.59E-04	1.08E-04	4.52E-05	5.82E-05	2.23E-05	1.01E-05
	Median	1.20E-02	5.28E-03	2.15E-03	2.53E-03	1.03E-03	4.41E-04	4.28E-03	1.83E-03	8.13E-04	5.95E-03	2.50E-03	1.04E-03	8.78E-05	3.71E-05	1.58E-05
	75th quartile	4.86E-02	2.03E-02	8.72E-03	2.36E-02	9.66E-03	4.28E-03	2.96E-02	1.27E-02	5.74E-03	3.48E-02	1.42E-02	6.50E-03	1.31E-04	6.00E-05	2.57E-05
R3	25th quartile	9.071E-04	4.09E-04	1.74E-04	3.78E-05	1.53E-05	7.35E-06	1.83E-04	8.08E-05	2.95E-05	2.86E-04	1.05E-04	4.85E-05	7.76E-05	2.92E-05	1.31E-05
	Median	1.152E-02	4.90E-03	2.15E-03	2.23E-03	8.51E-04	4.00E-04	5.24E-03	2.09E-03	8.95E-04	6.03E-03	2.51E-03	1.04E-03	1.35E-04	5.54E-05	2.43E-05
	75th quartile	4.720E-02	1.97E-02	8.31E-03	2.27E-02	9.44E-03	4.15E-03	3.33E-02	1.34E-02	5.87E-03	3.42E-02	1.53E-02	6.41E-03	2.00E-04	8.81E-05	3.77E-05
R4	25th quartile	1.28E-03	4.75E-04	2.32E-04	4.11E-05	2.01E-05	8.11E-06	2.96E-04	1.24E-04	5.07E-05	2.92E-04	1.21E-04	4.99E-05	1.19E-04	4.70E-05	2.05E-05
	Median	1.38E-02	5.46E-03	2.44E-03	2.40E-03	9.52E-04	4.08E-04	6.18E-03	2.67E-03	1.18E-03	6.32E-03	2.56E-03	1.20E-03	1.69E-04	7.14E-05	3.17E-05
	75th quartile	5.07E-02	2.12E-02	8.87E-03	2.40E-02	9.01E-03	4.12E-03	3.49E-02	1.58E-02	6.20E-03	3.69E-02	1.57E-02	6.57E-03	2.44E-04	1.09E-04	4.59E-05
R5	25th quartile	1.17E-03	4.52E-04	1.88E-04	4.29E-05	1.99E-05	7.67E-06	2.06E-04	8.80E-05	3.90E-05	2.53E-04	1.08E-04	4.87E-05	1.09E-04	4.03E-05	1.83E-05
	Median	1.33E-02	5.55E-03	2.37E-03	2.27E-03	9.27E-04	4.15E-04	5.21E-03	2.21E-03	1.07E-03	5.87E-03	2.60E-03	1.09E-03	1.45E-04	6.09E-05	2.57E-05
	75th quartile	4.91E-02	2.02E-02	8.67E-03	2.38E-02	1.04E-02	4.33E-03	3.40E-02	1.42E-02	6.24E-03	3.53E-02	1.50E-02	6.09E-03	1.82E-04	8.74E-05	3.60E-05
R6	25th quartile	1.85E-03	7.70E-04	3.48E-04	4.64E-05	2.00E-05	8.07E-06	7.45E-05	3.19E-05	1.27E-05	2.86E-04	1.13E-04	5.07E-05	3.09E-05	1.27E-05	5.42E-06
	Median	1.67E-02	6.51E-03	2.79E-03	2.32E-03	1.01E-03	4.27E-04	3.15E-03	1.32E-03	4.95E-04	6.43E-03	2.64E-03	1.17E-03	8.99E-05	3.80E-05	1.68E-05
	75th quartile	5.30E-02	2.21E-02	1.01E-02	2.44E-02	9.79E-03	4.41E-03	2.68E-02	1.05E-02	4.80E-03	3.57E-02	1.56E-02	6.14E-03	2.08E-04	9.17E-05	3.70E-05

	25th quartile	1.26E-03	5.06E-04	2.13E-04	4.00E-05	1.82E-05	7.63E-06	1.08E-04	4.63E-05	1.74E-05	3.00E-04	1.26E-04	6.00E-05	3.59E-05	1.49E-05	6.46E-06
R7	Median	1.34E-02	5.73E-03	2.58E-03	2.25E-03	9.28E-04	4.03E-04	3.96E-03	1.56E-03	7.46E-04	6.52E-03	2.61E-03	1.14E-03	1.00E-04	3.91E-05	1.78E-05
	75th quartile	4.89E-02	2.08E-02	9.07E-03	2.40E-02	9.97E-03	4.47E-03	2.88E-02	1.21E-02	5.28E-03	3.66E-02	1.54E-02	6.21E-03	2.19E-04	9.32E-05	3.99E-05
	25th quartile	1.79E-03	6.89E-04	3.31E-04	5.10E-05	2.20E-05	8.47E-06	7.19E-05	3.10E-05	1.30E-05	3.23E-04	1.35E-04	5.17E-05	4.53E-05	1.63E-05	7.32E-06
R8	Median	1.68E-02	6.71E-03	3.06E-03	2.59E-03	1.09E-03	5.17E-04	3.11E-03	1.34E-03	5.07E-04	6.37E-03	2.65E-03	1.19E-03	4.91E-05	2.08E-05	8.97E-06
	75th quartile	5.43E-02	2.16E-02	9.77E-03	2.42E-02	9.97E-03	4.67E-03	2.66E-02	1.09E-02	4.82E-03	3.65E-02	1.50E-02	6.86E-03	5.35E-05	2.70E-05	1.11E-05
	25th quartile	1.43E-03	7.13E-04	2.48E-04	4.64E-05	1.96E-05	8.07E-06	1.82E-04	7.65E-05	1.26E-05	3.81E-04	1.37E-04	6.70E-05	9.14E-05	3.61E-05	1.56E-05
R9	Median	1.47E-02	6.24E-03	2.89E-03	2.48E-03	9.63E-04	4.35E-04	5.04E-03	2.10E-03	5.32E-04	7.04E-03	3.16E-03	1.30E-03	1.51E-04	6.16E-05	2.62E-05
	75th quartile	5.15E-02	2.23E-02	9.34E-03	2.42E-02	1.04E-02	4.34E-03	3.25E-02	1.39E-02	5.14E-03	3.86E-02	1.61E-02	7.24E-03	2.07E-04	9.35E-05	3.99E-05
	25th quartile	1.72E-03	6.72E-04	3.06E-04	5.08E-05	1.82E-05	8.80E-06	7.59E-05	3.41E-05	1.27E-05	2.78E-04	1.10E-04	5.06E-05	3.14E-05	1.23E-05	5.47E-06
R10	Median	1.55E-02	6.56E-03	2.92E-03	2.58E-03	1.06E-03	4.75E-04	3.10E-03	1.24E-03	5.91E-04	6.46E-03	2.85E-03	1.18E-03	8.90E-05	3.66E-05	1.63E-05
	75th quartile	5.23E-02	2.16E-02	9.37E-03	2.39E-02	1.01E-02	4.31E-03	2.65E-02	1.19E-02	4.64E-03	3.62E-02	1.54E-02	6.78E-03	2.09E-04	9.00E-05	3.81E-05
	25th quartile	1.71E-03	7.13E-04	3.23E-04	4.41E-05	2.24E-05	8.85E-06	3.48E-05	1.55E-05	6.60E-06	1.51E-04	6.15E-05	3.03E-05	4.52E-05	1.61E-05	7.23E-06
R11	Median	1.58E-02	6.52E-03	2.88E-03	2.48E-03	1.11E-03	4.37E-04	2.18E-03	8.71E-04	3.97E-04	4.59E-03	1.75E-03	8.15E-04	4.93E-05	2.07E-05	9.05E-06
	75th quartile	5.34E-02	2.23E-02	9.67E-03	2.46E-02	9.63E-03	4.41E-03	2.32E-02	9.62E-03	4.27E-03	3.15E-02	1.29E-02	5.56E-03	5.35E-05	2.68E-05	1.11E-05
	25th quartile	1.24E-03	5.33E-04	3.15E-04	4.14E-05	1.83E-05	7.36E-06	2.25E-04	9.27E-05	4.11E-05	2.98E-04	1.24E-04	4.92E-05	9.07E-05	3.62E-05	1.61E-05
R12	Median	1.35E-02	5.80E-03	2.95E-03	2.27E-03	9.05E-04	4.08E-04	5.85E-03	2.29E-03	1.09E-03	6.42E-03	2.62E-03	1.20E-03	1.42E-04	5.74E-05	2.57E-05
	75th quartile	4.96E-02	2.09E-02	9.48E-03	2.32E-02	1.00E-02	4.40E-03	3.36E-02	1.51E-02	6.33E-03	3.58E-02	1.52E-02	6.61E-03	1.96E-04	8.77E-05	3.73E-05

Table 22 : Exposure to TCM and BDCM through inhalation and dermal absorption

		TCM Inhalation			**BDCM Inhalation**			**TCM Dermal absorption**			**BDCM Dermal absorption**		
		<0.5 years	**0.5 – < 5 years**	**20+ years**	**<0.5 years**	**0.5 – < 5 years**	**20+ years**	**<0.5 years**	**0.5 – < 5 years**	**20+ years**	**<0.5 years**	**0.5 – < 5 years**	**20+ years**
R1	25th quartile	2.73E-07	6.37E-07	1.85E-07	4.33E-09	8.53E-09	2.30E-09	2.13E-07	1.19E-07	4.22E-08	2.27E-10	9.29E-11	7.03E-11
	Median	3.77E-06	8.42E-06	2.40E-06	2.35E-07	5.24E-07	1.35E-07	3.08E-04	2.63E-04	1.05E-04	3.36E-05	3.00E-05	1.38E-05
	75th quartile	1.55E-05	3.37E-05	9.96E-06	2.36E-06	5.11E-06	1.66E-06	3.25E-03	2.67E-03	1.10E-03	1.19E-03	1.11E-03	4.48E-04
R2	25th quartile	3.12E-07	7.38E-07	1.80E-07	4.34E-09	8.07E-09	2.77E-09	1.19E-07	1.37E-07	5.67E-08	1.23E-10	1.43E-10	5.26E-11
	Median	3.63E-06	8.62E-06	2.41E-06	2.42E-07	5.04E-07	1.43E-07	3.42E-04	3.15E-04	1.03E-04	4.24E-05	3.17E-05	1.23E-05
	75th quartile	1.54E-05	3.49E-05	1.07E-05	2.40E-06	5.24E-06	1.52E-06	3.75E-03	3.33E-03	1.19E-03	1.59E-03	1.22E-03	4.25E-04
R3	25th quartile	3.23E-07	5.99E-07	1.73E-07	3.51E-09	8.38E-09	2.28E-09	1.82E-07	1.07E-07	5.41E-08	2.12E-10	1.48E-10	5.51E-11
	Median	3.54E-06	8.57E-06	2.66E-06	2.18E-07	5.01E-07	1.32E-07	4.06E-04	3.12E-04	1.07E-04	3.98E-05	2.92E-05	9.12E-06
	75th quartile	1.66E-05	3.44E-05	1.04E-05	2.44E-06	5.18E-06	1.51E-06	4.30E-03	3.15E-03	1.01E-03	1.41E-03	9.83E-04	4.13E-04
R4	25th quartile	4.28E-07	9.78E-07	2.57E-07	4.07E-09	1.00E-08	2.47E-09	4.13E-07	3.48E-07	4.20E-08	4.75E-10	1.28E-10	7.02E-11
	Median	4.44E-06	9.61E-06	2.95E-06	2.28E-07	5.60E-07	1.57E-07	4.77E-04	3.43E-04	1.44E-04	3.41E-05	2.95E-05	1.29E-05
	75th quartile	1.66E-05	3.76E-05	1.04E-05	2.59E-06	5.22E-06	1.48E-06	4.50E-03	3.15E-03	1.20E-03	1.40E-03	1.34E-03	4.64E-04
R5	25th quartile	3.81E-07	8.03E-07	2.32E-07	4.21E-09	8.20E-09	2.58E-09	2.23E-07	2.07E-07	6.67E-08	2.41E-10	1.07E-10	3.17E-11
	Median	4.45E-06	9.80E-06	2.85E-06	2.51E-07	5.12E-07	1.44E-07	4.58E-04	3.69E-04	1.40E-04	3.19E-05	2.50E-05	1.01E-05
	75th quartile	1.64E-05	3.53E-05	1.07E-05	2.38E-06	5.25E-06	1.53E-06	4.14E-03	3.16E-03	1.13E-03	1.50E-03	1.11E-03	4.46E-04
R6	25th quartile	5.59E-07	1.23E-06	3.40E-07	4.74E-09	8.75E-09	2.68E-09	5.00E-07	5.69E-07	2.78E-07	2.93E-10	1.97E-10	3.85E-11
	Median	5.47E-06	1.22E-05	3.47E-06	2.53E-07	5.12E-07	1.50E-07	4.61E-04	4.79E-04	1.89E-04	3.41E-05	2.95E-05	9.06E-06

	75th quartile	1.83E-05	3.91E-05	1.19E-05	2.39E-06	5.49E-06	1.59E-06	4.33E-03	3.64E-03	1.28E-03	1.19E-03	1.23E-03	4.07E-04
R7	25th quartile	3.81E-07	7.50E-07	2.00E-07	3.61E-09	8.66E-09	2.19E-09	1.80E-07	1.42E-07	5.74E-08	3.61E-11	1.99E-10	5.40E-11
	Median	4.17E-06	9.50E-06	2.86E-06	2.17E-07	4.99E-07	1.35E-07	4.77E-04	3.31E-04	1.31E-04	4.10E-05	2.71E-05	1.09E-05
	75th quartile	1.66E-05	3.66E-05	1.05E-05	2.41E-06	5.17E-06	1.51E-06	3.89E-03	3.15E-03	1.19E-03	1.42E-03	1.42E-03	4.14E-04
R8	25th quartile	6.26E-07	1.10E-06	3.26E-07	4.49E-09	1.00E-08	3.27E-09	1.98E-07	9.25E-07	1.44E-07	3.10E-10	6.15E-10	9.71E-11
	Median	5.24E-06	1.13E-05	3.46E-06	2.54E-07	5.81E-07	1.56E-07	5.23E-04	4.33E-04	1.42E-04	4.30E-05	3.83E-05	1.35E-05
	75th quartile	1.80E-05	3.99E-05	1.14E-05	2.72E-06	5.57E-06	1.63E-06	4.78E-03	3.70E-03	1.35E-03	1.65E-03	1.26E-03	4.86E-04
R9	25th quartile	4.87E-07	1.01E-06	3.13E-07	4.76E-09	9.89E-09	2.75E-09	3.37E-07	2.26E-07	1.22E-07	2.48E-10	1.70E-10	1.27E-10
	Median	4.66E-06	1.14E-05	3.17E-06	2.52E-07	5.43E-07	1.57E-07	4.27E-04	3.71E-04	1.37E-04	4.42E-05	3.37E-05	1.05E-05
	75th quartile	1.70E-05	3.82E-05	1.12E-05	2.39E-06	5.60E-06	1.64E-06	4.26E-03	3.52E-03	1.25E-03	1.74E-03	1.58E-03	4.18E-04
R10	25th quartile	5.08E-07	1.20E-06	3.37E-07	3.95E-09	1.06E-08	2.77E-09	5.55E-07	3.25E-07	1.30E-07	3.13E-10	4.28E-10	5.91E-11
	Median	5.20E-06	1.10E-05	3.50E-06	2.23E-07	5.61E-07	1.51E-07	5.29E-04	4.67E-04	1.62E-04	5.09E-05	4.35E-05	1.24E-05
	75th quartile	1.76E-05	3.84E-05	1.14E-05	2.37E-06	5.64E-06	1.52E-06	5.00E-03	3.80E-03	1.31E-03	1.60E-03	1.23E-03	4.53E-04
R11	25th quartile	5.54E-07	1.23E-06	3.54E-07	4.29E-09	9.33E-09	2.84E-09	3.57E-07	2.99E-07	1.49E-07	2.12E-10	2.99E-10	2.15E-11
	Median	4.93E-06	1.24E-05	3.36E-06	2.70E-07	5.44E-07	1.68E-07	5.40E-04	5.02E-04	1.64E-04	3.90E-05	3.95E-05	1.32E-05
	75th quartile	1.84E-05	3.79E-05	1.17E-05	2.46E-06	5.14E-06	1.69E-06	4.38E-03	3.72E-03	1.48E-03	1.63E-03	9.90E-04	4.58E-04
R12	25th quartile	3.94E-07	8.85E-07	2.48E-07	3.49E-09	7.76E-09	2.22E-09	2.31E-07	2.49E-07	7.18E-08	2.13E-10	1.15E-10	5.37E-11
	Median	4.42E-06	9.57E-06	2.86E-06	2.33E-07	5.53E-07	1.57E-07	4.10E-04	3.75E-04	1.14E-04	4.55E-05	2.68E-05	1.12E-05
	75th quartile	1.63E-05	3.58E-05	1.05E-05	2.40E-06	5.71E-06	1.57E-06	4.32E-03	3.06E-03	1.18E-03	1.64E-03	1.05E-03	4.34E-04

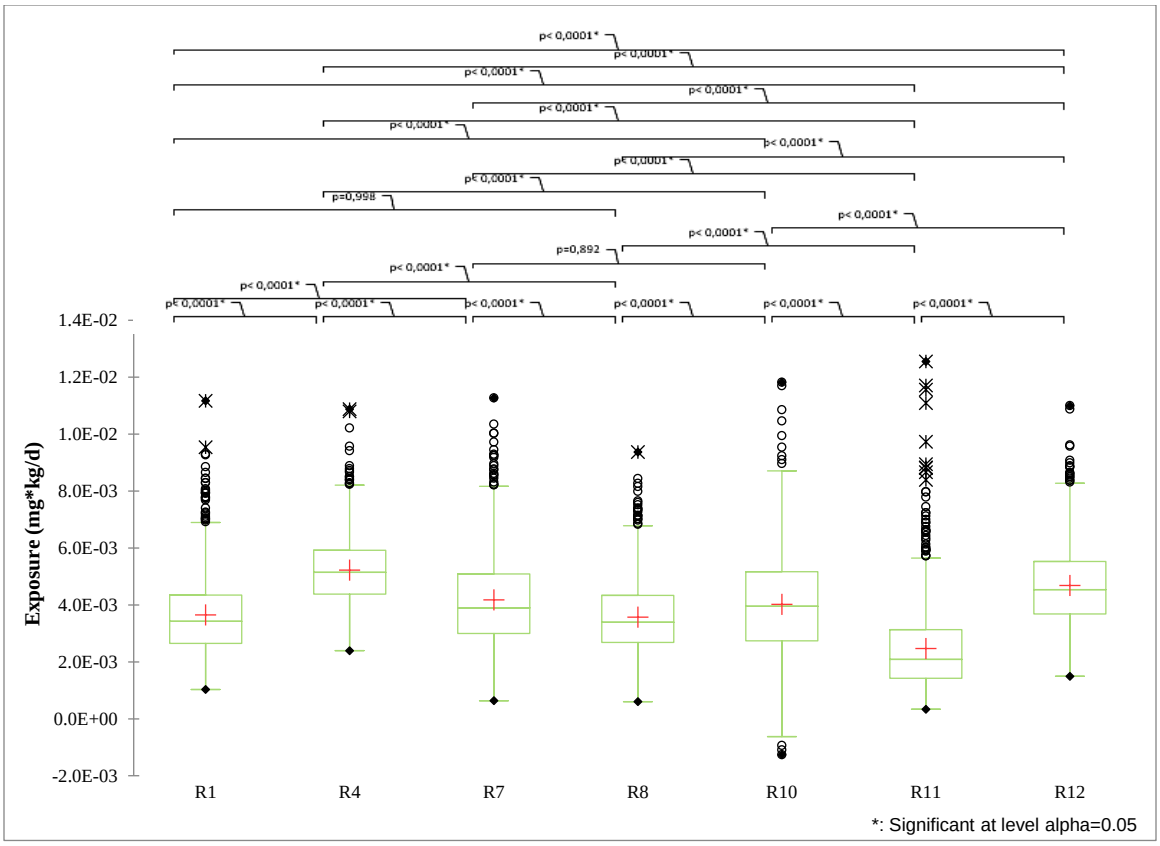

Figure 24: Kruskal-Wallis test for HAA_6 concentrations between different sampling points (α=0.05) having different estimated hydraulic residence times. R1: locations with estimated residence times between ≥0 and <4h, R4: locations with estimated residence times between ≥4 and <12h, R7, and R12: locations with estimated residence times between ≥12 and <16h, R8, R10, R11): locations with estimated residence times between ≥16 and <24h.

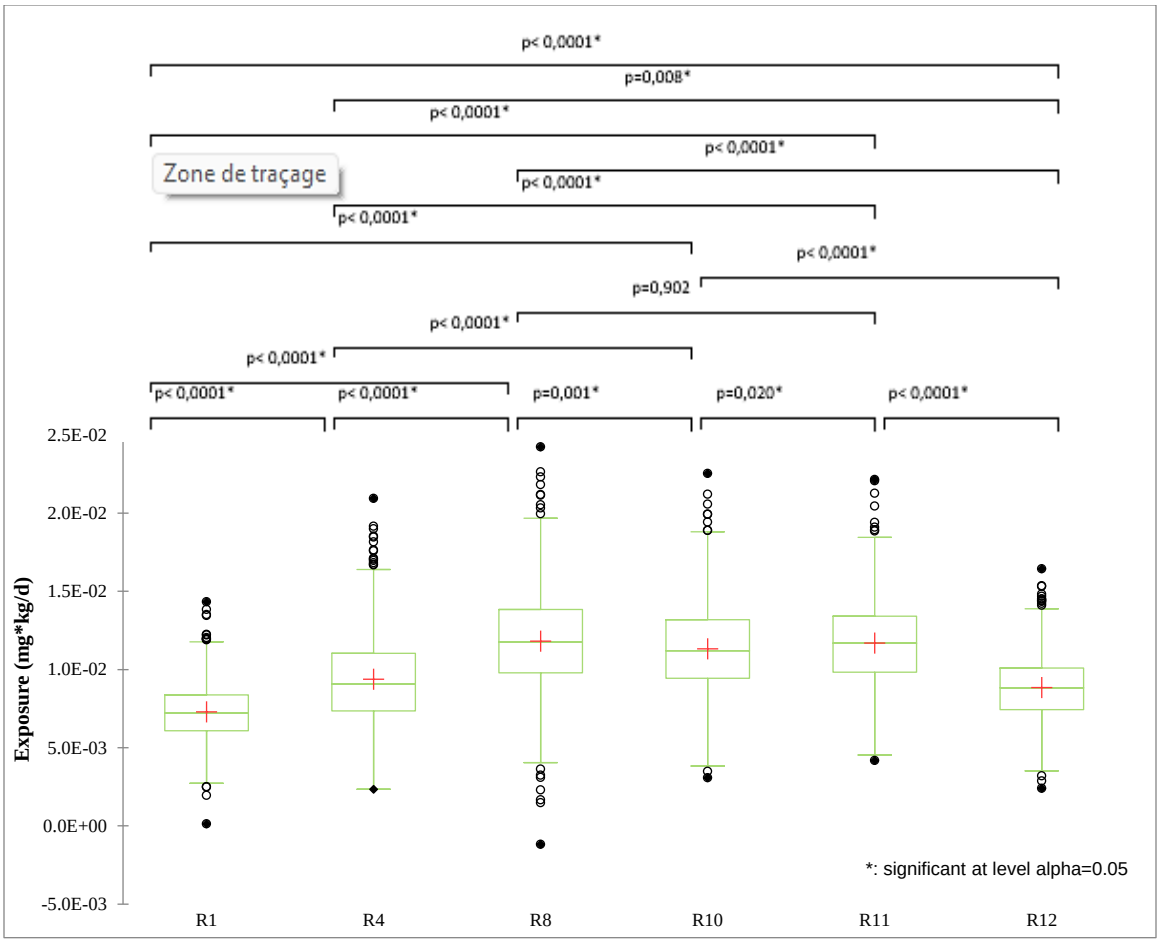

Figure 25: Kruskal-Wallis test for THM_4 concentrations between different sampling points (α=0.05) having different estimated hydraulic residence times. R1: locations with estimated residence times between ≥0 and <4h, R4: locations with estimated residence times between ≥4 and <12h, R7, and R12: locations with estimated residence times between ≥12 and <16h, R8, R10, R11): locations with estimated residence times between ≥16 and <24h.

Probability density functions for TCM subchronic risks calculated using different sampling approaches (grouped by HRT)

HRT: 0-4h (R1) and 4-12h (R2, R3, R4)

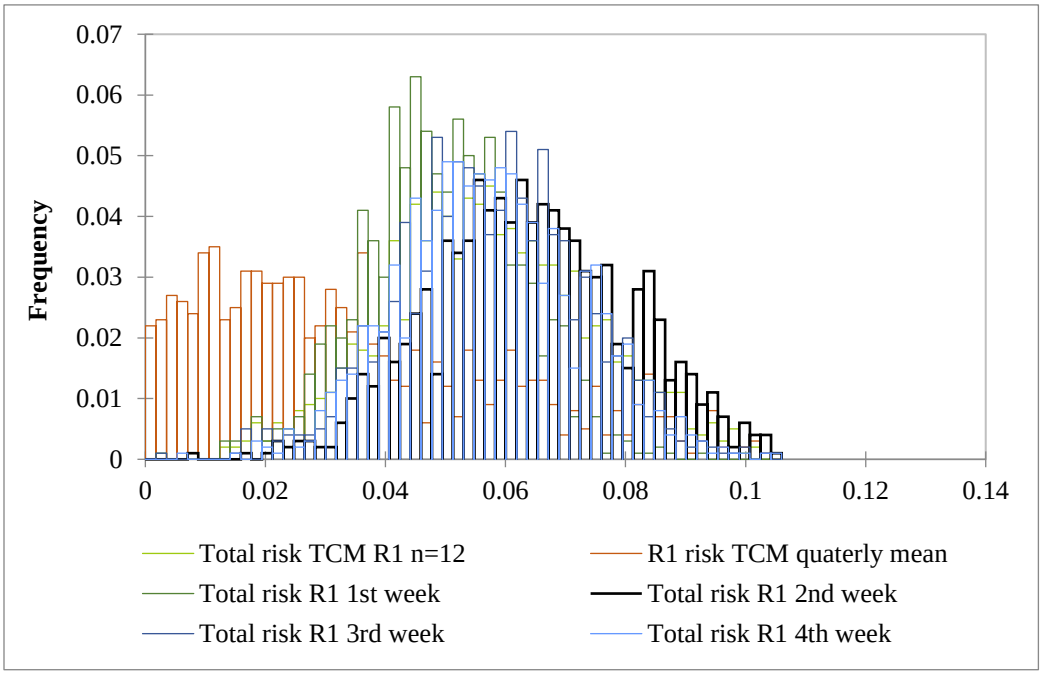

Figure 26 : Probability density functions for TCM subchronic risks (R1)

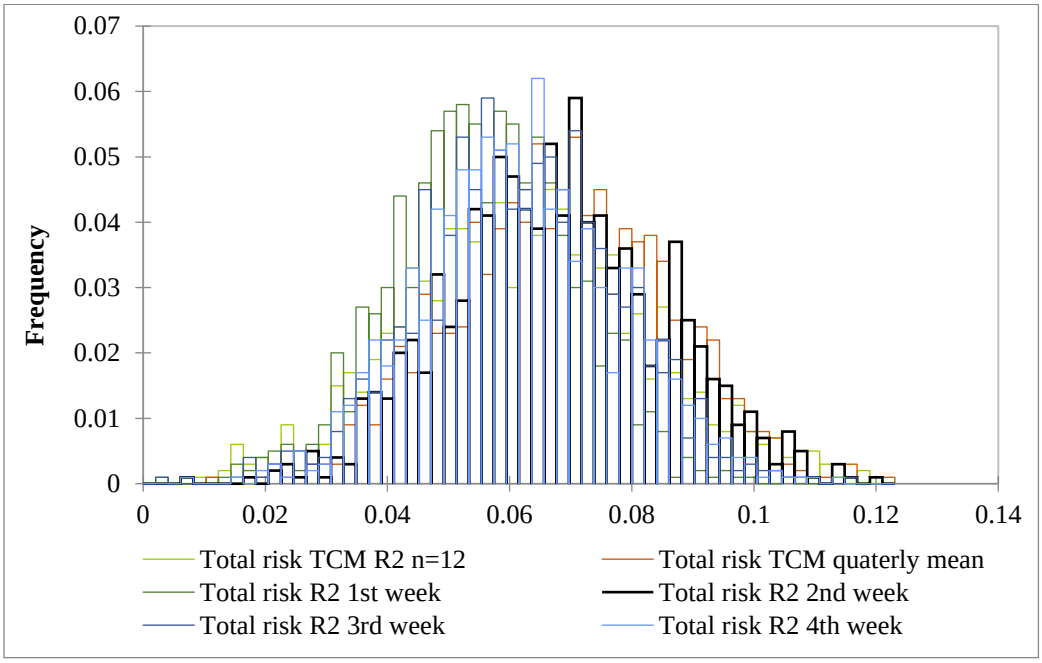

Figure 27 : Probability density functions for TCM subchronic risks (R2)

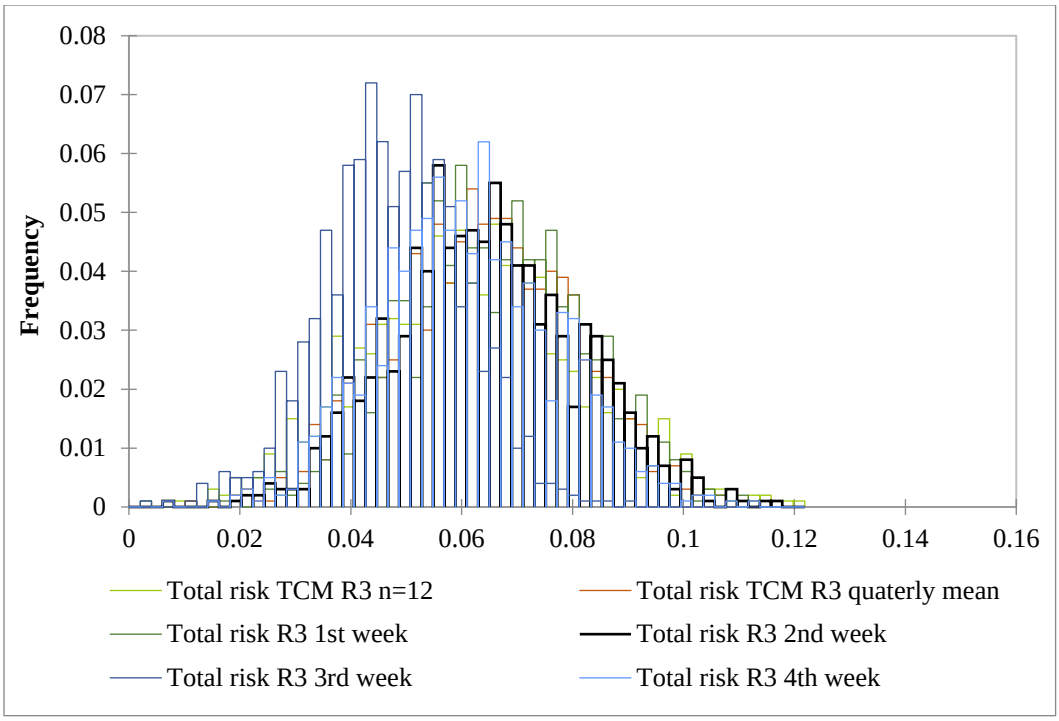

Figure 28 : Probability density functions for TCM subchronic risks (R3)

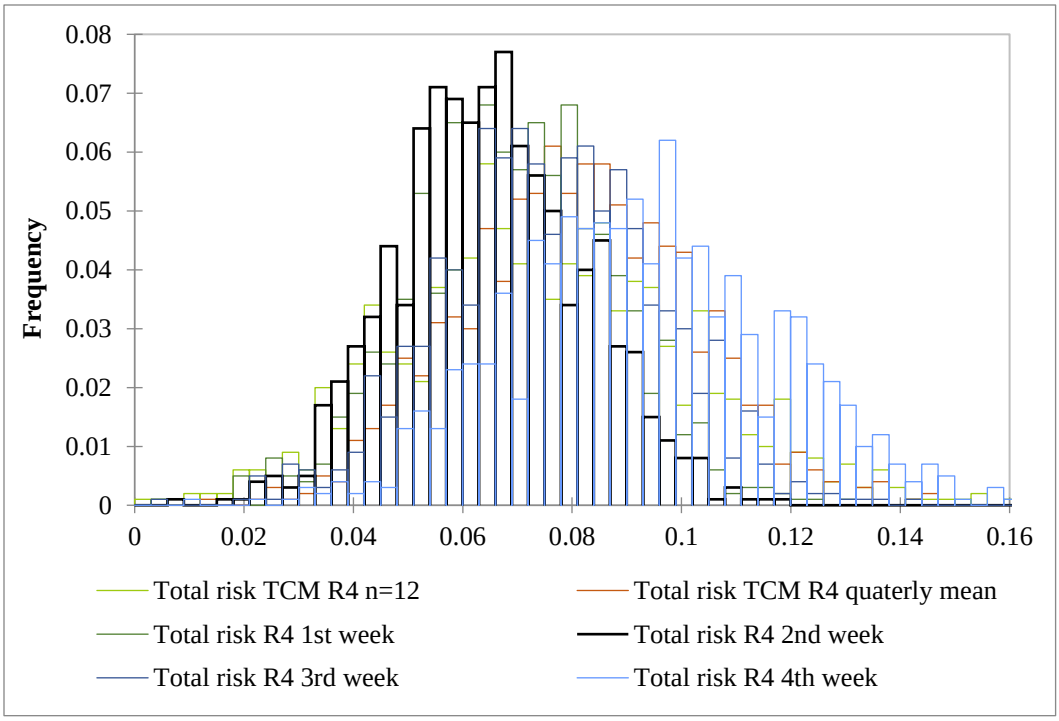

Figure 29 : Probability density functions for TCM subchronic risks (R4)

HRT: 12h – 16h (R5, R7, R12)

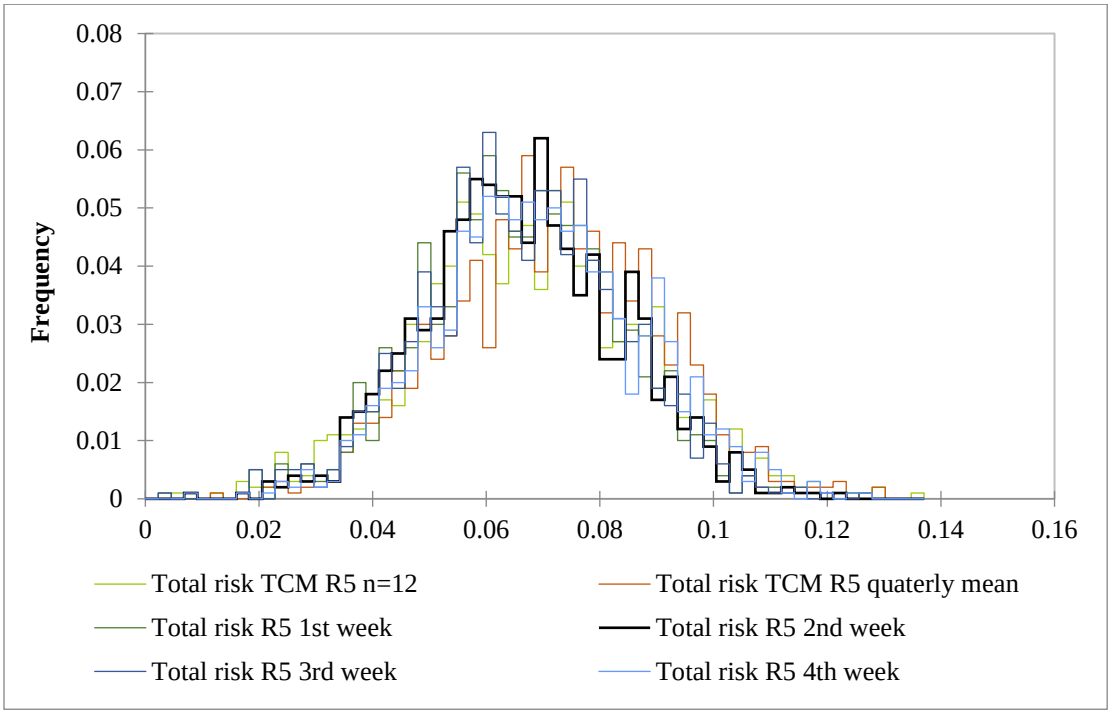

Figure 30 : Probability density functions for TCM subchronic risks (R5)

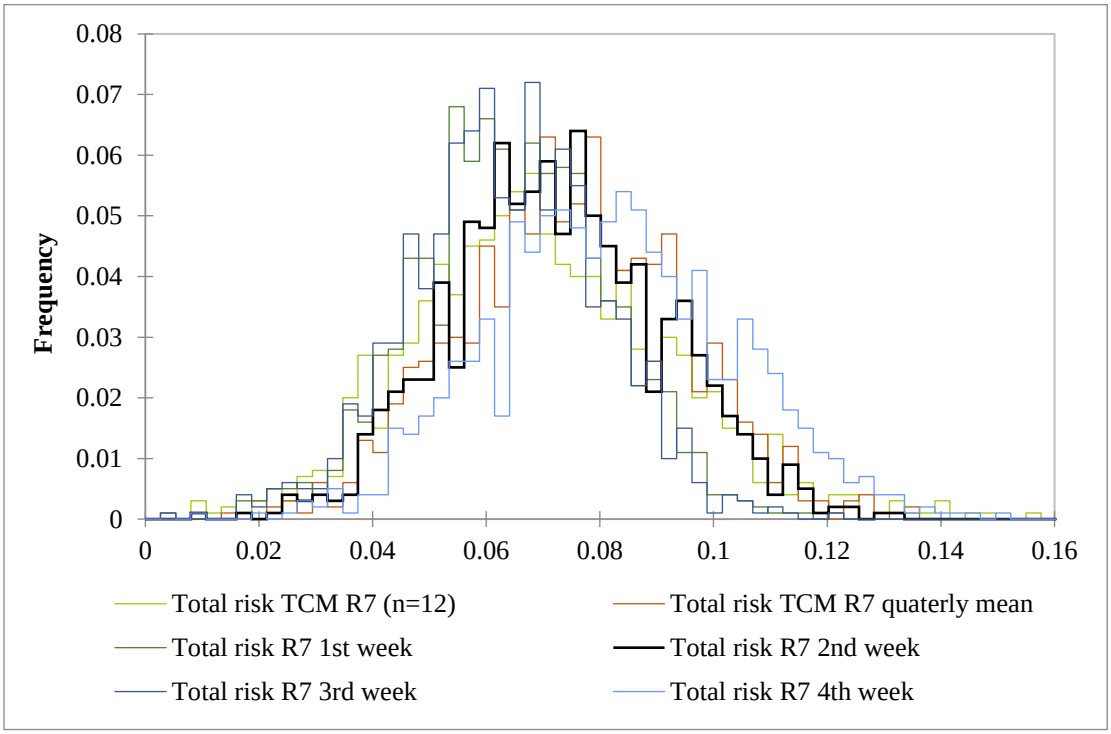

Figure 31 : Probability density functions for TCM subchronic risks (R7)

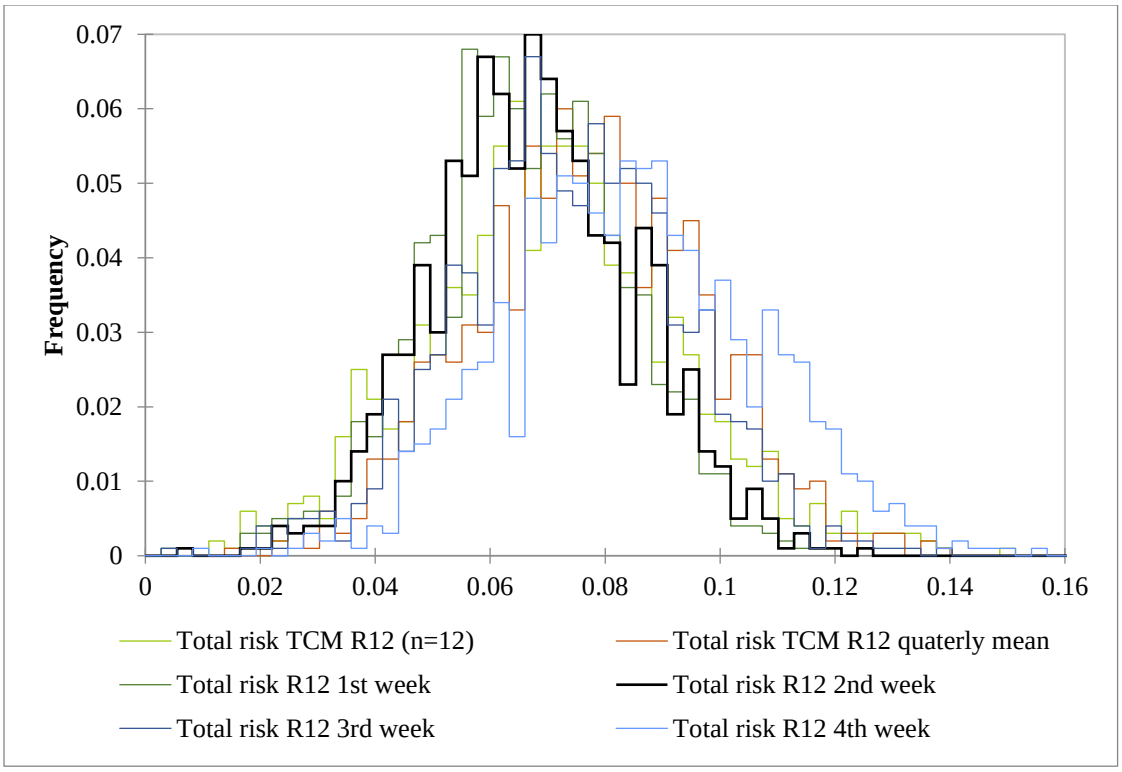

Figure 32 : Probability density functions for TCM subchronic risks (R12)

HRT: 16h – 24h (R6, R8, R9, R10, R11)

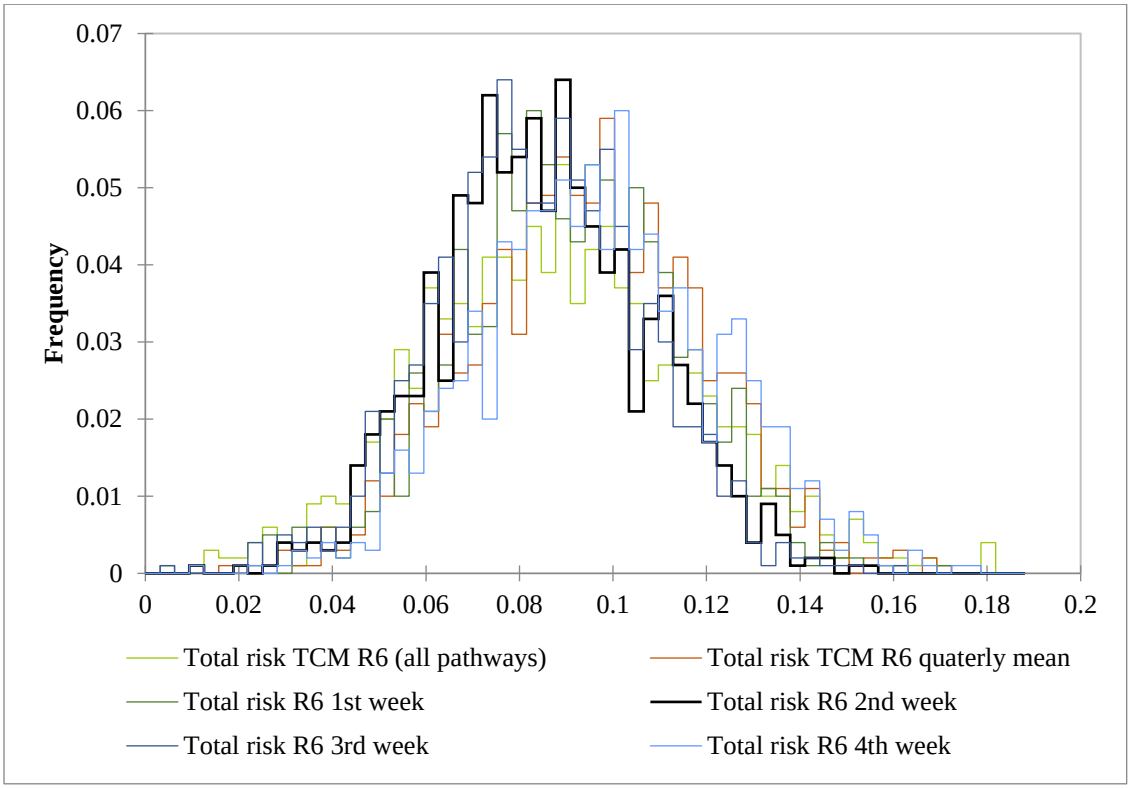

Figure 33 : : Probability density functions for TCM subchronic risks (R6)

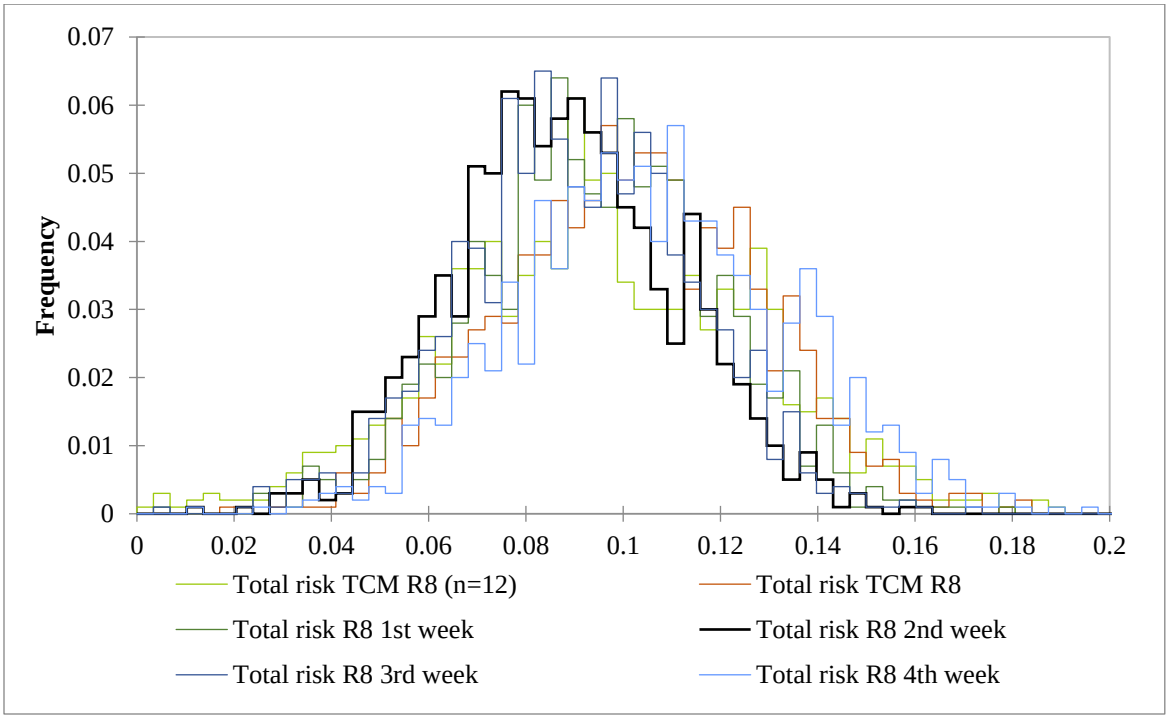

Figure 34 : Probability density functions for TCM subchronic risks (R8)

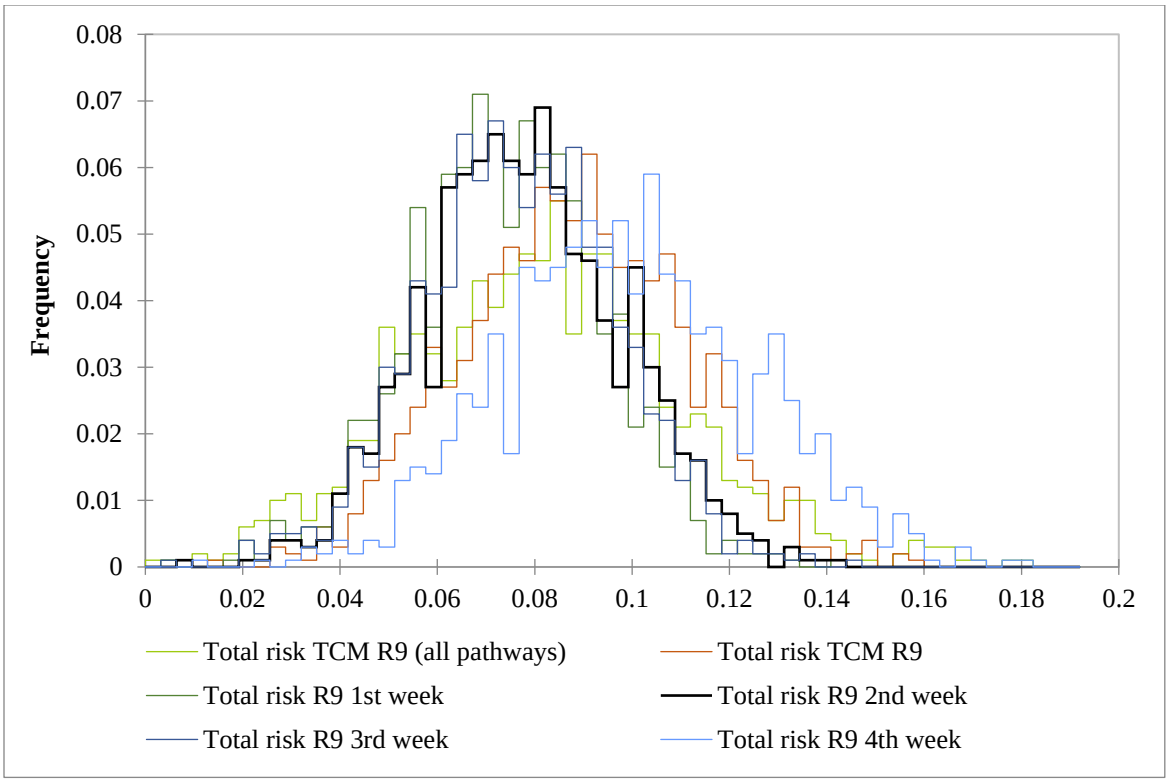

Figure 35 : Probability density functions for TCM subchronic risks (R9)

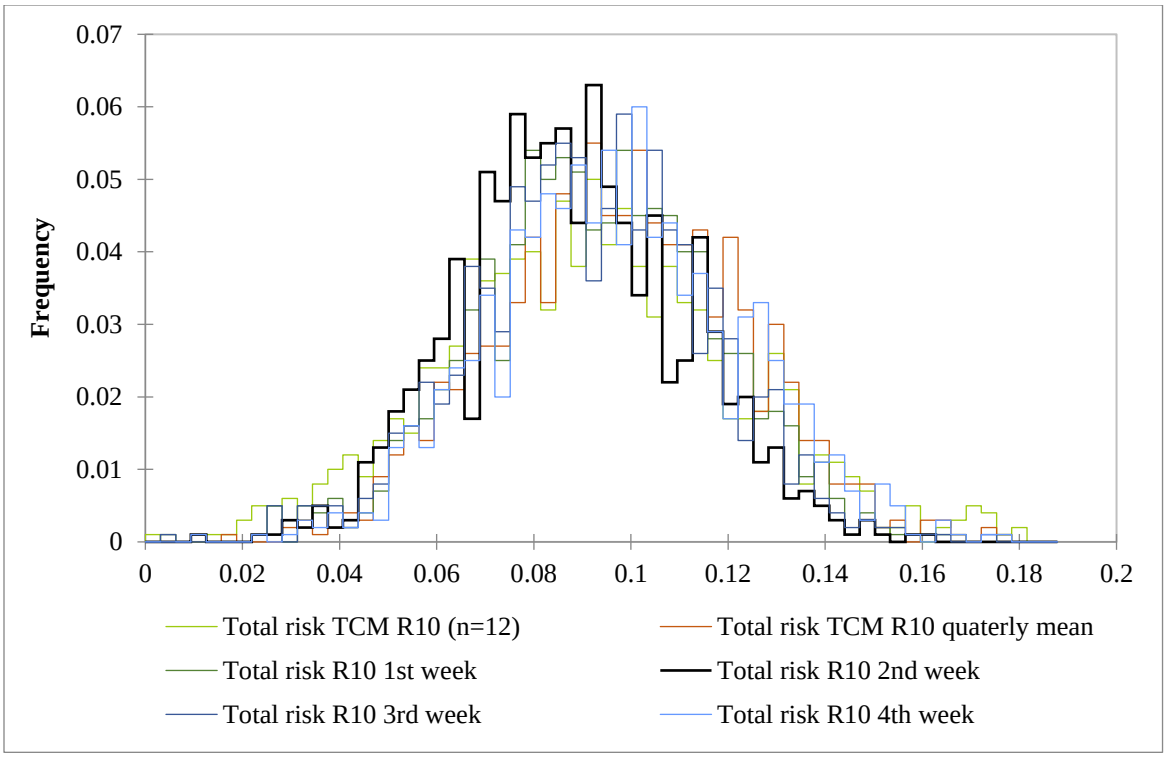

Figure 36 : Probability density functions for TCM subchronic risks (R10)

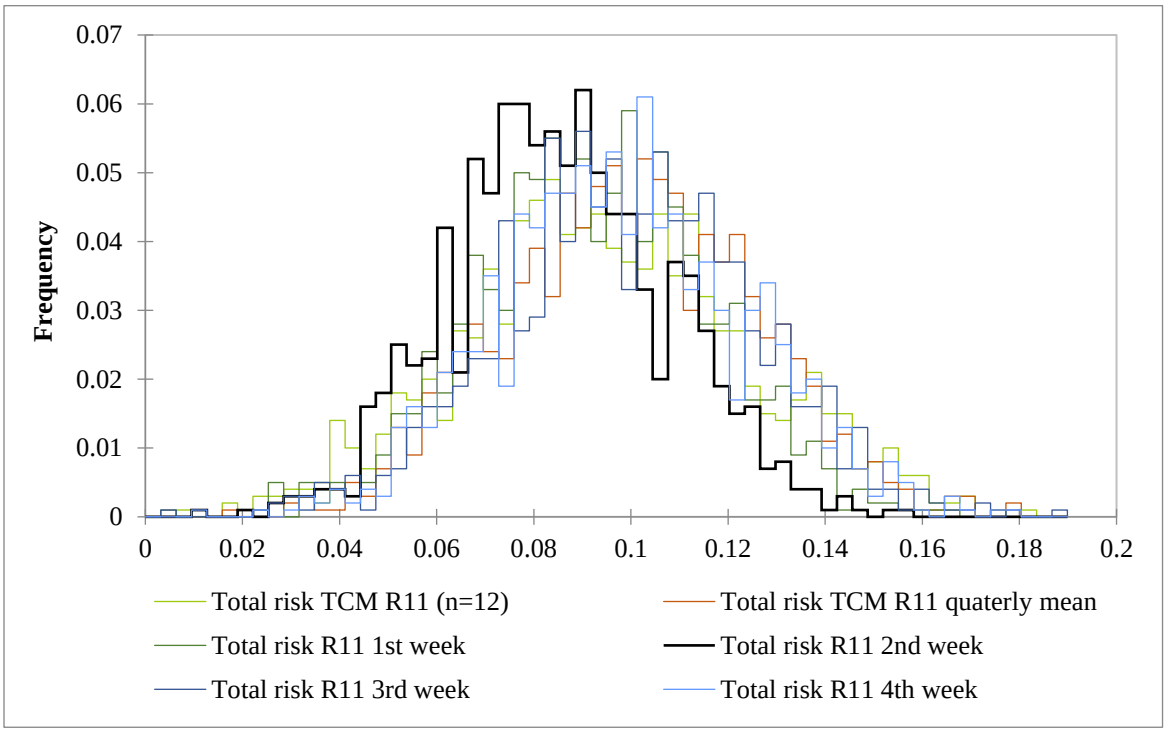

Figure 37 : Probability density functions for TCM subchronic risks (R11)

Table 23 : Descriptive statistics for R1, R2, R3 and R4 for the different calculation methodologies

	Risk R1 n=12	R1 risk quarterly mean	Risk R1 1st week	Risk R1 2nd week	Risk R1 3rd week	Risk R1 4th week	Risk R2 n=12	Risk quarterly mean	Risk R2 1st week	Risk R2 2nd week	Risk R2 3rd week	Risk R2 4th week	Risk R3 n=12	Risk R3 quarterly mean	Risk R3 1st week	Risk R3 2nd week	Risk R3 3rd week	Risk R3 4th week	Risk R4 n=12	Risk R4 quarterly mean	Risk R4 1st week	Risk R4 2nd week	Risk R4 3rd week	Risk R4 4th week
N observations	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Minimum	0.010	-0.032	0.003	0.008	0.003	0.007	0.007	0.012	0.003	0.008	0.004	0.007	0.009	0.012	0.004	0.008	0.003	0.007	0.001	0.014	0.004	0.008	0.004	0.011
Maximum	0.126	0.117	0.094	0.118	0.109	0.105	0.133	0.123	0.106	0.124	0.117	0.113	0.126	0.116	0.124	0.118	0.091	0.112	0.198	0.146	0.131	0.119	0.144	0.170
1st Quartile	0.046	0.011	0.041	0.053	0.048	0.047	0.049	0.056	0.046	0.056	0.051	0.051	0.049	0.053	0.054	0.053	0.040	0.050	0.058	0.066	0.058	0.054	0.063	0.076
Median	0.057	0.026	0.049	0.064	0.057	0.057	0.062	0.068	0.056	0.067	0.061	0.061	0.061	0.064	0.065	0.063	0.048	0.060	0.074	0.081	0.069	0.064	0.076	0.092
3rd Quartile	0.069	0.049	0.058	0.076	0.068	0.067	0.075	0.081	0.066	0.079	0.072	0.072	0.074	0.076	0.077	0.075	0.056	0.072	0.092	0.095	0.082	0.076	0.089	0.109
Mean	0.057	0.032	0.049	0.064	0.057	0.057	0.063	0.068	0.056	0.067	0.061	0.062	0.062	0.064	0.065	0.064	0.048	0.061	0.075	0.081	0.069	0.065	0.076	0.093
Standard deviation	0.018	0.027	0.013	0.017	0.015	0.015	0.020	0.018	0.015	0.018	0.016	0.016	0.019	0.017	0.017	0.017	0.012	0.016	0.027	0.021	0.018	0.017	0.020	0.024

Table 24 : Descriptive statistics for R5, R7, and R12 for the different calculation methodologies

Statistique	Risk R5 n=12	Risk R5 quarterly mean	Risk R5 1st week	Risk R5 2nd week	Risk R5 3rd week	Risk R5 4th week	Risk R7 (n=12)	Risk R7 quarterly mean	Risk R7 1st week	Risk R7 2nd week	Risk R7 3rd week	Risk R7 4th week	Risk R12 (n=12)	Risk R12 quarterly mean	Risk R12 1st week	Risk R12 2nd week	Risk R12 3rd week	Risk R12 4th week
N observations	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Minimum	0.006	0.013	0.004	0.008	0.004	0.008	0.009	0.013	0.004	0.009	0.004	0.010	0.012	0.014	0.004	0.008	0.004	0.010
Maximum	0.175	0.129	0.125	0.122	0.126	0.127	0.156	0.135	0.123	0.133	0.121	0.150	0.165	0.139	0.126	0.124	0.140	0.155
1st Quartile	0.055	0.059	0.055	0.055	0.055	0.057	0.055	0.062	0.054	0.060	0.053	0.068	0.057	0.063	0.055	0.056	0.062	0.070
Median	0.068	0.072	0.066	0.066	0.066	0.069	0.069	0.075	0.064	0.072	0.063	0.081	0.071	0.077	0.066	0.067	0.074	0.084
3rd Quartile	0.080	0.085	0.078	0.078	0.078	0.081	0.084	0.089	0.076	0.085	0.075	0.096	0.085	0.091	0.078	0.080	0.087	0.099
Mean	0.068	0.072	0.066	0.066	0.066	0.069	0.070	0.075	0.065	0.073	0.064	0.082	0.071	0.077	0.067	0.068	0.074	0.085
Standard deviation	0.020	0.019	0.017	0.017	0.017	0.018	0.022	0.019	0.017	0.019	0.017	0.021	0.022	0.020	0.017	0.018	0.019	0.022

Table 25 : Descriptive statistics for R6, R8, and R9 for the different calculation methodologies

Statistic	Risk TCM R6 (all pathways)	Risk TCM R6 quarterly mean	Risk R6 1st week	Risk R6 2nd week	Risk R6 3rd week	Risk R6 4th week	Risk TCM R8 (n=12)	Risk TCM R8	Risk R8 1st week	Risk R8 2nd week	Risk R8 3rd week	Risk R8 4th week	Risk TCM R9 (all pathways)	Risk TCM R9	Risk R9 1st week	Risk R9 2nd week	Risk R9 3rd week	Risk R9 4th week
N observations	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Minimum	0.011	0.017	0.005	0.010	0.005	0.012	0.002	0.018	0.006	0.010	0.005	0.013	-0.014	0.016	0.004	0.009	0.005	0.012
Maximum	0.204	0.170	0.172	0.156	0.160	0.178	0.213	0.183	0.179	0.162	0.172	0.194	0.180	0.158	0.142	0.143	0.146	0.182
1st Quartile	0.068	0.077	0.075	0.070	0.070	0.080	0.073	0.083	0.079	0.073	0.076	0.087	0.062	0.072	0.062	0.064	0.064	0.082
Median	0.088	0.094	0.090	0.084	0.084	0.096	0.094	0.102	0.094	0.087	0.091	0.105	0.081	0.088	0.074	0.077	0.077	0.098
3rd Quartile	0.107	0.111	0.107	0.100	0.099	0.114	0.118	0.120	0.111	0.104	0.107	0.125	0.099	0.104	0.088	0.092	0.090	0.117
Mean	0.089	0.094	0.090	0.085	0.084	0.097	0.096	0.102	0.094	0.088	0.091	0.106	0.081	0.088	0.075	0.078	0.077	0.099
Variance (n-1)	0.001	0.001	0.001	0.000	0.000	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.000	0.000	0.000	0.001
Standard deviation (n-1)	0.029	0.024	0.024	0.022	0.022	0.025	0.032	0.026	0.025	0.023	0.024	0.028	0.029	0.023	0.019	0.020	0.020	0.026

Table 26 : Descriptive statistics for R10 and R11 for the different calculation methodologies

Statistic	Risk TCM R10 (n=12)	Risk TCM R10 quarterly mean	Risk R10 1st week	Risk R10 2nd week	Risk R10 3rd week	Risk R10 4th week	Risk TCM R11 (n=12)	Risk TCM R11 quarterly mean	Risk R11 1st week	Risk R11 2nd week	Risk R11 3rd week	Risk R11 4th week
N observations	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Minimum	0.001	0.017	0.005	0.010	0.005	0.012	-0.002	0.018	0.005	0.010	0.006	0.012
Maximum	0.212	0.176	0.176	0.161	0.174	0.178	0.203	0.180	0.175	0.156	0.188	0.180
1st Quartile	0.071	0.080	0.077	0.073	0.076	0.080	0.076	0.082	0.077	0.070	0.082	0.081
Median	0.091	0.098	0.093	0.087	0.092	0.096	0.094	0.100	0.092	0.084	0.099	0.097
3rd Quartile	0.111	0.115	0.110	0.103	0.108	0.114	0.114	0.118	0.109	0.100	0.117	0.115
Mean	0.092	0.098	0.093	0.088	0.092	0.097	0.095	0.100	0.092	0.085	0.099	0.098
Variance (n-1)	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.000	0.001	0.001
Standard deviation (n-1)	0.030	0.025	0.024	0.023	0.024	0.025	0.030	0.026	0.024	0.022	0.026	0.025