Université de Montréal

Approche multidisciplinaire pour l'amélioration de l'estimation de l'exposition aux sous-produits de désinfection de l'eau en milieu domestique et en piscine

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Cette thèse intitulée :

Approche multidisciplinaire pour l'amélioration de l'estimation de l'exposition aux sous-produits de désinfection de l'eau en milieu domestique et en piscine

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RÉSUMÉ

La désinfection de l'eau de consommation et des piscines induit la formation de sous-produits (SPD) potentiellement nocifs pour la santé, parmi lesquels les trihalométhanes (THM), les acides haloacétiques (HAA) et les chloramines (CAM). La difficulté d'estimer l'exposition humaine à ces SPD empêche de cerner précisément les risques sanitaires possiblement associés (i.e., cancérigènes, reprotoxiques, irritatifs). Nos travaux s'articulent autour d'une méthodologie consistant à intégrer des données d'occurrence environnementales à des modèles toxicocinétiques à base physiologique (TCBP) pour améliorer les mesures de l'exposition aux SPD. Cette approche multidisciplinaire veut prendre en compte de manière aussi appropriée que possible les deux composantes majeures des variations de cette exposition : les variations spatio-temporelles des niveaux de contamination environnementale et l'impact des différences inter- et intra-individuelles sur les niveaux biologiques. Cette thèse, organisée en deux volets qui explorent chacun successivement des aspects environnemental et biologique de la problématique, vise à contribuer au développement de cette stratégie innovante d'estimation de l'exposition et, plus généralement, à des meilleures pratiques en la matière.

Le premier volet de la thèse s'intéresse à l'exposition en milieu domestique (i.e., résultant de l'utilisation de l'eau potable au domicile) et est consacré au cas complexe des THM, les plus abondants et volatils des SPD, absorbables par ingestion mais aussi par inhalation et voie percutanée. Les articles I et II, constitutifs de ce volet, documentent spécifiquement la question des variations inter- et intra- journalières de présence des SPD en réseau et de leurs impacts sur les estimateurs de l'exposition biologique. Ils décrivent l'amplitude et la diversité des variations à court terme des niveaux environnementaux, présentent les difficultés à proposer une façon systématique et « épidémiologiquement » pratique de les modéliser et proposent, de manière originale, une évaluation des mésestimations, somme toute modestes, des mesures biologiques de l'exposition résultant de leurs non-prise en compte.

Le deuxième volet de la thèse se penche sur l'exposition aux SPD en piscine, d'un intérêt grandissant au niveau international, et se restreint au cas jugé prioritaire des piscines publiques intérieures. Ce volet envisage, pour quantifier l'exposition dans ce contexte particulier, l'extension de l'approche méthodologique préconisée, élaborée originellement pour application dans un contexte domestique : d'abord, à travers une analyse approfondie des variations des niveaux de contamination (eau, air) des SPD en piscine en vue de les modéliser (article III); puis en examinant, dans le cas particulier du chloroforme, le THM le plus abondant, la possibilité d'utiliser la modélisation TCBP pour simuler des expositions en piscine (article IV). Les résultats mettent notamment en évidence la difficulté d'appréhender précisément la contamination environnementale autrement que par un échantillonnage *in situ* tandis que la modélisation TCBP apparait, sur le plan toxicologique, comme l'outil le plus pertinent à ce jour, notamment au regard des autres approches existantes, mais qu'il convient d'améliorer pour mieux prédire les niveaux d'exposition biologique.

Finalement, ces travaux illustrent la pertinence et la nécessité d'une approche multidisciplinaire et intégratrice et suggère, sur cette base, les pistes à explorer en priorité pour mieux évaluer l'exposition aux SPD et, *in fine*, cerner véritablement les risques sanitaires qui en résultent.

Mots clés : estimation de l'exposition, sous-produits de désinfection, trihalométhanes, eau potable, piscine, variations environnementales spatio-temporelles, modélisation toxicocinétique à base physiologique.

ABSTRACT

Disinfection of drinking and swimming pool waters disinfection is unavoidable but induces the formation of by-products (DBPs), such as trihalomethanes (THMs), haloacetic acids (HAAs) and chloramines (CAMs), that could be harmful to human health. The still challenging DBP exposure assessment prevent their suspected adverse effects (i.e., cancers, adverse pregnancy outcomes, irritations) to be clearly established. A methodology has been conceptualized which consists of integrating environmental occurrence data with physiologically based toxicokinetic (PBTK) modeling to improve DBP exposure assessment. It was designed to allow both spatial and temporal variations of the environmental contamination and the biological impacts of between- and within-individual differences to be accounted for. This thesis comprised of two parts. Each one investigates successively both environmental and biological aspects. The objective is to contribute to the development of an innovative integrated strategy and to the definition of best practices for DBP exposure assessment.

The first part of the thesis, comprising papers I and II, focuses on household exposure (i.e., resulting from drinking water use at home) and on THMs, the most abundant and volatile DBPs that can be absorbed not only by ingestion but also by inhalation and dermal absorption. These two papers investigate particularly the short-term (day-to-day and within-day) variations of THM levels in the drinking water and then their impact on the internal exposure indicators. They described the amplitudes and the diversity of the environmental variations, failed to model them in a systematic and practical way for epidemiological purposes but assessed, for the first time, their impacts on the predicted biological levels which appeared quite low.

The second part concerns the exposure to DBPs in swimming pool which is of a growing international interest. Only the allegedly worrying case of public indoor swimming pool was regarded. This section focuses on the feasibility of using the previously mentioned approach, which was first designed for dealing with household exposure, for DBP exposure assessment in swimming pools. First, Paper III investigated the occurrence and spatial and temporal variations of DBPs in both water and air of swimming pools to

model them. Focusing on chloroform, the most abundant THM, Paper IV examined the ability and reliability of PBTK modeling to simulate various swimming pool exposure events and predict the resulting biological levels in individuals. The results show, among other things, the difficulty of explaining precisely the environmental contamination and point out the necessity to carry out a minimal *in situ* sampling to monitor the environmental levels of DBPs. Compared to other approaches, PBTK modeling is a powerful but still to be improved tool for predicting swimming pool exposure.

Eventually, these works underline the relevance and the necessity of a multidisciplinary and integrating approach for better estimating exposure to DBPs and therefore health risks. Further issues that should be addressed are recommended.

Keywords : exposure assessment, disinfection by-products, trihalomethanes, drinking water, swimming pool, spatio-temporal environmental variations, physiologically based toxicokinetic modeling.

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LISTES DES SIGLES ET ABRÉVIATIONS

AFSSET	Agence française de sécurité sanitaire de l'environnement et au travail
AHA	Acide haloacétique
BCA	Acide bromochloroacétique
BDCA	Acide dichlorobromoacétique
CAM	Chloramine
CDBM	Chlorodibromométhane
CMA	Concentration maximale admissible
DBA	Acide dibromoacétique
DBCA	Acide dibromochloroacétique
DCA	Acide dichloroacétique
DCAM	Dichloramine
DCBM	Dichlorobromométhane
IRSST	Institut de recherche Robert-Sauvé en santé et en sécurité du travail
MBA	Acide monobromoacétique
MCA	Acide monochloroacétique
MCAM	Monochloramine
MDDEP	Ministère du développement durable, de l'environnement et des parcs
MO	Matière Organique
RQEP	Règlement sur la qualité de l'eau potable
RRSE	Réseau de recherché en santé environnementale
SPC	Sous-produits de la chloration
SPD	Sous-produits de la désinfection

SPDe	Sous-produits émergents
TBM	Tribromométhane (bromoforme)
TBA	Acide tribromoacétique
TCA	Acide trichloroacétique
TCAM	Trichloramine
TCBP	Toxiciocinétique à base physiologique
TCM	Trichlorométhane (chloroforme)
THM	Trihalométhanes
TTHM	Trihalométhanes totaux (sommes des quatre principaux composés)
USEPA	United States Environment Protection Agency

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INTRODUCTION GÉNÉRALE

Préambule : Exposition en « milieu domestique » et Exposition en « piscine »

On distinguera tout au long de ce document l'exposition en « milieu domestique » et l'exposition en « piscine » à nos contaminants d'intérêt, les sous-produits de désinfection (SPD). L'exposition en milieu domestique désignera l'exposition relative à l'utilisation de l'eau distribuée par les réseaux d'aqueducs au domicile des consommateurs (ex., consommation de l'eau ou des boissons à base d'eau, prise de douche, prise de bain, vaisselle, lavage). Dans le cadre de ces travaux,, l'étude de la seconde problématique sera consacrée essentiellement au cas des piscines publiques intérieures (couvertes) bien que l'appellation générique « exposition en piscine » puisse aussi être évoquée pour désigner l'exposition (récréative et/ou professionnelle) advenant dans d'autres lieux où l'eau est utilisée à des fins ludiques ou de remise en forme (ex., piscines publiques extérieures, piscines privatives, centres aquatiques, spas).

La présente section introductive vise à mettre en avant, après une rapide présentation des différents SPD, les raisons qui motivent l'intérêt pour ces composés, notamment dans le domaine de la santé publique et de l'analyse du risque. Elle dresse également un aperçu des techniques et méthodes mises en œuvre pour contrôler et estimer les deux types d'exposition susnommés et met en exergue les principaux résultats qui ressortent de la littérature quant aux facteurs environnementaux et biologiques de variation de ces expositions. Avant d'énoncer les objectifs de cette thèse, la dernière partie de cette introduction définit le cadre conceptuel autour duquel se sont articulés nos travaux et qui a été développé pour améliorer les méthodes d'estimation de l'exposition aux SPD sur la base d'une approche intégrant des outils de différentes disciplines.

1. La désinfection de l'eau

1.1. Importance de la désinfection de l'eau pour la santé publique

La désinfection de l'eau a sans aucun doute constitué une avancée primordiale et demeure un procédé absolument indispensable au regard de son impact pour la santé publique. Des règles visant à rendre l'eau plus saine à la consommation étaient déjà prescrites en 2000 av J.C (ex., exposition à la lumière du soleil, filtration sur charbon de bois, ébullition). Les mécanismes régissant la désinfection n'ont été véritablement explorés que beaucoup plus tard, et les effets des désinfectants n'ont été établis qu'au milieu du XIX^{e} siècle. La désinfection s'est ensuite rapidement répandue et est devenue monnaie courante dès les années 1900 (LENNTECH, 2011). Cet essor a incontestablement contribué à la réduction drastique des maladies d'origine hydrique, notamment des maladies graves et mortelles comme le choléra ou la fièvre typhoïde (Santé Santé Canada, 2006). L'effet des désinfectants tient à leur action oxydante. Leur emploi a différentes utilités (ex. améliorer goût et couleur, améliorer l'efficacité des traitements de l'eau) mais l'objectif premier reste l'inactivation (élimination ou neutralisation) des microorganismes pathogènes (ex., bactéries, virus, protozoaires) (Sadiq & Rodriguez, 2004; U.S.E.P.A., 1999). En ce sens, les bénéfices de la désinfection sur le plan sanitaire la rendent nécessaire pour ne pas dire tout bonnement incontournable.

1.2. Aperçu des méthodes de désinfection

1.2.1. En réseau

Différents agents et/ou procédés peuvent être utilisés pour désinfecter l'eau distribuée par les réseaux hydrauliques (ex., ozone, chloramines, dioxyde de chlore, ultraviolets) (Sadiq and Rodriguez, 2004). Le chlore demeure entre tous le plus prisé notamment du fait de ses propriétés oxydantes hautement bactéricides et propices à l'inactivation des virus (Vandentorren et al., 2004). D'un point de vue pragmatique, la chloration s'avère un procédé moins coûteux et plus pratique à mettre en œuvre. En outre, cette technique

permet, par rapport aux autres à l'efficacité plus limitée dans le temps, de maintenir un résiduel de désinfectant dans le réseau, depuis la station de traitement et idéalement jusqu'au robinet du consommateur. Il s'agit de l'effet de rémanence qui protège notamment le réseau face à une éventuelle recroissance microbienne (Santé Canada, 2006).

1.2.2. En piscine

Les piscines sont alimentées en eau neuve par le réseau d'eau publique ou à partir d'une source privée. Cette eau neuve n'est bien évidemment pas directement introduite dans les bassins (Lagadec, 2005). De manière générale, elle transite d'abord par un système de bacs qui doit permettre de réguler l'apport d'eau dans le bassin et d'appliquer les traitements supplémentaires nécessaires pour rendre cette eau de baignade saine. L'eau neuve rejoint au niveau d'un bac tampon l'eau venant du bassin qui doit être traitée en vue de sa recirculation. L'eau du bassin à traiter est généralement reprise par les goulottes tandis que l'apport d'eau traitée s'effectue par le fond du bassin. En pratique, on procède à un renouvellement journalier, en moyenne, de 50 à 80 litres d'eau par jour dans le bassin. En France, les piscines couvertes doivent être entièrement vidangées au moins deux fois par an (Lagadec, 2005). Au Québec, le règlement sur la qualité de l'eau des piscines et autres bassins artificiels ne pose pas d'exigence quant à la fréquence minimale des vidanges complètes mais le guide d'exploitation des piscines et autres bassins artificiels qui accompagne ledit règlement stipule qu'une vidange peut s'avérer nécessaire pour éviter des difficultés de traitement dues à l'accumulation de produits divers dans l'eau (Ministère du Développement Durable, Environnement et Parcs, 2005).

Avant la désinfection, l'eau peut subir un traitement permettant une épuration préalable (ex, filtration, coagulation). La désinfection s'effectue ensuite généralement par application de produits chlorés (ex., chlore gazeux Cl_2, eau de javel NaClO, l'hypochlorite de calcium $Ca(ClO)_2$), de brome, d'ozone ou bien encore d'ultraviolets. La chloration demeure encore la technique de désinfection la plus prisée pour les piscines, tout comme en réseau. Les contraintes de stockage et les difficultés d'approvisionnement limitent l'utilisation de brome également envisageable (Lagadec, 2005). L'ozonation ne se suffit pas à elle seule car elle n'offre pas d'effet rémanent. Qui

plus est, avant d'être introduite dans le bassin, l'eau doit généralement subir une désozonation pour supprimer l'excès d'ozone. Des solutions alternatives consistent encore en l'emploi de rayonnement UV (rayonnement à 254 nm), ou de sels d'argent. Mais l'emploi de l'une ou l'autre de ces méthodes ne saurait totalement se substituer dans un futur proche à celui de la chloration (Zwiener et al., 2007).

2. Les sous-produits de désinfection (SPD)

2.1. Historique et formation des sous-produits

C'est au début des années 1970 que l'on met en évidence la présence de chloroforme ou trichlorométhane (TCM) dans l'eau ayant été traitée alors que cette substance n'était pas présente à la source (Bellar et al., 1974). C'est le premier exemple connu de l'induction de sous-produits suite au traitement de l'eau pour la consommation. Rook (1974; 1976; 1977) propose, par la suite, un modèle de formation des SPD à partir d'une molécule de résorcinol, basée sur l'ouverture du cycle aromatique du fait de l'action oxydante de l'agent désinfectant et sur un clivage subséquent de la dite molécule.

La formation des SPD s'explique ainsi par des réactions chimiques entre le désinfectant et la matière organique (MO) présente dans l'eau. De nombreux paramètres influencent ce processus de formation et la spéciation des SPD, à savoir : la charge en MO de l'eau à désinfecter et plus généralement sa qualité initiale (ex., charge en ions bromures), ainsi que les conditions opérationnelles du traitement de l'eau (température, pH, dose de désinfectant, temps de réaction) (Tardif et al., 2011).

2.2. Les composés identifiés et leurs propriétés physico-chimiques

Plus de six cents SPD ont été identifiés à ce jour et la liste des sous-produits dits « émergents » ne cesse de s'allonger (Richardson et al., 2007; Richardson et al., 2010). Entre tous ces nombreux SPD, les trihalométhanes (THM), les acides haloacétiques (AHA) et les chloramines (CAM) sont les plus communs, particulièrement quand la

désinfection s'effectue par chloration. On parle alors plus spécifiquement des sous-produits de chloration (SPC).

2.2.1. Les trihalométhanes (THM)

Les THM sont les mieux connus des SPC et des SPD, car les plus étudiés : d'une part, ils furent les premiers à être découverts dans les eaux chlorées; d'autre part, ils sont les plus abondants. Les THM sont constitués de l'association de trois atomes d'halogènes (chlore Cl, brome Br, fluor F, ou iode I) à un radical méthane (CH). Les THM les plus communs sont le chloroforme ou trichlorométhane (TCM/Cl_3CH), le bromodichlorométhane (BDCM/$BrCl_2CH$), le dibromochlorométhane (DBCM/Br_2ClCH), le bromoforme ou tribromométhane (TBM/Br_3CH). TTHM est l'abréviation utilisée couramment pour renvoyer à la somme de ces quatre composés.
Les THM sont reconnus comme des composés particulièrement volatils qui peuvent se diffuser facilement dans l'air. Ils peuvent ainsi être absorbés par ingestion, inhalation mais aussi par voie percutanée étant également grandement lipophiles (Weisel & Jo, 1996; Xu et al., 2002; Xu & Weisel, 2003).

2.2.2. Les acides haloacétiques (AHA)

Les AHA sont des composés constitués d'une molécule d'acide acétique (CH_3COOH) sur laquelle un (ou des) halogène(s) se sont substitués à un (ou des) hydrogène(s) attaché(s) à un (ou des) carbone(s). On dénombre neuf principaux acides haloacétiques : l'acide monochloroacétique (MCA), l'acide dichloroacétique (DCA), l'acide trichloroacétique (TCA), l'acide monobromoacétique (MBA), l'acide dibromoacétique (DBA), l'acide tribromoacétique (TBA), l'acide bromochloroacétique (BCA), l'acide bromodichloracétique (BDCA) et l'acide dibromochloroacétique (DBCA). AHA5 désigne généralement la somme des cinq premiers composés cités et AHA9 la somme de tous ces composés.
Les AHA sont stables et facilement solubles dans l'eau. Ils sont en revanche peu volatils à la différence des THM. On considère traditionnellement l'ingestion comme l'unique voie d'absorption des AHA (Xu et al., 2002).

2.2.3. Les chloramines (CAM)

Les chloramines (ou chlore combiné) résultent de la réaction de l'agent désinfectant avec des matières azotées. Peuvent notamment se former la monochloramine (MCAM/NH_2Cl), la dichloramine (DCAM/$NHCl_2$) et la trichloramine (TCAM/NCl_3).
Les chloramines se diffusent facilement dans l'air sous forme de TCAM. L'exposition à cette dernière forme s'effectue ainsi essentiellement par inhalation (Héry et al., 1994).

2.2.4. Autres composés

De nombreux autres composés existent. L'U.S.E.P.A (1999) inventoriait les SPD connus et les principaux résidus de désinfection d'intérêt en termes de santé publique parmi lesquels on trouve également les haloacétonitriles, les halocétones, les chlorophénols. Les progrès de la chimie analytique permettent aujourd'hui d'identifier de nouveaux composés, présents en très petites quantités mais qui suscitent un intérêt grandissant (Krasner et al., 2006) : les THM iodés, les halométhanes, les halonitrométhanes, les haloamides sont de ceux-ci.
La question de l'exposition à ces composés ne sera pas abordée dans le cadre de cette thèse.

3. Les risques sanitaires relatifs aux SPD : effets, incertitudes et contrôles

3.1. Les effets sanitaires suspectés

Sur la base d'une importante revue de la littérature, l'Agence française de sécurité sanitaire de l'environnement et au travail (AFSSET) a rendu compte, dans un récent rapport, des dangers potentiels liés à chacun des différents composés préalablement cités (AFSSET, 2010). Une récente revue a également été publiée par un autre groupe de chercheurs français (Florentin et al., 2011).
De manière globale, on peut distinguer quatre types d'effets qui font encore l'objet de suspicions plus ou moins marquées et retiennent l'attention des chercheurs :

(i) La cancérogénicité associée aux AHA et surtout aux THM reste source de questionnement mais les données pour appuyer ce lien demeurent limitées. Le risque de cancer du colon, du rectum et de la vessie sont les seuls qui semblent encore véritablement d'actualité (Rahman et al., 2010; Villanueva et al., 2004). Rahman et al. (2010) ont estimé, dans un méta-analyse incluant treize études épidémiologiques, des risques relatifs de 1,27 (IC à 95% : 1.08-1.50) pour le cancer du colon et de 1,30 (IC à 95% : 1,06-1,59) pour le cancer du rectum. Les auteurs soulignent toutefois que le poids de la preuve demeure limité et que le lien de cause à effet entre l'exposition aux SPD et ces cancers ne peut être établi tenant compte des insuffisances de l'étude. L'étude de Villanueva et al. (2007a) a conclu à une association positive et significative, notamment chez l'homme, entre le développement de cancer de la vessie et l'exposition aux THM sur le long terme ([OR= 2.10 / IC à 95% : 1.09- 4.02] pour des expositions à niveaux >49µg/L dans l'eau en comparaison à des expositions à des niveaux <8µg/L). Cett effet n'est toutefois pas spécifique aux THM et l'étude ne précisait pas si des expositions à d'autres substances potentiellement toxiques, par exemple, en milieu de travail, avaient été considérées. La même étude a trouvé une association signficative spécifiquement entre la fréquentation des piscines et ce type de cancer ([OR=1.59 / IC à 95% :1.18-2.09]). Suite à une méta-analyse de trois études épidémiologiques conduite en Europe, la même équipe a observé un risque significatif de cancer de la vessie pour les hommes exposés à des niveaux >50µg/L de THM par rapport à ceux exposés à des niveaux <5µg/L (Costet et al., 2011). Cantor et al. (2010) ont suggèré que le polymorphisme de certains gènes (GSTT1, GSTZ1, CYP2E1) régulant le métabolisme des THM entrainerait des risques accrus chez certains individus. Panyakapo et al. (2008) ont, de leur côté, estimé un risque de cancer au-delà de celui usuellement considéré comme acceptable par l'United States Environmental Protection Agency (U.S.E.P.A) pour des nageurs exposés aux THM sur le long terme. L'étude demeure toutefois perfectible, tenant compte entre autres que toutes les voies d'exposition n'ont pas été considérées et que des fréquences d'exposition élevées ont été assumées.

(ii) La question d'un possible risque reprotoxique attribuable aux AHA et aux THM concerne essentiellement les retards de croissance intra-utérine et les bébés de petits poids à la naissance pour les femmes exposées durant leur grossesse (Graves et al.,

2001; Levallois et al., 2012; Porter et al., 2005; Tardiff et al., 2006). Nieuwenhuijsen et al. (2002) n'ont toutefois pas mis en évidence d'association entre la pratique de la natation chez les femmes enceintes et le poids à la naissance.

(iii) un intérêt croissant porte depuis peu sur le potentiel génotoxique et mutagène de ces mêmes composés, et notamment des substances bromées (Kogevinas et al., 2010; Liviac et al., 2010; Plewa et al., 2010; Richardson et al., 2007; Richardson et al., 2010). Richardson et al. (2010) ont estimé les pouvoirs mutagénes de l'eau de consommation et de l'eau de piscine équivalente, cette dernière s'avèrant plus concentrée en THM et CAM mais contenant des composés non détectés dans la première. L'étude de Kogenivas et al. (2010) mesurant des marqueurs d'effets génotoxiques chez des nageurs suggère un potentiel génotoxique spécifiquement associé aux composés bromés.

(iv) le pouvoir irritant (respiratoire et oculaire) des CAM, et plus spécifiquement de la TCAM abondamment présente dans l'air des piscines, est sans aucun doute l'effet sanitaire indésirable le mieux renseigné et le mieux établi, et semble indubitablement concerner tant les sauveteurs que les nageurs, et notamment les compétiteurs (Gérardin & Subra, 2004; Goodman & Hays, 2008; Héry et al., 1995; Jacobs et al., 2007; Kaydos-Daniels et al., 2007; Kohlhammer & Heinrich, 2007; Lévesque et al., 2006; Massin et al., 2001; Nemery et al., 2002; Parrat, 2008; Thickett et al., 2002; Thoumelin et al., 2005). Des travaux belges, à fort écho médiatique, ont insisté sur la probabilité forte d'un lien entre cette exposition et l'apparition d'allergies et d'asthme chez un jeune public, et plus particulièrement chez les bébés (Bernard et al., 2006; Bernard & Nickmilder, 2006; Bernard, 2007; Bernard et al., 2008; Bernard et al., 2009; Nickmilder & Bernard, 2007; Voisin & Bernard, 2008), suscitant un intérêt international pour le sujet (Font-Ribera et al., 2009; Font-Ribera et al., 2011; Schoefer et al., 2007; Weisel et al., 2009). Florentin et al. (2011) souligne toutefois l'inconsistence entre différentes études du lien entre l'exposition à la TCAM et des altérations pulmonaires (épithélium). Les études de Font-Ribera (2010, 2011) n'ont, en revanche, pas montré d'impact d'une pratique de 40 minutes de natation sur les biomarqueurs d'effets respiratoires, ni d'association entre la pratique de la natation durant la prime enfance et des symptomes allegiques ou asthmatiques plus fréquents à 7 et 10 ans. Au contraire, l'étude la plus

récente associe à la pratique de la natation des risques moindres de présenter des symptômes d'asthme.

3.2. Moyens de contrôle des risques sanitaires relatifs à l'exposition aux SPD

3.2.1. Réglementations

Les réglementations des teneurs en SPD en vigueur à travers le monde concernent essentiellement les réseaux de distribution d'eau potable. Les niveaux ambiants de SPD en piscine ne sont légiférés que dans un nombre très restreint de pays. Dans tous les cas, il est communément admis que l'on doit viser les niveaux de contamination en SPD les plus faibles possibles sans toutefois jamais compromettre l'efficacité de la désinfection sur le plan microbiologique.

3.2.1.1. Réseaux de distribution

Les normes québécoises concernant les concentrations maximales acceptables (CMA) de SPD dans les réseaux suivent essentiellement les recommandations de Santé Canada, elles-mêmes très proches de celles de l'U.S.E.P.A (MDDEP, 2006, 2012; U.S.E.P.A., 2006). Le Québec impose ainsi que la moyenne annuelle des concentrations maximales d'échantillons prélevés en des points représentatifs du réseau chaque trimestre ne dépasse pas la limite de 80 µg/L pour les TTHM. Cette CMA est légèrement plus sévère que celle recommandée par Santé Canada (100 µg/L) mais équivalente à celle imposée par l'U.S.E.P.A.

L'U.S.E.P.A a introduit une CMA à 60 µg/L pour les AHA5 en 2006. Santé Canada a dans le même ordre d'idée recommandé une CMA à 80 µg/L pour ce même groupe de composés. Au Québec, une modification au Règlement sur la qualité de l'eau potable (RQEP), en date de février 2012, a vu l'entrée en vigueur d'une norme pour les AHA (concentration moyenne maximale en AHA5 calculée sur quatre trimestre : 60µg/L) et impose une surveillance accrue également pour les THM (MDDEP, 2012).

Pour les CAM, la CMA au Québec est celle de Santé Canada à savoir 3 mg/L.

3.2.1.2. Piscines

L'Allemagne est, parmi les quelques pays à réglementer la teneur en THM dans l'eau des piscines, le plus sévère avec l'adoption d'une norme de 20 µg/L, juste avant la Suisse (30 µg/L, pour les piscines intérieures). Le Royaume-Uni, la Finlande et le Danemark recommandent des concentrations inférieures à 100 µg/L. La Belgique a fixé, pour sa part, une valeur limite à 100 µg/L pour le seul TCM. Aucune législation ne porte sur la teneur en AHA des eaux de piscine. Au Québec, la législation veut que Les teneurs en CAM doivent rester inférieures à 0.5mg/L dans l'eau des bassins intérieurs et à 1mg/L dans celle des bassins extérieurs. Aucun pays n'applique de réglementation spécifique à la tricholoramine dans l'eau malgré la recommandation de l'Organisation Mondiale de la Santé (0.5 mg/L).

Il n'y a pas de réglementation concernant les teneurs en THM ou TCAM dans l'air des piscines intérieures. Toutefois, une étude suisse, l'une des plus complètes et des plus robustes menées jusqu'à maintenant sur le sujet, a recommandé récemment la fixation à 0,3mg/m^3 d'une valeur limite d'exposition au poste de travail pour ce contaminant (Parrat, 2008). Cette valeur est en dessous de la « valeur de confort » de 0,5mg/m^3 en deça de laquelle les employés ne rapportaient pas de gêne respiratoire ou d'irritation oculaire qui avait été proposée par les français dans les années 90 et qui faisait depuis lors référence (Héry, 1994; Thoumelin et al., 2005).

3.2.2. Moyens techniques de mitigation

On peut distinguer quatre principaux axes (Bhardwaj, 2006) autour desquels peuvent s'articuler les moyens d'action pour minimiser la formation ou l'occurrence des SPD dans l'eau (Bhardwaj, 2006; Krasner et al., 2006) : (i) enlever les précurseurs organiques des SPD avant d'injecter le désinfectant (ce qui requiert notamment de développer des procédés de filtration très efficace et à coût raisonnable, ou plus spécifiquement en piscine, d'imposer des règles d'hygiène strictes pour réduire le plus possible l'apport de matière organique par les baigneurs) ; (ii) diminuer et ajuster au mieux les doses de désinfectants injectés (ce qui est en pratique difficile à régler) ; (iii) retirer les SPD formés (ce qui nécessite des filtres ou des procédés particulièrement efficaces) ; (iv) envisager des solutions alternatives au chlore pour la désinfection (alors que les coûts financiers et le rapport avantages/inconvénients sont souvent en faveur de la chloration).

L'adoption d'options autres que la chloration peut toutefois déplacer le problème, modifiant les types de SPD formés ou leurs proportions relatives.

Par exemple, en piscine plus spécifiquement, où l'exposition aux CAM, et plus exactement à la TCAM, est préoccupante, l'application d'ultraviolets s'est développée en tant qu'elle permettait de réduire l'occurrence de ces composés (déchloramination). Il a toutefois été établie que cette technique induisait en contrepartie une formation accrue de TCM (Cassan et al., 2006; Gérardin et al., 2005; Lagadec, 2005). Des procédés mécaniques (strippage et brassage de l'eau dans le bac tampon) ont aujourd'hui le vent en poupe du fait d'une efficacité, semble-t-il, redoutable pour limiter la volatilisation de la TCAM dans le bassin principal (Gérardin et al., 2005).

De manière générale, il reste toutefois, malgré des avenues encourageantes, encore du chemin à faire pour résoudre les difficultés rencontrées dans le développement ou la mise en œuvre de méthodes efficaces de mitigation. En un sens, ceci fait prévaloir la nécessité de mieux documenter et estimer l'exposition aux SPD pour *in fine* mieux cerner les risques réels pour la santé.

3.3. Éléments d'incertitudes pour l'analyse du risque relatif aux SPD

S'il existe des données plus ou moins probantes attestant des différents effets sanitaires indésirables susnommés et que celles-ci doivent ainsi inciter à une certaine prudence, il demeure délicat, voire hâtif, de conclure catégoriquement à l'existence (ou non) de liens causaux entre l'occurrence de risques sanitaires et l'exposition aux différents SPD. Toxicologues et épidémiologistes se heurtent ainsi à plusieurs difficultés qui compliquent l'établissement d'un portrait clair de cette problématique (Vandentorren et al., 2004).

Au niveau toxicologique, outre les inévitables et souvent pesantes incertitudes relatives aux extrapolations des résultats des études conduites chez l'animal à l'humain (ex., problèmes associés à l'adéquation des doses et voies d'exposition et des voies métaboliques entre les espèces), les mécanismes diversifiés suivant lesquels nos contaminants d'intérêt pourraient exercer leurs actions toxiques doivent encore être mieux élucidés. Si l'action toxique topique des CAM, sur le système respiratoire notamment, semble la mieux établie, les modalités de la toxicité systémique des autres

SPD demeurent à clarifier. Il est par exemple toujours question de savoir si les effets sanitaires présumés seraient davantage liés à des composés (produit mère ou métabolite) en particulier ou à mélange inévitable de tous (ou, au moins, de plusieurs d'entre eux) dans le médium environnemental. Dans ce même ordre idée, Zwiener et al. (2007) rapportent que, selon plusieurs études, le risque sanitaire relatif aux THM dépendrait de la voie d'exposition. L'absorption possible des THM par inhalation et par voie percutanée pourrait ainsi résulter en une éventuelle activation mutagénique des composés bromés dans certains organes.

Les limites méthodologiques des mesures d'exposition restent le principal point faible des investigations épidémiologiques. Cet aspect est abordé dans la section suivante de l'introduction et sera plus largement développé dans le corpus de cette thèse. Cette insuffisance à approcher convenablement l'exposition à ces contaminants pèse de tout son poids sur la caractérisation précise du risque sanitaire relatif aux SPD et se répercute évidemment sur la mise en place de mesures de contrôle véritablement efficaces. L'adéquation et la pertinence des contrôles réglementaires, lorsque prescrits, sont sujettes à caution (Sadiq & Rodriguez, 2004): la question de savoir si la fréquence des échantillons environnementaux suffit à prendre en compte raisonnablement les variations spatiales et temporelles pourtant significatives des concentrations des différents SPD est fondamentale. Elle a d'ailleurs focalisé l'attention des experts américains lors de la révision de la réglementation étatsunienne relative aux SPD en réseau (U.S.E.P.A., 2006).

Comme nous l'évoquions plus haut déjà, en réponse aux exigences réglementaires, les moyens techniques de mitigation consistent essentiellement à mettre en œuvre des procédés alternatifs de désinfection qui viennent se substituer à des procédés plus traditionnels, au risque toutefois de générer d'autres SPD moins connus ou juste d'en modifier la spéciation. Dans ce contexte, l'amélioration des méthodologies de mesurage ou d'estimation de l'exposition nous apparaît comme une priorité pour, outre cerner les risques sanitaires potentiels, fournir des indications pour mieux envisager la maîtrise des risques les plus avérés.

4. Mesure de l'exposition aux SPD : stratégies, facteurs de variations et insuffisances

Outre le fait que les quantités de SPD, tant dans les média environnementaux (i.e., eau, air) que dans les compartiments biologiques (ex., sang, foie), demeurent relativement faibles avec tout ce que cela sous-tend en termes de difficultés à appréhender l'exposition et à la lier à des effets sanitaires subséquents, deux principaux problèmes complexifient l'évaluation de l'exposition aux SPD : 1/ la variabilité spatio-temporelle des niveaux de contamination environnementale et 2/ les particularités comportementales et physiologiques des individus exposés au regard de cette exposition. Ce sont essentiellement les impacts de ces deux aspects sur les mesures d'exposition aux SPD qui nous intéresseront dans cette thèse, d'abord dans le contexte d'une exposition domestique puis dans celui d'une exposition en piscine.

4.1. Éléments relatifs à l'exposition domestique

4.1.1. Facteurs de variation de l'exposition

En termes d'exposition domestique, les investigations menées jusqu'à maintenant ont exclusivement concerné les THM et les AHA au regard des effets susmentionnés (cf. 3.1).

On propose la classification suivante pour distinguer les éléments susceptibles d'influencer la précision des mesures de l'exposition : (i) la localisation géographique et la situation temporelle du consommateur sur le réseau qui lui fournit l'eau potable ; (ii) les caractéristiques particulières du contexte domestique de la personne exposée, incluant l'agenda d'utilisation de l'eau, la présence d'appareillage de traitement de l'eau, les conditions d'aération de la maison et le nombre d'occupants de la maison.

La localisation géographique du robinet et la situation temporelle du consommateur sont bien sûr à mettre en relation avec les variations spatio-temporelles des concentrations de SPD dans le réseau hydraulique, elles-mêmes dépendantes à la fois de la qualité de l'eau brute, du système de traitement et des caractéristiques du réseau. Sur le plan spatial, ces variations se font ainsi ressentir aussi bien à une échelle internationale qu'à une échelle locale, renvoyant aux différences de conditions climatiques entre différent(e)s

régions/pays. Les variations sont également observables à l'intérieur d'un même réseau. Dans la région de Québec, Rodriguez and Serodes (2001) ont ainsi observé que la concentration de THM en bout de réseau pouvait être entre 1,3 à 2,5 fois celle en sortie d'usine. Sur le plan temporel, à Québec toujours , Rodriguez et al. (2003) ont fait ressortir des concentrations en extrémités de réseau variant entre l'hiver et l'été d'un facteur compris entre 2,5 à 5. Les variations spatiales, saisonnières et mensuelles ont été abondamment étudiées depuis lors (Coulibaly & Rodriguez, 2003; Legay et al., 2010b; Legay et al., 2011a; Legay et al., 2011b). Des données, recueillies par Sadik (2002) ont également mis en avant des variations horaires et journalières dans les concentrations de THM. Cet aspect, autrement abordé seulement par Chaib et Moschandreas (2008) à notre connaissance, sera développé sur la base des données de Sadik (2002) dans le premier volet de cette thèse.

Les caractéristiques du contexte domestique concernent essentiellement les habitudes d'utilisation et de manipulation de l'eau, notamment les particularités d'usage susceptibles de modifier la concentration en contaminants (i.e., entreposage au réfrigérateur, ébullition avant consommation, filtration au robinet ou sur pichet) (Levesque et al., 2006). Cela renvoie également aux conditions d'exposition différentes d'un individu à l'autre selon la fréquence, les moments et la durée des périodes d'exposition. Qui plus est, tout cela est à mettre en relation avec les variations des concentrations des SPD volatils dans l'air ambiant qui vont contribuer à l'exposition via l'inhalation. Gordon et al. (2006) et Nuckols et al. (2005) ont mis en évidence comment les activités domestiques (ex., douches, bains, lessives, vaisselles) pouvaient induire une contamination subséquente de l'air en SPD influençant ainsi l'exposition des individus. Évidemment, cette contamination va dépendre des conditions d'aération des différentes pièces du domicile qui gouvernent l'évacuation de l'air contaminé (Kerger et al., 2005).

L'exposition aux SPD va bien évidemment dépendre aussi des caractéristiques physiologiques de l'individu, des voies par lesquelles il est exposé (i.e., percutanée, respiratoire, digestive) et de son métabolisme. Les changements physiologiques qui peuvent s'opérer chez un sujet sont susceptibles d'induire des modifications au niveau des processus d'absorption, de distribution, de biotransformation et d'élimination. A titre d'exemple, on peut évoquer le cas des femmes enceintes dont la physiologie évolue

ostensiblement au cours des neuf mois de grossesse ou les nageurs qui déploient d'intenses efforts physiques.

4.1.2. Stratégies de mesure de l'exposition et insuffisances

Des efforts ont été particulièrement investis au cours des dernières années pour améliorer la robustesse des méthodologies d'évaluation de l'exposition domestique dans le cadre d'investigations épidémiologiques. Celles-ci ont longtemps reposé seulement sur des associations écologiques s'appuyant tout au plus sur quelques prélèvements d'eau. Souvent ces données étaient issues de contrôles réglementaires qui se sont révélés depuis lors inappropriés pour rendre compte correctement de l'exposition (cf., à titre d'exemple, la modification précédemment évoquée de la réglementation des SPD par l'U.S.E.P.A). Les pistes suivantes ont été explorées pour améliorer l'estimation de l'exposition externe (concentrations des SPD dans le médium environnemental) : (i) choisir un territoire d'étude où les variations de concentrations environnementales sont les plus faibles possibles (Hinckley et al., 2005; Savitz et al., 2005); (ii) développer des outils permettant d'appréhender les données géographiques relatives au territoire à l'étude (J. Nuckols et al., 2004; J. R. Nuckols et al., 2004; Whitaker et al., 2005); (iii) mettre en place une stratégie d'échantillonnage optimale (Weinberg et al., 2006); (iv) considérer l'impact des particularités d'utilisation (manipulation avant usage, entreposage de l'eau) susceptibles de modifier la concentration effective d'exposition aux SPD par rapport à celle dans l'eau du réseau d'alimentation (Kerger et al., 2005; Krasner & Wright, 2005; Li & Sun, 2001; Wright et al., 2005). A notre connaissance, seuls Villanueva et al. (2011) et Savitz et al. (2005) ont essayé de raffiner, dans leurs investigations épidémiologiques, l'estimation de l'exposition jusqu'au niveau interne (concentrations ou doses de SPD dans l'organisme). Pour ce faire, ils ont proposé l'utilisation de facteurs d'absorption standard spécifiques à chaque activité (i.e., douche, bain, ingestion) pour calculer, tenant compte de la concentration dans l'eau et de la durée de l'activité, des indices quantitatifs de l'exposition des individus. Toutefois, cette approche, bien que pratique d'utilisation, souffre notamment de ne pas distinguer la contribution spécifique de chaque voie d'absorption dans la quantification globale de l'exposition, et de ne pas prendre en compte les particularités physiologiques des

individus exposés. Ces études demeurent toutefois des références dans le soin pris à essayer de préciser autant que possible la délicate mesure de l'exposition aux SPD. L'utilisation alternative ou complémentaire de biomarqueurs dans le cadre d'une étude épidémiologique n'est pas la panacée du fait de l'importance (dans tous les sens du terme) du nombre de participants. L'étude de Levallois et al. (2012), à laquelle est directement rattachée une partie des travaux de cette thèse et dont nous aurons l'occasion de rediscuter, propose indubitablement une des méthodologies d'estimation de l'exposition les plus minutieuses et rigoureuses mises en œuvre jusqu'ici. Elle se base sur l'approche, qui sera décrite dans la section 5 de cette introduction, autour de laquelle se sont articulés nos travaux.

4.2. Éléments relatifs à l'exposition en piscine

4.2.1. État des recherches

En termes d'exposition aux SPD en piscine, les investigations ont essentiellement été menées jusqu'à maintenant dans des piscines publiques couvertes (intérieures). Une majorité d'entre elles ont concerné les CAM au regard des possibles effets susmentionnés (cf. 3.1), notamment en France et Belgique (Bernard et al., 2003; Bernard et al., 2005; Bernard et al., 2006; Bernard & Nickmilder, 2006; Bernard, 2007; Bernard et al., 2007; Bernard et al., 2008; Bernard et al., 2009; Carbonnelle et al., 2008; Héry et al., 1995; Massin et al., 1998; Massin et al., 2001; Nickmilder & Bernard, 2007; Thoumelin et al., 2005). L'intérêt pour l'exposition aux AHA dans ce milieu a été jusque-là bien moindre. La thèse de Kim (1997) est, à notre connaissance, un des rares documents à s'être intéressés à l'exposition aux AHA dans ce milieu en documentant l'absorption percutanée du DCA et du TCA pendant une pratique de natation et estimant que le ratio de l'exposition par ingestion par rapport à l'exposition percutanée pouvait varier entre 1.3 et 5.9. Les coefficients de perméabilité estimés dans cette étude restent beaucoup plus faibles que celui du TCM. Tout dernièrement, quelques études ont porté un regain d'intérêt aux AHA (Cardador & Gallego, 2010, 2011; Lee et al., 2010). L'intérêt demeure limité tenant compte que l'ingestion est la voie prédominante d'absorption des AHA et que les quantités d'eau ingérées par les baigneurs en piscine

demeurent elles-mêmes faibles. Dufour et al. (2006) ont estimé à 37 mL d'eau le volume ingéré par un adulte au cours d'une pratique de natation. Le fait que les THM soient également absorbables par voies respiratoire et percutanée a justifié un intérêt plus marqué pour ces composés. A ce sujet, les études ont visé (a) soit à renseigner l'occurrence environnementale de ces composés dans ce milieu particulier (Chu & Nieuwenhuijsen, 2002), (b) soit, à des fins d'exploration toxicologique, à enquêter sur les modalités d'absorption et d'élimination des dits produits par l'organisme humain (Lévesque et al., 1994), (c) soit à fournir des estimations quant à l'exposition globale de différentes catégories de personnes fréquentant, occasionnellement ou assidûment, ce type de milieu (Aggazzotti et al., 1993; Fantuzzi et al., 2001; Lindstrom et al., 1997). Les premières études s'étant intéressées spécifiquement aux THM dans les eaux de baignade ont été engagées dans les années 1980 par Beech à Miami (Beech, 1980; Beech et al., 1980). Par la suite, de nombreuses études ont été conduites, notamment pour examiner les modalités de formation et d'occurrence dans l'eau et dans l'air et s'inquiétant des charges corporelles des nageurs, notamment en Allemagne et Pologne (Botzenhart et al., 1988; Cammann & Hubner, 1995; Eichelsdörfer et al., 1981; Erdinger et al., 1997a; Erdinger et al., 1997b; Glauner et al., 2005; Grohmann, 1984; Hasselbarth, 1988; Jessen, 1986; Lahl et al., 1981; Schöler & Schopp, 1984; Schösner & Koch, 1995; Stottmeister, 1999). Les nombreuses et réputées recherches italiennes sur le sujet, impliquant notamment Gabriella Aggazzotti, se sont essentiellement intéressées à valider l'utilisation du sang et de l'air alvéolaire comme marqueur d'exposition et à fournir des indications quantitatives des niveaux biologiques en THM chez différentes catégories de population (nageurs, visiteurs, personnel en charge de la maintenance ou personnel administratif de piscines intérieures) (Aggazzotti & Predieri, 1986; Aggazzotti et al., 1987; Aggazzotti et al., 1990; Aggazzotti et al., 1993; Aggazzotti et al., 1995, 1998; Fantuzzi et al., 2001; Fantuzzi et al., 2003; Fantuzzi et al., 2007; Fantuzzi et al., 2010a, 2010b; Olivo et al., 1989). En Espagne, plusieurs groupes de recherches ont poursuivi des travaux dans le même ordre idée et pour, également, améliorer les procédés d'échantillonnage. Ils ont examiné l'utilisation de l'urine comme biomarqueur et également la question de la génotoxicité/mutagénicité des SPD (Cardador & Gallego, 2010; Caro et al., 2006; Caro & Gallego, 2007, 2008a, 2008b; Font-Ribera et al., 2010;

Kogevinas et al., 2010). Au Royaume-Uni, sous l'égide de Mark Nieuwenhuijsen, des études avaient été entreprises dans les années 2000 par Chu pour notamment renseigner les niveaux environnementaux en SPD dans les piscines londoniennes et envisager la possibilité des effets sur la santé des femmes enceintes (Chu, 2000; Chu & Nieuwenhuijsen, 2002). En France, les travaux de thèse d'Hamel (2007) et de Bessonneau (Bessonneau et al., 2011) ont fourni des données d'intérêt quant à l'occurrence des THM dans l'eau et l'air de différentes piscines tandis que l'Agence Française de Sécurité Sanitaire de l'Environnement et du Travail (AFSSET) a publié un rapport, qui fait référence, quant aux risques liés aux baignades, incluant notamment le risque chimique associé à l'exposition au SPD (AFSSET, 2010). Au Québec, des études majeures ont été conduites par Lévesque et al. (1994; 2000) sur l'exposition aux THM dans le milieu des piscines. La première visait à quantifier la contribution des voies percutanée et d'inhalation à l'exposition globale. La seconde regardait les risques de cancer chez les nageurs de compétition et chez les nageurs occasionnels liés à l'exposition au TCM. Avec une troisième étude du même auteur portant sur la TCAM (Lévesque et al., 2006), ce sont, à notre connaissance, les seules études publiées jusqu'ici sur l'exposition aux SPD en piscine au Québec. Les travaux de maîtrise de Simard (2009) et ceux engagés dans le cadre de cette thèse par notre équipe veulent contribuer à documenter la question. D'ailleurs, dans le contexte particulier des piscines, et dans une perspective d'évaluation de l'exposition, les différentes habitudes culturelles et sociales des populations peuvent être particulièrement contrastées, notamment sur les points suivants : entretien des locaux, techniques de désinfection, procédés de ventilation, statistiques de fréquentation, habitudes des nageurs (ex., hygiène, cosmétiques).

4.2.2. Particularités et complexité de l'exposition en piscine : facteurs aggravants

Les piscines sont des lieux à fort potentiel d'achalandage où l'on peut présumer que les conditions contribuent à une exposition conséquente. De nombreux facteurs (liés aux exigences techniques d'entretien et/ou aux comportements individuels) peuvent en effet concourir à accroitre (i) la formation et la diffusion des contaminants en grande quantité

dans les médias environnementaux (i.e., eau, air), ainsi que (ii) leur absorption par les personnes.

4.2.2.1. Sur le plan de l'occurrence environnementale.

De nombreux éléments portent à croire que la formation des SPD puisse être « exacerbée » dans les piscines par rapport à celle qui peut être observée dans les réseaux de distribution d'eau potable. La recirculation de l'eau, pratique hydraulique inévitable pour limiter le gaspillage, favorise la concentration des contaminants dans les bassins. À ceci s'ajoute l'application de doses importantes d'agents désinfectants, précurseurs des SPD, rendu nécessaire par l'achalandage important desdits sites pour garantir la qualité d'une eau saine sur le plan microbiologique. Souvent pointée du doigt, la non-conformité aux règles d'hygiène basiques ne permet pas de minimiser l'apport continu par les baigneurs des matières organiques ou azotées, autres précurseurs des SPD. Il est improbable que les conditions de ventilation, notamment en piscines couvertes, garantissent toujours une évacuation efficace des SPD volatils (en particulier en hiver, au Québec, où les apports d'air frais peuvent avoir tendance à être limitée) alors même que les turbulences engendrées par l'activité des baigneurs peuvent accentuer le transfert de ces contaminants de l'eau du bassin à l'air du milieu (aérosols, fines gouttelettes). Dans le même ordre d'idée, la prise de douches, recommandée pour les raisons hygiéniques précédemment évoquées, a été identifiée comme une source majeure d'exposition des individus à certains SPD volatils, d'autant que cela doit pouvoir indéniablement contribuer à accroitre les niveaux de contamination de l'air ambiant.

Un des défis à relever dans l'évaluation de l'exposition tient, comme dans la problématique de l'exposition domestique, à appréhender la stabilité, ou au contraire l'instabilité, temporelle et spatiale des concentrations environnementales. La littérature laisse entrevoir des variations importantes des niveaux de contamination observées dans une même piscine selon le moment de l'année (Aggazzotti et al., 1990; Aggazzotti et al., 1998). Des discordances quant aux variations intra-journalières et horaires sont à noter : certaines études rapportent une faible variation des concentrations dans une même

journée (Lindstrom et al., 1997), alors que d'autres résultats laissent entendre que les niveaux varient grandement dès lors que le nombre de baigneurs et l'intensité de leurs activités varient (Aggazzotti et al., 1998). Qui plus est, de plus amples différences 'intra piscines' qu''inter piscines' ont été observées à Londres (Chu & Nieuwenhuijsen, 2002). Par ailleurs, la concentration de contaminants dans l'air peut varier selon la configuration et le lieu où l'on se situe dans le « bâtiment piscine ». Cela amène notamment à distinguer le niveau d'exposition des différentes catégories d'employés présents sur ces sites où l'exposition repiratoire dans les vestiaires diffère de celle autour du bassin (Fantuzzi et al., 2001). L'intensité de l'activité physique et le type de nage (Aggazzotti et al., 1993; Cammann and Hubner, 1995; Lévesque et al., 1994; Lévesque et al., 2000) peuvent, via les turbulences induites, modifier les concentrations environnementales auxquelles est exposé spécifiquement un individu (et par suite, les concentrations globales dans le lieu d'étude), de même que jouer sur l'absorption des contaminants volatils (Aggazzotti et al., 1993; Cammann & Hubner, 1995).

4.2.2.2. Concernant la détermination des concentrations biologiques.

Les niveaux de contaminant dans le sang, l'air alvéolaire et l'urine sont autant de biomarqueurs d'exposition envisagés pour les THM (Aggazzotti et al., 1990; Aggazzotti et al., 1993; Aiking et al., 1994; Caro & Gallego, 2008b). Des concentrations sanguines dépassant les 5 ug/L pour ces contaminants ont été recensées dans la littérature (Cammann & Hubner, 1995). Les concentrations dans l'air alvéolaire peuvent atteindre aisément les 100 ug/m^3 (Lévesque et al., 1994; Lindstrom et al., 1997). On note, dans l'étude de Lindstrom, que le niveau biologique de base en THM chez des nageurs de compétition (c'est-à-dire avant même le début de l'entraînement) est plus élevé que celle de la population générale. La contribution relative des différentes voies d'absorption à l'exposition aux THM fait débat. Tandis que, par exemple, Erdinger et al. (2004) ont fait ressortir l'importance de l'inhalation, de même que Lévesque et al. (1994) suivant une méthodologie comparable, Lindstrom et al. (1997) attribuent 80% de l'exposition à l'absorption percutanée. L'importance de catégoriser les différents sujets selon leurs activités durant la période d'exposition (employés présents tous les jours, visiteurs occasionnels, etc.), leurs niveaux d'effort physique pendant leurs pratiques (nage de

compétition, baignade de loisir, etc), leurs âges (jeunes, moins jeunes, etc.), et voire peut-être même leurs genres, transparaît. En outre, la prise en compte de leurs caractéristiques physiologiques n'est sans doute pas à négliger.
Des mesures biologiques de AHA peuvent être effectuées dans l'urine (Kim, 1997; Wu, 2002). Les récents travaux de Cardador et al. (2010; 2011) pour améliorer les méthodes d'analyse des AHA dans l'urine ont permis d'estimer pour la première fois l'exposition de nageurs et de travailleurs en piscine. Des niveaux pouvant aller jusqu'à 6800 ng/L, 6200 ng/L et 880 ng/L ont été mesurés respectivement pour le TCA, le DCA et le MCA.

4.3. Perspective comparative entre les expositions domestique et en piscine

La fréquentation des piscines n'avait, avant récemment, jamais été intégrée dans aucune enquête épidémiologique portant sur l'exposition aux THM ou aux AHA. Il convient pourtant de noter que les efforts entrepris dans ce sens soulignent l'importante contribution de la baignade en piscine par rapport à l'exposition globale aux THM : des travaux récents suggèrent que la dose interne acquise sur une période de plusieurs mois provient principalement de la prise de douche puis de la pratique de la natation (Villanueva et al., 2007b). Ce défaut d'intégration de la problématique « piscine » dans le cadre « domestique » plus global est à mettre en relation avec l'absence de technique de quantification simple et standard permettant d'estimer quantitativement l'exposition, autrement que par des campagnes d'échantillonnage et/ou la collecte de biomarqueurs d'exposition – stratégies à la fois complexes, contraignantes et coûteuses. Ce manque renvoie à la nécessité de mettre en place des stratégies reproductibles et optimisées : il s'agit de minimiser les efforts à entreprendre lors de la collecte des données tout en maximisant *in fine* la qualité de l'estimation de l'exposition. A notre connaissance, une alternative a été proposée jusqu'ici (Villanueva et al., 2007b). Elle consiste à calculer un indice pour estimer la dose d'exposition acquise en piscine par un individu (toutes voies d'exposition confondues), à partir de la concentration moyenne de THM dans l'eau, du temps passé par l'individu dans la piscine et d'un facteur d'absorption semblable à ceux évoqués précédemment (cf. paragraphe 4.1.2). Comme nous le soulignons déjà dans le cadre de l'exposition domestique, cette approche souffre notamment de ne pas distinguer la contribution spécifique de chaque voie d'absorption dans la quantification globale de

l'exposition, et de ne pas prendre en compte les particularités physiologiques des individus exposés.

5. Une approche multidisciplinaire novatrice pour estimer l'exposition aux SPD

Dans le contexte esquissé, il apparait nécessaire de développer davantage les méthodes d'estimation de l'exposition aux SPD tant en milieu domestique qu'en piscine afin de mieux cerner les risques sanitaires encourus. Si le cas des CAM est essentiellement préoccupant en piscine (action topique suite à une exposition par inhalation), et celui des AHA retient davantage l'attention en milieu domestique (action systémique suite à une exposition par ingestion), le cas des THM volatils et lipophiles est plus complexe à envisager et requiert une perspective intégrative des deux problématiques (piscine et réseau). Nous formalisons dans cette section une stratégie conceptuelle pour améliorer les méthodes d'estimation de l'exposition à ces contaminants sur la base de la combinaison d'outils de modélisation environnementale et toxicologique.

5.1. Outils de modélisation environnementale et toxicologique

Le lecteur est invité à consulter en annexe I de la présente thèse un chapitre publié par notre équipe dans *Encyclopedia of Environmental Health* pour de plus amples détails et des exemples quant aux modèles environnementaux et toxicologiques mis à contribution (Tardif et al., 2011). Nous nous contenterons ici de décrire sommairement leurs fondamentaux et leur intérêt.

5.1.1. Outils de modélisation environnementale

Les spécialistes en ingénierie de l'eau font jouer leurs compétences en matière de traitement des eaux et de fonctionnement des réseaux de distribution pour mieux comprendre quand, comment et dans quelles quantités les contaminants se forment puis se « propagent » dans les canalisations. Dans le cas qui nous intéresse, il s'agit de développer des méthodologies pour évaluer les concentrations de SPD dans le réseau et, *in fine*, au robinet du consommateur afin de permettre une meilleure estimation de

l'exposition externe (potentielle) des individus à ces composés. Dans cette optique, les recherches entreprises au fil des années par l'équipe de Manuel Rodriguez, co-directeur de cette thèse, et qui se sont nourris de nombreuses et intensives campagne d'échantillonnage d'eau, ont permis de générer d'imposantes bases de données dans la grande région de Québec où les conditions climatiques, extrêmes et changeantes, ont des répercussions inévitables sur la « vie » des réseaux hydrauliques qui jalonnent le territoire. De telles séries de données présentent un intérêt « descriptif » évident dans l'analyse du réseau de distribution d'eau potable et permettent de déterminer les paramètres principaux expliquant l'évolution des concentrations de SPD. Elles conduisent au développement et à la validation de modèles prédictifs de l'occurrence des SPD en différents points d'un réseau et en différents moments (Sadiq & Rodriguez, 2004). Ces données peuvent ainsi être utilisées pour mettre au point des modèles statistiques, basés sur des régressions linéaires multi-variées, permettant d'estimer les concentrations de SPD en fonction des principaux facteurs d'influence pondérés selon leurs impacts relatifs apparents. Parmi ces modèles, on distinguera les modèles « sites » et les modèles « usine ». Les premiers sont spécifiques à un site particulier : ils sont générés à partir des données cueillies en un lieu donné. Ils permettent donc d'estimer les concentrations en THM en un point précis du réseau connaissant, en ce point, les différents facteurs déterminants. Les modèles « usine » sont basés sur les paramètres accessibles au niveau de l'usine de traitement de l'eau : ils sont générés à partir de données terrain et/ou résultant d'expérimentation en laboratoire et permettent d'estimer les concentrations en THM en un point du réseau localisé en fonction du temps de séjour, c'est-à-dire du temps mis par l'eau pour atteindre ce point depuis sa sortie d'usine. Ils ne sont pas aussi linéaires que les modèles « site » mais s'ajustent un peu mieux aux niveaux réels mesurés.

5.1.2. Outils toxicologiques

Les travaux des toxicologues visent, entre autres, à décrire le lien entre l'exposition interne d'un individu et l'apparition d'effets sur l'organisme. Dans cette optique, le développement de la modélisation toxicocinétique à base physiologique (TCBP) a ouvert une voie particulièrement prometteuse. La modélisation TCBP est un système

d'équations mathématiques décrivant les processus d'absorption, de distribution, de biotransformation, et d'élimination d'une substance chimique qui détermine son comportement dans un organisme vivant. Elle s'appuie sur une représentation conceptuelle de l'organisme comme un assemblage de compartiments correspondant à des groupes d'organes, et inter reliés par la circulation sanguine. Les équations mathématiques traduisent les bilans de masse entre la quantité de substance qui entre dans chaque compartiment et la quantité qui en sort, tenant compte de la capacité du tissu considéré à « capturer » le contaminant. La modélisation intègre également dans ces équations les caractéristiques physiologiques de l'organisme à l'étude, en utilisant notamment la taille et le poids du sujet, et considère les propriétés toxicocinétiques du composé étudié. L'intégration de ces équations permet de décrire ou de prédire l'évolution en fonction du temps des concentrations internes de la substance étudiée, ainsi que de calculer les quantités métabolisées.

Dans le cadre des travaux du réseau de recherche en santé environnementale (RRSE), Haddad et al. (2006) ont développé, pour un contexte d'exposition domestique, des modèles TCBP chez l'humain pour chacun des quatre principaux THM. Ont été inclus les compartiments suivants dans la conceptualisation du modèle : poumon, peau, foie, tissus pauvrement perfusés, tissus richement perfusés, tissus adipeux. Les trois voies d'absorption possibles sont prises en compte : ingestion, inhalation, absorption percutanée. La biotransformation est réduite à la seule action du foie, compte tenu qu'au niveau de la peau et des poumons les quantités de composé métabolisées sont apparemment beaucoup plus faibles. L'élimination se fait par excrétion urinaire des métabolites ou par exhalation dans l'air expiré. Un modèle statique de volatilisation des THM, construit sur la base des travaux de McKone (McKone, 1987), a été intégré dans le modèle TCBP afin d'estimer la concentration de contaminant dans l'air de la maison et de la douche à partir de celle présente dans l'eau, et prenant en compte des facteurs relatifs à la ventilation de la pièce.

En somme, cet outil permet de déterminer, chez un individu, les niveaux internes de THM à partir de la concentration de ces contaminants dans l'eau et/ou dans l'air.

5.2. Stratégie conceptuelle pour estimer l'exposition aux SPD

La stratégie que nous préconisons repose sur l'exploitation synergique de la modélisation TCBP et de données d'occurrence environnementale collectées ou prédites. L'utilisation combinée des informations générées à partir de ces deux sources doit permettre de mieux appréhender l'exposition en considérant, simultanément ou indépendamment, l'aspect environnemental (exposition externe) et l'aspect biologique (exposition interne) de la problématique.

L'approche s'articule plus précisément en trois étapes (Figure 1) : [1] prédictions des concentrations environnementales (par application de modèles statistiques de la variabilité spatio-temporelle des SPD) ; [2] ajustements des concentrations d'exposition externe (par application de facteurs correctifs) ; [3] estimation des concentrations internes (en utilisant la modélisation TCBP).

Cette stratégie d'évaluation de l'exposition par modélisation a d'abord été pensée pour s'appliquer en contexte domestique, notamment en vue de sa mise en œuvre dans le cadre d'une étude épidémiologique menée dans la région de Québec portant sur les risques de retards de croissance intra-utérine. Le lecteur trouvera en Annexe II de la présente thèse l'article illustrant la mise en œuvre de la méthodologie et présentant les résultats de cette étude (Levallois et al., 2012).

L'étape [1], concernant fondamentalement l'intégration des variations spatio-temporelles, a été le sujet central des travaux de thèse de Christelle Legay (Legay et al., 2010a, 2010b; Legay et al., 2011a; Legay et al., 2011b). La mise en œuvre de l'étape [1] débouche sur la prédiction d'une concentration moyenne en SPD dans une zone définie du réseau et dans un intervalle de temps délimité par la fréquence des échantillonnages (généralement mensuels ou au mieux bimensuels) permettant de recueillir les données nécessaires au modèle. Effectivement, l'utilisation desdits modèles nécessite la connaissance de certains paramètres à intervalles de temps réguliers. Prenons l'exemple où les paramètres nécessaires sont évalués mensuellement, on pourra alors prédire, chaque mois, une concentration de THM pour la zone et on considérera que cette valeur sera la référence moyenne pour tous les jours du même mois.

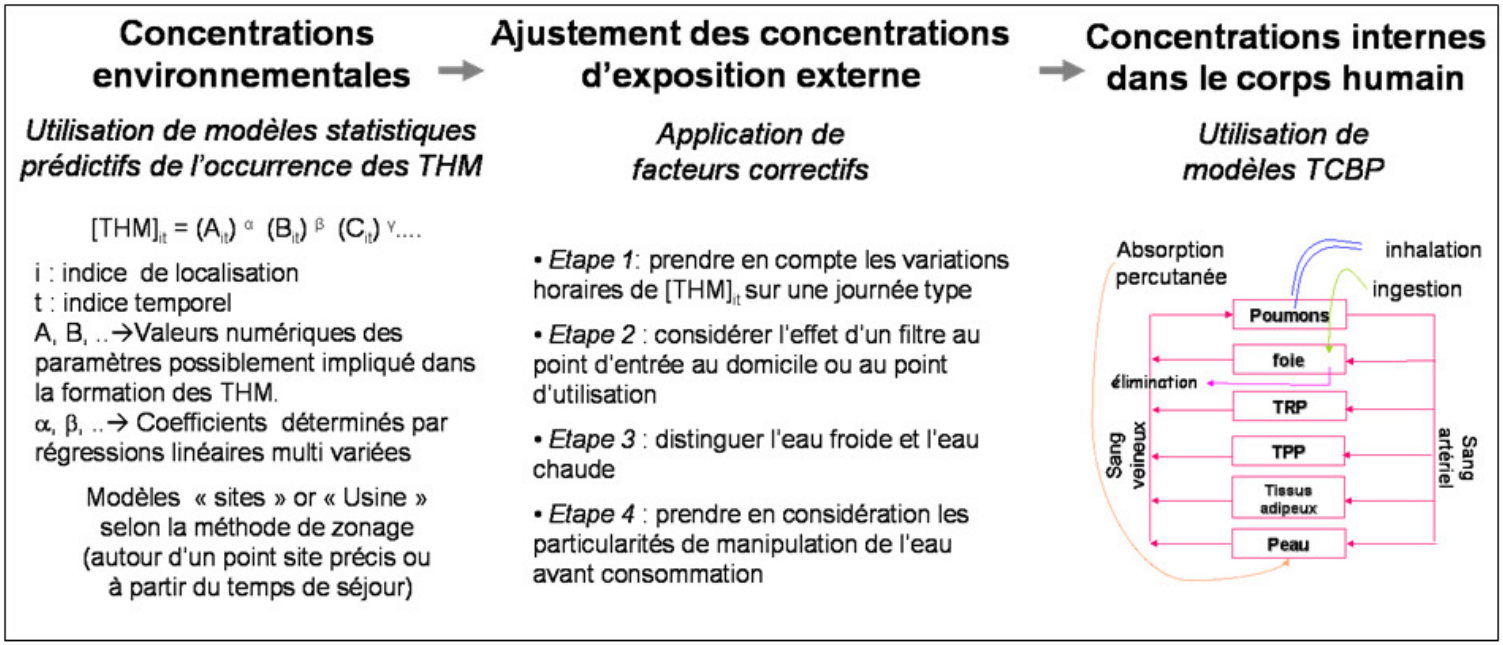

Figure 1. Schéma conceptuel d'évaluation de l'exposition par modélisation intégrée

L'étape [2] intermédiaire doit permettre de préciser autant que possible les concentrations de SPD auxquelles est véritablement exposé un individu (et qui seront en fait les entrants de l'étape [3]) en ajustant les concentrations de SPD dans l'eau du réseau prédite dans l'étape [1]. C'est une étape cruciale pour estimer convenablement l'exposition mais pour laquelle il n'existe que peu, voire pas, de données dans la littérature et qui doit être explorée davantage. Ainsi, il s'agit d'abord de considérer les variations intra-journalières des concentrations laissées pour compte dans l'étape [1] pour voir s'il convient de les appréhender pour estimer convenablement l'exposition et, le cas échéant, d'envisager la façon de faire. La question de la prédiction de ces variations intra-journalières et de leurs impacts sur l'estimation de l'exposition est l'objet du premier volet de cette thèse. Subséquemment, à cette étape [2], il faut aussi envisager les particularités d'usage et les manipulations domestiques qui peuvent induire des modifications parfois considérables de la teneur de l'eau en contaminant. Ceci implique d'appliquer des facteurs de corrections pour tenir compte, entre autres, de la présence d'appareils domestiques de traitement de l'eau au robinet ou à l'entrée d'eau, de l'impact du chauffe-eau, de l'entreposage avant sa consommation, de l'application de traitement thermique (ex, ébullition) ou de l'emploi de filtres (ex, Brita). Ces aspects ne seront qu'effleurés dans la présente thèse.

L'étape [3] permet de finaliser la démarche en estimant l'exposition au niveau interne chez un individu spécifique sur la base de la connaissance de son agenda d'exposition (durée, fréquence, moments des évènements y contribuant) et ses particularités physiologiques. L'article présenté en Annexe II fournit des précisions sur ces aspects qui ne seront pas approfondis dans le corps de cette thèse.

Finalement, le développement d'une stratégie similaire pour le contexte particulier des piscines en adaptant les outils disponibles ou en en développant de nouveaux n'est pas exclu et est l'objet du deuxième volet de cette thèse

6. Objectifs de la thèse

Cette thèse vise à contribuer à l'amélioration des méthodes d'estimation de l'exposition aux différents SPD en milieu domestique et en piscine via le développement d'une approche intégrée combinant des données d'occurrence environnementale à des modèles TCBP.

Plus spécifiquement, elle vise à :

i. documenter et modéliser les variations temporelles inter- et intra-journalières des THM dans l'eau des réseaux de distribution (article I)
ii. estimer l'impact de ces variations sur les prédictions des niveaux biologiques de THM (article II)
iii. documenter et modéliser les variations temporelles inter- et intra-journalières des THM, AHA et CAM dans l'eau et l'air des piscines (article III)
iv. évaluer la capacité (i.e., faisabilité et fiabilité) des modèles TCBP à prédire des scénarii d'exposition au TCM en piscine (article IV)

Le premier volet concerne spécifiquement l'exposition domestique. Les deux articles qui le constituent s'intéressent à l'étape [2] jugée prioritaire pour améliorer l'approche que nous préconisons. Le deuxième volet envisage l'application de cette approche, dans le contexte des piscines, en explorant d'abord l'adaptabilité à ce contexte des outils à employer dans les étapes [1] et [3] présentés dans la section 5.2. L'ensemble des travaux sont conduits en vue de mettre en perspective ces deux types d'exposition et la contribution de chacune à l'exposition globale aux SPD.

VOLET I : L'EXPOSITION AUX SOUS-PRODUITS DE DÉSINFECTION EN MILIEU DOMESTIQUE

Deux articles constituent ce premier volet de la thèse :

- Article I: *Accounting for the impact of short-term variations in the levels of trihalomethane in drinking water on exposure assessment for epidemiological purposes. Part I: environmental aspects*.
  Par : Catto C., Rodriguez M. et Tardif R.

La version ci-jointe est en soumission à *Environmental Monitoring and Assessment* (EMA).

- Article II: *Accounting for the impact of short-term variations in the levels of trihalomethane in drinking water on exposure assessment for epidemiological purposes. Part II: biological aspects*.
  Par : Catto C., Charest-Tardif G., Rodriguez M. et Tardif R.

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ARTICLE I - Accounting for the impact of short-term variations in the levels of trihalomethane in drinking water on exposure assessment for epidemiological purposes. Part I: environmental aspects.

Accounting for the impact of short-term variations in the levels of trihalomethane in drinking water on exposure assessment for epidemiological purposes.
Part I: environmental aspects.

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1. Abstract

Multi-route exposure assessment to trihalomethanes (THMs) in drinking water can be addressed using an original 3-tiered modeling approach. The strategy consists of integrating environmental occurrence modeling ([Tier 1]: estimation of THM water concentrations in a distribution system) and physiologically based toxicokinetic (PBTK) modeling ([Tier 3]: prediction of DBP biological levels in humans). Such integration requires an intermediate critical step ([Tier 2]) to adjust outputs of environmental models and inputs of PBTK models, namely the levels of THMs in drinking water. So, one main concern in [Tier 2] focuses on the within-day and day-to-day variations of these levels. In this context, this study examines whether any typical pattern exists in variations of THM levels in order to model them. Intensive sampling campaigns conducted in 2001 on Québec City's distribution networks included measurements of THM concentrations six times per day for seven successive days over four campaigns at four different sites (n=592). In addition to typical descriptive analyses, mixed ANOVA models were adjusted to the THM concentrations (mean =39.2±11.9µg/L; range=10.34-86µg/L) and autocorrelations were computed to detect possible periodicity of any other trend in the available time-series. The results highlighted the well-known and clear impact of the spatial (by site) and seasonal (by months) variations. Day-to-day and within-day variations are recurrent, but we were unable to establish repeated patterns (e.g., same site between days of a same week or same day wherever the site) or clear trends (e.g., diurnal versus nocturnal hours) that could help to model them easily for epidemiological purposes. Further investigation (Part II paper) is aim at estimating the impact of these actual, but unpredictable, fluctuations on the biological levels of exposed individuals.

Keywords: Disinfection by-products, Trihalomethanes, Exposure assessment, Spatial and temporal variations, Environmental modeling, Toxicokinetics modeling

2. Introduction

Household water use activities contribute to human exposure to trihalomethanes (THMs) – including chloroform (TCM), dichlorobromomethane (DCBM), chlorodibromomethane (CDBM) and bromoform (TBM) –, not only through ingestion but also through dermal and respiratory pathways (Nuckols et al., 2005). An accurate assessment of the multi-route and multi-source exposure to these disinfection by-products (DBPs) is critical in epidemiological investigations concerning potential health outcomes (e.g., cancer, reproductive and developmental effects) (Graves et al., 2001; Grellier et al, 2010; Nieuwenhuijsen et al, 2009; Tardiff et al., 2006; Villanueva et al, 2007). Exposure assessment to THMs is usually achieved through environmental or biological monitoring involving the measurement of concentrations of these substances in drinking water and/or sampling of biomarkers (e.g., alveolar air), respectively (Savitz et al, 2005). These strategies remain time-consuming, complex and expensive to achieve. Thus, epidemiological investigations must cope with certain limitations in order to suitably account for the environmental and biological variability of this exposure (Legay et al., 2010). Variations in THMs in drinking water can be great within the same distribution system as well as between different ones, due to changes in source and distributed water quality (i.e., composition), the treatment process, or the network's characteristics (Rodriguez et al., 2003). Furthermore, many differences exist between individuals in the amount and ways in which they use water (e.g., frequency and duration of showering, type and quantity of consumed water, and the use of domestic treatment devices), resulting mainly in great disparities in the relative contribution of each route of exposure (Castano-Vinyals et al., 2011; Forssen et al., 2009; Grazuleviciene et al., 2011; Wright et al., 2005). Eventually, physiological, biochemical, or physicochemical characteristics (e.g., body weight and pulmonary ventilation depending on the level of physical activity) can influence the absorption, distribution, metabolism, and excretion of THMs among individuals (Haddad et al., 2006). Therefore, an interesting way to challenge THM exposure assessment consists of implementing modeling approaches that integrate these main sources of exposure variations, namely spatial and temporal variations in THMs in drinking water (and subsequently in the

ambient air), differences in water use habits between individuals and individual characteristics influencing the fate of THM in the body.

Useful models have been developed to predict THM concentrations within a distribution system, as well in the human body (Tardif et al., 2011). On the one hand, statistically-based environmental occurrence modeling allows water concentrations of THM to be predicted from a set of operational data and quality parameters (e.g., disinfectant residuals, pH, temperature, distribution system characteristics, hydraulic residence time) (Legay et al., 2011; Rodriguez et al., 2004; Sadiq and Rodriguez, 2004). These water concentrations can be estimated in a precise area of a distribution system, weekly or monthly (depending on the availability of data to input). Physiologically based toxicokinetic (PBTK) modeling has been developed to predict the internal concentrations of a specific species of THM in various compartments of a body and the levels of other interesting endpoints (e.g., absorbed dose, metabolized quantity, relative contribution of each exposure pathway) usually by inputting the properties of the compound (e.g., molecular weight), the characteristics of the exposed individual (e.g., body weight and surface), and conditions of exposure (Haddad et al., 2006; Tan et al., 2007). These conditions include DBP concentrations in the water and the ambient air (the latter can be estimated from the first through a volatilization model [VTM module]), the duration and timing of showering/bathing, and the amount and timing of water consumption (Haddad et al., 2006).

Our research team conceptualized a 3-tiered integrated modeling approach based on these two types of tools to assess exposure to THMs for epidemiological purposes. This approach was developed primarily in the course of a current investigation conducted in Québec City on intra-uterine growth retardation and exposure among pregnant women (Levallois, et al., 2012). First, [Tier 1] predicts environmental concentrations in a distribution system by using previously described models for DBP occurrence. Eventually, [Tier 3] evaluates an individual's internal exposure to a specific THM with a PBTK model. Between these two steps, an intermediate but critical [Tier 2] is required to adjust outputs of the environmental models and inputs of the PBTK models (namely the levels of THMs in drinking water), by applying suitable corrective factors to ensure an appropriate and efficient integration of the environmental and PBTK models. As a

matter of fact, [Tier 2] involves considering all factors that can modify DBP concentrations between the "distributed" water (i.e., DBP water concentration in the distribution network estimated weekly or monthly as output of [Tier 1]) and the actual water really "used" (i.e., the DBP tap water concentration at a precise time, which is the required input for [Tier 3]). In our conceptual scheme, [Tier 2] is composed of four successive sub-steps. We arbitrarily chose to consider a first sub-step, which like [Tier 1], concerns variations of THMs in the distribution system. However, this first sub-step of [Tier 2] considers variations in estimated DBP concentrations in the distribution system over shorter periods of time (i.e., hourly and daily) than the periods usually addressed in [Tier 1] (i.e., weekly or monthly). Technically, it is not unfeasible, but very improbable that the models used in [Tier 1] can be programmed with enough readily available data to predict DBP variations on the short term. Thus, we suggest envisioning an alternative way of modeling these variations in an independent step. The second sub-step of [Tier 2] considers the potential effect of filtering at the home point-of-entry or household point-of-use. The distinction between cold and hot tap water is the main concern in the third sub-step, which also accounts for the possible use of bottled water rather than tap water. Finally, the fourth sub-step takes into account the potential effects of particular water handling before consumption, including pouring, heating, boiling and storage.

This study focuses specifically on the first sub-step of [Tier 2].Short-term variations have been investigated very little, contrary to seasonal variations (i.e., annual and monthly) (Chaib and Moschandreas, 2008; Drugeon, 2001; Smith et al., 1980). Smith et al. (1980) were the first to document this issue by measuring THM levels and other water quality parameters including temperature, pH, residual chlorine every four hours for 49 days. However, all samples were collected at one site only, which obscured the spatial dimension, and during seven consecutive weeks only in November and December 1980, meaning a relatively limited period of time. The investigations by Drugeon (2001) addressed the spatial dimension by considering various sampling sites, but sampling occurred three times per week during winter only. Chaib and Moschandreas (2008) used the dataset collected by Smith et al. (1980) and proposed a model predicting total THM levels within a 24-h period. However, the model requires

the average value of THM concentrations within the 24-h cycle and the water temperature, data not easily available for epidemiological studies.

This paper further explores such aspects by considering a robust database of short-term variations of THMs and other parameters measured in a distribution system of Québec City (Canada). It aims at describing the day-to-day and within-day variations of THM levels in various locations of this water network and during various months. The objective is also to determine whether any typical or repeatable patterns exist in these variations in order to use such profiles to model them in a practical manner for sub-step 1 of [Tier 2].

3. Methodology

3.1. Québec database

In 2001, intensive sampling campaigns were conducted in the Québec City distribution network (water source: Lake Saint-Charles; conventional treatment: pre-chlorination, coagulation, flocculation, decantation, ozonation, post-chlorination) (Sadik, 2002). The database used in this study was extracted from four campaigns (C1, C2, C3, C4) carried out during the months of May, June, July and August, respectively. Each campaign included measurements of THM concentrations six arbitrarily chosen times a day (1 a.m., 5 a.m., 9 a.m., 1 p.m., 5 p.m. and 9 p.m.) during seven consecutive days (Mon, Tues, Wed, Thur, Fri, Sat, Sun) at four different locations (S1, S2, S3, S4). S1 was located at the drinking water treatment plant (treated water following post-chlorination). S2 through S4 corresponded to sites where hydraulic residence times were estimated experimentally at 5 hours, 9 hours and 17 hours respectively (based on a fluoride-based tracer study). Sample collection occurred from Saturday at 9 a.m. to the following Saturday at 5 a.m., apart from the campaign in July which occurred between two consecutive Mondays. In addition to THM levels, water temperature, UV_{254} absorbance (as an indicator for natural organic matter which is the main precursor of THMs) and free residual chlorine were also measured.

3.2. Analytical methods (preparation, collection, storage and analysis)

Water samples for THM were collected in pre-treated 300 mL glass bottles (washed with nitric acid (10%), rinsed with ultra-pure water and oven-heated at 100 °C). Sodium thiosulfate solution (10%) was added to the bottles (1.5mL) to stop DBP formation after collection. The faucet was turned on for five minutes before sampling to ensure that the water came directly from the distribution system and not from the building's plumbing system. Water was collected carefully to avoid any air bubbles in the samples which were then stored at 4 °C in the dark. The analyses for THM were carried out within 10 days on the basis of EPA method 551.1. Samples were extracted with pentane and the analyses were conducted using a Perkin Elmer autosystem XL gas chromatograph with electron capture detectors (GC-ECD) (Rodriguez and Serodes, 2001).

3.3. Data analysis and statistical treatment

Preliminary analyses examined the spatial (between sites) and temporal (month-to-month, day-to-day and within-day) variations in THM levels separately using box plots and one-way analyses of variance (ANOVA) with R software (The R project for statistical computing, 2011). The analyses of spatial variations were conducted using data of all sampling sessions and then for each session independently. Temporal variations were examined using data from all sampling sites and then for each site independently.

A mixed analysis of variance (Mixed ANOVA) model was also adjusted to the THM concentrations. The fixed factors were the sampling site, campaign and hour. The random factor was the sampling day. The MIXED procedure of the SAS program (SAS Institute Inc., 2009) was used for the analyses and run three times. First, we considered all data together; then we separated the data collected during the days of the week only and the data collected the days of the weekend only. The homogeneity of variance was met however the Shapiro-Wilk normality test was rejected except for the last case while considering the days of weekend only. No transformation can be found to meet the normality assumption due to the presence of (nine) outliers. The Mixed ANOVAs were

then conducted separately with and without outliers and lead to the same conclusions. The significance levels used for all the statistical analyses were 0.01.

The possibility of drawing standard patterns of within-day variations from one reference value was studied by classifying days into sub-groups (e.g., on every Mondays). The THM level at 9 a.m. each day was arbitrarily chosen as a reference value. It was used to calculate the percentages of variations of the other concentrations measured during this entire day (i.e., at 1 a.m., 5 a.m., 1 p.m., 5 p.m. and 9 p.m.)

Data were missing for the first and third campaigns (C1 and C3) due to technical problems while collecting or analyzing samples. No data was missing for the second and the fourth campaigns. Thus we could analyze the database excerpted from these campaigns as time-series. Lagged autocorrelations were computed using R to detect any systematic periodicity on the variations of the THM levels. Through these analyses, we tested the hypothesis that a typical pattern of daily variations can be drawn and systematically used to predict THM water levels.

4. Results

The results of the analysis of 592 water samples are included in this study. TBM was not detected in any sample. The mean concentrations (± standard deviation) of TCM, DCBM and CDBM were 34.6 ± 11.3 µg/L, 2.95 ± 1.09 µg/L and 1.80 ± 1.60 µg/L. The 95% confidence intervals (IC95%) were [33.7-35.5], [2.8-3.0] and [1.5-1.8], respectively. These occurrences are within ranges usually reported by studies conducted in this geographical area (Legay, Rodriguez, Serodes and Levallois, 2010; Rodriguez, Vinette, Serodes and Bouchard, 2003). On average, total trihalomethanes (TTHMs, i.e., the sum of the four compounds) comprised 88%, 8% and 5% of TCM, DCBM and CDBM, respectively. Given the high prevalence of TCM, further statistical analyses were carried out for TTHM only. Table 1 summarizes the THM levels for all sampling sessions and sites and Figure 1 displays their variations in each case. No obvious periodicity exists in theses variations. Their amplitudes remain quite moderate (approximately around 20 µg/L); any rapid change appears to occur due to operations at the treatment plant or hydraulic conditions in the distribution system. At a same site, the

patterns of variations over an entire week clearly differ between each campaign, as do the range of TTHM levels. The patterns of variations are more similar from one sampling site to the next during a same campaign.

Figure 2 illustrates the spatial variations of TTHM levels for all campaigns. TTHM concentrations were lower in the treatment plant after final chlorination (S1) than in the rest of the distribution system ($p<<0.01$). This result is also statistically significant for each campaign separately. The highest concentrations were observed in the extremity (S4). Indeed, it is well known THM levels increase with longer water residence time (Rodriguez et al., 2004; Simard et al., 2011; Symanski et al., 2004). The variability inside each box-plot is related to temporal variations.

As shown in Figure 3, the mean TTHM concentrations tend to increase between May (C1) and August (C4) which may be attributed to an increase in water temperature (from 13.5°C to 22°C)($p<<0.01$). Slightly lower concentrations measured on July may be linked to the associated lowest load in organic matters reported in previous analyses of this database by Sadik (2002). The difference between the months is also significant on each site separately except for S1 while the time for the formation of THMs is the shortest. Slight day-to-day variations appear in Figure 4 with higher concentrations measured on Tuesday and on Saturday but they are not statistically significant ($p=0.0385$). Figure 5 does not reveal any clear differences between each hour ($p=0.1427$). However, for these two last figures, we combined the data from all sites and all campaigns, which may mask some specific spatial or month-to-month effects.

The mixed ANOVA shows a significant effect of the interaction Site-Campaign ($p<0.0001$) (see Table 2). It indicates that the effect of the site depends on the campaign, or conversely that the effect of the campaign depends on the site. From further examination of the slice effects associated with this interaction, it would appear that there was a strong effect at the site during C2, C3 and C4 and slightly weaker effect during C1. The levels of TTHMs were significantly lower in S1 for all campaigns; as previously mentioned, this is most certainly caused by shorter water residence times. Likewise, a strong effect of the campaign was observed for all sampling sites apart from S1. , It statistically validates again the previous observation that TTHM levels tend to

increase during the summer months when the study occurred while increasing temperature may promote THM formation into the distribution system.

Similar mixed ANOVAs were also carried out for days of week (i.e., Mon, Tues, Wed, Thur and Fri) and weekend days (i.e., Sat and Sun) separately. The interaction Site-Campaign remains but the effect of the site during C1 is no longer significant ($p=0.1385$) in the first case. There are clearly independent effects ($p<0.0001$) of both campaign and site that can be linked to lower concentrations measured during C1 and in S1 in the second case. In any cases, the hours of sampling show a significant effect but only a trend at a threshold $p=0.0293$ while considering all data together. This is clearly linked to higher TTHM levels at 1 a.m, which may be explained by the fact that water consumption and water flow is probably less important during the night. The water remains in the distribution system longer resulting in further THM formation. However, this trend disappears ($p=0.1512$) when the few outliers are excluded. Actually, this is logical, given most outliers were values measured at 1 a.m.. Nevertheless, in our opinion, these measurements are plausible enough to be considered, especially compared to other previous and following samples.

Classification of days into sub-groups was carried out to identify typical patterns of within-day variations. Illustrative, randomly chosen examples showed no obvious common or recurring trend of variations (i) between the days of a same week (or campaign) at a same sampling site (Figure 6), (ii) between one same day of various weeks at a same sampling site (Figure 7), (iii) between the various sampling sites during one same day of same weeks (Figure 8). The magnitudes of these variations may cause changes from day after day, but they range approximately between $\pm$ 20%, which is not very high for the quite low environmental levels measured.

No data was missing during C2 and C4. Thus, the 42 equally spaced values of TTHM levels measured at each site (S1, S2, S3, S4) every four hours during these campaigns (six per day during seven days) could be considered as eight different time-series. For each, autocorrelations were computed considering 4-h lags to establish whether there was any periodic trend in the variations of TTHM levels or, on the contrary, these fluctuations were actually random. The plots of these autocorrelations, namely the autocorrelation functions (acf), are shown in Figure 9. Contrary to Chaib and

Moschandreas (2008), no statistical evidence for a periodic fluctuation of TTHM levels appears.

5. Discussion and conclusion

In the course of developing a 3-tiered strategy to exposure assessment to DBPs, and especially to THMs, this Part I study further explored the sparingly investigated issue of short-term variations in drinking water concentrations of THMs. These variations and their impacts on exposure might be of interest although the sanitary risk of THMs is mainly associated to long-term chronic exposure. It is well acknowledged that short showering/bathing events may be responsible for most of exposure over a whole day (Haddad et al., 2006). If such activities occur while THM levels are maximal, individual exposure may be highly underestimated by ignoring these environmental variations and by considering mean concentration.

This study used an important database generated from intensive sampling campaigns, the design of which allowed us to address spatial and temporal variations in the meantime. The descriptive analyses highlighting the great variability of the concentrations of THMs in drinking water were consolidated as rigorously as possible by statistical analyses. Unsurprisingly, the results mirrored the well-known and solid impacts of sampling places (site) and seasons (month) on THM occurrence, especially in large distribution systems in locations with high climatic fluctuations, as is the case in the Province of Quebec, and despite seasonal variations should have been better addressed by additional data from autumn and winter sampling. These impacts, dependent primarily on both water residence time and temperature, have already been widely addressed (Legay et al., 2010; Rodriguez et al., 2004). The acknowledgement of these impacts has great implications for better exposure assessments to DBPs. Yet, accounting for spatial variations of THMs in drinking water remains challenging for epidemiological investigations. Unless the study takes place in a distribution system with low residence time or where variations may be regarded as low, demanding monitoring and/or modeling strategies should be implemented with caution (Legay et al., 2011; Legay et al., 2004; Savitz, et al., 2005). In all cases, the imprecise definition of an

appropriate hydraulic zone where THM water concentrations can be assumed to be quite homogeneous is particularly crucial for a reliable assessment of exposure to these contaminants. Accounting for monthly variations is also challenging, since it requires enough data available (or to predict other data) over the whole study period.

Day-to-day and within-day variations are far more complicated to address in the course of epidemiological investigations directed at carcinogenic or adverse reproductive effects relative to long-term exposure to THMs (various months or years). Nevertheless, there is little available information about these short-term variations, and their actual impacts on exposure assessment remain unknown. To deal with them in any way other than modeling would certainly require considerably expensive efforts. Indeed, to our knowledge, short-term variations have never really been fully addressed from this perspective to date. The relevance of accounting or not for them is the main and original focus of this paper and the Part II paper.

The results of this paper suggest the existence of some actual short-term variations of THMs. Although these variations usually remain quite moderate, sudden fluctuations in THM water concentration, which can increase or decrease subsequent exposure, may sometimes occur due to unavoidable maintenance operations at the treatment plant (e.g., boost of chlorination) and to the continuously changing flow of water associated with successive high- or low-consumption periods. Additional information about these aspects was previously reported elsewhere (Sadik, 2002). However, the statistical analyses did not allow identifying any systematic or periodic trends which could help to model such variations.

The validity of the analysis of THM concentrations as time-series should be viewed with caution, given that such analysis should be conducted with at least 50 equally spaced data (Chaib and Moschandreas, 2008). Only 42 values were available in our study (i.e., at each site and each campaign). In any case, our autocorrelation did not show results the same results as Chaib and Moschandreas (2008) who, as indicated previously, identified a 24-h cycle in the fluctuation of TTHM levels and subsequently proposed a predictive model for THM concentrations during a day depending on the water temperature. Chaib and Moschandreas (2008) had access to a longer time-series with numerous data from a same site which may have strengthened their analyses. We, on the other hand, generated

and used several short time-series from various sites and campaigns. The autocorrelation function does not reveal any positive result for possible periodicity in any instance for this distribution system. These considerations may again point to the "space-specific" behaviour of THMs within and between various distribution systems, and the difficulty of modeling it systematically without a minimal local approach. Overall, a main issue relative to the modeling of such variations are their strong link to the within-day variability of water residence time (which depends on the consumption of water). Modeling the latter in a specific distribution system may be needed to model the first in this same site. There exist some simulation tools for such modeling but their use is demanding and time-consuming.

To conclude with, this study provides information that may interest regulators as well as treatment plant and distribution system managers. Its implications also concern exposure assessment to DBPs. As has been pointed out, it may be particularly delicate to specify and model the short-term environmental variations of THM levels in water (sub-step 1 of [Tier2]); the necessity resides in the need to estimate the actual impact of accounting or not accounting for these variations on resulting biological levels among exposed individuals. This biological aspect is dealt with in the Part II paper. Obviously, similar studies should explore DBPs other than THM.

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6. Tables and Figures

Figure 1. Evolution of TTHM concentrations (expressed as µg/L in y-axis) along each campaign (C1 to C4) on each site (S1 to S4). The x-axis (unitless) indicates the numbers (from 1 to 42) of the samples in the order in which they were collected every 4h (6 times a day) during 7 consecutive days..

Figure 2. Spatial variations of TTHM levels (µg/L) for each sites (S1 to S4) during overall campaigns

Figure 3. Month-to-month variations (by campaign) of TTHM levels (µg/L) for overall sites.

Figure 4. Day-to-day variations of TTHM levels (µg/L) for overall campaigns and sites

Figure 5. Within-day variations of TTHM levels (µg/L) for overall campaigns, sites and days. The x-axis indicates the sampling time (hour).

Figure 6. Profiles of variations in TTHM levels between days of a same week (C2) and in a same site (S2). The x-axis indicates the time (hour).

Figure 7. Profiles of variations in TTHM levels between different weeks (campaigns) on a same day (We) and in a same site (S2). The x-axis indicates the time (hour).

Figure 8. Profiles of variations in TTHM levels between different sites on a same day and during the same week (campaign). The x-axis indicates the time (hour).

Figure 9. Autocorrelation functions of TTHM levels measured in the various sampling sites during C2 and C4. The y-axis indicates the coefficient of correlation. The x-axis indicate the lag (1 unit correspond to 4 hours).

Table 1. Average THM levels (µg/L) in the various sampling sites during each campaign.

Site	Campaign	Variable	n	Mean	Std	Med	Min	Max	IC95%
S1	C1	TCM	26	22.42	10.32	20.67	7.77	64.80	18.45-26.39
		DCBM	26	3.31	0.33	3.28	2.98	4.77	3.18-3.44
		CDBM	25	1.90	0.33	1.78	1.58	2.75	1.77-2.03
		TTHM	26	27.55	10.63	25.68	12.65	71.32	23.46-31.64
	C2	TCM	42	27.35	9.99	24.51	18.55	78.96	24.33-30.37
		DCBM	42	1.67	0.70	1.50	1.13	5.55	1.46-1.88
		CDBM	40	0.99	1.43	0.34	0.02	5.89	0.55-1.43
		TTHM	42	29.96	10.73	27.65	20.02	86.00	26.71-33.21
	C3	TCM	36	23.39	9.92	21.52	9.89	58.37	20.15-26.63
		DCBM	35	1.80	0.62	1.80	0.08	4.44	1.59-2.01
		CDBM	30	1.49	1.75	0.81	0.01	5.83	0.86-2.12
		TTHM	36	26.38	10.36	24.72	11.96	66.44	23.00-29.76
	C4	TCM	42	24.40	3.72	23.93	17.72	32.83	23.27-25.53
		DCBM	42	1.65	1.09	1.82	0.17	4.34	1.32-1.98
		CDBM	42	2.14	1.62	1.80	0.09	5.96	1.65-2.63
		TTHM	42	28.20	4.15	27.74	19.37	37.34	26.94-29.46
S2	C1	TCM	27	27.95	7.54	26.53	12.48	54.05	25.11-30.79
		DCBM	27	4.03	0.27	3.95	3.66	4.74	3.93-4.13
		CDBM	27	1.92	0.30	1.90	1.59	2.53	1.81-2.03
		TTHM	27	33.90	7.75	32.17	18.15	60.77	30.98-36.82
	C2	TCM	42	41.94	7.28	40.14	31.52	67.93	39.74-44.14
		DCBM	42	2.94	0.60	2.80	2.21	5.31	2.76-3.12
		CDBM	36	1.03	1.66	0.26	0.03	6.33	0.49-1.57
		TTHM	42	45.76	7.52	44.83	35.05	73.65	43.49-48.03
	C3	TCM	37	35.84	8.89	33.98	22.17	56.72	32.98-38.70
		DCBM	36	3.44	0.70	3.44	1.59	5.66	3.21-3.67
		CDBM	31	1.36	1.44	0.98	0.01	5.66	0.85-1.87
		TTHM	37	40.33	9.15	38.66	23.76	62.78	37.38-43.28
	C4	TCM	42	41.23	5.31	40.94	30.43	53.46	39.62-42.84
		DCBM	42	2.94	1.16	3.13	1.18	5.77	2.59-3.29
		CDBM	41	2.51	1.58	2.38	0.27	5.91	2.03-2.99
		TTHM	42	46.62	5.81	46.86	33.42	60.22	44.86-48.38

Table 1. (continued) Average THM levels (µg/L) in the various sampling sites during each campaign.

Site	Campaign	Variable	n	Mean	Std	Med	Min	Max	IC95%
S3	C1	TCM	27	23.69	7.19	23.54	5.32	36.80	20.98-26.40
		DCBM	27	3.77	0.21	3.80	3.36	4.08	3.69-3.85
		CDBM	27	2.04	0.58	1.88	1.54	3.95	1.82-2.26
		TTHM	27	29.50	7.43	29.17	10.34	42.41	26.70-32.30
	C2	TCM	42	36.16	11.94	34.16	23.03	78.59	32.55-39.77
		DCBM	42	2.77	0.88	2.56	1.76	6.15	2.50-3.04
		CDBM	36	0.98	1.59	0.24	0.09	6.28	0.46-1.50
		TTHM	42	39.77	12.53	36.97	26.56	85.33	35.98-43.56
	C3	TCM	38	31.91	8.37	31.10	16.53	63.47	29.25-34.57
		DCBM	38	3.06	0.91	3.00	0.05	6.45	2.77-3.35
		CDBM	32	1.09	1.14	0.73	0.06	5.17	0.70-1.48
		TTHM	38	35.88	9.06	35.63	18.99	70.60	33.00-38.76
	C4	TCM	42	45.46	6.65	45.47	35.64	67.20	43.45-47.47
		DCBM	42	3.10	1.20	3.24	1.36	6.17	2.74-3.46
		CDBM	42	2.65	1.78	2.20	0.24	6.34	2.11-3.19
		TTHM	42	51.21	7.43	50.86	37.42	75.83	48.96-53.46
S4	C1	TCM	27	30.18	8.67	27.33	20.21	62.77	26.91-33.45
		DCBM	27	4.09	0.38	4.01	3.75	5.63	3.95-4.23
		CDBM	27	2.08	0.44	2.03	1.56	2.88	1.91-2.25
		TTHM	27	36.35	9.15	33.50	26.44	71.28	32.90-39.80
	C2	TCM	42	43.42	8.07	42.18	31.11	66.90	40.98-45.86
		DCBM	42	2.98	0.59	2.92	2.12	5.24	2.80-3.16
		CDBM	39	1.36	1.65	0.60	0.11	5.91	0.84-1.88
		TTHM	42	47.66	8.50	46.03	34.06	70.37	45.09-50.23
	C3	TCM	38	40.09	7.09	39.55	24.77	59.23	37.84-42.34
		DCBM	38	3.82	0.54	3.77	2.77	5.28	3.65-3.99
		CDBM	30	1.90	1.95	1.19	0.20	6.13	1.20-2.60
		TTHM	38	45.41	7.31	45.26	27.74	64.92	43.09-47.73
	C4	TCM	42	44.39	5.08	43.29	36.88	55.14	42.85-45.93
		DCBM	42	3.02	1.23	2.89	1.30	5.75	2.65-3.39
		CDBM	42	3.03	1.83	2.97	0.25	5.79	2.48-3.58
		TTHM	42	50.44	5.44	50.17	39.13	61.23	48.79-52.09

Table 2. Mixed analysis of variance model adjusted to total THM levels considering all data (Fixed factors: the sampling site, campaign and hour; random factor: sampling day)

Effect	**Num DF**	**Den DF**	**F value**	**Pr>F**
Site	3	96	67.19	<0.0001
Campaign	3	96	32.07	<0.0001
Site*Campaign	9	96	4.83	<0.0001
Hour	5	400	2.52	0.0293
Site*Hour	15	400	0.62	0.8595
Campaign*Hour	15	400	1.59	0.0737
Site*Campaign*Hour	45	400	0.80	0.8240

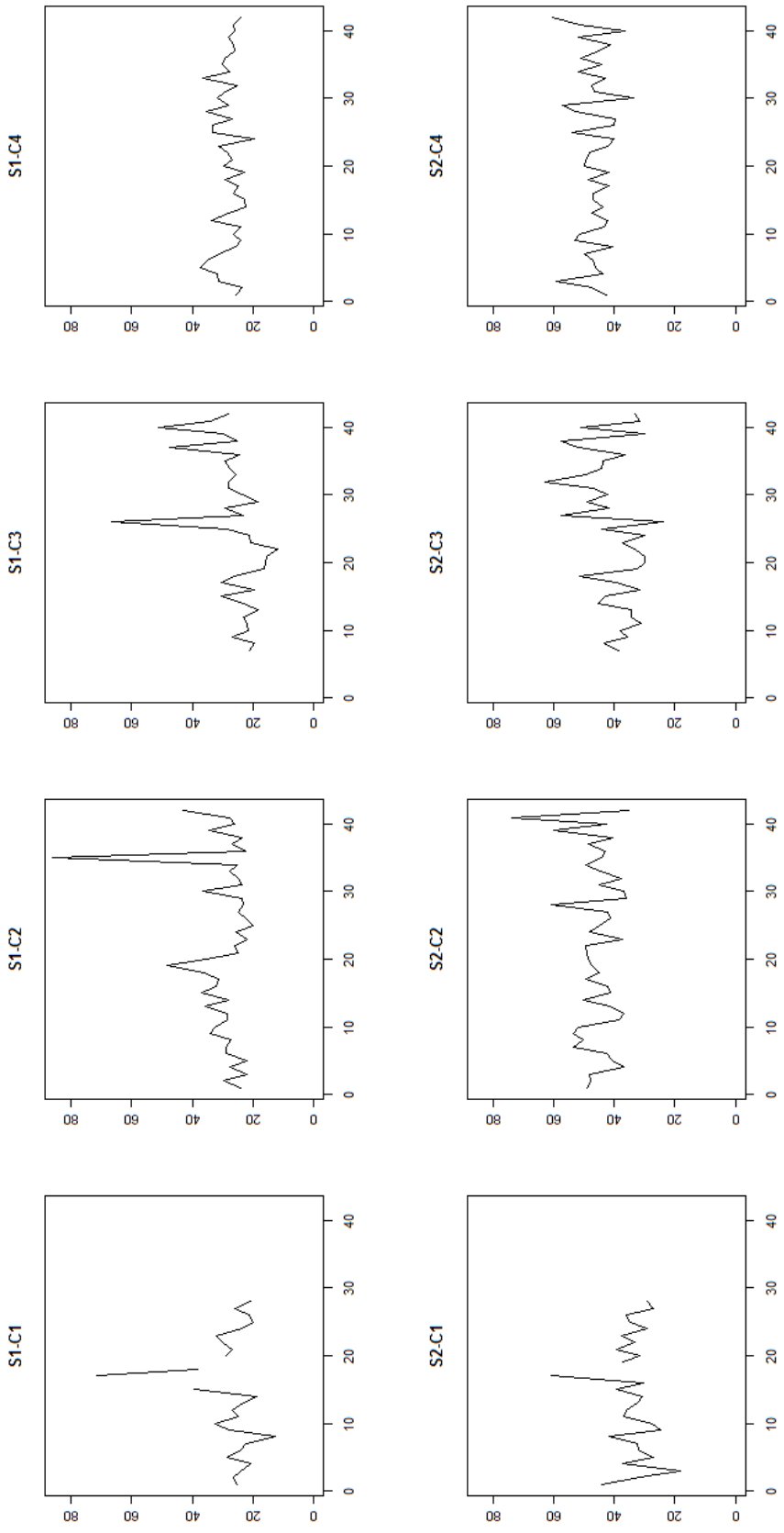

Figure 1. Evolution of TTHM concentrations (expressed as µg/L in y-axis) along each campaign (C1 to C4) on each site (S1 to S4). The x-axis (unitless) indicates the numbers (from 1 to 42) of the samples in the order in which they were collected every 4h (6 times a day) during 7 consecutive days.

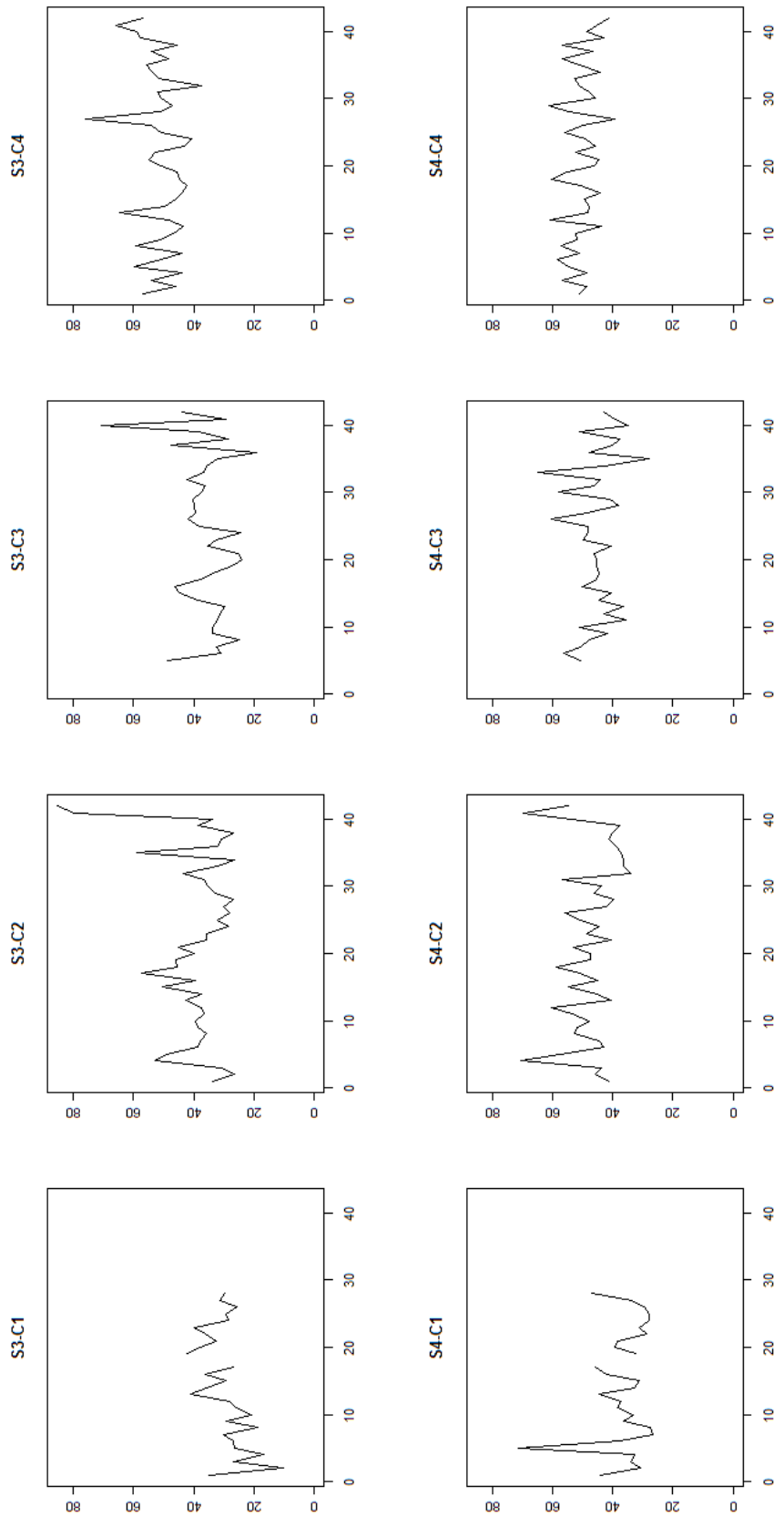

Figure 1. (continued) Evolution of TTHM concentrations (expressed as µg/L in y-axis) along each campaign (C1 to C4) on each site (S1 to S4). The x-axis (unitless) indicates the numbers (from 1 to 42) of the samples in the order in which they were collected every 4h (6 times a day) during 7 consecutive days.

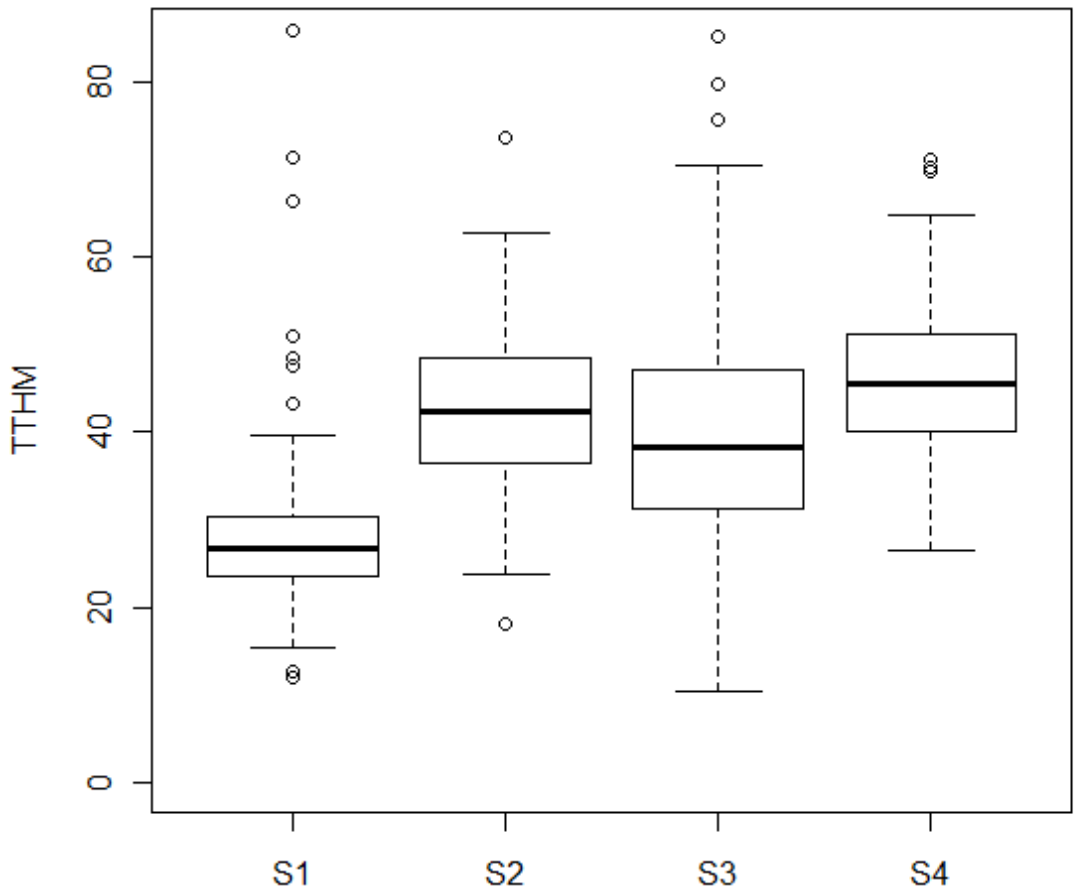

Figure 2. Spatial variations of TTHM levels (µg/L) for each sites (S1 to S4) during overall campaigns

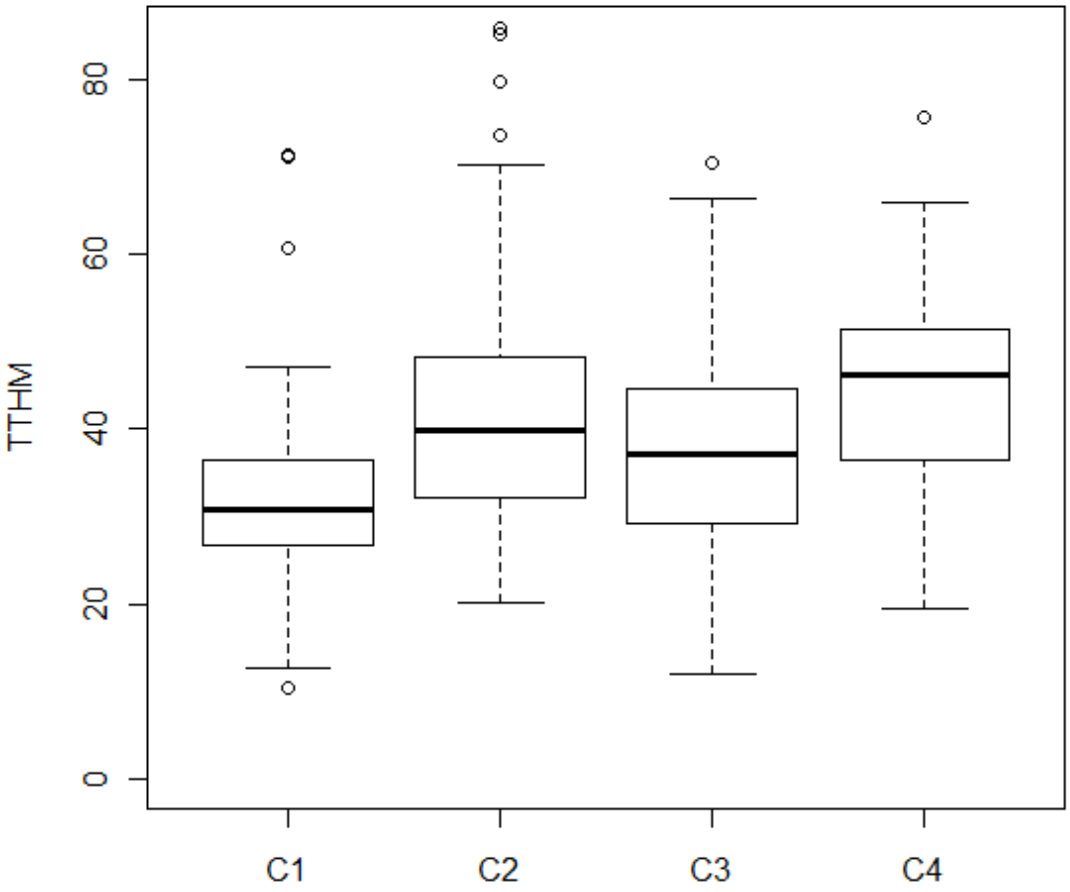

Figure 3. Month-to-month variations (by campaign) of TTHM levels (µg/L) for overall sites.

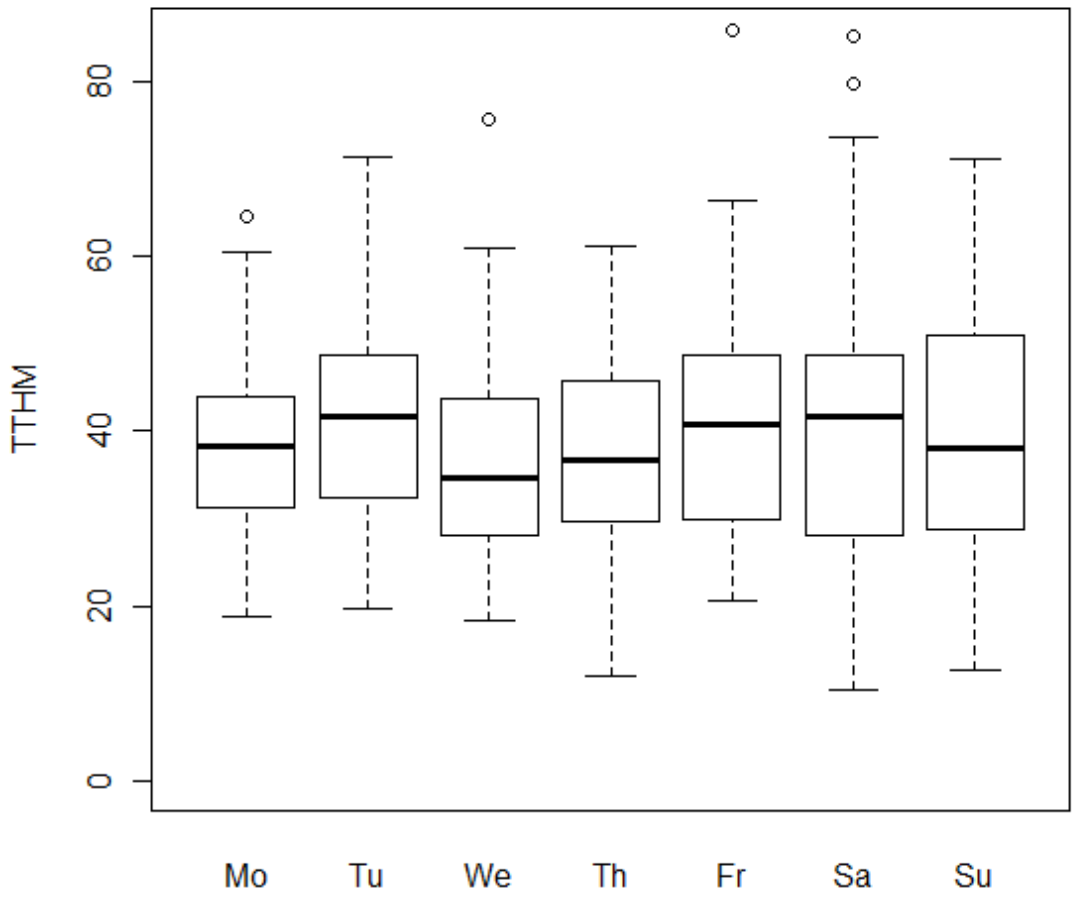

Figure 4. Day-to-day variations of TTHM levels (µg/L) for overall campaigns and sites

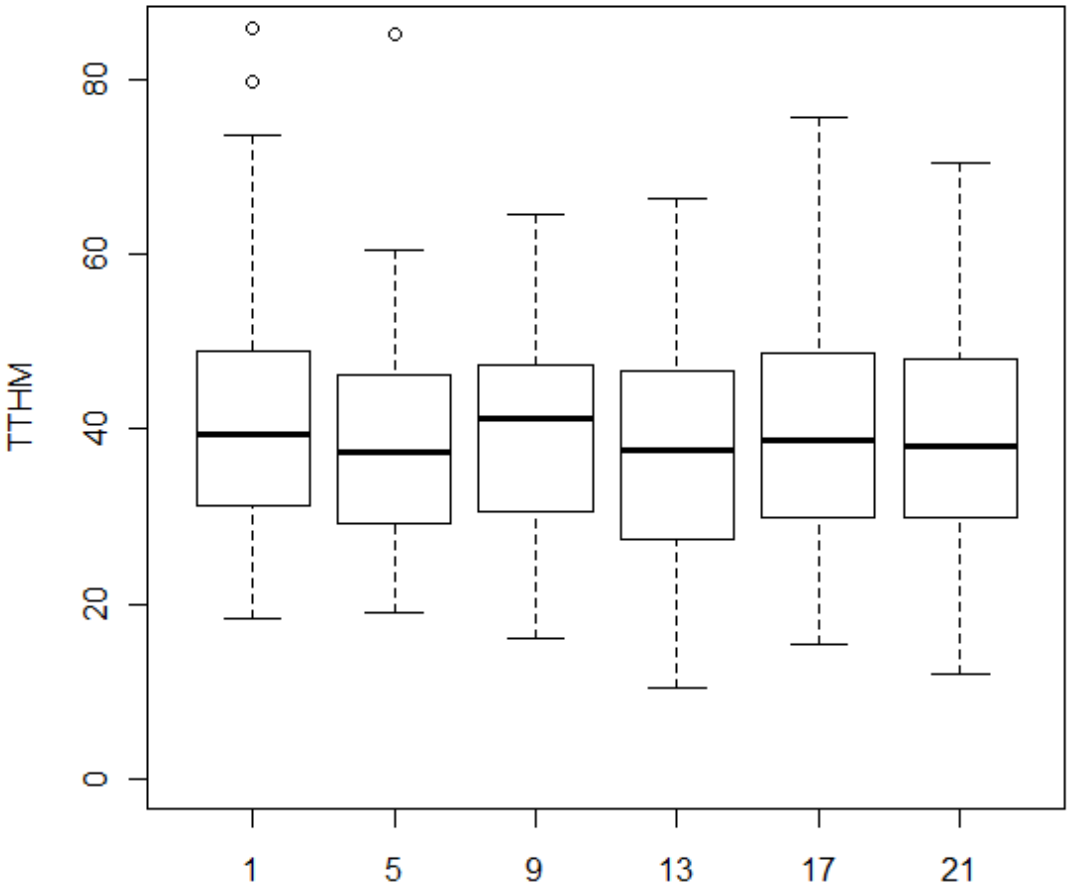

Figure 5. Within-day variations of TTHM levels (µg/L) for overall campaigns, sites and days. The x-axis indicates the sampling time (hour).

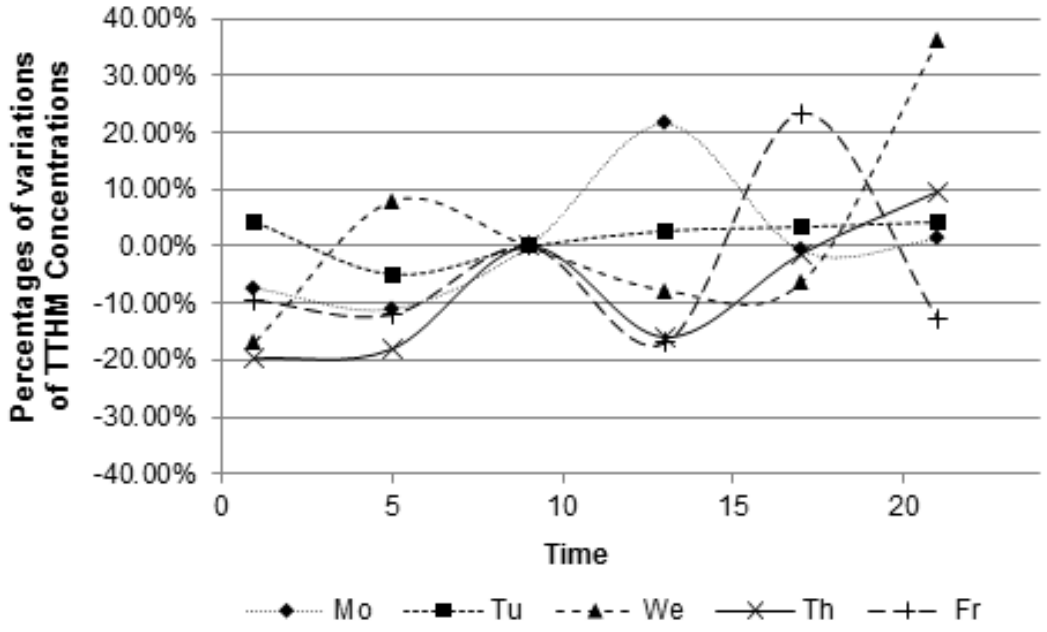

Figure 6. Profiles of variations in TTHM levels between days of a same week (C2) and in a same site (S2). The x-axis indicates the time (hour).

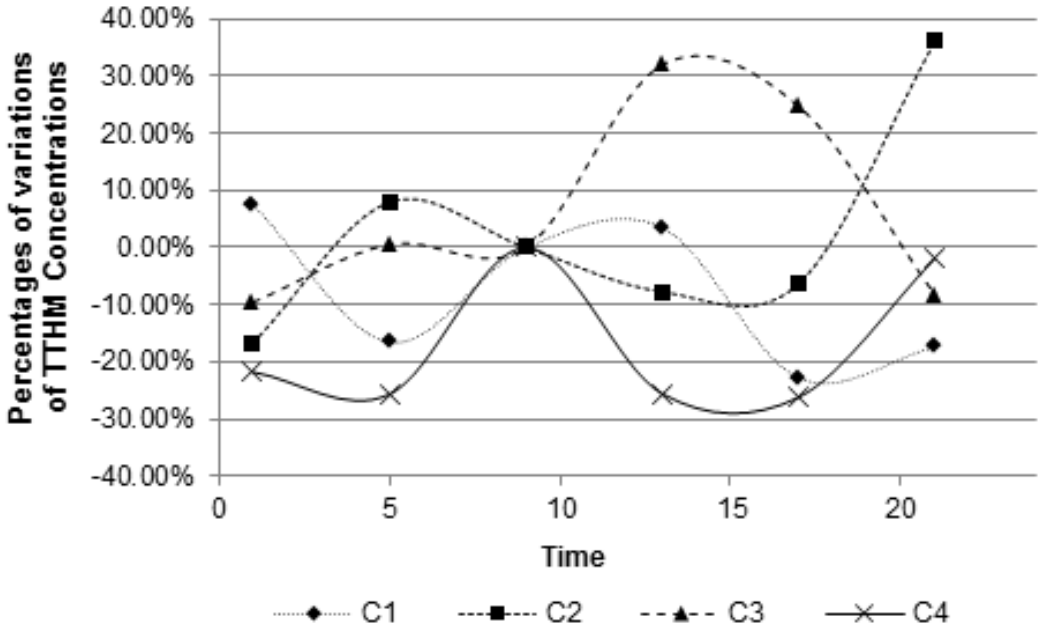

Figure 7. Profiles of variations in TTHM levels between different weeks (campaigns) on a same day (We) and in a same site (S2). The x-axis indicates the time (hour).

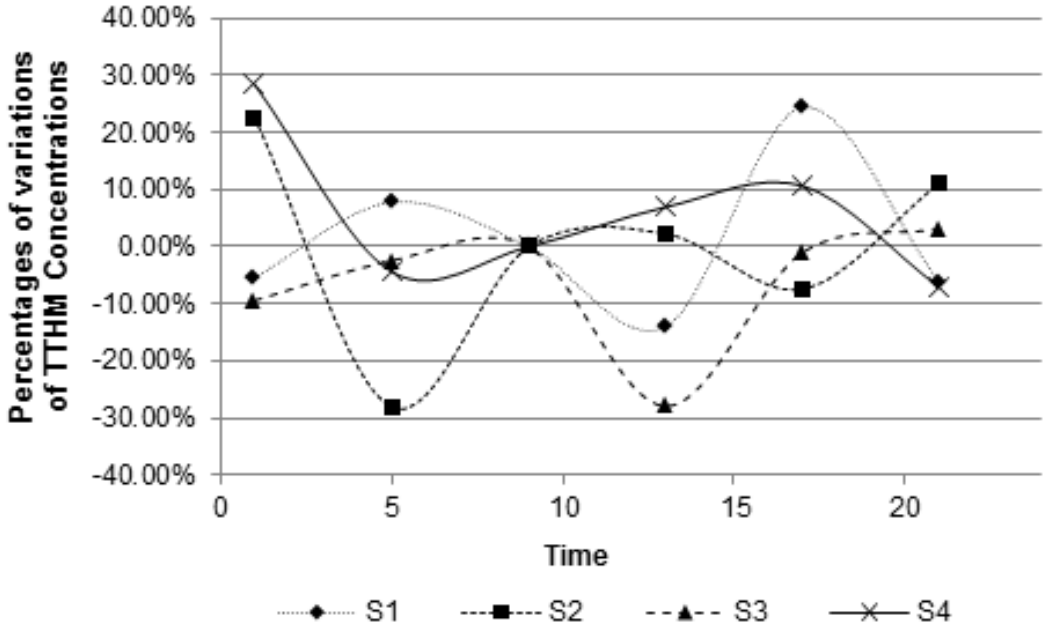

Figure 8. Profiles of variations in TTHM levels between different sites on a same day and during the same week (campaign). The x-axis indicates the time (hour).

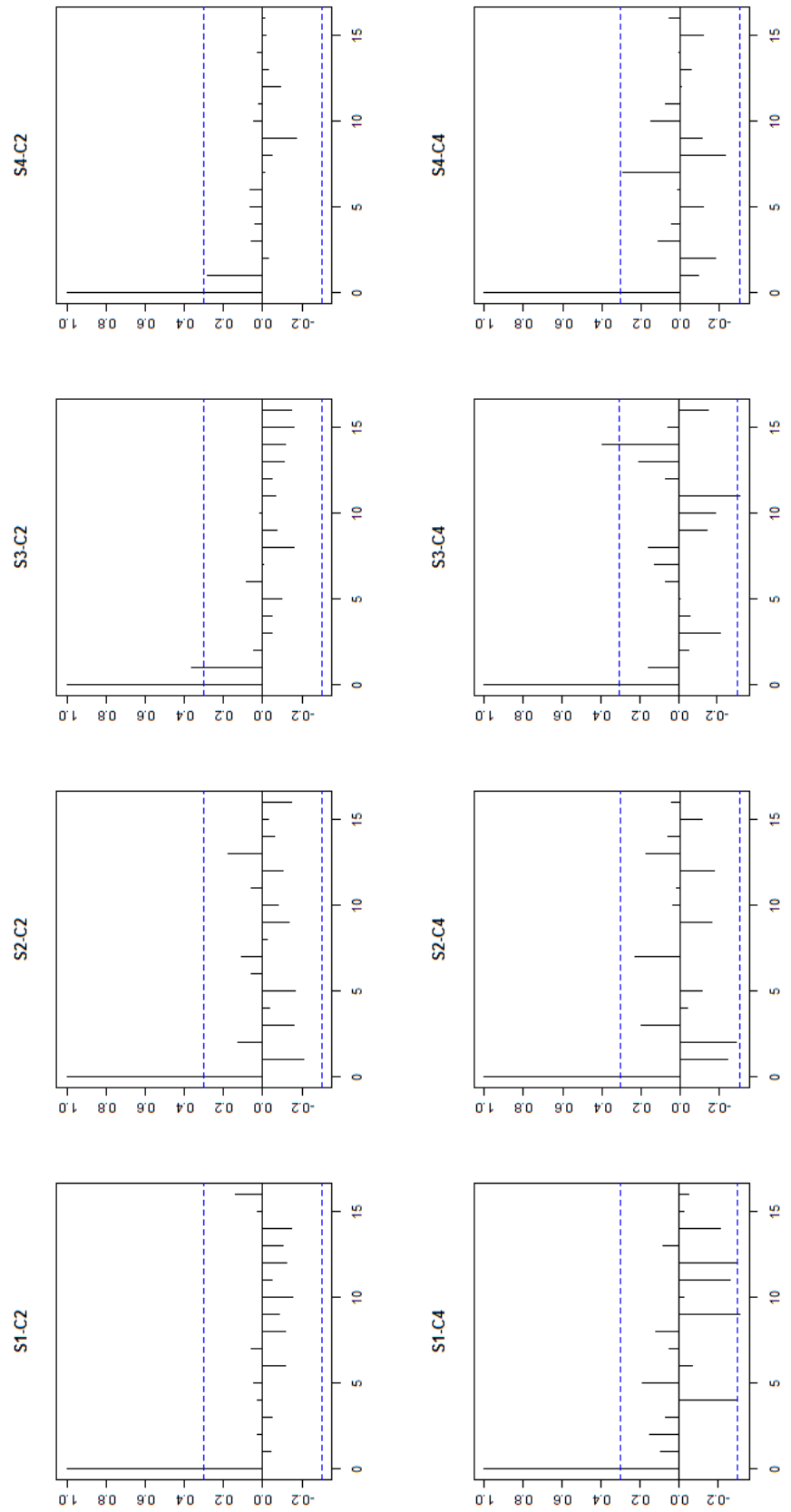

Figure 9. Autocorrelation functions of TTHM levels measured in the various sampling sites during C2 and C4. The y-axis indicates the coefficient of correlation. The x-axis indicate the lag (1 unit correspond to 4 hours).

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ARTICLE II - Accounting for the impact of short-term variations in the levels of trihalomethane in drinking water on exposure assessment for epidemiological purposes. Part II: biological aspects.

Accounting for the impact of short-term variations in the levels of trihalomethane in drinking water on exposure assessment for epidemiological purposes. Part II: biological aspects.

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1. Abstract

The variability of trihalomethane (THM) levels in drinking water raises the question of whether or not short-term variations (within-day) should be accounted for when assessing exposure to contaminants suspected of being carcinogenic and reprotoxic agents. The purpose of this study was to determine the magnitude of the impact on predicted biological levels of THMs (internal doses) exerted by within-day variations of THMs in drinking water. A database extracted from a campaign in the Québec City distribution system served to produce 81, 79 and 64 concentration profiles for the three most abundant THMs, namely chloroform (TCM), dichlorobromomethane (DCBM) and dibromochloromethane (CDBM), respectively. Using a physiologically based toxicokinetic (PBTK) modeling approach, we simulated exposures (1.5 L water/day and a 10-min shower) based on each of these profiles and predicted, for 2000 individuals (Monte-Carlo simulations), maximum blood concentrations (Cmax), areas under the time versus blood concentrations curve (24hr-AUCcv) and total absorbed doses (AD). Three different hypotheses were tested: [A] assuming a constant THM concentration in water (e.g., mean value of a day); [B] accounting for within-day variations in THM levels; and [C] a worst-case scenario assuming within-day variations and showering while THM levels were maximal. For each exposure profile, exposure indicator and individual, we calculated the ratios of values obtained according to each hypothesis (e.g., CmaxB/CmaxA and CmaxC/CmaxA) and the values corresponding to the 5^{th} and 95^{th} of these ratios. The closer these percentiles are to the value of 1, the smaller the error associated with assuming constant THM concentrations rather than their actual variability. Results showed that the minimal gap between these percentiles was TCM-AD[B]/TCM-AD[A] (5th; 95th = 0.91; 1.09), whereas the maximal gap was CDBM-Cmax[C]/CDBM-Cmax[A] (5th; 95th = 0.50; 3.40). Overall, TCM and AD were the less affected (TCM<DCBM<CDBM and AD<AUCcv<Cmax) when accounting for within-day variations in water levels.

Keywords: Disinfection by-products, Trihalomethanes, Exposure assessment, Within-day variations, Biological exposure, Physiologically based Toxicokinetic modeling

2. Introduction

Trihalomethanes (THMs), including chloroform (TCM), dichlorobromomethane (DCBM), chlorodibromomethane (CDBM) and bromoform (TBM), are the most abundant drinking water disinfection by-products (DBPs) that arise from chemical disinfection of source waters. Exposure assessment remains a challenge for epidemiological studies investigating the potential health impacts of these DBPs (i.e., mainly adverse reproductive outcomes and cancer), since they can be absorbed through ingestion, inhalation and/or dermal absorption (Backer et al., 2000; Haddad et al., 2006; Lynberg, et al., 2001; Nieuwenhuijsen et al., 2000; Nuckols et al., 2005; U.S.E.P.A., 2006; Villanueva, et al., 2006; Wallace, 1997; Weisel and Jo, 1996). In addition, the spatial and temporal variation of THM levels in drinking water is another especially problematic issue. Seasonal variations in particular have been studied at great length (Legay et al., 2010; Richter et al., 2009; Rodriguez and Serodes, 2001; Rodriguez et al., 2003; Rodriguez et al., 2004; Singer et al., 1995). While developing an integrated 3-tiered strategy to improve exposure assessment of THMs by combining environmental occurrence models ([Tier 1]) with physiologically based toxicokinetic (PBTK) models ([Tier3]), the short-term (day-to-day and within day) variations of THM concentrations in water were identified as a critical and poorly documented aspect of the intermediate step ([Tier 2]) (Tardif et al., 2011).

In a companion paper (Catto et al., 2012), we illustrated the magnitudes of such variations and pointed out the difficulty of modeling them in a practical manner for epidemiological investigations. Efforts to define typical profiles of within-day variations in THM water levels, which would have allowed us to consider the variations, continue to remain inconclusive. As a result, and given that no other practical alternatives are available, the issue then consisted of determining the error associated with failing to account for these variations in assessing exposure to THMs.

In this context and for the first time, this study attempted to estimate the impacts of actual within-day environmental variations on internal exposure biomarkers (e.g., absorbed doses, blood levels), using PBTK modeling as recommended in the final step [Tier 3]. More precisely, the objective of this study was to determine the magnitude of

the differences between the predicted biological levels taking into account within-day variations and levels calculated while ignoring within-day variations. For this purpose, PBTK modeling appeared as an extremely powerful and appropriate tool (Krishnan and Andersen, 2008). Modeling can describe the absorption, distribution, metabolism and elimination of a contaminant within an organism, thereby serving to estimate biological exposure indicators or assess the effect of various factors on their levels (Sari-Minodier et al., 2009). The relevance and usefulness of such assessments have been investigated several times in recent years (Berthet, et al., 2010; Tardif et al., 2002; Truchon et al., 2006; U.S.E.P.A., 2006; Valcke and Krishnan, 2010).

3. Method

3.1. Database

The same database of THM water concentrations extracted from an intensive campaign conducted in 2001 in the distribution system of Québec City (water source: Lake Saint-Charles; conventional treatment: pre-chlorination, coagulation, flocculation, decantation, ozonation, post-chlorination) and previously described in the companion paper was used for this study. Briefly, this database comprised the results of the analyses for THM levels of six samples per day (one sample every four hours) during seven consecutive days for four successive months and at the four same sites each time. From this database, actual profiles of within-day variations in THM water concentrations were produced for each sampling day and each site. Each profile describes the evolution of THM levels during 24 hours from midnight on a specific sampling day and at a specific site. These profiles were produced for each THM. Each comprised six reported data per day, i.e., measured THM concentrations at 1 a.m., 5 a.m., 9 a.m., 1 p.m., 5 p.m. and 9 p.m., respectively. Only complete profiles of within-day variations were considered for this study. Days presenting one (or more) unavailable measurement (i.e., lacking or below the limit of detection) were excluded.

3.2. MC-PBTK simulations

3.2.1. Materials.

PBTK models were previously developed by our team for each THM using Advanced Continuous Simulation Language Xtreme software (ACSLXtreme®) (Haddad, Charest-Tardif and Tardif, 2006). The models are based on mathematical equations describing the fate of a chemical in a living organism characterized by physiological parameters (e.g., body weight and body surface area) and represented by various compartments linked together by blood circulation. Actually, these equations express mass balances between inputs and outputs of the studied chemical at each compartment. In addition to the lungs, the developed models comprise five compartments: skin; richly perfused tissue; poorly perfused tissue; adipose tissue and the liver. The amount of chemical accumulated in each compartment (At, µg) is calculated from the following equations:

$$\frac{dAt}{dt} = Qt\left(Ca - \frac{Ct}{Pt}\right) \qquad \text{Eq.1}$$

Where Qt: blood flow through compartment t (L/min)

Ca: arterial blood concentration (µg/L)

Ct: concentration in the compartment t (µg/L)

Pt: tissue:blood partition coefficient (unitless)

The models assume that elimination occurs either by exhalation, or mainly through biotransformation in the liver , assuming a saturable process described as follows:

$$\frac{dAmet}{dt} = \frac{VMAX \times Cvl}{KM + Cvl} \qquad \text{Eq.2}$$

Where Amt: the amount of metabolized chemical (µg)

VMAX: maximal metabolic rate (µg/min)

Cvl: concentration in the venous blood from liver (µg/L)

KM: Michaelis-Menten affinity constant (µg/L)

The models consider multi-route absorption (i.e., ingestion, dermal absorption, and inhalation). Pulmonary exchanges describing inhalation are modeled with the following steady-state equation:

$$Ca = \frac{Qc \times Cv}{Qc + Qalv / PRB} + \frac{Qalv \times Ci}{Qc + Qalv / PRB} \quad \text{Eq.3}$$

Where Ca: arterial blood concentration (µg/L)

Qc: cardiac output (L/min)

Cv: venous concentration (µg/L)

Qalv: pulmonary ventilation (L/min)

PRB: blood:air partition coefficient (unitless)

Ci: concentration in inhaled air (µg/L) (Cair)

The two terms of this equation represent the portion of arterial blood from the systemic circulation (actually absorbed) (Ca_a) and the portion from inhaled air (unabsorbed) (Ca_{na}), respectively. The latter allows the calculation of the actual dose absorbed through inhalation (Di, µg) using a mass balance equation similar to Eq.1:

$$\frac{dDi}{dt} = Qalv\left(Ci - \frac{Ca_{na}}{Pb}\right) \quad \text{Eq.4}$$

Cv is the result of the mixture of venous blood from each compartments and is calculated as follows:

$$Cv = \frac{\sum_t (Cvt * Qt)}{Qc} \quad \text{Eq.5}$$

where Cvt: concentration in the venous blood from compartment t (µg/L)

The amount of dermally absorbed chemical (Dder, µg) is calculated with the following equation:

$$\frac{dDder}{dt} = (Kp \times SURF / 1000) \times \left(Cwat - \frac{Csk}{Psw}\right) \quad \text{Eq.6}$$

where Kp: permeability constant (cm/min)

SURF: body surface (cm^2)

Cwat: concentration in the water (µg/L)

Csk: concentration in the skin (µg/L)

Psw: skin:water partition coefficient (unitless)

The models also integrate volatilization modules (VTM) which can serve to predict THM ambient air concentrations from water concentrations. The VTM model assumes, under steady-state conditions, that the concentration in the air of a room depends

primarily on the ventilation rate of the room and the chemical input into the room, the latter depending on the concentration of the chemical in the water, the volume of water used and the duration of water use. For each THM, efficiency factors were used to quantify the water-to-air transfer. For this study, we used the by-default parameterizations of the VTM models as originally assumed by Haddad et al. (2006) to predict the THM concentrations into the air of the shower room and of the remainder of the house.

Eventually, the integrated PBTK models allow the prediction of concentrations of the contaminant versus time in each compartment, as well as in the systemic circulation. They can also be used to estimate the amount of a given contaminant that has been absorbed, metabolized and eliminated, as well the residual amount of its metabolites in the human body. The choice of the exposure indicator depends on the kind of effects associated with a given contaminant (or of its metabolite) considered. For instance, whereas peak concentrations would concern cases of contaminants that exert effects, such as central nervous effects, following acute exposure; the area under the curve of the concentration of a contaminant in a compartment is an indicator that accounts not only for the quantities of this contaminant, but also for the time it spends in the human body (i.e., it considers the quantity that has been eliminated and the quantity still remaining in systemic circulation).

3.2.2. Parameterization and simulations.

Three series of simulations of a single typical 24-h exposure scenario were performed for each day when a complete profile of within-day variations was available. The scenario included the consumption of five glasses of water (one glass contains 300 mL) at 7 a.m., 10 a.m., 1 p.m., 4 p.m. and 7 p.m., respectively, a 10-min shower at 8 a.m. and a 24-h inhalation of THM levels in ambient air (estimated from the THM water concentration using the integrated VTM).

The first case (reference case [A]) assumed a constant THM concentration in water during the 24-h exposure. More precisely, the average of the six measured concentrations available for one day was used. The second case (studied case [B]) considered the particular observed profiles of within-day variations in THM

concentration. The value measured at sampling time t (i.e., 1 a.m., 5 a.m., 9 a.m., 1 p.m., 5 p.m. and 9 p.m.) was used and assumed constant between t-2h and t+2h. The last case (worst case [C]) also accounted for these within-day variations in THM water concentrations, but with a slight modification to the exposure scenario; in this case, showering was assumed to occur during the period when THM water concentration reached its peak each day, rather than at 8 a.m. as presumed by default in [A] and [B]. Figure 1 describes the various exposure conditions corresponding to each case.

For each case [A], [B] and [C], simulations were run for the same 2 000 virtual individuals using a Monte-Carlo process on the "key parameters" of the PBTK model. These "key parameters", for which any change in their initial values produce a significant change on the model's outputs, were identified by a previous sensitivity analysis, as described by Tardif et al. (2002). The changes in the area under the curve of the blood concentrations of each THM were evaluated after increasing each initial PBTK parameter by 10%. These changes are mathematically described with normalized sensitivity coefficients (NCS). As shown in Figure 2, the "key parameters" (i.e., those with the higher NCS) included body weight (BW), cardiac outflow (KQCR), alveolar ventilation (KQALV), blood/air partition coefficients (PRB)_ and the metabolic constants (i.e., maximal velocity (VMAX) and affinity constant (KM)). Table 1 shows the characteristics of the distributions and the coefficients of variation (CV) used to generate specific data for each individual. Apart from body weight, all distributions were truncated (+/-1.96 S.D. or +/-1.96 G.S.D according to the type of the distribution) to reduce the chance of considering individuals with unrealistic characteristics in the simulation process. Body surface (SURF) was extrapolated from body weight (BW), expressed in kg, using the following empirical formula proposed by Costeff (1966):

$$SURF(m^2) = \frac{4 \times BW + 7}{BW + 90}$$

Likewise, the same random values generated for cardiac output were attributed to the alveolar ventilation.

3.2.3. Endpoints.

The three following typical internal exposure indicators (IEIs) provided outputs for each simulation (i.e., for each THM, each individual and each simulated day): the peak of blood concentration (Cmax, in µg/L), the area under the curve of blood concentration versus simulation time (24h-AUCcv, in (µg× h/L)) and the total absorbed dose (AD, in µg/kg). To quantify the impact of within-day variations on internal exposure assessment based on one of the three indicators identified above, for all of them and for each simulation, we calculated the ratios of the values resulting from the studied case [B] and from the worst case [C] on the corresponding estimate resulting from the reference cases [A], respectively:

$$R(IEI)_{i,j}[B/A]=\frac{IEI_{i,j}[B]}{IEI_{i,j}[A]} \quad \text{and} \quad R(IEI)_{i,j}[C/A]=\frac{IEI_{i,j}[C]}{IEI_{i,j}[A]}$$

where $IEI_{i,j}$ is an endpoint (i.e., Cmax, AUCcv or AD) predicted following the assumptions of scenario [A], [B] or [C] for a specific compound i (i.e., TCM, DCBM or CDBM) and for a particular individual j (from 1 to 2000).

The 5^{th} and 95^{th} percentiles of these ratios were determined for each IEI and each compound i.

4. Results

4.1. Profiles of within-day variations.

Table 2 indicates the numbers (N) of complete actual profiles of within-day variations produced for each THM from the available database, as well the corresponding number (n) of related samples. When expressed as a percentage of all possible profiles, values are 72%, 70% and 57% for TCM, DCBM and CDBM, respectively. Table2 also presents the geometric mean of the THM levels considering all the selected data. As mentioned in a companion paper (Catto et al., 2012), where further analyses of these data were carried out, TCM was by far the most abundant of all THMs but its level of contamination was not particularly high in this database. No TBM was detected. Therefore, it was excluded

from the present investigation. The ranges [min-max] of air concentrations estimated in the air of the shower room are [4.6-843], [0.4-68] and [0.36-65] in $\mu g/m^3$ for TCM, DCBM and CDBM, respectively. They are [0.45-83], [0.004-0.5] and [$5x10^{-}4$ -0.1] in $\mu g/m^3$ in the air of the remainder of the house. Figure 3 illustrates the great variability of day-to-day and within-day variations of TCM. This aspect is more detailed in the companion paper. The selected profiles of Figure 3 were arbitrarily chosen among profiles showing a maximum or minimum concentration at one sampling time or another, as well as among profiles presenting the highest and lowest amplitudes of variations.

4.2. Internal exposure indicators.

A total of 1 344 000 simulations were run. Tables 3 to 5 present the averages and ranges of values of the IEIs predicted by PBTK modeling for each of the cases [A], [B] and [C] previously described. Unsurprisingly, the mean TCM-Cmax was far greater in the worst case scenario [C] than in the scenarios [B] and [A], since this peak is known to appear while showering (Haddad et al., 2006) . The difference, however, was less noticeable for DCBM and CDBM-Cmax due to the typically low water concentrations of these compounds. The same tendency IEI[C]>IEI[B]>IEI[A] was observed for 24h-AUCcv and AD and was clearer for TCM than for the other THMs. Nevertheless, the mean values of IEI[C] were not very different compared to IEI[B] and IEI[A] than for the case where Cmax was considered.

Tables 6.I and 6.II indicate the 5^{th} and 95^{th} percentiles of the ratios calculated between the various IEIs estimated in the study [B], worst case [C] simulations and simulations from the reference case [A]. The closer these percentiles are to the value of 1, the smaller the error associated with assuming constant THM concentrations rather than considering their actual variability.

5. Discussion and conclusion

This study presents an original and useful approach that, for the first time, allows short-term variations in THM environmental levels (i.e., within-day variations of concentrations in water) to be investigated on the basis of their predicted impacts on the assessment of internal exposure using a PBPK approachand risk assessment. This is an issue that may have tremendous implications for an appropriate DBP exposure assessment but which, to our knowledge, has never actually been documented or considered in epidemiological studies. In the companion paper, we address the practically unfeasibility of modeling these daily variations in a practical way for epidemiological purposes because no typical pattern or any specific tendencies might be detected despite the importance of a large variability. Therefore, it is crucial to raise the question of the relevancy of accounting for these variations or not. In this perspective, the main strength of this study is certainly to have accounted for both actual environmental and biological variability, thanks to the combined use of a huge (and perhaps unique) database of environmental occurrence data and a robust MC-PBTK modeling, approach Results show that the minimal gap between these percentiles was TCM-AD[B]/TCM-AD[A] (5th; 95th = 0.91; 1.09), whereas the maximal gap was CDBM-Cmax[C]/CDBM-Cmax[A] (5th; 95th = 0.50; 3.40). Overall, TCM and AD appear respectively as the compound and the IEI least affected when not accounting for THM within-day variations, and therefore as the compound and the IEI most reliable (i.e., to prefer) for estimating internal exposure. Likewise, and unsurprisingly, the deviations increase while comparing simulations [C] to the simulation [A].

The fact that the deviations between the predictions appear to be lower with TCM than with DCBM and CDBM may be explained by their lower levels compared to TCM. Indeed, given the really low levels of DCBM and CDBM, even small differences between the IEIs estimated with and without consideration of the within-day variations would result to apparently high deviations.

Among IEI, AD is clearly the least affected when not accounting for within-day variations. AUCcv appears to be less affected than Cmax. It may be linked to the very nature of these different IEIs: each corresponds to a higher degree of precision in estimating internal exposure. AUCcv is a more precise indicator than AD from a

toxicological point of view, since it reflects not only absorption, but also the accumulation and elimination of the compound during the day. The increasing imprecision noted for Cmax is obviously linked to the fact that the peak of the concentrations depends greatly on the timing of exposure events.

Indeed, the impact of the timing of exposure in the case of wide THM within-day variations clearly appears while comparing the range of the ratios [B]/[A] with [C]/[A]. Naturally, matching shower times with times when water concentrations of THM are maximal during a day results in much greater differences between the IEIs accounting for THM variations and the IEIs not accounting for them. Nevertheless, these differences remain quite moderate for the best predicted compound, namely the TCM. Likewise, maximal water concentration times are not necessarily realistic or usual shower times for most people. In fact, 35% of the selected profiles of TCM within-day variations present their peak concentrations during nocturnal hours (i.e., 1 a.m., 5 a.m.). However, we should keep in mind that some of important differences we pointed out probably correspond to exposure conditions that may never occur (or at least only occasionally).

Obviously, the exposure scenario was arbitrarily defined and some other scenario may be considered for further investigations. However, we did assume, and do believe, that the scenario we used is quite representative of a typical exposure encountered in epidemiological investigations. Further investigations should be directed at modifying the reference value adopted for the reference simulations [A] (e.g., value of THM concentration at a precise time a day, or a monthly average, rather than the mean daily concentration). Such investigations will contribute to identify the best trade-offs associated with THM sampling efforts for improving precision in exposure assessment of epidemiological studies. In this perspective, the present works point out the impact on exposure assessment of considering a constant exposure concentration all along a day (instead of the actual variation) seems to be limited. So, it does not invalidate the usual and hardly avoidable, practice which consists of ignoring these within-day environmental variations. Nevertheless, although our analyses involved an important database, the limited number of profiles available for simulations does not allow the external validity to be totally ensured. While it is not possible to confirm it, we believe

this database gives a good idea and may be quite well representative of typical within-day variations, at least in the studied distribution system and periods of time. Another limitation of this study regards the THM air concentrations estimated from THM water concentrations using a volatilization model (VTM module), the reliability of which might be improved. No air measurements were available to check the estimates of this study However, given the current state of knowledge, other alternatives would possibly have introduced many more uncertainties. The use of empirical data of THMs in the air reported in the literature would have introduced a bias in the prediction of the IEIs since they would have not been necessarily linked to the actual and fluctuating levels in the water. Besides, no attempt was made to adjust the VTM model accounting for various conditions of ventilation associated with particular household characteristics.

To conclude, accounting for within-day variations in THM water levels does not necessarily appear to be relevant or absolutely crucial, when considering their rather weak impacts on predicted internal exposure levels, particularly on AD. Nevertheless, it is important to remember that these impacts can quickly increase in importance, particularly with respect to the kind of IEIs to estimate. Overall, this study presents a relevant illustration of how integrating environmental data and PBTK modeling can improve exposure assessment practices.

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6. Tables and Figures

Figure 1. Description of the three scenarios of 24h-exposure investigated to predict three IEIs (i.e., Cmax, AD, 24h-AUCcv) among 2000 virtual individuals for each THM and for each available within-day profile of variation.

Figure 2. Normalized sensitivity coefficients (NSC) for the parameters used in the PBTK model for TCM, DCBM, CDBM and TBM.

Figure 3. Examples of actual profiles of within-day variations (TCM levels in µg/L) for six different days. Each line corresponds to one day. The symbols indicate the measured concentrations in the collected samples during each day.

Table 1. Parameters used in PBTK models for Monte-Carlo simulations

Parameters		**Values**	**Distributions** [1]	**CV** [7] **(%)**
Body weight [2] *(kg)*	BW	70	L	13
Constant for Cardiac Output [2] *(L/h/(kg)$^{0.7}$)*	KQCR	18	L	30
Constant for Alveolar ventilation [6] *(L/h/(kg)$^{0.7}$)*	KQALVR			
Fraction of Qc to Liver [2] *(L/h/(kg)$^{0.7}$)*	KQF	0.25	N	22
Partition coefficients blood:air *(no unity)*	PRB			
TCM [3]		10.7	L	6.5[+]
DCBM [5]		26.6	L	20
CDBM [5]		49.2	L	20
TBM [5]		10.4	L	20
Metabolic constants				
Maximal velocity *(mg/h/(kg)$^{0.75}$)*	KVmax			
TCM [4]		12.68	L	30[++]
DCBM [5]		8.01	L	30
CDBM [5]		13.7	L	30
TBM [5]		102.3	L	30
Affinity constant *(mg/L)*	KM			
TCM [4]		0.448	L	30[+]
DCBM [5]		0.302	L	30
CDBM [5]		0.72	L	30
TBM [5]		0.42	L	30

[1] type of distributions : L (lognormal), N (normal)
[2] (Tardif et al., 2002)
[3] (Batterman et al. 2002)
[4] (Corley et al., 1990)
[5] (Tan et al., 2007)
[6] Alveolar ventilation was assumed to be equal to cardiac output at rest (Tardif et al., 2002)
[7] Coefficient of variation
+ calculated from reported normal standard deviation (S.D.)
++ arbitrarily fixed

Table 2. Number of selected profiles (N) of within-day variations and number of samples (*n*), geometric mean (GM) and standard deviation (GSD) and range [Minimal-Maximal] of levels (µg/L) of each THM in water

THM		**GM**	**GSD**	**[Min-Max]**
TCM	*N = 81* *n = 486*	33.08	1.39	[7.77 , 78.96]
DCBM	*N = 79* *n = 474*	2.60	1.66	[0.05 , 6.45]
CDBM	*N = 64* *n = 384*	1.09	3.45	[0.01 , 6.33]

Table 3. Predicted venous blood concentrations (Cmax) of each THM for each scenario [A], [B] and [C]. (Av: Average; SD: Standard deviation; Min: minimum; Max: maximum)

Cmax (µg/L)	TCM		DCBM		CDBM	
	Av.(+/- SD)	[Min-Max]	Av.(+/- SD)	[Min-Max]	Av.(+/- SD)	[Min-Max]
Scenario [A]	0.375 (+/- 0.114)	[0.097 , 0.834]	0.042 (+/- 0.015)	[0.004 , 0.108]	0.021 (+/- 0.012)	[0.0006 , 0.099]
Scenario [B]	0.379 (+/- 0.127)	[0.093 , 0.957]	0.041 (+/- 0.018)	[0.001 , 0.144]	0.022 (+/- 0.021)	[0.0004 , 0.123]
Scenario [C]	1.072 (+/- 0.089)	[0.136 , 1.326]	0.051 (+/- 0.020)	[0.008 , 0.153]	0.036 (+/- 0.023)	[0.0007 , 0.123]

Table 4. Predicted areas under the curve of venous blood concentrations (24h-AUCcv) of each THM for each scenario [A], [B] and [C]. (Av: Average; SD: Standard deviation; Min: minimum; Max: maximum)

24h-AUCcv (µg/L)xh	TCM		DCBM		CDBM	
	Av.(+/- SD)	[Min-Max]	Av.(+/- SD)	[Min-Max]	Av.(+/- SD)	[Min-Max]
Scenario [A]	0.439 (+/- 0.128)	[0.120 , 0.972]	0.045 (+/- 0.016)	[0.006 , 0.115]	0.034 (+/- 0.191)	[0.001 , 0.148]
Scenario [B]	0.442 (+/- 0.134)	[0.119 , 1.024]	0.045 (+/- 0.017)	[0.004 , 0.118]	0.035 (+/- 0.027)	[0.001 ,0.160]
Scenario [C]	0.488 (+/- 0.154)	[0.152 , 1.293]	0.051 (+/- 0.019)	[0.011 , 0.144]	0.049 (+/- 0.028)	[0.001 , 0.160]

Table 5. Predicted total absorbed doses (AD) of each THM for each scenario [A], [B] and [C]. (Av: Average; SD: Standard deviation; Min: minimum; Max: maximum)

AD (µg/kg)	TCM		DCBM		CDBM	
	Av.(+/- SD)	[Min-Max]	Av.(+/- SD)	[Min-Max]	Av.(+/- SD)	[Min-Max]
Scenario [A]	1.465 (+/- 0.410)	[0.459 , 3.019]	0.123 (+/- 0.040)	[0.017 , 0.277]	0.084 (+/- 0.046)	[0.003 , 0.325]
Scenario [B]	1.469 (+/- 0.423)	[0.451 , 2.965]	0.122 (+/- 0.042)	[0.018 , 0.272]	0.086 (+/- 0.055)	[0.003 , 0.326]
Scenario [C]	1.568 (+/- 0.447)	[0.523 , 3.342]	0.132 (+/- 0.042)	[0.034 , 0.300]	0.107 (+/- 0.057)	[0.003 , 0.330]

Table 6. 5th, 50th and 95th percentiles of the ratios (unitless) between the estimates of each internal exposure indicator (IEI) predicted from simulations of scenarios [B] and [C] and IEI predicted from simulations of scenario [A] for each THM.

I. Scenario [B] vs Scenario [A]

Ratio (unitless) IEI [B/A]	**TCM**			**DCBM**			**CDBM**		
	5th	**50th**	**95th**	**5th**	**50th**	**95th**	**5th**	**50th**	**95th**
Cmax	0.81	0.99	1.29	0.57	0.95	1.17	0.11	0.86	2.70
24h-AUCcv	0.87	0.99	1.18	0.79	0.98	1.13	0.36	0.90	2.22
AD	0.91	1.00	1.09	0.86	0.99	1.10	0.51	0.96	1.72

II. Scenario [C] vs Scenario [A]

Ratio (unitless) IEI [C/A]	**TCM**			**DCBM**			**CDBM**		
	5th	**50th**	**95th**	**5th**	**50th**	**95th**	**5th**	**50th**	**95th**
Cmax	0.88	1.19	1.48	0.86	1.16	2.22	0.50	1.78	3.40
24h-AUCcv	0.80	1.12	1.35	0.81	1.10	1.83	0.54	1.51	2.66
AD	0.92	1.06	1.21	0.94	1.06	1.39	0.73	1.28	2.09

<table>
<tr><th rowspan="2">Conditions of each simulation</th><th rowspan="2">Exposure events</th><th colspan="2">Exposure concentrations</th></tr>
<tr><th>Water (Cwater)</th><th>Air (Cair)</th></tr>
<tr><td>Scenario [A]</td><td rowspan="3">Ingestion of Cwater drinking 5 glasses of water (300 ml each time) at 7 am, 10 am, 1pm, 4 pm and 7 pm

24h-Inhalation of ambient air Cair

Inhalation of Cair + dermal absorption of Cwater during a 10-min showering at 8 am</td><td>Constant

(mean of 6 samples a day)</td><td rowspan="3">Estimated from Cwater using VTM</td></tr>
<tr><td>Scenario [B]</td><td rowspan="2">Variable

(Cwater of the sample taken at t assumed to be constant between t-2h and t+2h)</td></tr>
<tr><td>Scenario [C]</td><td>Idem but showering time is assumed to be equal to time when Cwater is maximal</td></tr>
</table>

Figure 1. Description of the three scenarios of 24h-exposure which were investigated to predict three IEIs (i.e., Cmax, AD, 24h-AUCcv) among 2000 virtual individuals for each THM and for each available within-day profiles of variation. (Cwater : THM water concentration; Cair: THM ambient air concentration)

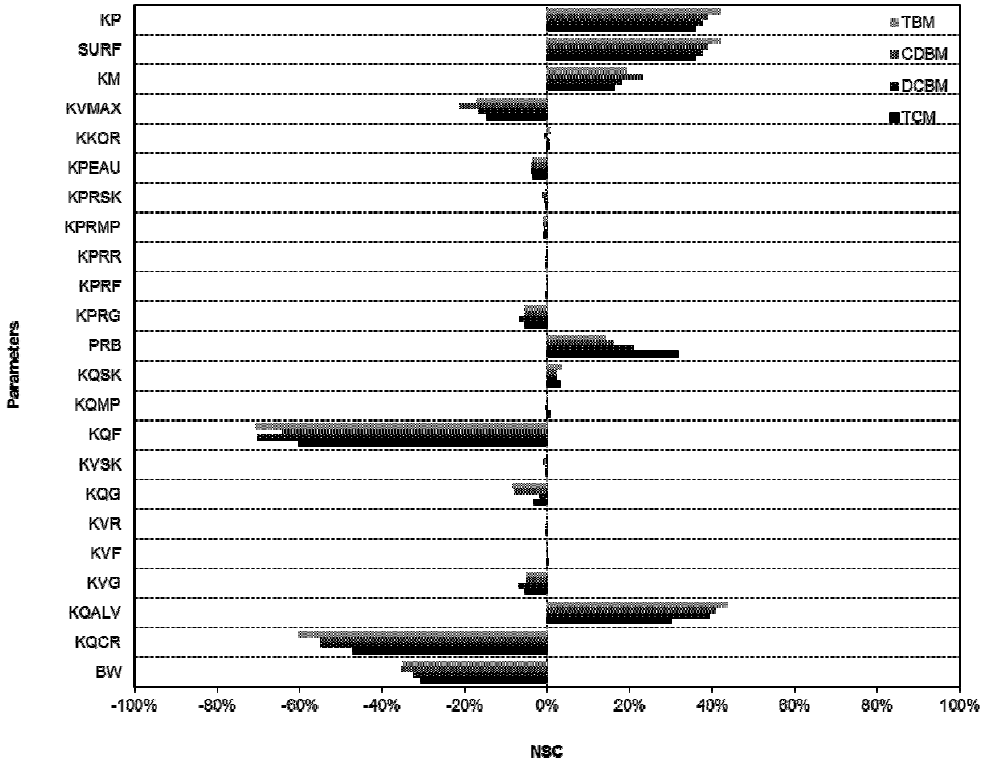

Figure 2. Normalized sensitivity coefficients (NSC) for the parameters used in the PBTK model for TCM, DCBM, CDBM and TBM.

KP: permeability constant; SURF: body surface area; KM: metabolic affinity constant; KVMAX: metabolic maximal rate; KKOR: oral absorption constant; KPEAU: water-air partition coefficient; KPRSK: skin-air partition coefficient; KPRMP : poorly perfused tissues-air partition coefficient; KPRR: richly perfused tissues-air partition coefficient; KPRF: liver-air partition coefficient ; KPRG: fat-air partition coefficient; PRB: blood-air partition coefficient; KQSK: fraction of blood flow to skin compartment; KQMP: fraction of blood flow to poorly perfused tissues; KQF: fraction of blood flow to liver; KQG: fraction of blood flow to fat; KVSK: volume of skin compartment (%BW); KVR: volume of richly perfused tissues (%BW); KVF: volume of liver (%BW); KVG: volume of fat (%BW); KQALV: alveolar ventilation rate; KQCR: cardiac output; BW: body weight.

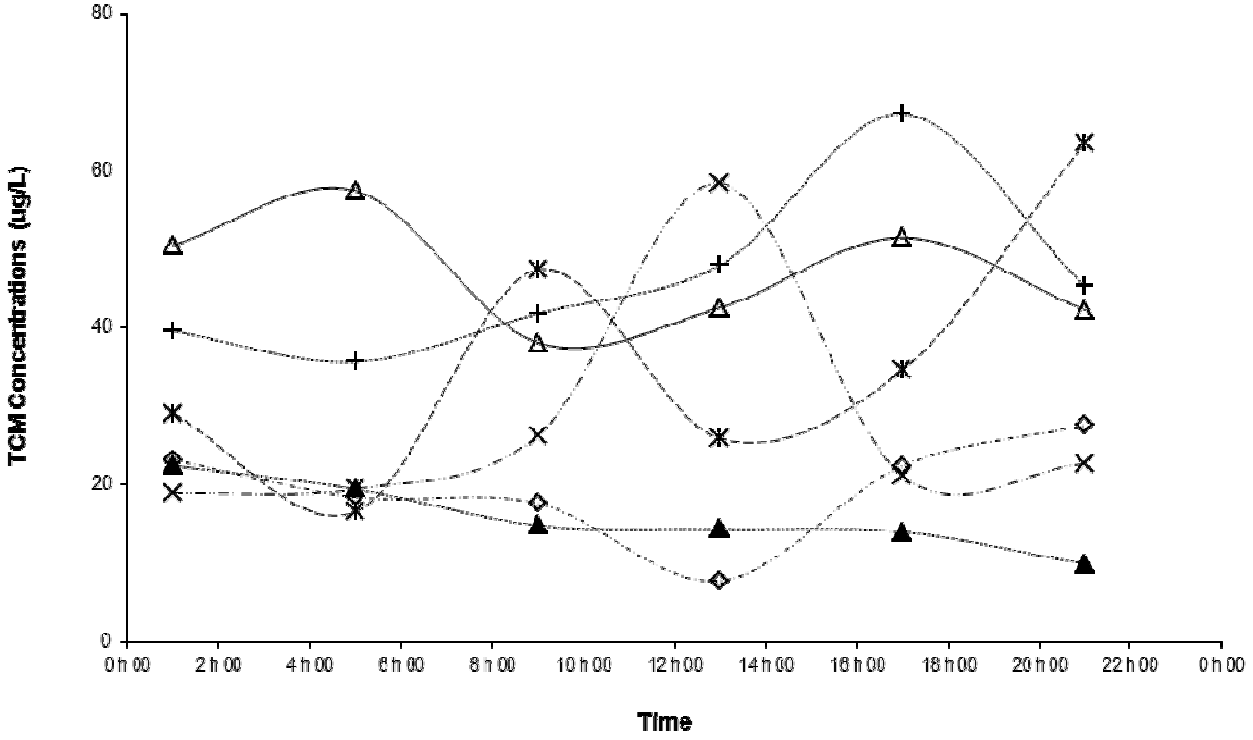

Figure 3. Examples of profiles of within-day variations (TCM levels in µg/L) for 6 different days. Each line corresponds to one day. The symbols indicate the measured concentrations in the collected samples during each day.

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VOLET II : L'EXPOSITION AUX SOUS-PRODUITS DE DÉSINFECTION EN PISCINE

Deux articles constituent ce second volet de la thèse :

- Article III*: Occurrence and spatial and temporal variations of disinfection by-products in the water and air of two indoor swimming pools.*
  Par : Catto C., Simard S., Charest-Tardif G., Rodriguez M. et Tardif R.

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- Article IV: *Assessing exposure to chloroform in swimming pools using physiologically based toxicokinetic modeling.*
  Par : Catto C., Charest-Tardif G., Rodriguez M. et Tardif R.

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ARTICLE III - Occurrence and spatial and temporal variations of disinfection by-products in the water and air of two indoor swimming pools

Occurrence and spatial and temporal variations of disinfection by-products in the water and air of two indoor swimming pools

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1. Abstract

In order to improve disinfection by-product (DBP) exposure assessment, this study was designed to document both water and air levels of these chemical contaminants in two indoor swimming pools and to analyze their within-day and day-to-day variations in both of them. Intensive sampling was carried out during two one-week campaigns to measure trihalomethanes (THMs) and chloramines (CAMs) in water and air, and haloacetic acids (HAAs) in water several times daily. Water samples were systematically collected at three locations in each pool and air samples were collected at various heights around the pool and in other rooms (e.g., changing room) in the buildings. In addition, the ability of various models to predict air concentrations from water was tested using this database. No clear trends, but actual variations of contamination levels, appeared for both water and air according to the sampling locations and times. Likewise, the available models resulted in realistic but imprecise estimates of air contamination levels from water. This study supports the recommendation that suitable minimal air and water sampling should be carried out in swimming pools to assess exposure to DBPs.

Keywords:
disinfection by-products; swimming pool; exposure assessment; water and air monitoring; spatial and temporal variations; volatilization model

2. Introduction

It is well known that the disinfection of swimming pool water generates by-products (DBPs) as a result of chemical interactions between chlorine and nitrogenous or organic matters that come from swimmers or are naturally present in water [1]. Indeed, both the high quantities of disinfectant required to ensure protection of bathers against microbiological risks and the continuous pool loading with organic and nitrogenous precursors (e.g., body fluids, skin particles, hair, and cosmetics) from bathers contribute to the formation of high quantities of these DBPs. Whereas water recirculation tends to concentrate the non-volatile DBPs in the pool, the turbulence generated by swimmers promotes the diffusion of volatile compounds from water into the ambient air [2]. Moreover, in indoor swimming pools in particular, ventilation conditions may not necessarily be sufficient enough to efficiently remove DBPs in the air.

Among numerous DBPs (n>600) and apart from the emerging ones newly discovered thanks to analytical progress [3, 4], three main classes are traditionally identified: trihalomethanes (THMs) – including chloroform (TCM), dichlorobromomethane (DCBM), chlorodibromomethane (CDBM) and bromoform (TBM) –, haloacetic acids (HAAs) and chloramines (CAMs) – including monochloramine (MCAM), dichloramine (DCAM) and trichloramine (TCAM). THMs are known to volatilize easily from water into ambient air, contrary to HAAs. As for CAMs, MCAM and TCAM are usually the main compounds encountered in water and air, respectively [5].

THMs and HAAs are suspected to have various health effects, mainly regarding carcinogenic risk (e.g., bladder cancer) or adverse reproductive outcomes (e.g., intra-uterine growth retardation) [6, 7]. However, these issues have been investigated primarily for exposure involving household drinking water use activities (e.g., consumption, showering) without (or seldom) accounting for exposure resulting from swimming pool attendance. Irritation (respiratory and ocular) associated with exposure to CAMs (particularly TCAM) among swimming pool attendees or workers are well acknowledged [8, 9, 10, 11, 12, 13, 14, 15]. Likewise, currently growing interest concerns potential allergic and asthmatic impacts of these contaminants, especially on the young population (e.g., baby swimmers) [16, 17, 18, 19, 20, 21, 22]. In this context,

various actions, such as the use of dechloramination devices, are currently considered to reduce CAM exposure which is of prime interest and worth to be evaluated first as short-term health effects could be produced. Nevertheless, some reports suggest that this technology could promote the formation of other DBPs, especially THMs [23, 24], and so the long-term health effects relative to a potential carcinogenic risk.

More recently, the potential mutagenicity and genotoxicity of swimming pool water, possibly linked to DBPs, have been considered [3, 4, 25, 26, 27] and there is growing international interest in assessing DBP exposure in swimming pools and related risks [20, 28, 29, 30, 31, 32, 33, 34, 35, 36].

In the Province of Quebec (Canada), few studies documented the occurrence of DBPs in swimming pools. To our knowledge, only one study by Lévesque et al. [37], comparing the occurrence of health complaints between two groups of swimmers and soccer players, reported levels of CAM in the water ([450µg/L-1030µg/L]) and air ([260µg/m^3-410µg/m^3]) of seven swimming pools. This study showed a link between irritation symptoms, more frequently reported among swimmers, and CAM concentrations in the air; it also showed that more respiratory complaints were experienced at levels above 370µg/m^3. This value, under the reference limit of 500µg/m^3 suggested by a French study [38], is close to, but still above, the value of 300µg/m^3 proposed by Parrat [39] and also above the toxicity reference value of 0.4 µg/m^3 proposed by Bonvallot et al. [40]. In another previous study, Lévesque et al. documented the water and air concentrations of TCM in eight various indoor swimming pools located in the Quebec City area while they were assessing associated exposure and risk among competitive and leisure swimmers [41]. Reported mean TCM water and air concentrations ranged from 18µg/L to 80µg/L and from 78µg/m^3 to 329µg/m^3, respectively. More recently, Simard reported the monthly evolution (during 12 months) of DBPs levels in water samples from 15 indoor and 39 outdoor swimming pools in Quebec City [5]. The THM levels ranged between 17.5µg/L and 113.5µg/L (mean = 44µg/L) in indoor swimming pools and reached up to 300µg/L in outdoor pools. These levels exceed the regulatory standard adopted in Germany that requires THM pool water concentration under 20µg/L. Simard reported CAMs ranging between 300 and 1700µg/L, and between 10 and 800µg/L for indoor and outdoor pools, respectively [5].

These authors also observed an important accumulation of HAAs with levels up to 1100µg/L and above 2200µg/L in indoor and outdoor pools, respectively. However, their study was limited to water contamination only. Indeed, only a limited number of studies have explored the relationship between air and water contamination by DBPs [29, 41, 42, 43, 44, 45]. The study of Hamel is of particular interest, as the authors examined the evolution of THM and CAM levels in the water and air of four swimming pools in France [42].

How DBPs are distributed into and between various media (i.e., water and air) of a swimming pool and the extent to which contamination fluctuates in time are issues that continue to require investigation in order to improve DBP exposure assessment through suitable environmental monitoring and/or predictive modeling strategies. HAAs, more particularly, should be investigated, since little data regarding these DBPs are currently available [5, 46, 47]. The modeling of THM volatilization and resulting levels in water and air, influenced by numerous factors (e.g., number of swimmers, ventilation, and water turbulence), is another challenging concern. Hsu et al. [48] and Dyck et al. [49] have proposed two interesting approaches which focus on TCM and whose reliability should be further explored. Hsu et al. have developed a robust mathematical model accounting for environmental conditions and occupant activities and using computational fluid dynamics to predict TCM concentrations into the indoor swimming-pool air. However, this model requires numerous assumptions, particularly concerning the description of the indoor airflow patterns, which make its use difficult. The works of Dyck et al. resulted in an easier equation as described in a following section.

In this context, the present study aimed at documenting the variability of the occurrence of the main DBPs in water (THMs, HAAs and CAMs) and in the ambient air (THMs, CAMs) of two indoor swimming pools in Quebec City through intensive monitoring campaigns. The study examined the spatial variations of DBPs (i.e., in the pool water, in the air around the pool and in premises) as well as within-day and day-to-day variations of DBPs in both the water and the air. The database developed was then used to test various THM volatilization models. We also sought to establish the extent to which frequent or occasional water and air samplings might be required in order to properly

assess DBP exposure in pools and/or for risk assessment and potential regulatory purposes.

3. Methodology

3.1. Sites of study

For this investigation, two public indoor swimming pools ([A] and [B]) in Quebec City (Canada) were selected among those previously investigated by Simard [5]. Sites with a basic configuration consisting of a single pool were preferred. Technical information relative to each swimming pool is presented in Table 1.

3.2. Sampling program for air and water

Two consecutive sampling sessions were carried out during the first week of June (S1) and that of July (S2) 2010, respectively. The same sampling programs were carried out at the same time in both swimming pools.

Air Sampling (THMs and TCAM)

Basically, the program of each session consisted of four 95min-sampling periods/day during five consecutive days (from Monday to Friday, between 9:30am and 4:30pm approximately). For each period, 95min-integrated sampling was used to estimate THM levels in the air. Samples were collected at 30 cm and 150 cm above the surface water on the pool edge in the middle of the swimming pool. Depending on the day, other air samples were also collected near the breathing zone (150 cm) in various rooms, including men's and women's changing rooms, lifeguard's office, administrative office or operational room. The air sampling strategy differed slightly for TCAM, whose concentrations in the air were measured only two times/day. For this parameter, 120-min integrated air samples were collected along the pool edge in the middle of the swimming pool 150 cm above the water surface once in the morning (through the first and second period) and once in the afternoon (through the third and fourth period).

Water Sampling (THMs, HAAs and CAMs)

For water, duplicate spot samples were collected at midway through each period in three different locations around the pool: the shallow end, the middle of the pool and the deep end. All water samples were taken at approximately 30 cm under the water surface and were analyzed for THMs and HAAs. Only samples in the middle of the pool were collected for CAM analysis (as well as for other physicochemical parameters: pH, temperature, free residual chlorine and total chlorine)

3.3. Analytical procedures

Air samples. Air samples for THM measurements were collected using a pump (AirLite Sampler Model 110-100, SKC Inc.) at 165mL/min flow rate for 95 min through adsorption into activated carbon tubes (ORBO™ 32 Small Activated Coconut Charcoal (20/40), 100/50 mg; Sigma-Aldrich, #cat 20267-U). Tubes were sealed and stored on ice for analysis within three days of sampling. A solution of carbon disulfide (1ml) was used for desorption (Carbon disulfide, ACS reagent, ≥99.9%; Sigma-Aldrich, #cat 180173). After ultrasound heating during 30 min (Branson Bransonic 1200 Ultrasonic Cleaner Heated Water Bath), 1µL was injected into a gas chromatograph combined with electron capture detector (CP-3800, Varian. He: 1.0 mL/min. column VF5ms 30m [L] X 0.25mm [ID] X 0.25µm [Film thickness]). The limits of detection (LOD) were 0.69, 0.102, 0.095 and 0.112 µg/m^3 for TCM, DCBM, CDBM and TBM, respectively. TCAM in air was analyzed according to the reference method developed by Héry et al. [38]. Requisite sampling cassettes were prepared and analyzed by the Laboratoire d'études et de recherche en environnement et santé of the École des hautes études en santé publique de Rennes (LERES, EHESP, France) following NF ISO 10304-1 procedure. The LOD was 50 µg/m^3. Air samples for TCAM measurements were pumped at a 1L/min flow rate for 120 min through the cartridges. All pumps were calibrated each morning prior to sampling.

Water samples. For THM and HAA analyses, 40-mL glass vials with screw caps and polytetrafluoroethylene-lined silicone septa were prepared beforehand with a chlorine-quenching agent (166 µl of ammonium chloride at 30g/l) to prevent further chlorinated

DBP formation. After careful collection to prevent bubble formation, the samples were kept in an icebox and then stored at 4°C in the laboratory until analysis. THMs in water were extracted by solid phase microextraction SPME technic with PDMS 100µm fiber (Supelco, # cat. 57341) and determined using a gas chromatograph (Varian GC model 3900; column Factor Four VF-5ms 30 m [L] X 0.25 mm [ID] X 0.25 µm [Film thickness]) with ion-trap mass spectroscopy detection Supelco, –(Varian MS model 2100T). HAAs were measured according to EPA method 552.2 [50] using gas chromatograph (Perkin Elmer Autosystem XL included column Zebron 1701: 30m [L] X 0,32 mm [ID] x 0,25 µm [Film thickness]) with electron capture detector (GC-ECD) (methane-argon gas with purety of 99.99%). HAAs were extracted using methyl-tert-butyl-ether (Fisher Scientific HPLC grade, #cat E127-4), using 2-bromopropionic acid as extraction standard "surrogate" (Supelco, #cat 47645). For quality assurance, field blanks, duplicate samples and internal standards (1,2,3 Tricholoropropane, Supelco #cat 47669-U) in each sample were conducted. The limits of detection (LOD) ranged between 0.6 and 1.1µg/L for THMs and between 0.1 and 1.6µg/L for HAAs. For CAMs, the LOD was 10 µg/L-Cl_2.

Water samples for physicochemical measurements were collected in 250mL plastic bottles (Nalgene). Inorganic CAMs in water were estimated by spectrophotometry (HACH DR 5000, 515nm-reading, 1cm-cell) according to 4500-Cl-G DPD method (*Standard Methods for examination of water and wastewater,* 1998). Solid DPD (DPD free chlorine reagent HACH, #cat 21055-28) was used instead of liquid DPD prescribed in the 4500-Cl-G method. Apart from CAMs, other physicochemical measurements carried out included pH (Denver instrument Model-AP 15), temperature (alcohol thermometer), and, according to 4500-Cl-F method, free residual chlorine (HACH DR 890-MTH 8021) and total chlorine (HACH DR 890-MTH 8167).

3.4. Volatilization models

Two tools were compared for the predictions of TCM air concentrations from water levels: (i) the volatilization model (VTM) integrated into the physiologically based toxicokinetic modeling developed by Haddad et al. [51] and based on the work of

McKone [52, 53] and (ii) the level III fugacity model (FUG) currently proposed by Dyck et al. [49]. The VTM model assumes, under steady-state conditions, that the concentration in the air of a room depends primarily on the ventilation rate of the room and the chemical input into the room, the latter depending on the concentration of the chemical in the water, the volume of water used and the duration of water use. An efficiency factor is used to quantify the water-to-air transfer. First, we used the by-default parameterization of the model as originally assumed by Haddad et al. and then we adjusted the following parameters to better fit its predictions on the empirical data: flow = 7.42 L/min; ventilation = 0.66 m^3/min; efficiency factor = 0.390 (unitless). The FUG was developed on the basis of Mackay's work [54] and is based on the concept of fugacity. It accounts for interactions between several multimedia environments (i.e., water, air and also human organism), including flow and non-equilibrium conditions. From this process, a linear equation was reported by Dyck et al. to predict TCM air concentration (TCMa in µg/m^3) from TCM water concentrations (TCM in µg/L): TCMa = - 0.039 + 4.229*TCM.

3.5. Statistical analysis

Student t-tests (with Satterthwaite correction for inequal variances) were used to compare DBP levels between [A] and [B] as well between S1 and S2. First, relationships between the various DBP concentrations were studied using scatter plots and secondly, by calculating the Pearson correlation coefficients. A mixed analysis of variance (ANOVA) model was adjusted to these concentrations separately for each pool. The fixed factors are the sampling place, time and day. The random factor is the session. The MIXED procedure of the SAS program was used for the analyses [55]. Variance was modeled with the GROUP statement of the function REPEATED to ensure that homogeneity of variance and degrees of freedom were adjusted accordingly. We selected the best model of variance using the Aikaike Information Criteria (AIC). In some cases, the normality assumption was not verified, due to some outliers. However the analysis without the outliers led to similar results and the same conclusion. The significance levels used for these analyses were 0.01 for the ANOVAs and 0.05 otherwise. Data under the LOD were substituted by LOD/(2^0.5). The comparisons

between the volatilization models were based on the calculation of least square residual means.

4. Results

Table 2 provides an overview of the concentrations of DBPs measured in pools [A] and [B] during the two sampling sessions. Table 3 presents the values of the physicochemical parameters and cumulative number of bathers during those sessions.

4.1. DBP levels in water

4.1.1. Occurrence and speciation

As shown in Table 2, TCM was the only THM found in water samples. No brominated THMs were detected. In the previous study by Simard [5], TCM was the most abundant THM (approximately 97% of all measured THMs). Among the nine HAAs usually measured (HAA9), mostly dichloroacetic acid (DCAA) and trichloroacetic acid (TCAA) were present in high concentrations. Only bromochloroacetic acid (BCAA) and bromodichloroacetic acid (BDCAA) were also detected at very low concentrations. MCAM and TCAM were the main species of CAMs found in water while DCAM was measured in very low levels and only in approximately 25% of samples.

4.1.2. Spatial variations

The levels of TCM and CAMs were significantly higher in [A] than in [B] ($p<0.0001$ in each case). Conversely, HAA9 concentrations (especially TCAA and DCAA) were significantly lower in [A] (Table 2). Figure 1 illustrates the DBP concentrations measured at the three different sites where the samples were collected (i.e., deep, medium or shallow end of the pool). No clear trend appears, as the levels measured were sometimes greater in the deep end but sometimes greater in the shallow end. The coefficients of variations of the concentrations measured between the various areas of the pool can reach up to around 40%. However, the average coefficients of variations

were quite similar for both pools, ranging between 5% and 15% for the water contaminants (Table 4).

Regarding TCM, the mixed ANOVA models did not indicate any effect relative to the sampling site for [B], but a slight effect depending on the day for [A] ($p=0.0176$) . In this last case, the samples collected in the shallow end of the pool tended to present slightly lower TCM levels than the samples collected at the deep end. Nevertheless, this effect was only significant at the beginning of the week (Monday and Tuesday). The ANOVA showed no effect of the sampling site on HAA9 levels.

4.1.3. Temporal variations

TCM concentrations were slightly but significantly higher during S2 than during S1 in both [A] and [B] 25.4 ± 4.5 µg/L for S1 vs 31.7 ± 6.04 µg/L for S2, in [A]; and 20.7 ± 3.95 µg/L for S1 vs 27.95 ± 4.4 µg/L for S2, in [B]) ($p<0.001$). HAA9 and CAM levels were also higher during S2 in each pool. For HAA9, they were: 193 ± 26.3 µg/L for S1 vs 242.2 ± 49.3 µg/L for S2, in [A]; and 245.1 ± 27.5 µg/L for S1 vs 270.5 ± 43.8 µg/L for S2, in [B]. For CAMs, they were: 583 ± 123 µg/L for S1 vs 791 ± 568 µg/L for S2, in [A]; and 419 ± 112 µg/L for S1 vs 509 ± 121 µg/L for S2, in [B]. Figures 1 and 2 illustrate the within-day and day-to-day variations of DBP concentrations, respectively. Figure 1 does not disclose any evidence of a typical pattern regarding the within-day variations in DBP levels. Mean TCM concentrations did not fluctuate much (around 10 µg/L approximately) between the five days of the week (Figure 2a). More variations were observed for HAAs, the levels of which increased constantly during the week (approximately 1.7-fold) (Figure 2b). Figure 3 presents day-to-day variations of the levels of CAMs in water. These variations were dependent primarily on TCAM levels, while the concentration of MCAM remained quite constant during the week.

Overall, the mixed ANOVA showed no effect relative to sampling day or time for CAMs or TCM. However, interestingly, the factor day was clearly significant in each pool for HAA9 ($p<0.0001$) (Figure 1b). For instance, in [A], the HAA9 levels were significantly lower on Monday, compared to the other days, and higher on Friday, compared to the first days of the week. This confirms the observation that HAA9

concentrations in pool water would tend to increase during the week. Indeed, the same trends are also observed in pool [B].

4.2. DBP levels in air

4.2.1. THMs

Only TCM was systematically detected above the limit of quantification. DCBM was detected in some samples, but at much lower levels than TCM (Table 2). CDBM and TBM levels remained under their LOD. TCM showed the highest levels in both [A] and [B]. Therefore, the interpretation of spatial and temporal variations of THMs in the air was restricted to TCM and DCBM.

4.2.1.1. Spatial variations

Significantly higher levels of THMs were measured in the air of pool [A] (Table 2). In addition, as shown in Table 4, the concentrations of THMs measured at 30 cm and 150 cm above the water surface in [A] were much more variable than in [B]. It may be due to usually higher swimmers' attendance in [A] (see Table 3) which cause more turbulence and therefore can contribute to higher volatilization of the THMs. Besides, Figure 4 clearly shows that the THM levels measured at 30 cm of pool [A]-session S2 are higher, compared to the levels measured at 150 cm. Indeed, the mixed ANOVA model for pool [A] indicates the factor sample site (height) is significant ($p=0.0176$). Such was not the case for pool [B].

Table 5 summarizes the concentrations of TCM measured in various premises of each swimming pool building. Values measured in the premises of pool [B] were clearly higher, compared to pool [A].

4.2.1.2. Temporal variations

Overall, total THM (TTHM) air levels around the pool were significantly higher during S2 (147.6 ±± 67.4 $\mu g/m^3$) than during S1 (113.4 ± 14.6 $\mu g/m^3$) in [A] ($p= 0.003$, $p= 0.0316$, $p= 0.0031$ for TCM, DCBM, TTHM, respectively) as it was also the case for water levels. Conversely, the level of contamination was surprisingly, but significantly

greater during S1 in [B] (112.5 ± 26.7 µg/m^3 vs 69.0 ± 23.4 µg/m^3) ($p<0.0001$ for each THM), as shown in Figure 4. However, no clear trends could be observed regarding day-to-day variations. Nevertheless, for [B] only, the mixed ANOVA showed an effect of the factor day ($p=0.0079$) due mainly to higher levels of contamination measured on Tuesday. The within-day variations of TTHM air levels were quite disparate as for water concentrations (Figure 5). No typical patterns could be drawn. However, differences as high as 60 µg/m^3 could be measured between two samples taken at two different times on the same day.

4.2.2. TCAM

4.2.2.1. Spatial variations

TCAM air levels around the pool were generally higher in [A] than in [B] (see Table 2) ($p = 0.0005$). Only two samples (both in [A]) were above the suggested protective threshold level of 300 µg/m^3 proposed by Parrat [39] (see Figure 6). TCAM were below this threshold in the few samples collected in the lifeguard's offices and even below the detection limit (50µg/m^3) in the changing rooms.

4.2.2.2. Temporal variations

In [A], the mean concentrations of TCAM were 243.3±47.0µg/m^3 and 199.0±79.4µg/m^3 during S1 and S2, respectively. In [B], they were 145.0±52.8µg/m^3 and 132.5±25.5µg/m^3. In both cases, differences between S1 and S2 were not statistically significant ($p=0.1626$ and $p=0.5487$, for [A] and [B] respectively). Figure 6 shows the day-to-day and within-day variability of TCAM concentrations during S1 and S2. It is not clear whether any trends exist regarding these variations. However, the ANOVA points to evidence of an effect relative to the factor day (with TCAM concentrations higher at the beginning of the week), but only for [B] ($p=0.0093$).

4.3. Relationships between the DBP concentrations

Pearson coefficients between the various DBP concentrations in each pool and for each session were calculated. No consistent correlations were observed between the various types of DBPs in water, i.e. HAAs, THMs and CAMs.

The results show that TCAM in air was correlated either with THM levels measured at 30 cm above the water surface or at 150 cm. However, this result was not consistent according to the pool and the session, making it difficult to explain. The relationships between THM levels at 30 cm and THM levels at 150 cm were also inconsistent. However, in general, correlations with mean THM levels were always better with THM levels at 30 cm rather than 150cm.

No clear relationship appeared between the DBPs in water and in the air (Table 6). Interestingly, HAA9 levels in water tended to be inversely correlated to air TCAM but the result was not statistically significant. Quite weak correlations were obtained between water CAMs and air THMs, but the relationships are inconsistent if each pool and session were considered independently.

4.4. Predicting TCM air concentrations from water concentrations

We further investigated the relationship between TCM in air and TCM in water and the possibility of predicting air levels from water levels. Figure 7 shows the disparity of TCM air concentrations according to the TCM water concentrations when measured at the same time. However, it is interesting to note in this figure, the paired water and air concentrations measured in one pool during the same week tended to aggregate in the same area that may be regarded as representative of this pool during this week.

Figure 8 shows the predicted TCM air concentrations using the integrated volatilization model (VTM) and the level III fugacity model (FUG) described previously, versus actual measurements. In all cases, the by-default setting did not allow very precise estimates. Nevertheless, the FUG modeling resulted, interestingly enough, in much more plausible estimates. Indeed, Table 7, where the lower mean indicates the best predictor, suggests a greater reliability of FUG model to predict TCM air concentrations, rather

than by-default set VTM model. Interestingly, the FUG estimates were clearly better for periods with no swimming pool attendance. In fact, the situation may be closer to an actual equilibrium state more suitable for such modeling, given that bathers' absence may cause less turbulence and DBP volatilization.

We adjusted the parameterization of VTM model to better fit its predictions on actual measurements. The Adjusted VTM model served to achieve a lower residual square means of 2758.33 (± 4816.76), which indicates more precise predictions. We also adjusted an empirical model (EMP) on our generated database, resulting in the following formula: TCMa = 49.44 + 2.646*TCM, where TCMa is the TCM air concentration predicted in $\mu g/m^3$ and TCM is the TCM water concentration in µg/L.

The FUG, adjusted VTM and EMP models were compared on the basis of data extracted from the literature and reported by Dyck and al. [49]. TCM air concentrations predicted using each model from reported TCM water concentrations were compared to reported TCM air measurements. Table 8 indicates FUG and EMP models are better predictive models than the adjusted VTM model.

5. Discussion

We investigated the environmental occurrence of DBPs in two typical swimming pools with particular interest directed at the short-term and spatial variations of both water and air contaminants. Moreover, the database created served to examine the reliability of volatilization models for TCM. It provided interesting information to try to define best practices to assess DBP exposure in swimming pools for risk analysis or regulatory purposes.

5.1. Occurrence of DBPs and health risks

The high levels of HAAs in the water of the visited pools require particular attention. Indeed, these levels are consistent with those reported in a limited number of studies that documented the occurrence of these compounds in similarly chlorinated pools and also identified DCAA and TCAA as the most abundant HAAs [5, 46, 47]. While ingestion of swimming pool water is usually considered quite low [56], the impact of the

consumption of even small quantities of water so highly loaded in HAAs should be further examined, especially compared to the levels to which people are exposed on a daily basis through drinking water consumption. Previously, Simard et al. indicated HAA levels in swimming pools that could be up to 80 times the HAA levels in the distribution system [5]. The levels of HAAs we measured in the present study remain lower but are approximately 3-4 times the norm of Québec for HAAs in drinking water (60µg/L) [57]. Among THMs, only TCM was detected in pool water at quite low levels, ranging close to those reported in the literature, but usually above the German standard of 20µg/L [2, 4, 5, 41, 44, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68]. TCM was measured in concentrations usually reported in the ambient air of swimming pools [2, 4, 41, 44, 58, 59, 60, 62, 64, 65, 66, 68]. DCBM was also detected but in much smaller concentrations in the air (up to 4.34µg/m^3 but usually 100 times less than TCM levels), while no brominated THMs were detected in the water (less than 0.6, 1.0 and 0.8µg/L for DCBM, CDBM and TBM respectively), perhaps due to differences in the sensitivity of analytical methods.

Air contamination was also assessed in various rooms surrounding the pool. To our knowledge, only two Italian studies by Fantuzzi et al. have reported this type of information by measuring THM air concentrations in the reception area or in the engine room [65, 66]. Interestingly, TCM levels in the various rooms of the swimming pool building was high, compared to typical household baseline contamination levels ranging between 1 and 10 µg/m^3 reported by Nuckols et al. [69]. They are comparable to contamination levels resulting from other household water use activities (i.e., clothes washing [7-33µg/m^3], dishwashing [2-28µg/m^3], hand washing [19-85µg/m^3], bathing [21-98µg/m^3]) which the same author points out as potentially significant contributors to daily exposure to TCM._Moreover, swimming pool attendees or workers may spend a much longer time in these premises; therefore, they may even be more exposed to DBPs in these locations than during their usual household water use activities.

The levels of TCAM in ambient air did not comprise a range that seems to be particularly problematic for human health according to the suggested guideline of Parrat [39]. Likewise, it is important to note that for technical reasons we did not take samples during the periods when higher attendance might result in increasing DBP

formation and then exposure. In addition, sampling was carried out in summer only; the results may have been greater in winter, especially for air contamination.

5.2. Monitoring and integrated modeling for exposure assessment

Defining best practices for DBP exposure assessment in swimming pools must consider two main aspects: the first deals with the feasibility of using one particular DBP in a particular medium as a surrogate for the occurrence of other DBPs in other media; the second concerns the availability, ease of use and reliability of *in-situ* monitoring methods and/or predictive environmental modeling, since no standard sampling strategy for DBP exposure in swimming pool exists for attendees or workers.

To use a single DBP as an indicator of the levels of other DBPs would appear unfeasible, given the few correlations obtained in this study, which implies separate monitoring of each DBP. Indeed, contrary to Lee et al. [47] or Bessonneau et al. [29], we did not observe any consistent correlation between DBPs. Likewise, the analysis of spatial and temporal variations of both water and air contaminant levels pointed to a considerable potential for random disparities that make it inconceivable to predict their presence without using a minimal *in-situ* monitoring campaign.

Regarding the spatial variations, given the differences observed within and between the swimming pools, no location (at a fixed height for air or in a particular zone for water) could be identified as the most representative of the pool contamination for sampling; thus, neither should be regarded as suitable for one-shot monitoring. In the particular case of air TCAM, Parrat [39] points to the different conclusions drawn in the literature regarding possible decreases of contamination levels according to the height of sample collection. The author assumes that numerous different conditions between pools (e.g., ventilation and attendance) may explain this. Our results, and particularly the differences observed between [A] and [B], support his assumption. In fact, collecting at least two samples of water and two samples of air is recommended, rather than taking some spot samples alone. Systematically collecting two samples of water in the deep and shallow ends of the pool and two samples of air at approximately 30 cm and 150cm above water surface (i.e., breathing zones of a swimmer and of a man standing at the edge of the pool) could be an interesting strategy for a better assessment of environmental exposure.

Indeed, in this study, all air samples were collected in the middle on the poolside and we focused on the "vertical" variations without considering "horizontal" ones. This latter can occur actually as shown by Hsu et al [48]. Nevertheless, in the current state of knowledge, we believe sampling air at the center of the pool may be the most representative sampling place to account for horizontal variations, but further investigations should address that.

Temporal variations can be important within a day, despite the fact that no typical pattern was drawn. Day-to-day variations in one swimming pool appeared to be quite limited in the course of the same week, apart from HAAs that tended to increase over the week in each pool and in each session; this may be due to a water change (back wash) in the pool. As for spatial variations, an appropriate monitoring should account for temporal variations by sampling at least twice a day. To take into account the variations of the number and activities of pool attendants, sampling just after opening and just before closing should be considered. The potential impact of such variations on DBP absorption and internal exposure assessment (and the error measurement associated to accounting for it or not) should be addressed in further investigations.

The issue of modeling the DBP volatilization is another challenging point to address for two reasons. On the one hand, analytical methods to measure TCAM and THMs in the air are not easy to carry out, despite the apparent necessity, given the sanitary impact associated with air TCAM and the allegedly high contribution of inhalation to THM exposure. On the other hand, as previously mentioned, numerous factors influence the formation and the volatilization of DBPs (e.g., number of swimmers, ventilation, and water turbulence) and make the development of alternative modeling tools particularly challenging. So far predicting TCM air concentrations from water levels does not appear to be very reliable, irrespective of the model used, which enforces the need of minimal sampling for both water and air. Between the various models tested, the FUG model proposed by Dyck et al. [49] and the EMP model we developed from the data collected in this study resulted in the more realistic predictions but their precision still needs be greatly improved.

6. Conclusion

This study indicates that a minimal sampling strategy should be used for each DBP separately. The water-to-air models available for TCM require further improvement, but given the current state of knowledge where data for TCM air concentrations are not available, the use of the FUG model or the EMP model are alternatives. Overall, accurate DPB exposure assessment in swimming pool still remains very challenging, given the great number of variables (e.g., number of bathers or attendants, turbulence, organic precursors, ventilation) which may influence the amount of each compound and can produce the remarkable differences that this paper relieved within the same environment (water and air). Further research on DBP exposure should deal with the impact on bathers of such high levels of HAAs in the swimming pool water, integrate both swimming pool and household exposure to DBPs in risk assessment and look at the impact of such exposure on swimming pool workers as they represent the potentially highest exposed population.

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7. Tables and Figures

Table 1. Technical information on configuration and water treatment in each studied swimming pool.

	Pool [A]	Pool [B]
Dimensions ([m] x [m])	25 x 14,4 (360 m²)	25 x 12 (300 m^2)
Pool volume (L)	682 000	860 000
Water Desinfectant	Sodium hypochlorite (automated injection)	
Indicative DBP concentrations in water (µg/L) reported by Simard et al. [5]		
THM	26,1	28,6
HAA	267,0	388,9
CAM	574,9	493,1

Table 2. DBP concentrations in pool water and air of [A] and [B] (all samples)

	Pool [A]			Pool [B]		
	n [a]	**Mean (+/- SD)**	**[min-max]**	***n*** [a]	**Mean (+/- SD)**	**[min-max]**
TTHMs[b] in water (µg/L)	119	28.8 (+/- 5.8)	[13.3 – 46.0]	116	24.3 (+/- 5.5)	[10.4 – 38.1]
[b]*TCM*		28.8 (+/- 5.8)	[13.3 – 46.0]		24.3 (+/- 5.5)	[10.4 – 38.1]
HAA9[b] in water (µg/L)	120	217.6 (+/- 46.5)	[111.3 – 390.4]	120	257.8 (+/-38.6)	[138.6 – 365.0]
[c]*DCAA*		93.3 (+/-28.6)	[48.0 – 191.5]		112.1 (+/- 21.8)	[69.1 – 163.2]
[b]*TCAA*		107.5 (+/- 23.0)	[54.0 – 190.7]		128.9 (+/- 22.2)	[59.2 – 201.0]
BCAA		1.81 (+/- 0.80)	[0.6 – 3.0]		1.8 (+/-0.9)	[0.4 – 2.9]
BDCAA		15.0 (+/- 6.7)	[<LOD – 23.6]		15.1 (+/- 6.2)	[6.1 – 23.5]
CAMs[c] in water (µg/L Cl_2)	39	689 (+/- 166)	[376 – 981]	40	526.9 (+/-113)	[268 – 802]
[c]*MCAM*		323 (+/- 55)	[188 – 434]		284 (+/- 81)	[<LOD – 450]
DCAM		25 (+/- 97)	[<LOD – 593]		11 (+/- 21)	[<LOD – 70]
[b]*TCAM*		341 (+/- 183)	[<LOD – 650]		232 (+/- 146)	[<LOD – 557]
TTHMs[c] in air (µg/m^3)	78	130.3 (+/- 49.1)	[47 – 311]	76	90.2 (+/- 33.1)	[33.7 – 180.3]
[c]*TCM*		128.7 (+/- 48.5.2)	[46.4 – 306.7]		89.1 (+/- 32.8)	[33.6 – 177.7]
[c]*DCBM*		1.55 (+/- 0.7)	[<LOD – 4.3]		1.1 (+/- 0.5)	[<LOD – 2.6]
TCAM[b] in air (µg/m^3)	19	220 (+/- 68)	[110-350]	18	139 (+/- 42)	[80-210]

[a] number of samples

[b] statistically significant for T-test (equal variances) ($p<0.05$)

[c] statistically significant for T-test (unequal variances) ($p<0.05$)

Table 3. Mean physicochemical parameter values and cumulative number of bathers in [A] and [B] during S1 and S2

	Pool [A]		Pool [B]	
	S1	**S2**	**S1**	**S2**
Temperature (°C)	27.8	28.5	27.9	27.6
pH	7.2	7.5	7.2	7.4
Free Chlorine (mg/L)	1.32	1.32	1.19	0.89
Total Chlorine (mg/L)	1.88	1.88	1.68	1.43
Cumulative number of bathers	239	862	122	530

Table 4. Coefficients of variations (%) between the levels of DBPs measured at the various sampling places into the pool (for water contaminants) and around the pool (for air contaminants)

		Pool [A]			**Pool [B]**	
	***n*[1]**	**Mean(+/- SD)**	**[min-max]**	***n*[1]**	**Mean(+/-SD)**	**[min-max]**
TTHMs in water (µg/L)	39	14.1 (+/- 7.4)	[2.6 – 31.1]	37	14.1 (+/- 8.15)	[2.4 – 38 .9]
TCM		14.1 (+/- 7.4)	[2.6 – 31.1]		14.1 (+/- 8.15)	[2.4 – 38 .9]
HAA9 in water (µg/L)	40	9.5 (+/- 9.5)	[1.3 – 38.2]	40	7.2 (+/- 5.0)	[0.9 – 26.2]
DCAA		10.0 (+/- 9.9)	[1.5 – 35.3]		6.6 (+/- 4.5)	[1.5 – 23.0]
TCAA		10.8 (+/- 9.9)	[0.5 – 40.5]		9.3 (+/- 6.0)	[0.8 – 30.9]
BCAA		6.7 (+/- 6.2)	[0.2 – 24.8]		6.6 (+/- 10.3)	[0.4 – 52.5]
BDCAA		6.5 (+/- 13.0)	[0.4 – 82.6]		5.6 (+/- 5.8)	[0.2 – 21.6]
TTHMs in air (µg/m^3)	38	22.1 (+/- 24.2)	[0.4 – 87.3]	37	12.9 (+/- 15.9)	[0.12 – 63.9]
TCM		22.1 (+/- 24.1)	[0.1 – 87.3]		12.8 (+/- 15.8)	[0.1 – 62.5]
DCBM		33.0 (+/- 32.0)	[0 – 128]		22.9 (+/- 30.2)	[0 – 133]

[1] n is the number of cases with all concentrations available at a same time in each sampling place

Table 5. TCM concentrations (µg/m^3) in the ambient air of various rooms of [A] and [B] (all samples)

	Pool [A]			Pool [B]		
Room	***N***	**median**	**[min-max]**	***n***	**median**	**[min-max]**
Men changing room	20	2.3	[<LOD – 4.5]	19	65.6	[43.8 – 115.5]
Women changing room	20	14.6	[4.6 – 28.2]	19	66.10	[47.5 – 111.5]
Lifeguards' office	18	13.10	[<LOD – 38.3]	20	59.3	[22.3 – 109.3]
Administrative office	-	-	-	11	27.1	[8.5 – 37.1]
Technical room	14	46.4	[4.7 – 99.2]	8	62.2	[43.8 – 117.8]
Bleachers	4	90.5	[81.4 – 117.9]	-	-	-

Table 6. Pearson coefficient of correlations between DBP concentrations in water and DBP concentrations in air overall sessions and pools

	TTHM	HAA9	CAM
Air TCAM	0.1821	-0.7139	0.3970
Air TCM	0.1657	-0.1819	* 0.3218
Air DCBM	0.1970	* -0.2708	* 0.2021
Air TTHM	0.1664	-0.1834	* 0.3207

* $p < 0.05$

Table 7. Means of square residuals between measured and predicted TCM air concentrations

Square residuals	*N*	Mean	STD	Minimum	Maximum
VTMs [a]	84	31240	22670	25.43	99610
-	32	34290	26320	5214.80	99610
+	52	29360	20140	25.43	79690
VTMh [b]	84	17170	16840	1688.42	87340
-	32	10740	7120	1688.42	33380
+	52	21120	19720	2277.11	87340
FUG [c]	84	2760	5060	0.36	27750
-	32	1810	2690	25.76	9930
+	52	3350	6030	0.36	27750

[a] volatilization model set by Haddad et al. to predict air concentration into the shower room

[b] volatilization model set by Haddad et al. to predict air concentration into the rest of the house

[c] equation from the fugacity model set by Dyck et al.

- : considering periods with no bathers in the pool

+: considering periods with bathers in the pool

Table 8. Comparison between adjusted VTM, EMP and FUG models for their abilities to predict TCM air concentrations from TCM water concentrations on the basis of data reported in the literature.

Square residuals	***n***	**Mean**	**STD**	**Minimum**	**Maximum**
Adjusted VTM [a]	31	83450	276000	0.12	1459500
EMP [b]	31	36220	145880	10.44	830500
FUG [c]	31	71480	232430	0.0017	1218600

[a] volatilization model set to fit with our dataset

[b] empirical model adjusted on our database

[c] equation from the fugacity model set by Dyck et al.

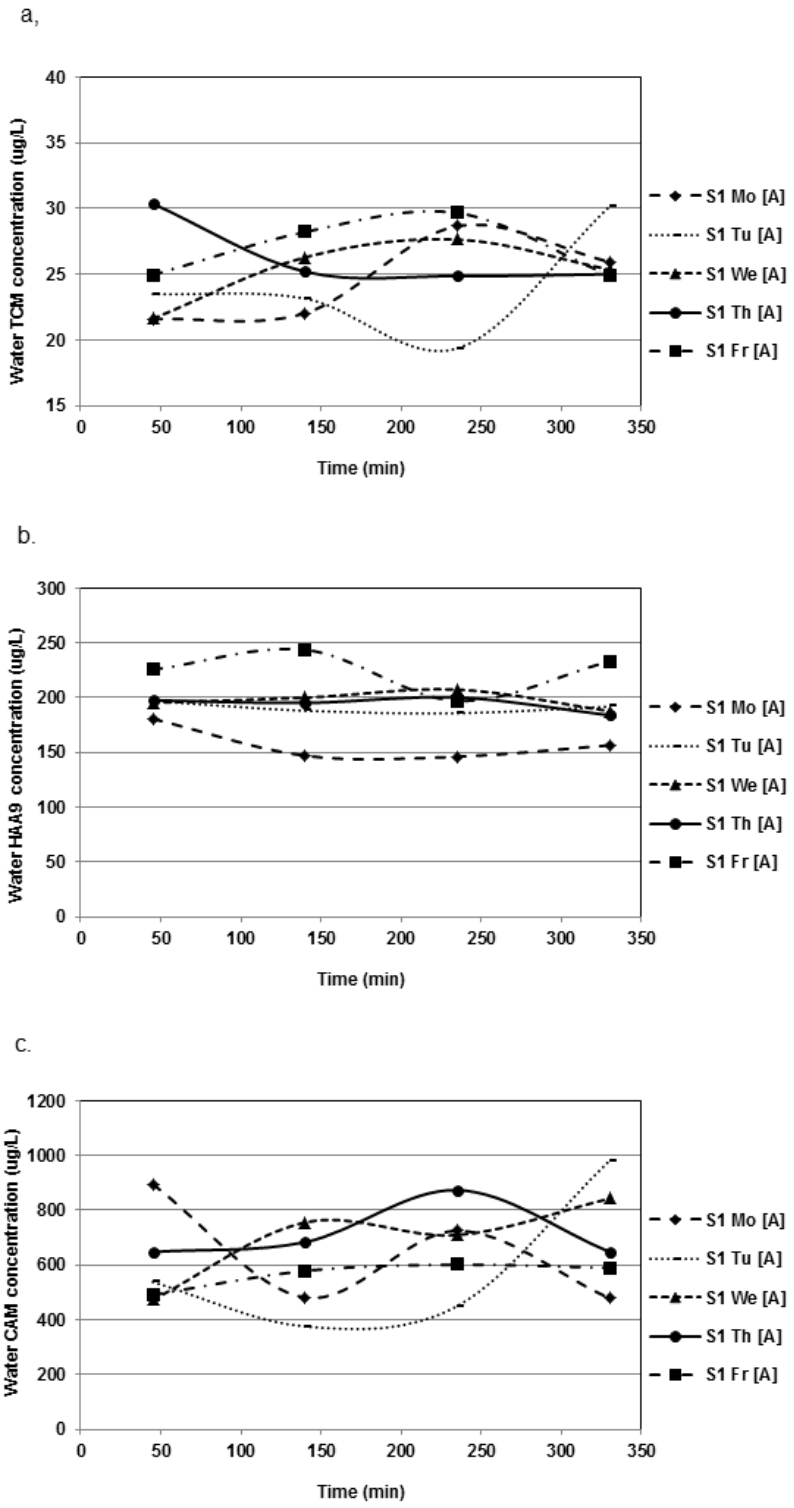

Figure 1. Mean DBP water concentrations (µg/L) in the swimming pool [A] during the four sampling periods of each day of the campaign S1 (Time = 0 min → 9a.m).

(a) TCM; **(b)** HAA9; **(c)** CAM

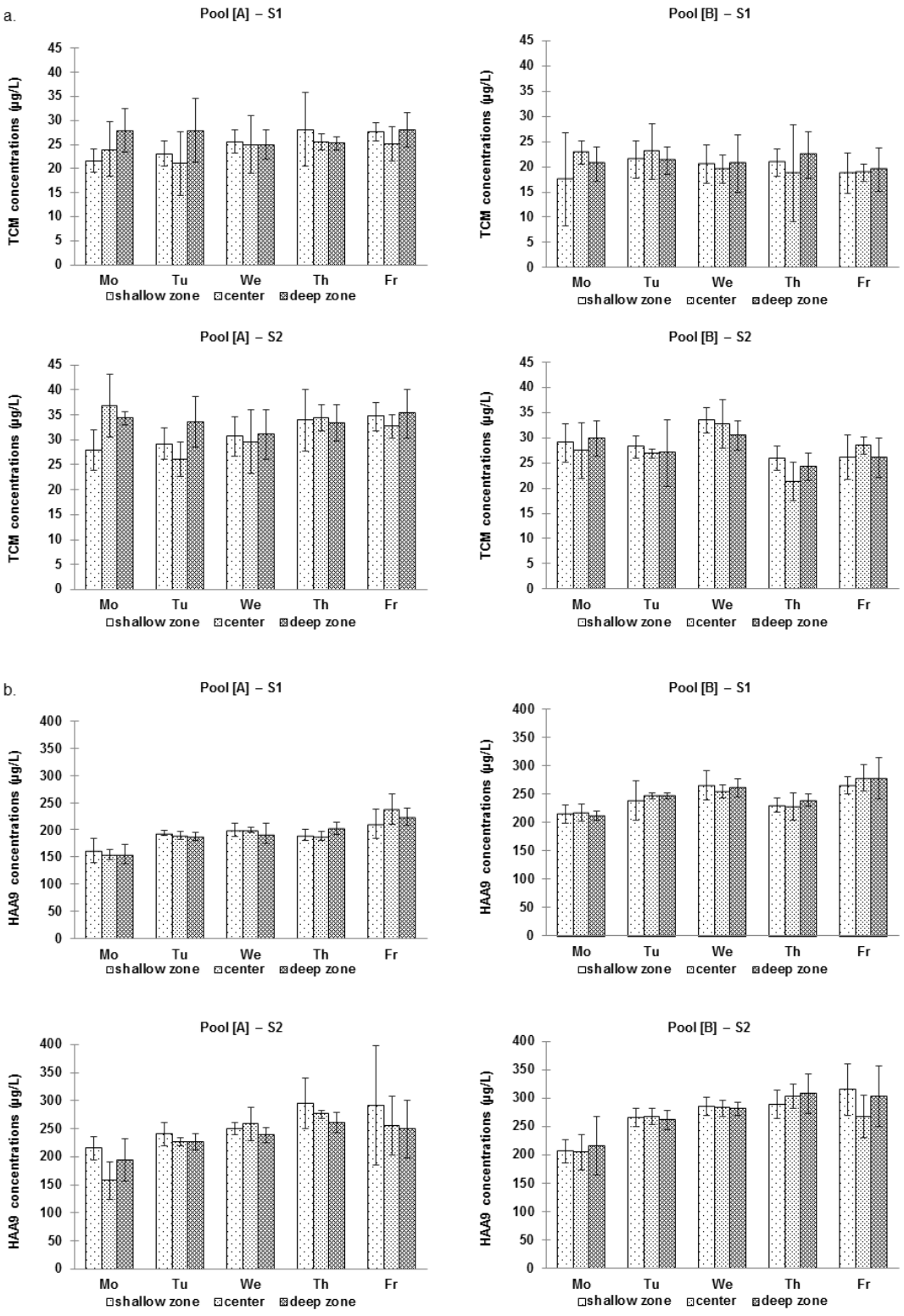

Figure 2. Mean DBP water concentrations (µg/L) in the various zones of pool [A] and [B] during session S1 and S2. **(a)** TCM; **(b)** HAA9

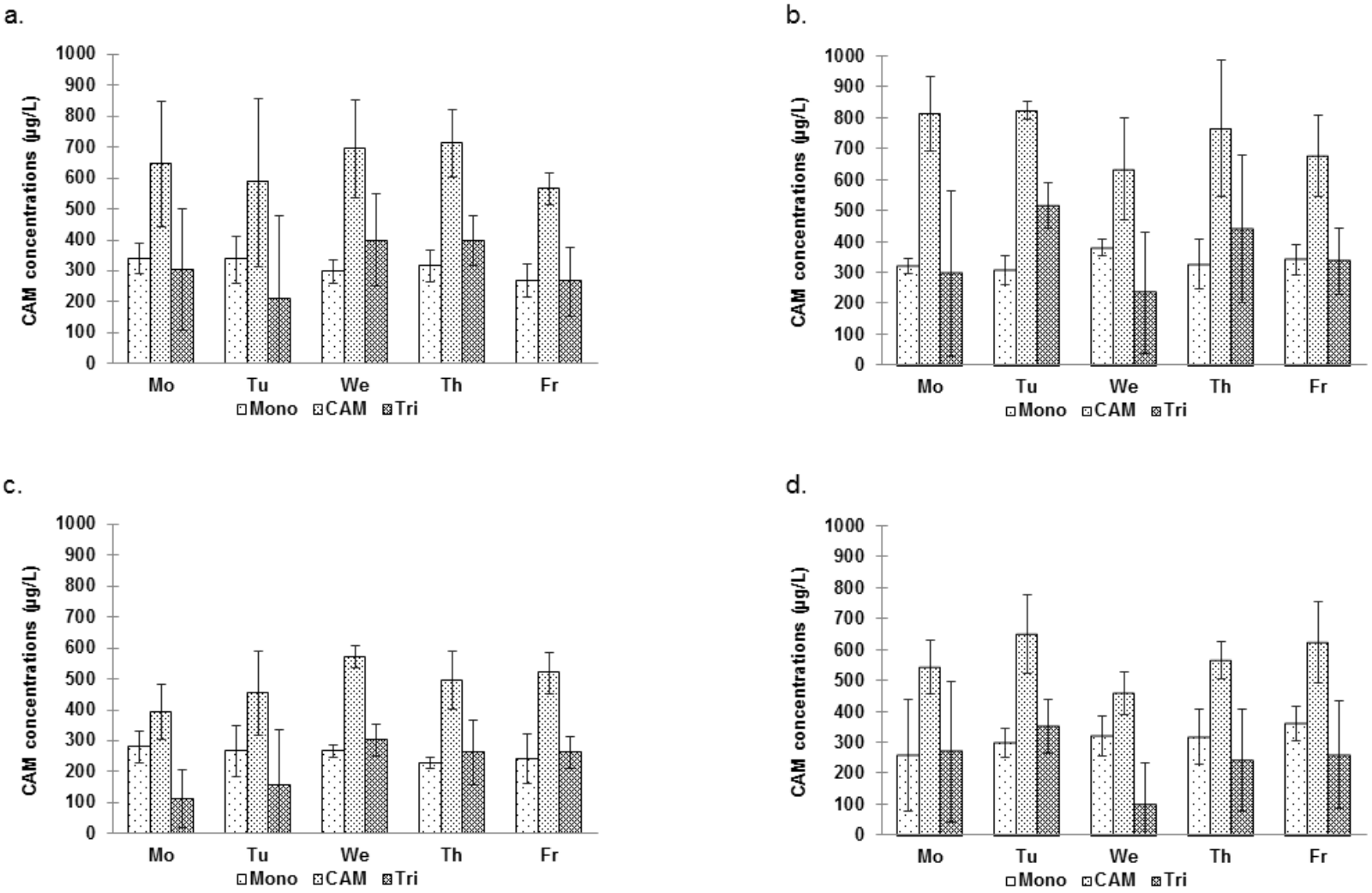

Figure 3. Mean daily concentrations of MCAM (Mono), TCAM (Tri) and Total CAM in water in [A] and [B] during S1 and S2. **(a)** [A] – S1; **(b)** [A] – S2; **(c)** [B] – S1; **(d)** [B] – S2

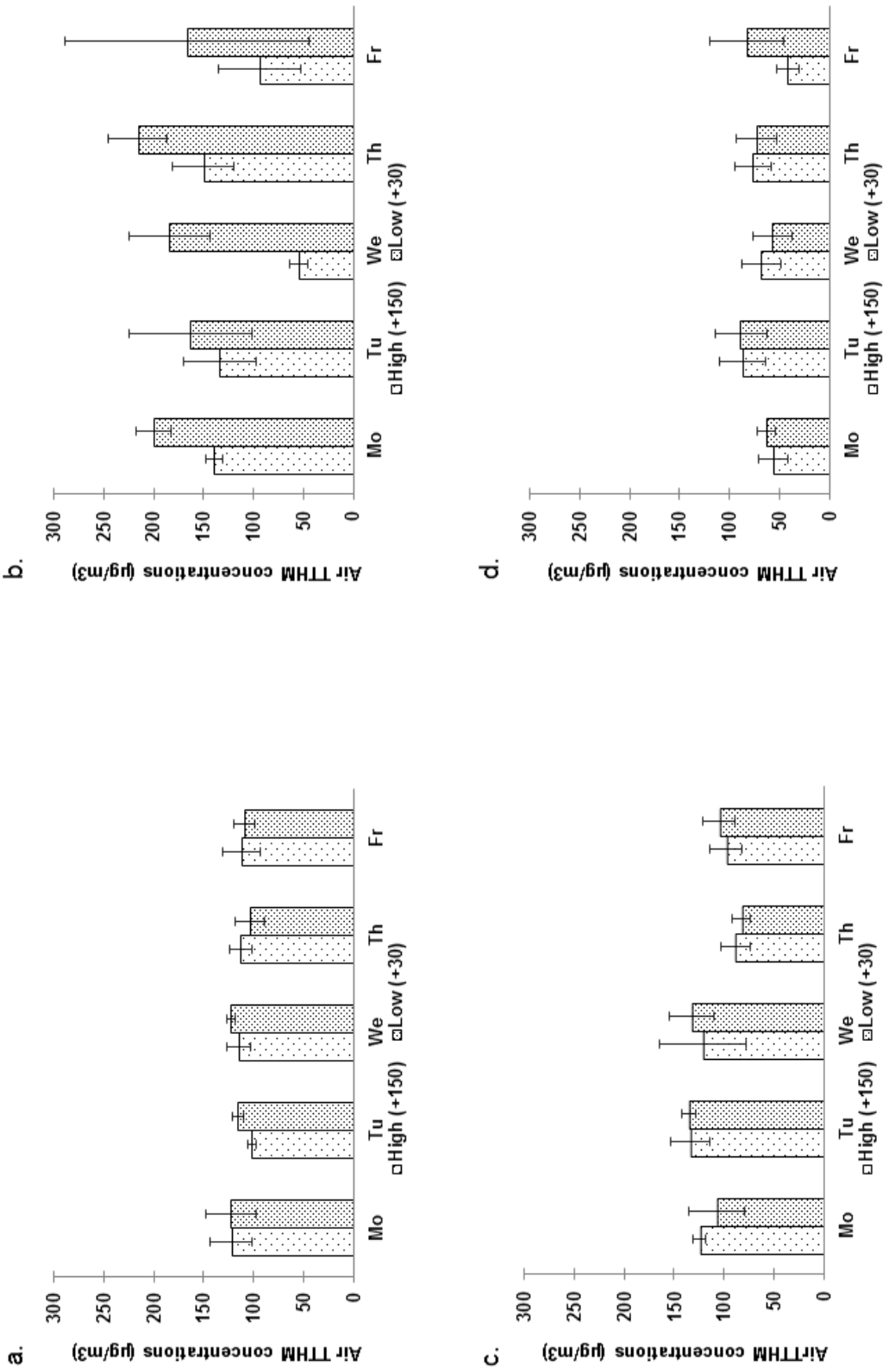

Figure 4. Mean concentrations (µg/L) of TTHMs in the pool air.

(a) [A] – S1; **(b)** [A] – S2; **(c)** [B] – S1; **(d)** [B] – S2

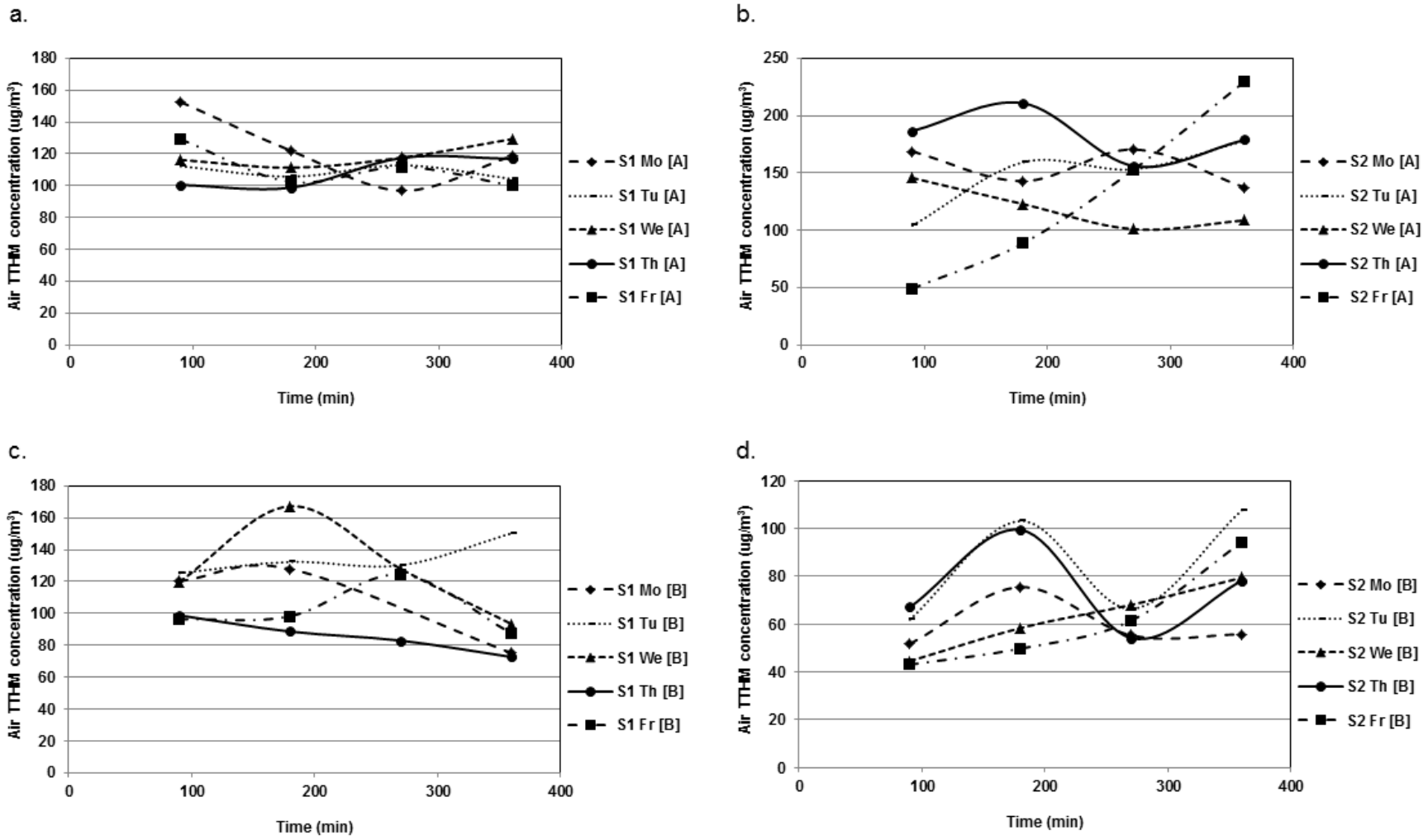

Figure 5. Mean TTHM concentrations (µg/m^3) in the air of [A] and [B] during the 4 sampling periods of each day (Time = 0 min → 9a.m). **(a)** [A] – S1; **(b)** [A] – S2; **(c)** [B] – S1*; **(d)** [B] – S2 *One data misses on Monday for [B]-S1

130

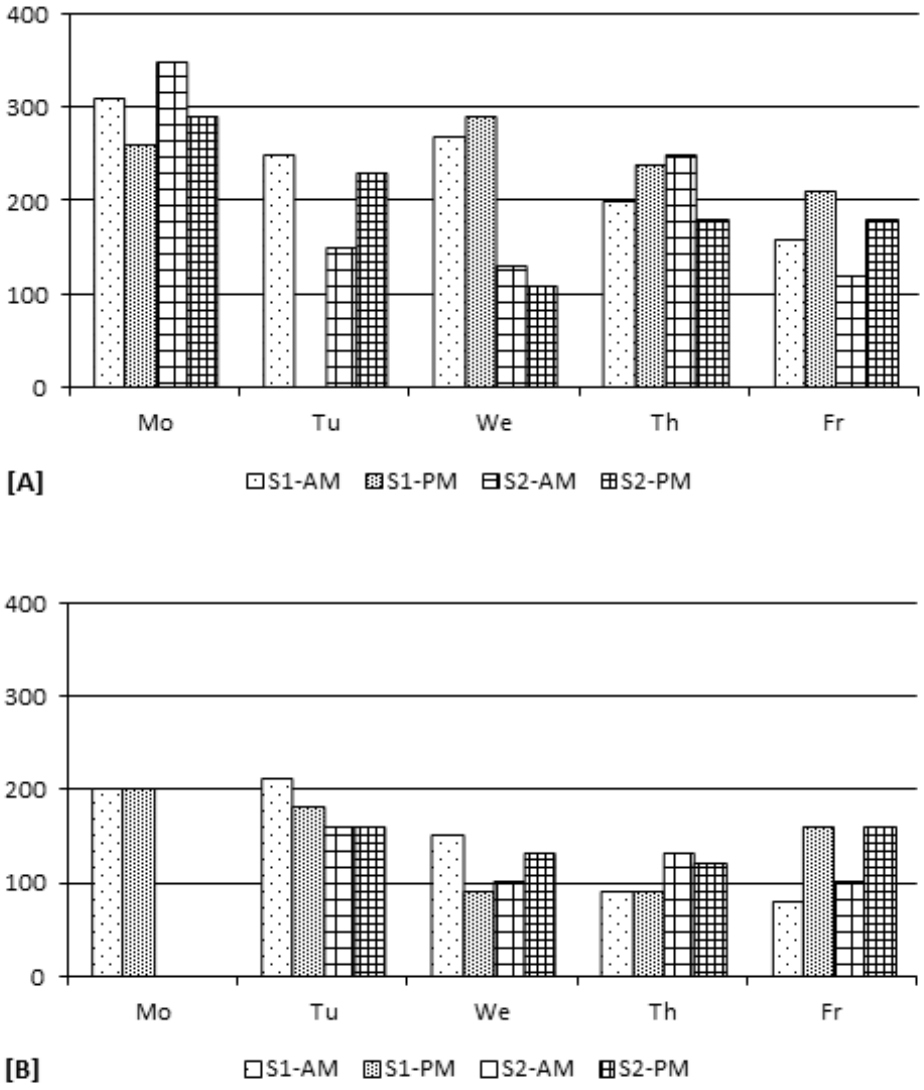

Figure 6. Concentrations (μg/m^3) of TCAM in the air of [A] and [B] in the morning (AM) and afternoon (PM) of each sampling day during S1 and S2.
(Missing data were due to broken samples)

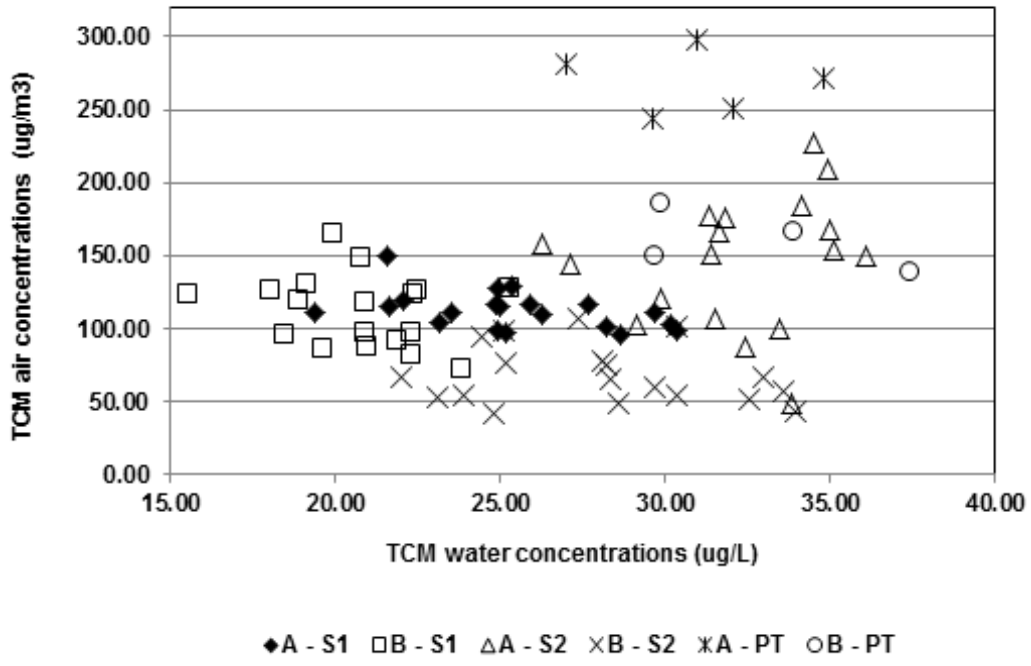

Figure 7. Concentrations ($\mu g/m^3$) of TCM in the air of [A] and [B] versus water concentrations ($\mu g/L$)

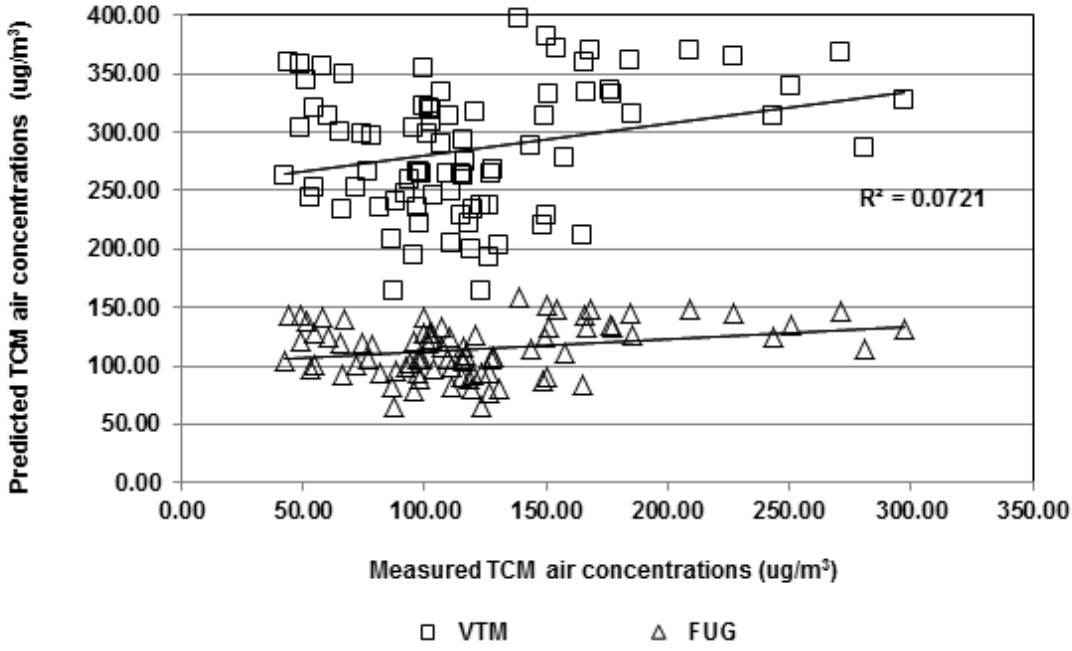

Figure 8. Predicted versus measured TCM air concentrations (μg/m^3) using VTM model and FUG model

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ARTICLE IV - Assessing exposure to chloroform in swimming pools using physiologically based toxicokinetic modeling

Assessing exposure to chloroform in swimming pools using physiologically based toxicokinetic modeling

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1. Abstract

This work examines the use of physiologically based toxicokinetic (PBTK) modeling to assess exposure to the most abundant disinfection by-product (DBP), chloroform (TCM), to be found in indoor swimming pools. Real exposure scenarios including environmental (water and air levels) and biological (alveolar air or blood levels) data extracted from the literature were simulated. Predicted biological data matched up well with the reported actual levels, thereby confirming the reliability of this approach. Relative contributions of inhalation and dermal absorption to the total body burden were estimated and compared to the inconsistent results of reported studies. The PBTK simulations served to explain this inconsistency, suggesting that the prevalence of each pathway depends on environmental concentrations and on the ratio between air and water levels in particular. Likewise, comparisons between 24-h typical household and typical 1- or 2-h swimming pool exposure scenarios point to the preponderance of the latter.

Keywords: Disinfection by-products, Trihalomethanes, Chloroform, Exposure assessment, Swimming pools, Biological exposure, Physiologically based toxicokinetic modeling

2. Introduction

Chloroform (TCM) is by far the most abundant drinking water contaminant among disinfection by-products (DBPs). It belongs to the category of the trihalomethanes (THMs) that raise public health concerns, given their potential adverse effects (i.e., carcinogenicity and reprotoxicity) (Grazuleviciene et al., 2011; Grellier et al., 2010; Nieuwenhuijsen et al., 2009; Tardiff, Carson, & Ginevan, 2006; Villanueva et al., 2007). It is a well known fact that exposure to volatile and lipophilic TCM can occur through ingestion, inhalation and dermal absorption (Weisel & Jo, 1996). Excluding ingestion, inhalation is commonly regarded as the main route of absorption (Erdinger et al., 2004; Lévesque et al., 1994), but it is also reported that dermal absorption might be dominant (up to 80%) (Lindstrom, Pleil, & Berkoff, 1997). Likewise, various sources can contribute to exposure to TCM: it can occur through household water use activities (e.g., showering, washing) (Nuckols et al., 2005) but also in swimming pools where conditions are conducive to a potentially high exposure to disinfection by-products (DBPs) for occasional or regular attendees (e.g., children, pregnant women, competitors), as well as workers (e.g., lifeguards) (AFSSET, 2010). As a matter of fact, numerous factors related to technical requirements or individual behaviors can contribute to increasing swimming pool exposure to these chemical contaminants, in particular their formation in high quantities and their absorption by the human body (e.g., water re-circulation, high doses of applied disinfectants, poor ventilation in indoor swimming pools, continuous DPB precursor loading from swimmers and the physiological impact of physical exercise resulting in greater pulmonary ventilation) (Zwiener et al., 2007).

Most studies dealing with the issue of exposure to THMs and especially to TCM in swimming pools examined the use of biological markers (e.g., blood, alveolar air and urine) to quantitatively assess this exposure among leisure and competitive swimmers (Aggazzotti, Fantuzzi, Righi, & Predieri, 1998; Aggazzotti et al., 1993; Aggazzotti, Fantuzzi, Tartoni, & Predieri, 1990; Cammann & Hubner, 1995; Caro & Gallego, 2008a, 2008b; Caro, Serrano, & Gallego, 2006, 2007; Faust, Faust, & Cammann, 1993; Lourencetti et al., 2010). Only a few studies investigated occupational exposure to TCM

among workers (Caro & Gallego, 2007, 2008a; Fantuzzi et al., 2001; Fantuzzi et al., 2010); however, health risks were rarely assessed (AFSSET, 2010; Lee, Ha, & Zoh, 2009; Lévesque et al., 2000; Panyakapo, Soontornchai, & Paopuree, 2008). Some studies aimed more specifically at quantifying the relative contributions of each exposure pathway to the total exposure (Beech, 1980; Erdinger, et al., 2004; Lévesque, et al., 1994), while others documented environmental occurrence only (Bessonneau, Derbez, Clement, & Thomas, 2011; Chu & Nieuwenhuijsen, 2002; Lee, Jun, Lee, Eom, & Zoh, 2010; Sa, Boaventura, & Pereira, 2011; Sacré, Schwenk, Jovanovic, Wallner, & Gabrio, 1996; Simard, 2009; Weaver et al., 2009). The relationship with biomarkers of genotoxicity and respiratory effects was investigated recently (Font-Ribera et al., 2010; Kogevinas et al., 2010).

So far, little effort has been devoted to account for swimming pool exposure in epidemiological investigations on potential adverse effects of TCM and other THMs. Indeed, most studies consider only household exposure (i.e., tap water use through ingestion, showering and bathing) and fail to address the potential contribution of swimming (i.e., frequency of pool attendance) as a possible source of additional exposure (Dodds et al., 2004; Gallagher, Nuckols, Stallones, & Savitz, 1998; Hinckley, Bachand, & Reif, 2005; Hoffman et al., 2008a, 2008b; MacLehose et al., 2008; Porter, Putnam, Hunting, & Riddle, 2005; Savitz et al., 2006). Recently, however, the potential importance of swimming pool exposure emerged as a growing concern (Font-Ribera, Kogevinas, Nieuwenhuijsen, Grimalt, & Villanueva, 2010; Villanueva et al., 2006; Villanueva, Gagniere, Monfort, Nieuwenhuijsen, & Cordier, 2007). As a result, new studies examine this contribution by at least documenting the time spent by attendees in the swimming pools (Levallois et al., 2012; Villanueva, Cantor, et al., 2007) and/or by using algorithms to estimate personal uptakes while swimming (Patelarou et al., 2011; Villanueva et al., 2011). Such algorithms consist of multiplying the TCM concentration in pool water and the time an individual spends swimming by an uptake factor proposed by Villanueva et al. (2007) on the basis of previous work by Whitaker et al. (2003) and using data from Aggazzotti et al.(1995). The result is the prediction of an indicator of internal exposure representative of the quantity of TCM absorbed in the blood while swimming.

To our knowledge, only two other methods can serve to quantify swimming pool exposure to TCMs. The swimmer exposure assessment model (SWIMODEL) is a tool developed by the United States Environmental Protection Agency (U.S.E.P.A) on the basis of previous work by Beech et al. (Beech, 1980). It uses typical equations describing the absorption of contaminants by an organism. It estimates the swimmer's chemical intake. Dyck et al. (2011) compared this model with a robust and powerful level III fugacity model they developed to estimate exposure to THMs in indoor swimming pools. However, like the SWIMODEL, it does not consider the kinetics of the contaminant entering the human body and only predicts absorbed doses.

Another interesting and more practical alternative is physiologically based toxicokinetic (PBTK) modeling (Krishnan, Haddad, Beliveau, & Tardif, 2002). It consists of simulating the fate of a toxicant in a living organism (animal or human) characterized with physiological parameters that consider the kinetic properties of the studied substance in terms of its absorption, distribution, metabolism and excretion. It is based on a conceptual representation of a body divided into several compartments. Blood (venous and arterial) circulation interconnects these compartments so that the chemical may circulate into the conceptual body. Differential equations express mass balances between input and output amounts of chemical in each compartment. Integrating these equations allows an estimation of contaminant concentrations versus time in each compartment.

In this context, this study examines the relevance, including feasibility and efficiency, of using PBTK modeling to simulate exposure to TCM in swimming pools and predict biological levels of this contaminant in individuals. Indeed, such an approach was previously developed in the course of field investigations by Lévesque, et al. (2000). More specifically, this paper: (i) compares the predictions of internal concentration using PBTK modeling with actual biological indicator levels and identifies the main factors influencing these estimates; (ii) compares the relative contributions of dermal and respiratory pathways to global TCM exposure while present at a swimming pool; and (iii) compares swimming pool exposure contributions with household exposure. Finally, a comparative perspective is outlined between the various approaches available to assess exposure to TCM in swimming pools.

3. Methodology

3.1. Database

Data were extracted from the literature among investigations involving exposure assessment to TCM of indoor swimming pool attendees (volunteers for an experiment or occasional visitors). We selected only studies that reported both TCM environmental levels (i.e., concentrations in the water and air) and TCM biological levels (i.e., blood or alveolar air concentrations). We then excluded studies that only reported the mean of TCM environmental levels over various sampling sessions or sites. We focused on cases of exposure resulting from short attendance (one or two hours) rather than on the longer occupational exposure of workers (shift of several hours). Table 1 briefly describes the five studies finally selected for simulation purposes. Each took place at a single indoor swimming pool. The wide range of reported environmental contamination levels is shown in Table 2. These data encompass various geographical areas and reflect possible cultural differences in swimming pool operational management.

3.2. PBTK Simulations

3.2.1. PBTK modeling

A PBTK model (ACSLXtreme®) for TCM developed by our team (Haddad et al. 2006) was used to simulate the various swimming pool exposure scenarios previously identified. It was initially developed to estimate household exposure through tap water consumption, showering and inhalation of ambient air (in the shower room and/or in the rest of the house). Indeed, a volatilization model for TCM (VTM) was developed and integrated into the PBTK model to predict TCM ambient air concentrations resulting from the volatilization of water.

The model is based on mathematical formulas explaining the fate of a chemical in a living organism characterized by physiological parameters (e.g., body weight and body surface area) and represented by various compartments linked together by blood circulation. Actually, these equations express mass balances between inputs and outputs

of the studied chemical at each compartment. In addition to lungs, the PBTK model comprises five compartments (e.g., skin, liver, adipose tissue, poorly and richly perfuse tissues) as shown in scheme 1. The amount of chemical accumulated in each compartment (At, µg) is calculated from the following equations:

$$\frac{dAt}{dt} = Qt\left(Ca - \frac{Ct}{Pt}\right) \quad (1)$$

Where Qt: blood flow through compartment t (L/min)

Ca: arterial blood concentration (µg/L)

Ct: concentration in the compartment t (µg/L)

Pt: tissue:blood partition coefficient (unitless)

Only liver metabolism was considered. It was assumed to be a saturable process described as follows:

$$\frac{dAmet}{dt} = \frac{VMAX \times Cvl}{Km + Cvl} \quad (2)$$

Where Amt: the amount of metabolized chemical (µg)

VMAX: maximal metabolic rate (µg/min)

Cvl: concentration in the venous blood from liver (µg/L)

Km: Michaelis-Menten affinity constant (µg/L)

This model considers multi-route exposure (e.g., inhalation, dermal absorption and ingestion), but also considers independently only one or two exposure pathways. Pulmonary exchanges describing inhalation are modeled with the following steady-state equation:

$$Ca = \frac{Qc \times Cv}{Qc + Qalv / Pb} + \frac{Qalv \times Ci}{Qc + Qalv / Pb} \quad (3)$$

Where Ca: arterial blood concentration (µg/L)

Qc: cardiac output (L/min)

Cv: venous concentration (µg/L)

Qalv: pulmonary ventilation (L/min)

Pb: blood:air partition coefficient (unitless)

Ci: concentration in inhaled air (µg/L) (Cinh or Cinhs)

The two terms of this equation represent the portion of arterial blood from the systemic circulation (actually absorbed) (Ca_a) and the portion from inhaled air (unabsorbed)

(Ca_{na}), respectively. The latter allows the calculation of the actual dose absorbed through inhalation (Di, µg) using a mass balance equation similar to Eq.1:

$$\frac{dDi}{dt} = Qalv\left(Ci - \frac{Ca_{na}}{Pb}\right) \quad (4)$$

Cv is the result of the mixture of venous blood from each compartments and is calculated as follows :

$$Cv = \frac{\sum_{t}(Cvt * Qt)}{Qc} \quad (5)$$

where Cvt: concentration in the venous blood from compartment t (µg/L)

The amount of dermally absorbed chemical (Dder, µg) is calculated with the following equation:

$$\frac{dDder}{dt} = (Kp \times SURF / 1000) \times \left(Cwat - \frac{Csk}{Psw}\right) \quad (6)$$

where Kp: permeability constant (cm/min)

SURF: body surface (cm^2)

Cwat: concentration in the water (µg/L)

Csk: concentration in the skin (µg/L)

Psw: skin:water partition coefficient (unitless)

For each scenario, we predicted TCM levels in alveolar air or blood versus time, the relative contribution of dermal and respiratory pathways to estimated total exposure and the total intake of TCM as absorbed quantity. Then appropriate estimates were compared to the actual field data reported in the literature. Prior to each simulation, we carried out a careful parameterization to define environmental concentrations, the physiological characteristics of the "modeled" individual and exposure conditions as realistic as possible to those actually reported.

3.2.2. Environmental parameterization

The data regarding the water and air levels reported by the authors of the selected studies (see Table 2) were used to set the PBTK model (the VTM module was never used to estimate environmental concentration; as previously mentioned, studies with missing environmental data were systematically excluded). When authors reported a pre- and/or

post-exposure periods in poorly contaminated areas for biological sampling before or following the main studied exposure event, we accounted for a slight inhalational exposure to a basic TCM level in ambient air. When this environmental level was not indicated by authors, we arbitrarily assumed it was equal to the baseline concentration measured before the exposure experiment in the alveolar air of the participants. The current work of Lourencetti et al. (2010) supports this assumption.

3.2.3. Physiological parameterization

When no other information was available, standard physiological characteristics for an individual were considered: (i.e., body weight of 70 kg and a body surface of 18 000 cm^2). In the cases when body surface (SURF) was unknown, it was estimated from body weight (BW) using a formula proposed by Costeff (1966). All other physiological parameters used for modeling were adjusted according to these two parameters based on classic allometric relationships and by assuming standard values of the percentages of body weight and cardiac output for the various compartments (Tardif, Droz, Charest-Tardif, Pierrehumbert, & Truchon, 2002). These values were sometimes adjusted to consider the physiological impact associated with a possibly demanding physical effort (e.g., intense training). By default, the "simulated" subjects were assumed to have standard physiology corresponding to rest. Physiological characteristics corresponding to a workload equivalent to 50W or 100W were occasionally considered to improve simulations according to the intensity of physical exercise reported in a given study (for instance, in cases of hard training) (Lévesque, et al., 2000).

3.2.4. Exposure conditions

Water ingestion during swimming is allegedly irrelevant (less than 50 mL of water might be swallowed) (Dufour, Evans, Behymer, & Cantu, 2006) and was consequently ignored, as were specific and low contributions relative to aural (both buccal and sublingual), as well as the orbital and nasal absorptions considered by Beech (1980).
Swimming was assimilated with showering, which consisted of accounting for dermal absorption (from TCM concentration in the water – C_{wat}) and inhalation of ambient air (from TCM concentration at the surface of the pool water – C_{inhs}). Resting, sitting on

pool edges or walking around the pool was simulated by considering only inhalation of ambient air (from suitable TCM concentration in the indoor air – C_{inh}), as were the pre- and/or post-exposure periods before and/or following reported monitored activities. When a particular experimental design was established by the authors to segregate a single route of exposure (e.g., with scuba tanks or diving suits to prevent respiratory or dermal exposure, respectively), other pathways were not taken into account in our simulations. Very precise information was available in the selected studies in terms of activity timing and duration. Only slight cases of imprecision (i.e., lack of information) emerged occasionally, for example the precise time between end of swimming, the exact timetable of biological sampling and departure from the swimming pool.

3.3. Comparative household exposure scenarios

The average scenario of exposure proposed by Haddad and al. (2006) was used as a reference to simulate a typical TCM exposure at home. This scenario comprised the consumption of five glasses of water (TCM water concentration [C_{wat}] = 50µg/L), a 10-minute shower (same TCM water concentration; TCM air concentration in shower [C_{inhs}] = 530µg/m^3) and inhalation, over a whole day (24h), at the level corresponding to ambient air (TCM predicted by the VTM from TCM water concentration [C_{inh}] ≈ 3µg/m^3). We also reconstructed and simulated some scenarios by adjusting household exposure conditions in cases involving low and high contamination (data not shown) corresponding to the data reported by Nuckols et al. (2005). The mean and maximal TCM blood levels and absorbed quantities predicted by our models in these two typical cases of household exposure were compared to those reported in the various study cases of pool water exposure previously simulated.

4. Results

A total of 23 scenarios involving swimmers exposed to TCM by both dermal and inhalational pathways during short period of exercise (from 45 to 120 min) were identified from the five selected studies described in Table 1 and simulated using PBTK

modeling. Table 2 summarizes the parameterization corresponding to each scenario. A scenario was defined each time both the levels of TCM in water and air during an exposure event and the average level in blood or exhaled air for a group of participants following this event were reported in the selected studies.

The PBTK model allowed a quite good fit of the experimental data. Figure 1 illustrates that the predictions of TCM alveolar air adequately estimate the biological measurements reported. However, while simulating additional scenarios involving a single route of exposure (i.e., dermal absorption or inhalation but not both), our predictions appear less reliable in the case of dermal absorption (Figure 1). Indeed, the worst match was for the data reported by Lindstrom (1997) (Figure 2), who estimated a very important contribution of dermal absorption while testing a new device for collecting self-administered breathed air samples. The very intense physiological effort involved by swimmers may have contributed to such a high contribution.

Erdinger et al. (2004) is the only selected case reporting measurements of blood levels of TCM. Figure 3 shows that the predictions of venous concentrations can be improved in the case of Erd_#1 by assuming increasing levels of physiological activities (50W or 100W). However, for this case, no particular efforts in swimming exercise were reported. Nevertheless, participants were all members of a scuba diving club and many were accustomed to intense training. Lindstrom et al. (1997) did not measure, but rather estimated, the blood concentrations at the end of the swimming exercise. Their predictions (1.81 and 2.08 µg/L for the man and the woman, respectively) are comparable to ours (1.70 and 1.71 µg/L, respectively).

Table 3 presents the results of the simulations of the exposure scenarios previously described (Table 2), including the peak venous concentrations (Cv max), the total absorbed dose (AD) and the relative contribution of dermal (DERM) and respiratory (INHAL) pathways. Although these indicator values vary highly between the different studies, Cv max and AD increase consistently with increasing water and air contamination levels. Cv max are in the range of levels reported in the literature (0.1-5.23µg/L) (Aggazzotti, et al., 1998; Aggazzotti, et al., 1990; Aiking, van Acker, Scholten, Feenstra, & Valkenburg, 1994; Cammann & Hubner, 1995). Even for the scenarios extracted from Lévesque et al. (1994) with forced contamination resulting in

extremely high environmental levels in comparison with typical measurements, the predicted ADs remain below the worst case TCM body burden of 128.8 µg/kg estimated by Beech (1980) while also assuming high water contamination (500µg/L). However, ADs are generally higher than those estimated by Dyck et al. (2011) based on a fugacity approach.

On the basis of their measurements of TCM in exhaled air, Wilson (1995), Lévesque et al. (1994) and Erdinger et al. (2004) concluded that inhalation was the major route of exposure to this compound. Lévesque (1994) and Erdinger (2004) estimated this contribution at approximately 24% and that one third of body burden resulted from dermal absorption. Our predictions are in good agreement with their estimates. Contrary to these authors, Lindstrom (1997) reported that the dermal route prevailed primarily over the respiratory route (80% of the blood concentration in TCM). PBTK modeling did not predict that dermal absorption contributed so greatly to the total exposure in this case, but estimated a contribution of this pathway clearly higher than that established for the previously mentioned studies. In the simulations carried out with data from Lindstrom et al. (1997), biological air alveolar predictions misestimated actually measured levels. This may be attributable to an underestimation of skin absorption by the PBTK model in this particular study case where swimmers in training were subjected to very intense physiological efforts. However, interestingly enough, we confirmed that dermal absorption could be more important than other studies suggested. Likewise, for scenarios from Caro and Gallego (2008a) and Wilson (1995), with either high water contamination and comparatively low air pollution or both low water and air contamination compared to usually reported levels, respectively, we predicted skin absorption could contribute more than 80% of total TCM intake, as reported by Lindstrom et al. (1994). Interestingly, as shown in Figure 4, the relative contributions of each route to TCM exposure resulting from approximately one hour swimming were determined by the ratio of air contamination (C_{inhs} in µg/m^3) on water contamination (C_{wat} in µg/L) (data from Lindstrom corresponding to a longer exposure were excluded). It appears that when TCM air concentration (in µg/m^3) is more than approximately eight times the TCM concentration in water (in µg/L), inhalation is the major exposure pathway. Above this value, the dermal route would prevail.

Finally, we compared Cv max and AD resulting from short-time (1-2h) swimming pool exposures versus following long-time (24 h) household exposure. Interestingly, the predicted quantities of contaminant absorbed in a few minutes in a swimming pool are at least equivalent to those absorbed over 24-h at home ([0.875-112.44] vs. [0.91-3.43] µg/kg, respectively). The same conclusion, addressed for the first time, applies to the maximal venous concentration ([0.26-31.25] vs [0.2-0.88] µg/L). Apart from the cases when low environmental contamination of pool were reported (Wil_#1, Wil_#2, Wil_#3 and Erd_#3), Cv max and AD are always higher following swimming pool exposure versus typical household exposure if the physiological impacts of effort for improving our predictions are considered, as shown in Figure 3.

5. Discussion and conclusions

5.1. Advantages and reliability of PBTK modeling

PBTK modeling is a powerful and practical tool that can facilitate the assessment of exposure in epidemiological investigations, especially when multi-route exposure is involved. It was used recently to estimate household exposure in a study on adverse reproductive outcomes and exposure to THMs (including TCM) (Levallois, et al., 2012). The use of PBTK modeling to assess additional or separate exposure to TCM resulting from swimming pool attendance is worth further exploring. The approach was tested earlier regarding TCM exposure in competitive swimmers (Lévesque, et al., 2000)

Our predictions using PBTK modeling appear to adequately simulate real swimming pool exposure scenarios and the relative biological measurements reported in the more detailed studies extracted from the literature. In all cases, the same tendencies and similar exposure profiles were found between modeled predictions and reported measurements, which tend to confirm the robustness of the PBTK model developed by Haddad et al. (2006) and its suitability to efficiently assess and easily predict multi-route exposures to TCM.

The PBTK modeling suggested that the relative proportions to TCM exposure attributable to dermal and pulmonary routes after one hour of swimming depend on

environmental concentrations. Nevertheless, this result should be regarded with caution. As a matter of fact, Lévesque et al. (1994) reported strong correlations between TCM concentrations in water and alveolar air, which is not necessarily contradictory to a prevalent contribution of inhalation to exposure. Conversely, a recent study by Font-Ribeira et al. (2010) established a significant correlation between TCM levels in exhaled air with levels in ambient air, but not with levels in water. This suggests that exposure may be influenced primarily by respiratory absorption. However, the mean contamination levels reported (16.1 +/- 3.4 µg/L in water and 35.0 +/- 12.3 µg/m^3 in the air) would indicate a higher contribution of dermal absorption, according to our statement. On the other hand, using a fugacity model, Dyck et al. (2011) previously demonstrated that the proportion of exposure attributable to dermal absorption can be just as important as inhalation for TCM, which is consistent with our results. These latter authors also established this proportion change according to the age of exposed individual and for other THMs.

5.2. Comparison with other approaches

Various approaches available to assess individual exposure to TCM in swimming pools include (i) the use of the SWIMODEL software (U.S.E.P.A., 2003), (ii) the use of uptake factors (UF) (Villanueva, Gagniere, et al., 2007) or (iii) fugacity modeling (Dyck, et al., 2011). However, PBTK modeling may offer an attractive balance between practicability, efficiency and reliability, although it is certainly the less easy-to-use approach and the most demanding for parameterization. However, it can serve to predict a greater number of different outputs (dose surrogates) than all other approaches. Additionally, PBTK modeling involves mechanisms that make it more plausible biologically and predictions more relevant. For instance, if we compare the predictions resulting from the UF approach with the same appropriate outputs from PBTK modeling for the 23 scenarios of swimming pool exposure previously examined, ratios between the estimates from each method vary between 0.17 and 3.25. Although interesting and very practical for epidemiological purposes, the UF approach does not suffice to distinguish the specific contributions of each absorption pathway in the total exposure

quantification, nor does it consider the particular physiological characteristics of the exposed individuals while generalizing a particular case. The PBTK modeling approach, on the other hand, allows consideration of the characteristics of individuals and exposure conditions (for example, adaptation of pulmonary ventilation), appearing, therefore, to be more suitable for assessing “real” exposure.

5.3. Limitations, challenges and perspectives

A main limitation of this study concerns the fact that swimming is actually simulated as showering or bathing. To date, only the duration of the activity serves to distinguish these various exposure events for PBTK modeling. Future research should address this issue, perhaps by exploring distinct ways of modeling skin absorption. In the current state of knowledge, such assumptions are unavoidable.

The intensity of physical activity and its impact on a subject’s physiological characteristics while swimming should be specified and accounted for to optimize the predictions of the internal concentrations. The feasibility and possibility of assessing the physical efforts of an individual during his/her swimming exercise in order to account for their potential impact on his/her physiology and improve prediction accuracy is particularly challenging from the perspective of standardizing the use of PBTK modeling for exposure assessment.

Precisely predicting the actual values of contaminant concentrations in water and air at the exact time of the exposure appears is another important issue, given that field measurements are often hard to obtain or not necessarily available. For the present investigation, we selected only studies documenting actual environmental levels for both water and air in order to mitigate any additional uncertainties. Other investigations should address the predictive modeling of these environmental levels.

Likewise, simulations for this preliminary exploration of PBTK modeling as a tool for swimming pool exposure assessment were performed for typical adult swimmers or competitors. Swimming pool exposure of other potentially sensitive populations (e.g., children, workers and pregnant women) should also be addressed. As mentioned earlier, the work of Dyck et al. (2011) in particular underlined the change in TCM exposure depending on the age of the exposed individual.

Obviously, similar studies should be reproduced for other THMs (whose specific chemical properties can modify the contaminant fate in the organism), but very few data are available in the literature which could serve to validate the models for other THMs.
Moreover, our study focused on alveolar air and blood as biomarkers. Further investigation could evaluate the predictions of TCM levels in urine using an upgraded PBTK model for comparison with the few data reported in the literature (Cammann & Hubner, 1995; Caro & Gallego, 2007, 2008a; Caro, et al., 2007).
Finally, the results of this study corroborate other investigations that point out the importance of swimming pool exposure compared to typical household exposure (Font-Ribera, Kogevinas, Nieuwenhuijsen, et al., 2010; Villanueva, et al., 2006; Villanueva, Gagniere, et al., 2007). Such results should lead to further investigation on exposure to TCM (and DBPs) in other places such as hot tubs.

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6. Tables and Figures

Scheme 1. Conceptual representation of PBTK modeling

Figure 1. Simulated (lines) and observed (symbols – mean ± SD) concentrations of TCM in alveolar air according to various scenarios previously described (A, D, F) and additional data extracted from literature (B, C, E). A: Wil_#1; B: Wil_#3 with inhalation only, Cwat=17µg/L, Cinhs= 39.8µg/m^3, Cinh= 4.2µg/m^3 and post-exposure at rest; C= Wil_#2 with dermal absorption only, Cwat=16.5µg/L, Cinhs= 65.3µg/m^3, Cinh= 4µg/m^3 and 75 min swimming; D: Lev_1#; ; E: Lev_1# with inhalation exposure only , Cwat= 567.5µg/L and Cinhs= 6 372µg/m^3; F: Car_1#

Figure 2. Simulated (line) and observed concentrations of TCM (triangles: male; circle: female) in alveolar air in swimmers. From Lindstrom et al. (1997)

Figure 3 Simulated (full line) and range of observed venous concentrations (symbol) of TCM in swimmers corresponding to scenario Erd_#1. Dotted lines represent the predicted levels assuming increasing physiological effort during swimming exercise (50W and 100W)

Figure 4. Relative contributions of dermal (DERM) and respiratory (INHAL) pathways according the ratio of environmental air (Cinhs) and water (Cwat) concentrations

Table 1. Description of selected published studies on swimming pool exposure assessment to TCM

Reference	Objective / Place	Design	Participants	Environmental sampling	Biological sampling
Lévesque et al., 1994	To evaluate dermal and respiratory TCM absorption. Québec, Canada	7 sessions of 55-min training (3 periods of 15 min separated by 5-min periods of rest) with forced increasing TCM water levels between each session. Experimental design investigating impact of physical activities and isolated impact of dermal exposure	11 males members of a scuba diving association (19-38 years old)	Every 10 minutes during experiment in the middle of the pool -Water at a depth of 20 cm -Air in respiratory zone of swimmers	Three alveolar air sampling for each swimmer before, during and at the end of the session
Wilson, 1995	To compare the relative contribution of dermal and inhalational pathways to TCM uptake. Albany, USA	7 breath sampling events regarding various activities (resting on the pool edge, walking, swimming) and considering single or multi-route exposure	7 males volunteers (29-42 years old)	- 3 concurrent water samples at a depth of 20 cm in various moments - air in respiratory zone	Alveolar air concentration of each subject before entering the pool and regularly during the exposure period (usually 7 and 30 min after beginning) and at the end
Lindstrom et al., 1997	To test a self-administered sample collection method to assess TCM alveolar air. Montana, USA	A 2h-typical and intense training session of elite college athletes	1 male and 1 female (23 and 22 years old)	- 2 water samples (no more precision) - 1 integrated whole-air sample (+30 cm above water surface at mid-pool) + 3 punctual whole-air grab samples	Intensive measurements of alveolar air concentrations during and following exposure
Erdinger et al., 2004	To investigate the relative contribution of the different pathways to TCM exposure. Heidelberg, Germany	3 distinct sessions of 60 min exercising period. Each session involved 3 groups: swimmers with or without scuba tanks, and persons normally dressed walking around the pool	Between 10 and 17 a session. All males, members of a scuba diving club (26-58 years old)	-Water : One sample by session at a depth of 10 cm -Air: samples at 20 and 150 cm above the water surface (respiratory zones of swimmers and lifeguards, respectively)	Venous blood concentrations measured before and at the end of the exposure
Caro and Gallego, 2008	To compare use of alveolar air and urine as biomarkers of exposure to TCM. Cordoba, Spain	One hour in the swimming pool water without any particular requirements	4 males and 8 females (25-45 years old)	-18 water samples for 2-4h - 5 air spot samples during the same time	Triplicate alveolar air samples within 5 min before and after swimming

Table 2. Simulated exposure scenarios for a typical swimmer exposed to TCM by all routes (dermal and inhalational) during short periods of exercise

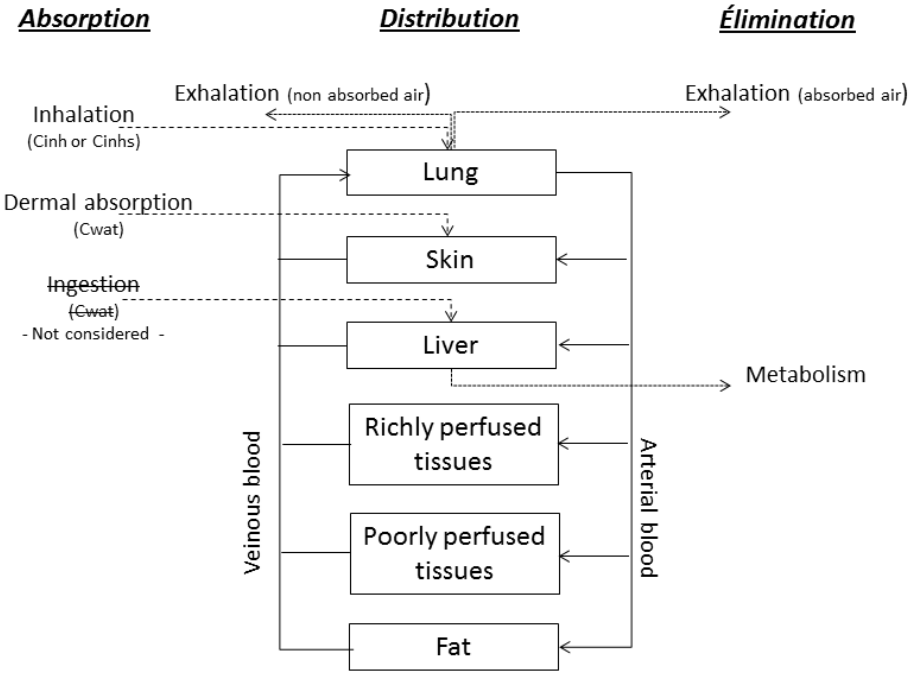
Scenario reference		Environmental parameterization			Physiological characteristics	Exposure conditions
		Cwat (µg/L)	Cinhs (µg/m^3)	Cinh (µg/m^3)		
Lévesque et al., 1994	Lev_#1	158.6	2 492	260	BW by default	5-min pre-exposure + 55-min swimming
	Lev_#2	200	7 325	260	BW by default	5-min pre-exposure + 55-min intense swimming (50W)
	Lev_#3	307.1	5 506	260	BW by default	5-min pre-exposure + 55-min swimming
	Lev_#4	553	7 222	260	BW by default	5-min pre-exposure + 55-min swimming
	Lev_#5	538.3	8 014	260	BW by default	5-min pre-exposure + 55-min swimming
Wilson, 1995	Wil_#1	30.5	35	6	Mean BW of 4 participants	5-min pre-exposure + 45-min swimming + 30-min post-exposure
	Wil_#2	20.3	29.3	20.5	Mean BW of 5 participants	5-min pre-exposure + 60-min swimming
	Wil_#3	21.3	122.1	31.3	Mean BW of 4 participants	5-min pre-exposure + 30-min swimming + 15-min intense swimming
Lindstrom et al., 1997	Lin_#1	70	145	2.5-4.5	Male BW	2h pre-exposure + 2h intense swimming (100W) + 3h post-exposure (50W)
	Lin_#2	70	145	2.5-4.5	Female BW	2h pre-exposure + 2h intense swimming (100W) + 3h post-exposure (50W)

Table 2. (continued) Simulated exposure scenarios for a typical swimmer exposed to TCM by all routes (dermal and inhalational) during short periods of exercise

Scenario reference		Environmental parameterization			Physiological characteristics	Exposure conditions
		Cwat (µg/L)	Cinhs (µg/m^3)	Cinh (µg/m^3)		
Erdinger et al., 2004	Erd_#1	20.7	235	285	BW by default	60-min swimming + 10-min post-exposure in the pool area
	Erd_#2	24.8	215	210	BW by default	60-min swimming + 10-min post-exposure in the pool area
	Erd_#3	7.1	125	83	BW by default	60-min swimming + 10-min post-exposure in the pool area
Caro and Gallego., 2008	Car_#1	125	241	2.9	BW by default	5-min pre-exposure + 60-min swimming
	Car_#2	115	195	3.3	BW by default	5-min pre-exposure + 60-min swimming
	Car_#3	145	305	4.5	BW by default	5-min pre-exposure + 60-min swimming
	Car_#4	100	136	3.8	BW by default	5-min pre-exposure + 60-min swimming
	Car_#5	120	218	2.4	BW by default	5-min pre-exposure + 60-min swimming
	Car_#6	85	92	3.3	BW by default	5-min pre-exposure + 60-min swimming
	Car_#7	130	254	4.2	BW by default	5-min pre-exposure + 60-min swimming
	Car_#8	155	340	5	BW by default	5-min pre-exposure + 60-min swimming
	Car_#9	150	324	4.8	BW by default	5-min pre-exposure + 60-min swimming
	Car_#10	110	187	4.6	BW by default	5-min pre-exposure + 60-min swimming

Table 3. Maximal venous concentrations (Cv max), absorbed doses (AD), and pulmanory (INHAL) and dermal (DERM) relative contributions to total absorbed doses predicted for the various simulated exposure scenarios

Simulation reference		Cvmax (µg/L)	AD (µg/kg)	INHAL (%)	DERMAL(%)
Swimming pool exposure (1h or 2h)					
Lévesque et al., 1994	Lev_#1	5.15	16.39	65	35
	Lev_#2	31.5	112.44	94	6
	Lev_#3	10.9	34.5	68	32
	Lev_#4	15.81	50.74	60	40
	Lev_#5	16.81	53.43	63	37
Wilson, 1995	Wil_#1	0.286	0.987	13	87
	Wil_#2	0,239	0.875	15	85
	Wil_#3	0.621	1.310	55	45
Lindstrom et al., 1997	Lin_#1	1.70	12.65	55	45
	Lin_#2	1.71	13.01	55	45
Erdinger et al., 2004	Erd_#1	0.61	2.11	61	39
	Erd_#2	0.58	2.13	54	46
	Erd_#3	0.26	0.92	70	30
Caro and Gallego., 2008	Car_#1	1.66	6.08	18	82
	Car_#2	1.49	5.47	16	84
	Car_#3	1.97	7.17	19	81
	Car_#4	1.25	4.68	13	87
	Car_#5	1.58	5.77	17	83
	Car_#6	1.02	3.81	11	89
	Car_#7	1.74	6.34	18	82
	Car_#8	2.12	7.72	20	80
	Car_#9	2.04	7.47	20	80
	Car_#10	1.43	5.24	16	80
Household exposure (24h)					
Scenario from Haddad et al. (2006)		0.65	2.27	32	21
Scenario from Nuckols et al. (2005)					
low contamination (30µg/L)		0.20	0.91	30	30
high contamination (100µg/L)		0.88	3.43	39	24



Scheme 1. Conceptual representation of PBTK modeling

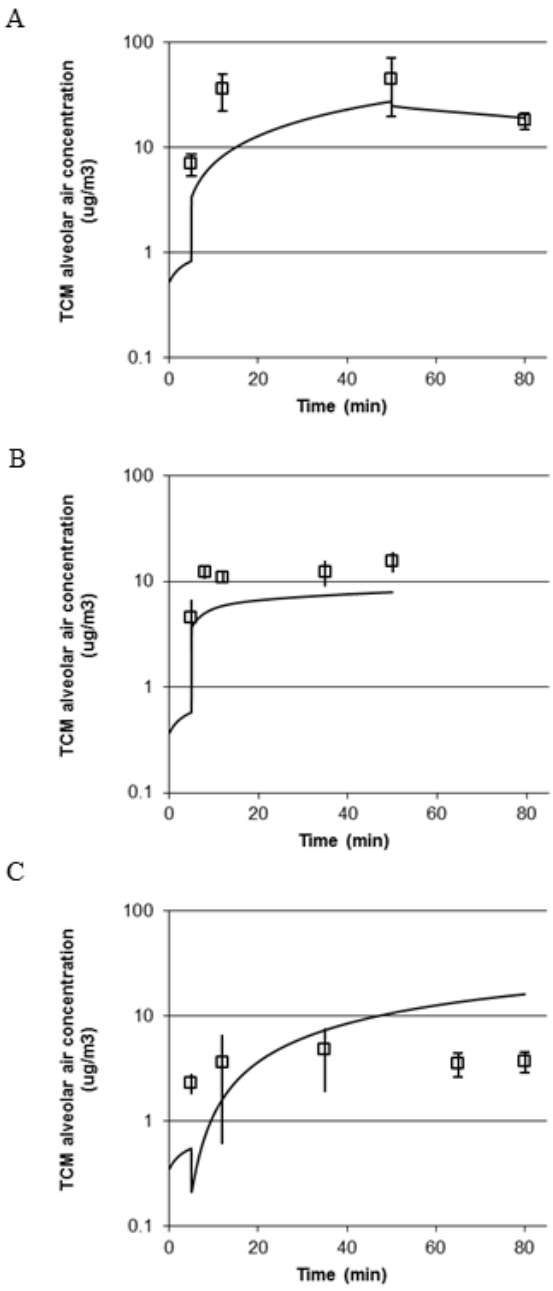


Figure 1. Simulated (lines) and observed (symbols – mean ± SD) concentrations of TCM in alveolar air according to various scenarios previously described (A, D, F) and additional data extracted from literature (B, C, E). A: Wil_#1; B: Wil_#3 with inhalation only, Cwat=17µg/L, Cinhs= 39.8µg/m^3, Cinh= 4.2µg/m^3 and post-exposure at rest; C= Wil_#2 with dermal absorption only, Cwat=16.5µg/L, Cinhs= 65.3µg/m^3, Cinh= 4µg/m^3 and 75 min swimming

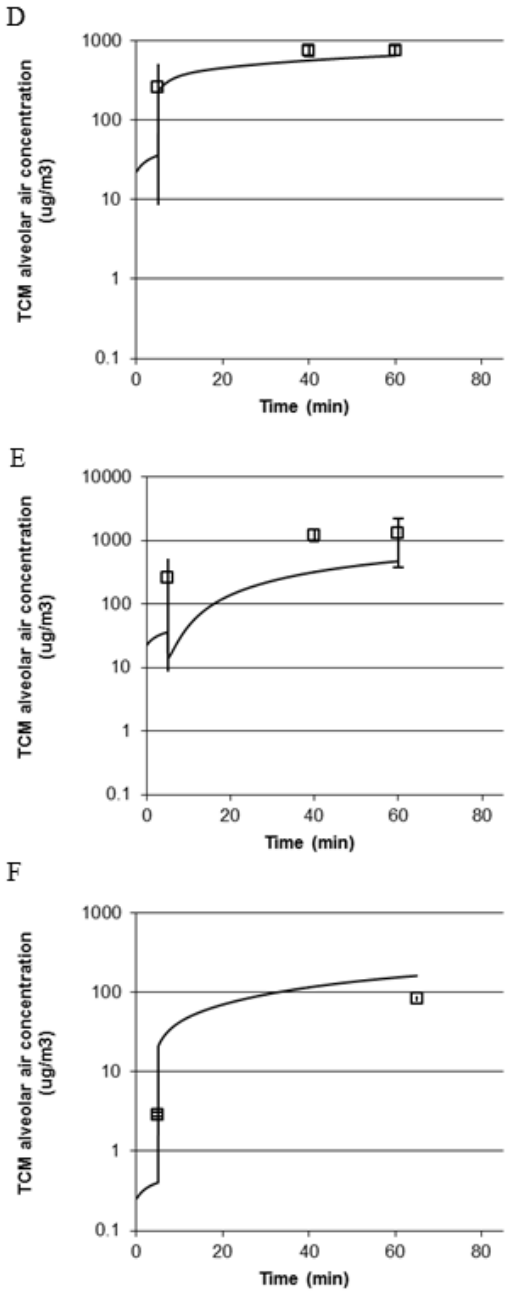


Figure 1. (continued) Simulated (lines) and observed (symbols – mean ± SD) concentrations of TCM in alveolar air according to various scenarios previously described (A, D, F) and additional data extracted from literature (B, C, E). D: Lev_1#; ; E: Lev_1# with inhalation exposure only , Cwat= 567.5µg/L and Cinhs= 6 372µg/m^3; F: Car_1#

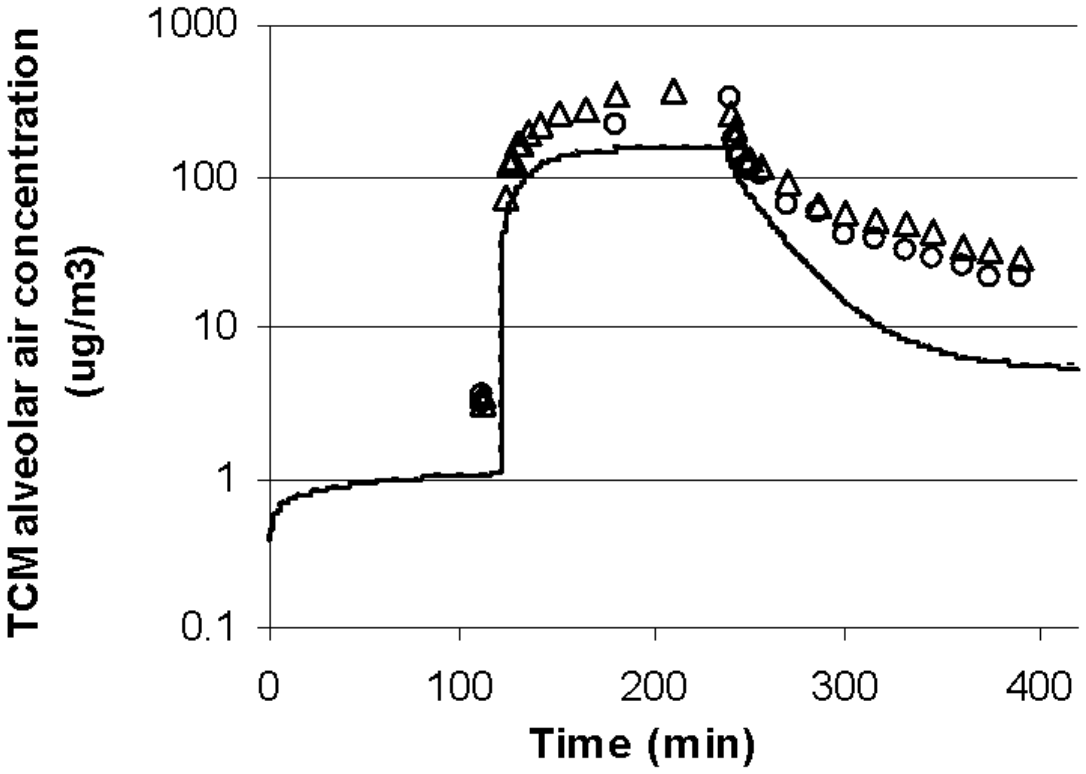


Figure 2. Simulated (line) and observed concentrations of TCM (triangles: male; circle: female) in alveolar air in swimmers. From Lindstrom et al. (1997)

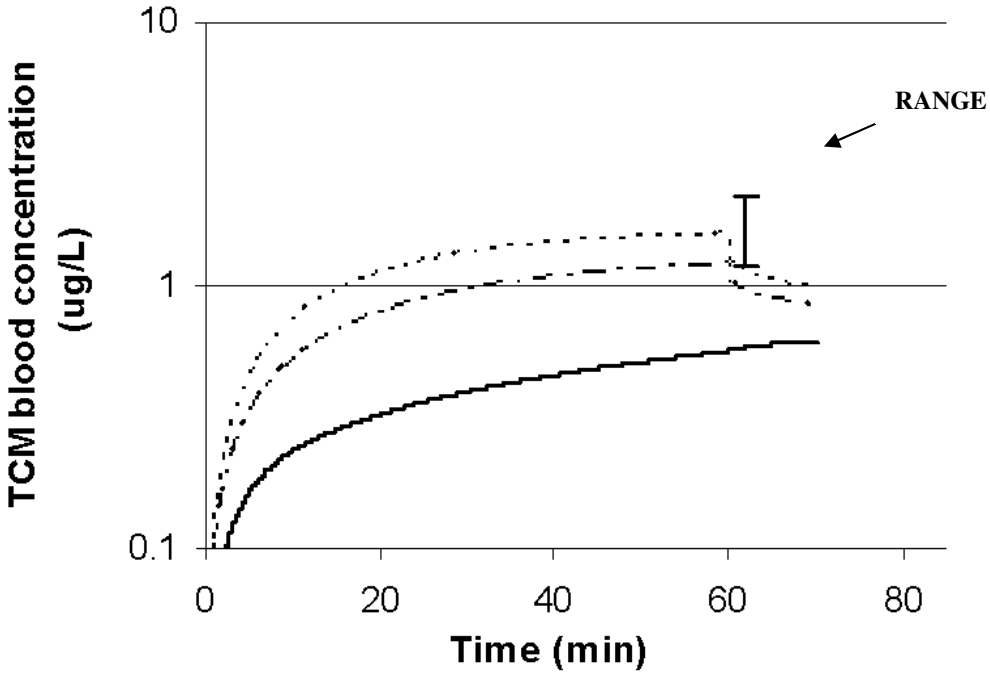


Figure 3. Simulated (full line) and range of observed venous concentrations (symbol) of TCM in swimmers corresponding to scenario Erd_#1. Dotted lines represent the predicted levels assuming increasing physiological effort during swimming exercise (50W and 100W)

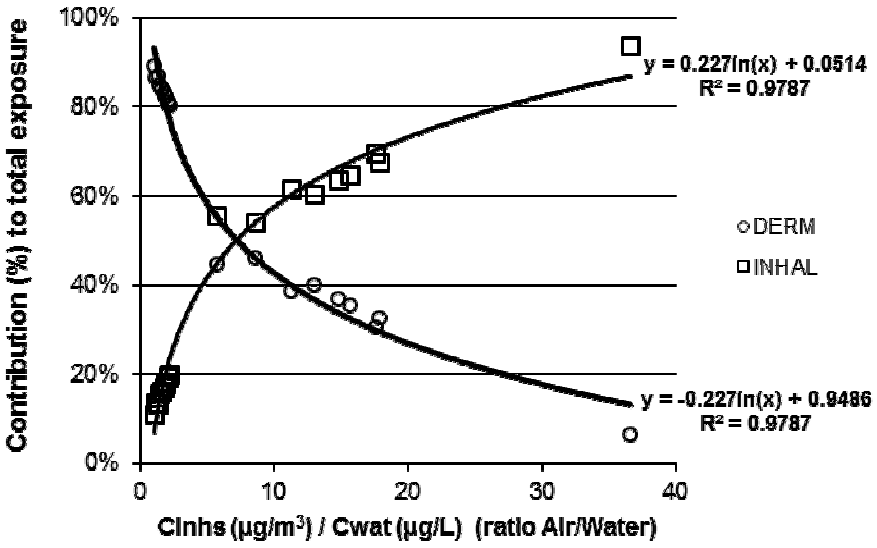


Figure 4. Relative contributions of dermal (DERM) and respiratory (INHAL) pathways according the ratio of environmental air (Cinhs) and water (Cwat) concentrations

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DISCUSSION GÉNÉRALE

La question de l'exposition aux sous-produits de désinfection (SPD) de l'eau soulève une problématique inévitable alors même que les bienfaits reconnus de la désinfection en font un processus définitivement incontournable et que les méthodes communément employées à cette fin résultent, chacune à leur manière, en la formation desdits SPD dans des quantités plus ou moins importantes et suivant différents panels de spéciations. La complexité d'estimer cette exposition se répercute sur la définition précise du risque sanitaire relatif, qui demeure encore, malgré certains faisceaux de preuves, incertain, et sur le contrôle de celui-ci en termes d'adéquation et de pertinence des mesures mises ou à mettre en place. Dans ce contexte, les travaux conduits dans le cadre de cette thèse se sont inscrits dans la perspective de développer de meilleures façons de mesurer cette exposition, notamment au travers de l'intégration stratégique d'outils et d'approches issus de différentes disciplines concernées par cette problématique foncièrement multidimensionnelle.

La démarche originale qui a orienté l'ensemble de ces travaux a reposé sur l'exploitation synergique de l'outil toxicologique éprouvé que constitue la modélisation TCBP et de données d'occurrence environnementale. Sur cette base, il convenait en priorité d'évaluer, en termes de capacité/validité/fiabilité/adaptabilité, l'utilisation simultanée ou indépendante de ces instruments sous divers angles. La thèse, dans son organisation, rend compte du souci particulier accordé à envisager la problématique non pas sous un angle spécifique mais le plus possible dans sa globalité en considérant à la fois les différents contextes où elle se pose (i.e., volet I et II de la thèse, s'intéressant respectivement à l'exposition domestique et à l'exposition en piscine) et ses différents aspects (environnemental et biologique qui réfèrent respectivement à la question de l'exposition externe et interne et qui font chacun l'objet d'un article spécifique dans les deux volets susmentionnés). Qui plus est, les travaux ont été essentiellement consacrés à la question peu documentée des variations à court terme des SPD par souci de cerner aussi précisément que possible l'exposition en « temps réel » des individus.

Dans cette dernière section, au regard des travaux préalablement exposés, nous mettrons successivement en exergue les différentes dimensions qui contribuent à complexifier la mesure de l'exposition aux SPD, les forces et faiblesses des outils utilisées et de

l'approche développée, notamment en vue d'identifier les recherches qu'il nous semble devoir être priorisées au regard du sujet qui nous occupe.

1. Les multiples dimensions de la problématique de l'exposition aux SPD

1.1. Multiples acteurs et multiples enjeux

La problématique de l'exposition aux SPD, du fait même de la multiplicité des différents acteurs qu'elle concerne, exige indubitablement d'être abordée avec une perspective multidisciplinaire pour être appréhendée de façon optimale. Enjeu de santé publique, elle intéresse effectivement non seulement épidémiologistes, toxicologues et autres intervenants en analyse des risques, pour lesquels elle constitue – comme l'illustre d'ailleurs cette thèse – un défi de taille, mais aussi le législateur et les gestionnaires de réseaux de distribution et de piscines qui doivent s'interroger sur la nécessité, la pertinence, et, le cas échéant, sur la faisabilité et sur les modalités de la mise en place d'un système de surveillance adéquat des niveaux de SPD. Ainsi, la problématique s'articule fondamentalement autour des points suivants : quel est le niveau de risque (s'il est avéré) associé à l'exposition aux SPD? Peut-on réglementer les SPD, c'est-à-dire le doit-on et en est-on capable en l'état actuel des connaissances? Cette deuxième question, intimement liée à la première, recouvrent en effet deux aspects : d'abord, celui de la légitimité de mettre en place une réglementation qui peut avoir aussi l' « effet pervers » d'inciter à la mise en œuvre de procédés alternatifs aux procédés de désinfection traditionnellement appliqués, mais aux impacts méconnus sur les systèmes et sur les expositions subséquentes; ensuite, celui de la capacité à mettre en place une réglementation adéquate, au sens d'imposer un système de surveillance approprié qui puisse rendre compte correctement de l'exposition des populations. Les travaux précédemment évoqués de l'U.S.E.P.A (2006), menés au cours des dernières années pour imposer un contrôle adapté des niveaux de THM et de AHA dans les réseaux d'eau

potable, tout en étant exemplaires, illustrent, au regard de ce dernier point, les difficultés rencontrées sous-jacentes à l'importante variabilité spatio-temporelle de ces composés, que les études décrites dans la présente thèse ont voulu davantage préciser (articles I et III). Actuellement, cette réglementation étatsunienne des SPD fait référence. Des questions restent toutefois en suspens : devrait-on envisager d'élargir la réglementation concernant les SPD aux piscines alors que seulement quelques pays ont choisi d'imposer des limites (mais alors draconiennes!) quant aux concentrations de THM admissibles dans l'eau des bassins? Ne devrait-on pas aussi envisager de contrôler la charge des SPD volatils dans l'air? Réglemente-t-on les bons « mauvais SPD »? D'autres devraient-ils être réglementés? Les travaux conduits dans le cadre de la présente thèse ne permettent pas de répondre à ces questions mais fournissent, dans les résultats auxquels ils ont menés, des éléments qui devraient pousser à s'attarder sur certaines. Ainsi, au regard des contributions comparées des expositions domestiques et en piscine aux SPD (article IV), et assumant pertinentes les réglementations en place pour les SPD en réseau, la question de la raison d'être d'une surveillance systématique des niveaux ambiants en piscine peut logiquement se poser. La question de la faisabilité de cette surveillance en est une autre. Elle se pose d'autant plus que les méthodes analytiques classiques (notamment pour l'analyse des contaminants de l'air), que nous avons eu l'occasion d'éprouver dans la cadre des investigations décrites dans l'article III, ne seraient vraisemblablement pas des plus pratiques à mettre en œuvre dans le cadre d'un usage systématique et fréquent. Reste à savoir si les recherches récentes axées sur le développement de nouvelles méthodes analytiques offriront des solutions mieux et véritablement adaptées dans cette optique (Caro & Gallego, 2008a).

Dans tous les cas, il convient de reconnaitre, qu'en l'état actuel des connaissances sur le sujet, la réglementation des SPD a un caractère essentiellement préventif, que l'élimination du risque microbiologique doit demeurer l'objectif primordial de la désinfection et que l'atteinte de cet objectif ne saurait souffrir de compromis qui prioriserait la réduction d'un éventuel risque chimique attribuable aux SPD. On voit ici comment cette problématique a évidemment un impact direct sur les opérateurs des stations de traitement des eaux pour la consommation et les gestionnaires municipaux de la qualité de l'eau potable, qui doivent trouver la meilleure façon de fournir une eau

saine sur le plan microbiologique tout en minimisant l'occurrence des SPD (et comment elle pourrait aussi ne pas simplifier la vie des gestionnaires de piscine en cas de mise en place d'une réglementation spécifique pour ces sites). Ce défi technique oblige les gestionnaires à penser le mieux possible l'organisation de la filière de traitement et à procéder, dans des conditions de moyens et de ressources qui ne s'y prêtent pas toujours, à sa gestion. Le souci est multiple pour eux : assurer une désinfection efficace en maintenant en tout temps un résiduel de désinfectant; limiter la formation des SPD autant que possible compte tenu de l'incertitude quant aux risques sanitaires qui y sont potentiellement associés; surveiller les niveaux de SPD dans les systèmes qu'ils exploitent que ce soit pour mieux les connaître ou en réponse à des exigences réglementaires; satisfaire le consommateur en fournissant une eau qui ne goûte pas trop le chlore ou le baigneur en veillant à une température adéquate dans le bassin, sans affoler ni l'un ni l'autre quant aux possibles risques chimiques induits par les SPD.

1.2. Multiplicité et particularité des SPD

A l'heure où les nouvelles catégories de SPD « émergents » suscitent un intérêt grandissant (Krasner et al., 2006; Liviac et al., 2009; Richardson et al., 2007; Richardson et al., 2010), cette thèse s'est consacrée exclusivement à l'étude des composés plus classiques et mieux connus que sont les THM, les AHA et les CAM. Il nous semblait opportun de prioriser l'étude de ces contaminants alors même que l'estimation de l'exposition à ces composés, pourtant les SPD les plus abondants, demeure imprécise (pour ne pas dire fallacieuse).

Les différences comportementales manifestes dans l'environnement de ces SPD (illustrées notamment dans les articles I et III) tendent à souligner la nécessité d'une approche « SPD-spécifique » de l'exposition, entendons par là une approche qui consiste à examiner séparément l'exposition (et par suite le risque relatif) à chaque SPD (ou à un mélange spécifique de SPD). Ceci parait d'autant plus judicieux que : (i) les propriétés de volatilité et lipophilicité propres à chaque SPD influent évidemment, chacune à sa mesure, sur le passage des polluants en question de l'eau à l'air et sur la possibilité de

leur absorption par les voies d'absorption autres que digestive; (ii) les mécanismes de toxicité qui permettraient d'associer à un SPD en particulier un effet sanitaire reste à établir. Qui plus est, en piscine, nous avons, dans l'article III, échoué à identifier, parmi les différents composés étudiés, un composé de type « surrogate » qui eusse pu faire office d'indicateur pour estimer l'exposition environnementale à tous ou, au moins, à une partie des autres SPD. Bien que cela n'ait pas été examiné dans le cadre de ces travaux, il ne semble guère plus probable, compte tenu de ce que l'on sait actuellement, de parvenir à identifier un tel indicateur d'occurrence environnementale pour les SPD en réseau où il a été, par exemple, mis en évidence, qu'à la différence des THM, dont les niveaux augmentent tout le long du réseau, les AHA ne sont pas nécessairement plus élevés à ses extrémités.

Évidemment, il est, d'autre part, sans doute utopique de parvenir un jour à être en mesure d'estimer l'exposition à chacun des plus de 600 SPD déjà identifiés (et auxquels s'ajouteront assurément d'autres grâce aux progrès de la chimie analytique). Il faut toutefois convenir qu'une majorité de ces produits se retrouvent dans des quantités infimes (de l'ordre du nanogramme par litre et moins) et que la plupart ne se prêtent sans doute qu'à la seule exposition par ingestion. Dans ces conditions qui devraient résulter en une exposition somme toute modeste à ces composés, voire plus que minime au regard de l'exposition aux THM, il faudrait que ces SPD émergents présentent un potentiel toxique exceptionnellement élevé pour contribuer à un risque majeur pour la santé humaine. Cela ne peut être rigoureusement exclu (Richardson et al., 2007).

Finalement, il convient d'évoquer à ce stade la possibilité qui existe à savoir que la toxicité (si avérée) des SPD ne résulte pas de l'exposition à un SPD en particulier mais de l'exposition à un mélange. La question de savoir à quel mélange exactement reste entière alors que l'on conçoit aisément la multitude de mélanges possible au regard du nombre faramineux de SPD. Il sera intéressant de suivre à ce sujet les résultats des travaux étatsuniens qui ont été engagés ces dernières années afin de documenter cette problématique des mélanges de SPD (Andrews et al., 2004; Pressman et al., 2010; Richardson et al., 2008; Simmons et al., 2004; L. Teuschler & Simmons, 2003; L. K. Teuschler et al., 2004). Sur la base de précédents travaux de Haddad et al. (2001) portant notamment sur l'utilisation des modèles TCBP pour l'analyse du risque associé à des

mélanges de contaminants, une voie qui envisagerait comment combiner les modèles développés suivant le schéma conceptuel décrit dans la dernière section de l'introduction pour différents SPD pourrait être explorée en vue de prédire l'exposition au mélange des SPD en question.

1.3. Les multiples sources d'exposition

Cette thèse, comme l'indique son intitulé même, avait vocation à documenter l'exposition domestique (volet I) et l'exposition en piscine (volet II), deux aspects qui ont jusqu'ici été abordés indépendamment l'un de l'autre dans la littérature. Rarement les études, en examinant une situation dans un de ces deux contextes, ont envisagé de tenir compte de l'autre. Tout au plus, on peut évoquer le soin pris dans certaines études incluant des volontaires en piscines, comme celle conduite par l'équipe d'Aggazzotti (1998), pour s'assurer qu'aucune activité domestique ne contribuait à une exposition conséquente desdits volontaires pendant le déroulement de l'étude en question. Dans le cas d'enquêtes épidémiologiques relatives à une exposition domestique, la contribution de l'exposition en piscine à l'exposition globale aux SPD n'avait été jusqu'à récemment pas considérée (Villanueva et al., 2007a). Pour autant, avec le bémol que le public exposé en piscine est un public différent, tout au moins plus restreint, que celui exposé via un usage domestique, il semblait opportun de consacrer des efforts à considérer l'intégration de ces deux sources d'exposition. Les résultats de l'article IV, qui font écho à ceux de Villanueva et al. (2007b), nous confortent en ce sens.

Au-delà ou au sein même de ces deux principales sources d'exposition, plusieurs autres sources mériteraient éventuellement d'être considérées ou du moins davantage documentées. Nuckols et al. (2005) ont déjà évoqué la contribution à l'exposition associée à différentes activités domestiques telles que l'utilisation d'un lave-linge ou d'un lave-vaisselle. L'exposition susceptible d'advenir sur le lieu de travail (sans doute essentiellement liée à de la consommation d'eau) devrait sans doute être plus systématiquement distinguée dans les études épidémiologiques, tenant compte que la

source d'eau et donc le niveau de contamination peuvent différer considérablement avec ceux à la maison.

Dans le volet II, nous nous sommes focalisés, comme l'essentiel de la littérature, sur l'étude des piscines publiques intérieures. Les piscines extérieures n'ont été étudiées que beaucoup plus rarement (Bernard et al., 2009; Font-Ribera et al., 2009; Simard, 2009), mais mériteraient sans doute un surcroit d'intérêt compte tenu notamment des niveaux de contamination parfois considérablement élevés qui ont pu être mesurés. Il est de même pour les spas et autres centres de remise en forme, objets d'un nombre très restreint d'études bien que, comme dans les piscines, de nombreuses conditions soient susceptibles d'y exacerber l'exposition aux SPD (Bartocha & Seidel, 1984; Rogers & Davis, 1995; Shaw, 1993; Wilson, 1995). Qui plus est, dans ce type de centre, de même qu'en piscine, la prise de douche fortement recommandée par souci hygiénique (et pour diminuer du même coup l'apport de précurseurs en SPD dans les bassins) est en soi une source considérable qui contribue sans doute à accroitre l'exposition, en premier lieu, de la personne qui se douche (qui va donc encore absorbée des SPD) mais aussi possiblement de toute les personnes dans le vestiaire en tant qu'elle va accentuer la contamination de l'air ambiant par les plus composés volatils. Dans l'article III, nous évoquions aussi les niveaux substantiels de contamination en SPD dans l'air des salles adjacentes aux bassins des piscines visitées comme pouvant contribuer significativement à l'exposition.

Quant à la question de l'occurrence des SPD et de l'exposition subséquente dans le cas de piscines privées, on n'en sait pour ainsi dire rien.

1.4. Les multiples média d'exposition

Un des éléments qui complexifient grandement la mesure de l'exposition aux SPD tient aux propriétés volatiles de certains d'entre eux. Ainsi, l'exposition aux THM en particulier ne se fait pas seulement via l'eau mais également via l'air. La TCAM est un autre SPD que l'on retrouve en piscine, peu soluble dans l'eau et qui va donc contaminer spécifiquement l'air. À la différence des THM dont les indésirables effets sanitaires potentiels sont vraisemblablement à mettre en relation avec une action systémique (i.e.,

via la circulation sanguine), l'effet mieux avéré de la TCAM est, comme cela a déjà été mentionné, lié à une action topique (i.e., consécutif au seul contact du contaminant avec l'organe cible, sans absorption interne du toxique).

Outre donc la nécessité précédemment évoquée d'appréhender le comportement spécifique de chaque SPD dont l'on souhaiterait mesurer l'exposition, s'ajoute à la complexité, mise en exergue dans les articles I et III, de déterminer la concentration dudit SPD dans l'eau, celle de déterminer sa concentration dans l'air.

Si les mesures des concentrations de SPD dans l'eau ou les modèles prédictifs pour les estimer sont relativement efficaces et faciles à mettre en œuvre, le développement de modèles de volatilisation pour estimer la concentration dans l'air à partir de celle dans l'eau doit se poursuivre, d'autant que les méthodes d'échantillonnage et d'analyse des SPD dans l'air sont moins pratiques et, de fait, difficiles à systématiser en l'état actuel des choses. Dans le cadre d'investigations épidémiologiques d'envergure, il serait excessivement chronophage et couteux d'envisager des mesures effectives des concentrations des différents SPD dans l'air ambiant. La stratégie que nous proposons en introduction de la thèse met à contribution un modèle de volatilisation intégrée à un modèle TCBP afin d'estimer (à défaut de pouvoir les mesurer) les concentrations de contaminants dans l'air. Ce modèle, valable pour les THM, est sans aucun doute mieux adapté à une application dans un contexte domestique pour lequel il a été initialement développé. Dans l'article III, nous avons envisagé, avec un certain succès, d'ajuster les paramètres de ce modèle pour l'appliquer en piscine et prédire les concentrations de THM dans l'air. Dans tous les cas, il conviendrait d'examiner davantage la validité de ces modèles qui constituent, en l'absence de véritables mesures des niveaux de ces composés dans l'air, une rare, si ce n'est pas la seule, alternative. A notre connaissance, deux autres approches existent pour modéliser les concentrations de THM dans l'air des piscine : une proposant d'utiliser un modèle de fugacité type III est abordée dans l'article III (Dyck et al., 2011); une autre, plus complexe et moins aisée à mettre en œuvre, a été suggérée par Hsu et al. (2009). En revanche, pour ce qui est du contexte domestique, nous n'avons pas connaissance d'autres façons de faire, mise à part le recours discutable et peu convaincant à la loi de Henry.

La prédiction des niveaux de TCAM dans l'air des piscines demande encore à être explorée. Les éléments recueillis dans le cadre de l'étude rapportée dans l'article III n'ont pas permis d'identifier de piste à privilégier en ce sens.

1.5. Les multiples voies d'exposition

L'exposition la plus délicate à cerner est sans aucun doute celle des THM qui peut advenir, outre par ingestion, par voie percutanée et par inhalation. Beech (1980), dans le cadre de travaux visant à estimer la dose de TCM absorbée par un enfant dans le pis des scénarii, a envisagé également les expositions par voies buccale et sublinguale, orbitale et nasale, et même auriculaire. Il est toutefois difficilement envisageable de tenir compte de manière systématique de ces voies spécifiques du fait des nombreuses hypothèses que cela peut nécessiter et des incertitudes en découlant. D'ailleurs, les résultats de l'étude citée ci-dessus indiquait une contribution minime de ces voies.

Haddad et al. (2006) ont documenté les contributions relatives des différentes voies classiques (i.e., digestive, respiratoire et percutanée) dans le cas de différents scénarii d'exposition domestique, mettant en évidence l'importance longtemps mésestimée de l'inhalation et de l'absorption percutanée dans ce contexte. Dans le cas des piscines, la part de l'exposition par ingestion est encore plus minime, voire souvent négligée. Dufour et al. (2006) ont estimé à 16mL et 37mL, respectivement, les volumes d'eau ingérés par les adultes et les enfants suite à une baignade de 45 min, ce qui conforte cette hypothèse.

Dans l'article IV, nous avons évoqué les contradictions de la littérature quant à savoir si l'exposition aux THM provient majoritairement de l'absorption percutanée ou de l'absorption par inhalation (Erdinger et al., 2004; Lévesque et al., 1994; Lindstrom et al., 1997). En reproduisant par simulation les expositions mesurées par les auteurs concernés, l'utilisation de la modélisation TCBP a permis de retrouver, si ce n'est les mêmes chiffres, au moins les mêmes tendances que celles rapportées par chacun desdits auteurs quant aux contributions respectives des voies respiratoire et percutanée à l'absorption totale des contaminants. La voie percutanée pourrait ainsi avoir une contribution plus substantielle que celle généralement attendue. Des efforts devraient

sans doute être investis pour explorer davantage et mieux appréhender cette voie d'exposition.

1.6. Les multiples populations exposées

Dans le cadre d'une analyse de risque, la mesure de l'exposition doit pouvoir cibler non seulement la population générale mais également les individus (ou au moins les groupes populationnels) présentant des sensibilités particulières et tenir compte des caractéristiques physiologiques parfois spécifiques et changeantes des différentes catégories de personnes exposées. Cet aspect n'a pas été spécifiquement analysé dans le cadre de cette thèse; tout au plus, a-t-il été rapidement entrevu dans les articles II et IV. Nous posons toutefois dans cette section quelques éléments relatifs à cette question fondamentale à envisager en vue de préciser davantage et de mieux évaluer les risques sanitaires associés aux SPD chez les populations exposées.

L'exposition domestique concerne l'ensemble de la population susceptible d'utiliser pour une activité ou une autre l'eau potable du réseau de distribution. Dans cette population, les femmes enceintes constituent la catégorie la plus préoccupante au regard d'un possible risque sanitaire et sur laquelle se sont concentrées les dernières enquêtes épidémiologiques (ex., Annexe II). Récemment, il a été évoqué également une susceptibilité particulière à l'exposition domestique aux THM des individus présentant un certain bagage génétique, avec la possibilité de risques accrus de cancer de la vessie selon les formes adoptées par différents gènes associés à des enzymes de biotransformation et/ou de détoxication (GSTT1, GSTZ1, CYP2E1) (Cantor et al., 2010).

L'ensemble des usagers des piscines (i.e., clients et professionnels) sont également exposés aux SPD à des niveaux non négligeables (article III). Le type et l'intensité des activités pratiquées, outre leurs impacts sur le plan des concentrations environnementales en contaminants volatils, sont des facteurs susceptibles d'induire des modifications temporaires de la physiologie des baigneurs et donc d'influencer le devenir biologique des SPD dans l'organisme. Dans la catégorie des clients, on

distinguera la clientèle fréquentant de manière occasionnelle lesdits lieux à des fins de loisir et la clientèle sportive présente assidument. Les femmes enceintes, qui peuvent être incluses dans le groupe des clients de loisir, subissent donc en piscine une exposition additionnelle à l'exposition domestique. Leur seule exposition en piscine ne semble pas résulter en un risque élevée pour elles si l'on se fie à l'évaluation des risques conduite par l'AFSSET (2010). L'effet combiné de l'exposition en piscine avec l'exposition domestique n'a en revanche pas été examiné. Les jeunes nageurs, chez qui Aiking et al (1994) avaient identifié des niveaux significativement élevés d'une enzyme indicatrice de dommages rénaux, sont une autre catégorie qui présente un intérêt particulier, et spécifiquement aussi celles des bébés nageurs (Bernard & Nickmilder, 2006; Nystad et al., 2003). L'étude de l'AFSSET (2010) conclut quant à elle que la population vraisemblablement la plus à risque entre toutes est celle des nageurs sportifs.

La catégorie des travailleurs regroupe les sauveteurs, le personnel administratif et d'entretien. Cette catégorie suscite aussi un intérêt particulier qui a motivé l'Institut de recherche Robert Sauvé en Santé au Travail (IRSST) à financer, dans la continuité des travaux menés par notre équipe, un projet visant à évaluer son exposition aux SPD [Tardif R., Haddad S., Rodriguez M. Évaluation de l'exposition des travailleurs aux sous-produits de désinfection en piscine au Québec (IRSST 2010-0010, 2011-2013)]. En effet, outre les niveaux de contamination relativement élevés dans le milieu (article III), la probabilité est forte qu'un travailleur en piscine pratique régulièrement plusieurs minutes d'activité physique dans ce milieu, et cela sans compter la dépense associée à ses interventions ou à l'accomplissement de ses tâches sur son lieu de travail (ex., cours de natation). L'impact de l'effort physiologique sous-tendu (ex., augmentation de la ventilation alvéolaire) peut, tel qu'évoqué dans l'article IV, renforcer la capacité d'absorption de certains contaminants par l'organisme et ne doit donc pas être négligé. Dans une autre perspective complémentaire, du fait de la diversité des tâches leur incombant durant leurs heures de services, il n'est pas évident que les employés présents sur le site puissent se prévaloir, à la différence des baigneurs, de la contrepartie immédiate et positive relative à la pratique ponctuelle et vraisemblablement bénéfique d'un exercice de natation. Il est à craindre que la balance risques (associés à l'exposition aux SPD) – bénéfices (associés à l'exercice physique) ne penche en fait en la défaveur

d'une population de travailleurs présents autrement plus longtemps que les visiteurs et, dans le cas spécifique des sauveteurs, soumis à un stress constant et éprouvant pendant leur travail. Par ailleurs, on peut raisonnablement présumer que les populations des travailleurs en piscines se composent essentiellement autour d'un public qui fréquente les lieux depuis un tout jeune âge, puis de manière assidue jusqu'à un âge plus avancé, et qui profite régulièrement des infrastructures pour sa convenance personnelle au-delà de son quart de travail. Cette présence prolongée sur les lieux ne peut, là encore, qu'amplifier les probabilités d'une exposition conséquente pour ces groupes d'intérêt.
Finalement, la question de la sensibilité des individus exposés en fonction de leur genre pourraient être examinée plus profondément tandis que les résultats décrits dans la littérature laissent tantôt entrevoir des différences homme/femme, tantôt non (Aggazzotti et al., 1998; Fantuzzi et al., 2001; Lindstrom et al., 1997; Villanueva et al., 2007a).

2. Forces et faiblesses du concept stratégique d'estimation de l'exposition

2.1. Une approche adaptée aux différentes dimensions de la problématique

Le concept stratégique d'évaluation de l'exposition, autour duquel s'articule cette thèse, a été développé pour tenir compte des différentes dimensions évoquées dans la section précédente. A date, sa mise en œuvre illustrée dans le cas concret présenté en Annexe II, bien qu'elle présente encore bien des imperfections (ex., prise en compte de la dimension spatiale et choix des facteurs de correction des concentrations dans l'eau discutables), a sans nul doute permis l'une des plus robustes et précises estimations de l'exposition comparativement à celles menées jusqu'alors dans les études épidémiologiques portant sur les SPD. Axée sur l'évaluation de l'exposition interne des individus exposés grâce au recours à la modélisation TCBP (au lu de l'Article IV, la plus crédible méthode d'estimation des niveaux biologiques), l'approche préconisée a, qui plus est, le mérite de tenir compte : (i) des variations spatio-temporelles des

concentrations environnementales (étapes [1] et [2]); (ii) des différences interindividuelles quant aux conditions d'exposition (étapes [2] et [3]); et (iii) des variations inter- et intra-individuelles des caractéristiques physiologiques (étape [3]).

La concrétisation de cette stratégie sous la forme d'un outil de modélisation pourrait fournir un instrument utile aux différents acteurs concernés par l'exposition des populations aux SPD. L'annexe II témoigne de cette utilité en épidémiologie environnementale, alors que des applications plus larges que la seule évaluation quantitative de l'exposition pourraient être envisagées en analyse du risque. Un tel outil pourrait servir également l'intérêt des gestionnaires municipaux au regard des attentes des législateurs et permettre une amélioration des stratégies de gestion des SPD dans les systèmes d'eau potable.

L'approche doit bien entendu être adaptée spécifiquement à chaque SPD. Elle a été développée en se concentrant sur le cas des THM, notamment sur celui du mieux connu et du plus abondant d'entre eux le TCM. Ainsi, par exemple, pour les THM bromés, la question de la validité des modèles TCBP de l'étape [3] demeure compte tenu du peu de données disponibles dans la littérature. La confiance que l'on peut accorder à ces modèles repose sur le fait qu'ils ont été développés suivant la même méthodologie que le modèle du TCM et avec des données provenant des mêmes laboratoires (Haddad et al., 2006). Pour la plupart des AHA, la pertinence de l'étape [3] peut se limiter à la considération de la voie d'exposition par ingestion (qui ne requiert pas nécessairement le développement d'un modèle TCBP). Pour l'exposition en piscine au TCAM, à l'action vraisemblablement topique, seules les étapes [1] et [2] sont pertinentes à développer.

L'approche demande à être développée indépendamment pour chaque source possible d'exposition, ce qui permet de les considérer chacune séparément (comme ici dans les volets I et II) mais qui n'exclut pas *in fine* d'intégrer les résultats de chacune pour estimer l'exposition globale (i.e., multi-source). Dans cet ordre d'idée, nous rappelons encore ici, compte tenu des résultats de l'article IV, l'importance de tenir compte de l'exposition en piscine au regard de l'exposition domestique si l'on souhaite établir un lien « juste » (et éventuellement fort) entre de possibles effets sanitaires et l'exposition aux SPD.

Un des grands avantages que propose l'approche repose sur la prise en compte (simultanément ou indépendamment les uns des autres) des différents média et voies d'exposition rendue possible par la modélisation TCBP développée par Haddad et al. (2006). L'annexe II illustre également la puissance de ces modèles qui peuvent être adaptés pour tenir compte des physiologies particulières de certaines catégories d'exposés (ex., femmes enceintes). L'article II ou encore les travaux de Tan (2007) montrent comment ils peuvent être utilisés en combinaison avec des approches populationnelles (ex., en l'occurrence, respectivement, Monte-Carlo ou Bayésienne).

2.2. Avancées et défis à surmonter : conclusions et perspectives

Le développement de l'approche proposée pose évidemment encore des défis majeurs. Dans cette thèse, nous avons tenté de contribuer à la résolution de certains d'entre eux, tout au moins de fournir des éléments nouveaux et pertinents en vue du développement de cette méthodologie et, de façon plus générale, en vue de l'amélioration des méthodes de mesures de l'exposition aux SPD. Nous avons notamment choisi de porter l'attention en priorité sur le cas fondamentalement plus complexe des THM et d'étudier plus particulièrement les variations des niveaux environnementaux et biologiques des SPD sur un court terme (une journée ou moins) afin de mieux cerner l'exposition « réelle » des individus. L'idée sous-jacente était d'explorer dans quelle mesure des outils de modélisation de ces variations à court-terme pourraient être utilisés ou développés pour préciser et renforcer l'estimation de l'exposition dans le cadre d'investigations épidémiologiques à grande échelle. Une autre préoccupation a été de considérer en parallèle l'exposition domestique et l'exposition en piscine aux SPD.

Le premier volet de la thèse a été consacré au premier type d'exposition susmentionné et exclusivement à l'étude des THM. En l'état actuel des connaissances, relativement à la stratégie conceptuelle d'estimation de l'exposition proposée, alors que les outils déployés dans les étapes [1] et [3] sont déjà largement éprouvés, nos efforts se sont porté sur l'étape intermédiaire.

Cette étape [2] vise à ajuster, autant que possible, la concentration environnementale en SPD prédite, le plus souvent sur base mensuelle, à l'issue de l'étape [1] à la concentration environnementale à laquelle est réellement exposée un individu au moment même de son exposition et qui sert d'entrant à l'étape [3]. Dans cette optique, il s'agissait, en priorité, de cerner l'ampleur des variations inter- et intra-journalières, d'envisager de les modéliser et de voir quel était l'impact de considérer (ou non) ses variations sur les estimations possibles des niveaux biologiques des individus.

L'article I, consacré à l'aspect environnemental, a mis en évidence les variations effectives des niveaux de contamination en SPD de l'eau. Ces variations sont apparues relativement modestes de manière générale mais ponctuellement de fortes amplitudes. Il n'a toutefois pas été possible de trouver de « pistes » pour les modéliser d'une façon qui se prête à une mesure pratique de l'exposition dans le cadre d'une étude épidémiologique. Contrairement à la seule étude conduite, à notre connaissance, sur les variations journalières des SPD (Chaib & Moschandreas, 2008), nous n'avons pas identifié de périodicité dans ces variations, pas plus que de profils type reproductibles.

Confronté à cette impossibilité de prédire les variations journalières des niveaux environnementaux de SPD, l'article II présente les résultats de la première étude à avoir évalué leurs impacts sur les indicateurs de l'exposition biologique. Les erreurs liées à la non-prise en compte de ces variations se sont traduites par des écarts de l'ordre de 30% entre les prédictions justes et les prédictions faussées. Les erreurs étaient moindres dans le cas du TCM que pour les THM bromés et la quantité de contaminant absorbé est apparue comme l'indicateur d'exposition le moins affecté. Des investigations complémentaires sur cette mésestimation difficilement contournable de l'exposition aux THM pourraient envisager de considérer d'autres scénarii d'exposition typiques que ceux que nous avons choisis arbitrairement aux fins de simulation. Il conviendrait également pour renforcer la validité de l'étude de mieux appréhender la volatilisation desdits composés dans l'air ambiant ou, comme déjà évoqué plus avant, de s'assurer de la fiabilité effective des modèles de volatilisations existants.

Dans le cadre de l'étape [2], d'autres questions devraient toutefois être aussi privilégiées. Elles concernent les sous-étapes subséquentes à la prédiction des variations spatio-temporelles à court terme des SPD dans l'eau du réseau. En premier lieu, la

question des variations des concentrations entre l'eau chaude et l'eau froide. Des travaux ont été engagés dans ce sens et ont mis en évidence l'impact conséquent du chauffe-eau sur les niveaux de SPD (Chowdhury et al., 2011; Dion-Fortier et al., 2009). Également, la question de l'impact de la manipulation de l'eau avant consommation (i.e., traitement thermique, entreposage et/ou filtration) revêt une importance fondamentale qui justifie un intérêt certain (Chowdhury et al., 2010; Levesque et al., 2006).

Au regard des autres étapes de ce volet, deux points mériteraient davantage de développement, quand bien même chacun constitue, en l'état actuel des choses et en ce qui le concerne, la meilleure façon de procéder. Le premier concerne l'étape [1] et la prise en compte de la dimension spatiale dans la prédiction des concentrations en SPD dans l'eau des réseaux. Legay et al. (2011a) ont proposé une façon de faire très originale mais qui comporte son lot d'incertitudes en tant qu'elle associe distance géographique et distance hydraulique. Le deuxième point a trait à l'étape [3] et concerne la modélisation TCBP qui ne distingue pas, dans sa forme actuelle, les bains et douches autrement que par la durée de l'exposition.

Le deuxième volet de la thèse s'est focalisé sur la question de l'exposition aux SPD en piscine qui fait l'objet d'un regain d'intérêt marqué ces dernières années. Il s'agissait notamment d'examiner comment le cadre stratégique conceptuel de mesure de l'exposition proposé et élaboré d'abord pour un contexte domestique pouvait être mis en œuvre dans le contexte particulier des piscines. Dans cette perspective, il convenait notamment de voir dans quelle mesure il était envisageable de développer des modèles prédictifs de l'occurrence des SPD dans les milieux en question (étapes [1] et [2]) et dans quelle mesure la modélisation TCBP (étape [3]) se prêtait à la prédiction des niveaux biologiques d'exposition suite à des exercices de natation.

L'article III a proposé un design d'étude original au regard des études traditionnellement conduites en piscines pour aborder la question de l'occurrence environnementale en procédant à un suivi intensif et prolongé des niveaux des différents SPD dans l'eau et dans l'air autour des bassins et dans les salles connexes. Cet article a permis de dresser les portraits de la contamination dans deux piscines et de mettre en relief la grande variabilité entre et au sein même de chaque piscine tant sur le plan temporel que spatial.

Cette variabilité a été constatée alors même que les piscines présentaient des caractéristiques assez similaires avec la même configuration à un bassin unique et que les échantillonnages ont été conduits hors de périodes de plus fort achalandage. Dans ce cas encore, nous ne sommes pas parvenus à identifier des profils reproductibles des variations des niveaux environnementaux qui puissent permettre de les modéliser. Tout au plus, des modèles de volatilisation permettant de prédire la concentration de TCM dans l'air à partir de celle dans l'eau ont été suggérés en l'absence de mesures. Un échantillonnage minimal *in situ* de l'eau et de l'air semblent toutefois incontournable pour estimer correctement les niveaux de chacun des différents SPD. En effet, nous n'avons identifié aucune corrélation entre les différents SPD étudiés, contrairement à d'autres études (Bessonneau et al., 2011; Lee et al., 2010).

Finalement, l'article IV, consacré au TCM a fourni plusieurs résultats très intéressants. Inspiré d'une démarche déjà mise en œuvre par Lévesque et al. (2000), l'efficacité prédictive du modèle TCBP pour simuler des exercices de natations a été éprouvée dans plusieurs cas. Comparativement à d'autres outils disponibles pour prédire l'exposition interne résultant d'activités de ce type (Dyck et al., 2011; U.S.E.P.A., 2003; Villanueva et al., 2007b), la modélisation TCBP est apparue comme particulièrement intéressante mais peut encore être améliorée, entre autres quant à la façon de simuler l'absorption percutanée (ce qui fait d'ailleurs écho également au point évoqué plus haut concernant la distinction bain/douche). Enfin, ce travail a permis d'établir l'importante contribution de l'exposition en piscine au regard de l'exposition domestique, au moins dans le cas du TCM.

En conclusion, une approche multidisciplinaire de l'exposition aux SPD qui intègre, telle qu'illustrée par cette thèse, la perspective d'ingénieurs de l'eau et de toxicologues conscients des besoins de l'épidémiologie et de l'analyse du risque, est sans aucun doute indispensable pour mesurer au mieux l'ampleur d'un problème qui reste à préciser. Sans avoir eu la prétention de résoudre toutes les difficultés encore nombreuses à surmonter pour estimer véritablement correctement l'exposition « réelle » des individus aux SPD au travers d'une telle approche, les résultats de nos travaux ont conforté assurément la

pertinence de la démarche préconisée, ont fourni des éléments de réflexion originaux quant à l'état de l'art et pourront contribuer – souhaitons-le – à orienter de manière stratégique les recherches à ce sujet.

Dans cette dernière perspective, nous recommandons d'investir en priorité les efforts autour des axes de recherches suivants :

- Étude de l'impact des manipulations de l'eau avant consommation (étape [2])
- Documentation de la volatilisation des THM dans l'air intérieur
- Développement de la modélisation de l'absorption percutanée
- Étude de l'exposition des travailleurs et des nageurs sportifs en piscine
- Intégration de l'exposition en piscine dans les études épidémiologiques
- Analyse du risque en piscine par le biais de la modélisation TCBP

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ANNEXE I

L'annexe I reproduit avec l'autorisation de l'éditeur et des autres coauteurs l'article suivant, publié le 10 février 2011 :

Tardif R, Haddad S, Catto C, Hamelin G and Rodriguez MJ (2011) **Modeling Exposure to Disinfection ByProducts.** In: Nriagu JO (ed.) *Encyclopedia of Environmental Health*, volume 3, pp. 810–819 Burlington: Elsevier.

Le lecteur y trouvera une description des différents outils de modélisation évoqués dans la thèse, qui sont notamment à la base de la stratégie conceptuelle d'estimation de l'exposition décrite en introduction et autour de laquelle se sont articulés les travaux présentés précédemment.

Ma contribution à ce document a exclusivement tenu à une participation à sa rédaction et à l'intégration des différentes parties pour la préparation de la version finale.

Modeling Exposure to Disinfection ByProducts

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Abbreviations

ANN	artificial neural network
AUC	area under the blood concentration versus time curve
BDCM	bromodichloromethane
C_{max}	maximal blood concentration
DBCM	dichlorobromomethane
DBP	disinfection by-product
DOC	dissolved organic carbon
HAA	haloacetic acid
NHANES	National Health and Nutrition Examination Survey
NOM	natural organic matter
OLS	ordinary least squares
PBTK	physiologically based toxicokinetic model
SPSS	Statistical Package for the Social Sciences
SUVA	specific ultraviolet absorbance
TBM	tribromomethane (bromoform)
TCM	trichloromethane (chloroform)
THM	trihalomethane
TOC	total organic carbon
UV	ultraviolet

Introduction

Sources and Routes of Exposure

Humans are exposed to a large number of disinfection by-products (DBPs) through drinking and water use activities. Significant exposure can occur not only through ingestion (e.g., consumption of tap water, prepared beverages, and food) but also through dermal or respiratory pathways while washing, showering, bathing, boiling water, using humidifiers or washing machines, dishwashing, and even, obviously, while swimming in pools.

The relevance of each exposure pathway also depends on the properties of each DBP. For instance, the haloacetic acids (HAAs), which are nonvolatile and have low skin permeability, are mainly absorbed through ingestion. In contrast, the importance of dermal and inhalation exposures to highly volatile and lipophilic trihalomethanes (THMs) is clearly acknowledged. This DBP multisource and multiroute exposure is particularly challenging.

Measuring Exposure to DBPs: Environmental versus Biological Monitoring

An accurate assessment of human exposure to DBPs is critical in establishing whether the suspected risks of adverse effects (e.g., cancer, reproductive and developmental effects) are substantiated. This assessment is usually done with either environmental or biological monitoring.

Environmental monitoring involves external exposure. It is mainly based on spot and periodic measurements of drinking water concentrations within a distribution system. Most of these data are collected to meet regulatory requirements. However, they are neither necessarily relevant nor numerous enough to assess adequately the DBP exposure of individuals in epidemiological studies, especially given the spatial and temporal variations of these compounds that are often observed in DBP drinking water distribution networks.

In contrast, the use of exposure biomarkers allows the rather precise assessment of an individual's internal level of exposure to DBPs, through biological measurements in blood, urine, or alveolar air. Obviously, this monitoring approach is more demanding to develop and carry out than the environmental one, not to mention expensive.

A common limit of these means of assessing DBP exposure involves quantification issues, given the usually low levels of DBPs commonly found in drinking water and subsequently absorbed by humans. Another limit is linked to the previously mentioned large number of different DBPs, which renders questionable the possibility of measuring one specific compound as a surrogate for all others or of identifying a suitable biomarker for each one.

Factors for Exposure Variations

In addition to the previously mentioned 'practical' difficulties in carrying out exposure assessment, numerous factors are sources of exposure variations that should be considered. Spatial and temporal variations in environmental concentrations (i.e., in water and, consequently, in ambient air following volatilization) have already been suggested. The range of these variations can be great within the same distribution system as well as between two different ones, due to changes in source and distributed water quality (i.e., composition), the treatment process, or the network's characteristics. Furthermore, many differences exist between individuals in the amount

and ways in which they use water (e.g., frequency and duration of showering, type and quantity of consumed water, and the use of domestic treatment devices), resulting mainly in great disparities in the relative contribution of each route of exposure. Eventually, physiological, biochemical, or physicochemical characteristics (e.g., body weight and pulmonary ventilation depending on the level of physical activity) can influence the absorption, distribution, metabolism, and excretion (ADME) of DBPs by individuals.

Complementary Modeling Approaches Challenging DBP Exposure Assessment

In the particular context of DBP exposure assessment, both environmental and biological monitoring present several deficiencies, related in part to the numerous factors previously suggested. In both cases, reliable modeling approaches exist to sustain and complement these time-consuming, complex, and expensive exposure assessment strategies. To properly estimate DBP exposure, the ideal methodology would consist of measuring continuously (over the duration of the assessment) the environmental concentrations (external exposure) in the drinking water and ambient air in the house of each subject, as well as the biological levels (internal exposure) in each subject, due to appropriate biomarkers for each DBP. Currently, this is still a utopia considering the microenvironment changes over the course of the day as daily activities are conducted, including work, recreation, and other activities outside the house and the impact of physical activity on pulmonary retention of volatile DBPs.

Therefore, the development of models to predict DBP concentrations in water treatment plants and within the distribution systems, as well as in the human body, is undeniably useful. On the one hand, the approach of modeling environmental occurrence allows the significance of the parameters that influence the formation of DBPs to be quantitatively identified and spatial and temporal variations in these compounds to be estimated. On the other hand, knowledge about the toxicokinetics of the various DBPs allows the fate of these contaminants in humans to be described/predicted while identifying the factors that have the greatest impact. Indeed, toxicokinetic modeling can also simulate the relative uptake from various exposure routes and be used to estimate the impact of differences between individuals.

The second section in this article discusses the modeling of environmental occurrences of DBPs in drinking water. The third section deals with the modeling of toxicokinetic profiles of THMs in humans. Throughout the document, THMs are the main focus, as they are the most investigated DBPs for multiroute absorption.

Modeling the Environmental Occurrence of DBPs in Drinking Water

Usefulness of Models of DBPs in Drinking Water

Environmental models of DBPs are useful as decision-making tools for minimizing DBP formation for various purposes including (1) operational control during the treatment process (e.g., adjustment of pH and disinfectant dose and control of hydraulic residence time in reservoirs), (2) selection of locations for boosting chlorination facilities for monitoring water quality within the distribution network, and (3) evaluation of the impact of regulation updating (e.g., in combination with other models simulating the removal of organic precursors and estimation of the infrastructure requirements to upgrade facilities in order to comply with regulations).

These models can also be applied to estimate human external exposure to DBPs by generating data at desired locations within the water distribution system. Since DBP regulation is relatively recent in some countries and the sampling frequency required for compliance is low, available data are often not sufficient historically and geographically for epidemiological purposes.

Description of Modeling Approaches

Models for DBPs have been developed using mechanistic and empirical approaches. With mechanistic models, the mechanisms and kinetics of the reactions of disinfectants with natural organic matter (NOM), the main DBP precursor, are considered sufficiently known to be mathematically represented. However, given the great complexity of these chemical reactions, empirical models have been preferred over mechanistic ones, despite the known limitations of the former. The main drawback is that they do not provide information about DBP formation mechanisms. Nevertheless, most research has focused on empirical approaches, particularly on multivariate regression techniques that consist of linking DBP concentrations statistically to various water quality and operational parameters associated with disinfection.

Experimental laboratory-scale or full-scale data can be used to develop these two types of models. Laboratory-scale simulations of disinfection allow useful data to be generated for estimating the potential for DBP formation under controlled disinfection conditions (bench-scale). However, most laboratory-scale chlorination studies published in the literature have been carried out under conditions that are different from those encountered in real water utilities (e.g., too high disinfectant doses and water temperature variations disregarded). In contrast, full-scale sampling allows the determination of data representing actual concentrations of DBPs in distribution systems.

Laboratory studies have been found to be more reliable than full-scale studies for developing empirical models because of controlled conditions (e.g., disinfectant dose, pH, and NOM quantity). The major drawback is that the actual effects of the distribution system are not accounted for. In contrast, this is not the case for field data-based models, but some parameters affecting DBPs are difficult to precisely estimate (e.g., the actual reaction time of water within the distribution system, which requires compelling tracer studies and hydraulic simulation models).

Multivariate regression has limitations in representing complex relationships between variables. To deal with such limitations, other techniques such as artificial neural networks (ANNs) have recently been used to develop DBP predictive models. Another recently applied technique for DBP modeling is fuzzy logic. Since multivariate regression models have demonstrated the usefulness of DBP prediction, the next two sections focus on this technique for DBP environmental occurrence modeling. Before presenting an example, the following section deals with model representation.

Representation of Multivariate Regression Models for DBPs

Regression-based modeling of DBPs aims to identify the significance of diverse operational and water quality parameters controlling the formation of DBPs. The main interest of research in the past two decades is to link DBP occurrence with total or dissolved organic carbon (TOC or DOC), ultraviolet(UV) absorbance at 254 nm (UV-254), pH, water temperature (T), concentration of bromide ion (Br^-), disinfectant dosage (D), and the reaction time of residual chlorine (t). TOC (or DOC), UV-254, and specific UV absorbance, i.e., SUVA (specific ultraviolet absorbance, the ratio between UV-254 and TOC) are the common surrogates of NOM. TOC and DOC are indicators of the mass of organic substance, whereas UV-254 accounts for the specific structure and functional groups. SUVA is an indicator of NOM reactivity. Other NOM indicators that have been used are chlorophyll-*a* and fluorescence. A longer reaction time (also known as contact time, residence time, or water age) generally leads to a higher consumption of residual disinfectant and results in the formation of more DBPs. This is one of the major reasons for the generally higher DBP concentrations observed at the extremities of water distribution systems compared to the finished water at the treatment plants. This is the case for THMs, for example. However, current research suggests, on the contrary, that other chlorinated DBPs such as HAAs may degrade at the extremities of distribution systems.

In multivariate regression models, the relationship between DBPs and the above-mentioned parameters can be described using an equation in the following form:

$$Y = \beta_0 + \sum_{i=1}^{m} \beta_i X_i \qquad (1)$$

where Y is the dependent variable (in this case DBP levels); X_1, X_2, …, X_n are the independent variables (disinfectant dose, TOC, SUVA, reaction time, etc.), with m being the number of independent variables considered; and β_0 is the intercept and β_1, β_2, …, β_n are the partial slope coefficients providing a partial explanation or prediction for the value of Y. Estimates of the intercept and regression coefficients are obtained mathematically using the method of ordinary least squares (OLS) estimation. When a relationship appears to be nonlinear, either the dependent variable or one or more of the independent variables can be transformed (using a logarithmic transformation, for example). In such a case, the modeled relationship becomes nonlinear even if the form of the model remains linear. Such a relationship is nonlinear in terms of its variables but linear in terms of its parameters. A model thus developed may therefore also be analyzed using the OLS estimation.

Modeling Example

An application of DBP modeling was done using full-scale data generated in the largest water distribution system in Quebec City (Canada). In this system, spatio-temporal variations in water quality are considerable. In fact, the region under study is characterized by sudden watershed runoff – associated with a rapid increase in ambient temperature and with snow melting in the spring – and by frequent rain and a relatively rapid decay of vegetation (a source of NOM in water) during the fall. All these events contribute to modifications in surface water quality and also require changes in operations during water treatment. Generation of data for modeling purposes was based on a full-scale 14-month sampling program intended to characterize water quality in various locations between the plant and the end of the distribution system. Samples were collected every 2 or 3 weeks. **Figure 1** presents the parameters measured at each location. Water residence times in distribution system locations were estimated through tracer studies based on fluoride monitoring. Two 2-day tracer studies were carried out – one in winter and the other in summer – in order to consider the possible impacts of seasonal differences in water consumption and of produced flow rates on residence times.

Model development consisted of establishing statistical relationships between THM or HAA concentrations in the distribution system based on data for P1, P2, P3, and P4 together, and water quality and operational conditions before postchlorination (i.e., conditions

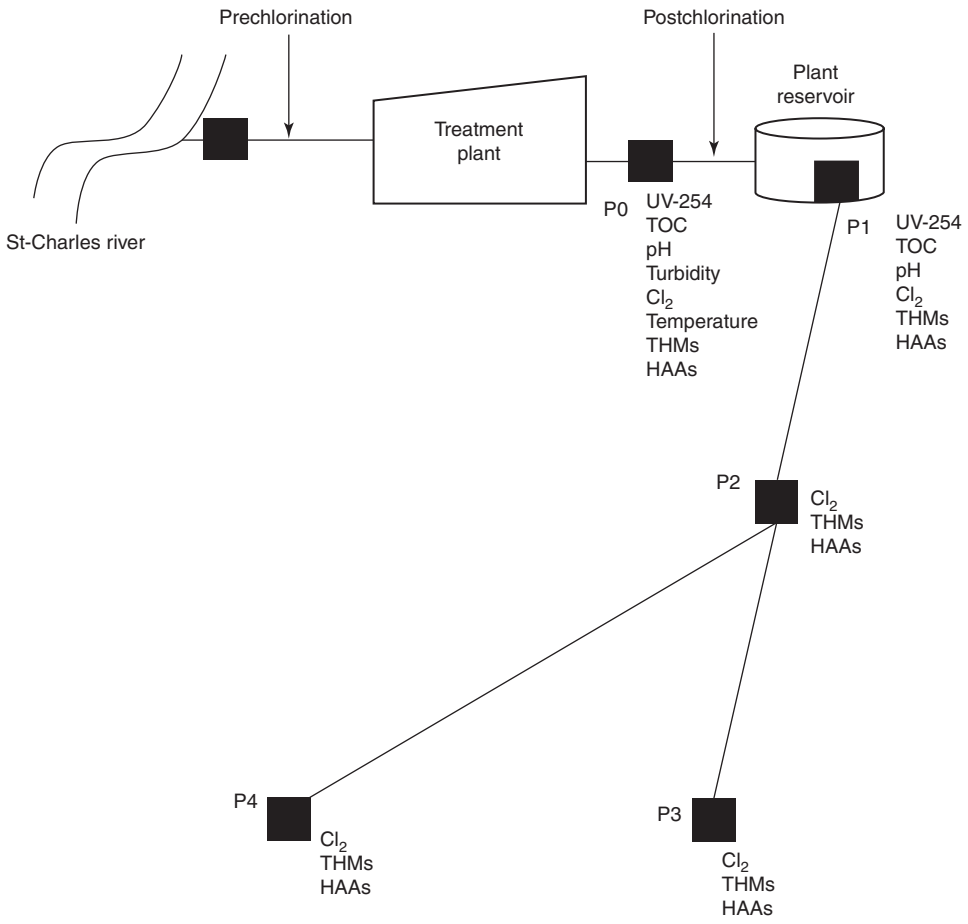

Figure 1 System under study, location of sampling points, and measured parameters. Rodriguez MJ Sérodes JB, Levallois P (2004) Behavior of trihalomethanes and haloacetic acids in a drinking water distribution system. *Water Research* 38: 4367–4382.

of prechlorinated water, represented by P0). The applied model was based on eqn [2], which is a transformation of the model in eqn [1] in which the variables were subjected to Ln–Ln transformation, as follows:

$$Y = \beta_0 \prod_{i=1}^{m} X_i^{\beta_i} \qquad (2)$$

The explanatory parameters considered in the model were the water quality parameters before postchlorination (at P0): the indicators of NOM (denoted TOC_0, $UV\text{-}254_0$, and $SUVA_0$ in $mg\,l^{-1}$, cm^{-1}, and l/cm.mg/, respectively); water pH (Ph_0); concentrations of DBPs (namely, $TTHM_0$ or $HAA2_0$ in $\mu g\,l^{-1}$); water temperature (T_0 in °C); postchlorination chlorine dose (D in $mg\,l^{-1}$); and the estimated residence time of water (t_r in h) between the postchlorination point and each of sampling points in question (P1, P2, P3, or P4). The parameters of the models in eqn [2] were estimated using the OLS method, which results in a line that minimizes the sum of the squared vertical distances from the observed data points to the line. Using the stepwise procedure in Stastistical Package for the Social Sciences (SPSS) statistical software, the method consists of first classifying the predictor variables according to their statistical significance (p) and then including one variable at a time in different steps.

Table 1 presents the modeling results. The criterion used to judge whether or not to consider selected variables in the models during the stepwise regression procedure was a significance level of 10%. This result shows that the nonlinear structure is generally able to adequately identify the spatial evolution of THMs and HAAs in the distribution system. Neither chlorine dose nor temperature was a significant variable in any of the models. Also, indicators for NOM only contribute to a moderate degree to seasonal variations in THMs. The concentration of DBPs already occurring before the postchlorination point (P0) has a significant effect on their fate in the distribution system. Actually, for the HAA model, this variable was the only significant one (giving a one-variable model). This can be explained by the fact that the variations in HAA levels between P0 and the next three locations (P1, P2, and P3) are relatively

Table 1 DBP model results (only variables that are significant in at least one model are shown)

	Variable significance (p-value)					*Statistical coefficients*					R^2
	b_0	$CDBP_0$	Ph_0	UV_0	t_r	b_0	$CDBP_0$	Ph_0	UV_0	t_r	
THMs	<0.01	<0.001	ns	ns	<0.001	286.9	0.745	na	na	0.298	0.68
HAAs	<0.001	<0.001	ns	ns	ns	5.34	0.571	na	na	na	0.70

ns: not significant; na: not applicable.
Note: Average values of the 2-day seasonal residence time were used within the model.

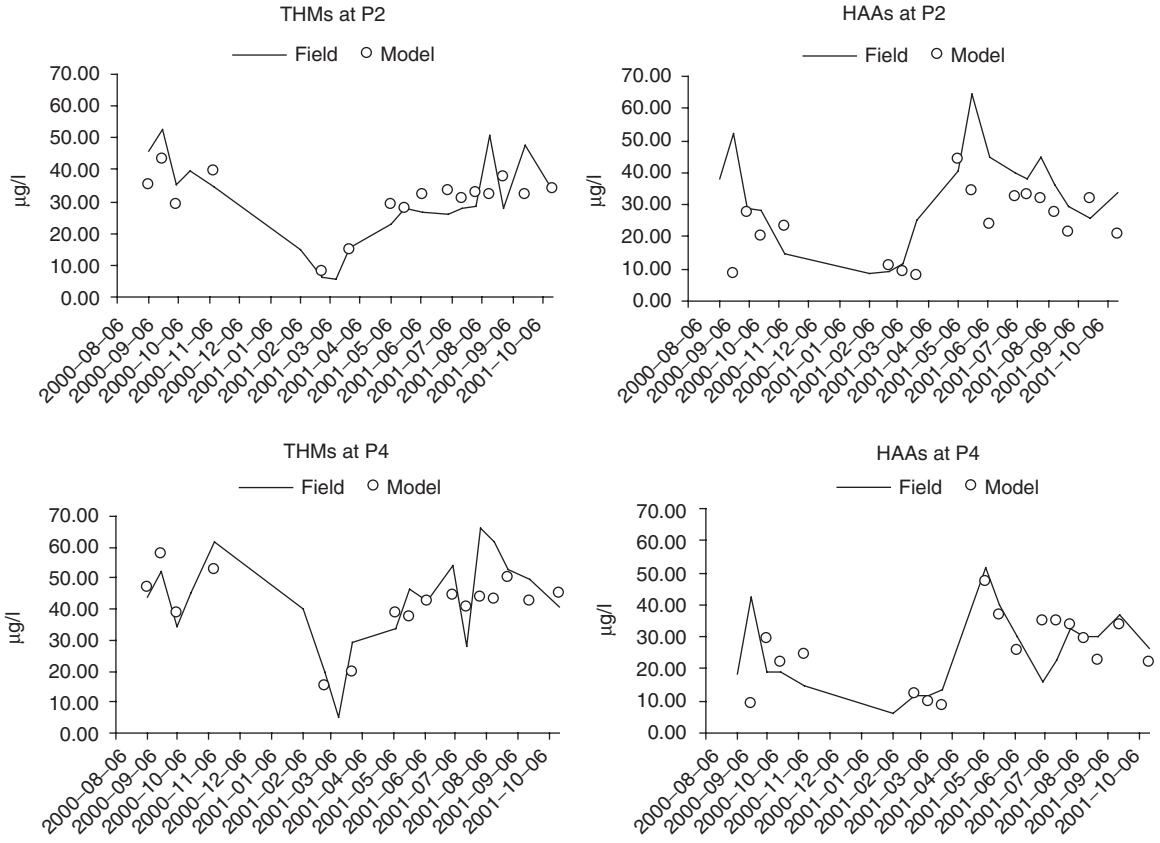

Figure 2 Comparison of field and modeled DBPs at selected locations in the distribution system.

minimal. The results also show that the residence time of water within the distribution system is a significant contributing variable for spatial variation in THMs. Figure 2 illustrates how the application of the models fits relatively well with measured data for DBPs.

Toxicokinetic Modeling Profile for Trihalomethanes in Humans

Description of Different Modeling Approaches

Two types of modeling approaches can be used to mathematically describe toxicokinetic data, which is how blood or tissue toxicant concentrations vary with time following exposure: (1) classical toxicokinetic modeling or (2) physiologically based toxicokinetic (PBTK) modeling. The first is based on compartmental modeling, which consists of determining the model structure and parameter values based strictly on the available toxicokinetic data, without necessarily reflecting any physiological/biological realism, but strictly describing the behavior of the data at hand. Hence, the use of such models should be restricted to interpolations. However, various toxicokinetic extrapolations (e.g., high-to-low dose, species-to-species, different exposure scenarios, route-to-route, interindividual differences) are needed for health risk assessment. PBTK modeling, which consists of describing all physiological, physicochemical, and biochemical processes affecting the ADME of a chemical, is particularly well suited to this context. Recently, there has been some effort to develop PBTK models for DBPs in humans and most notably for THMs, since PBTK

modeling allows multiroute exposure to be taken into account. In general, these models are similar in their structures, but the parameter values may differ slightly from one to another. This section focuses on how these models are constructed and shows various applications.

Physiologically Based Toxicokinetic Approach

Conceptual description (multiroute exposure)

These multiroute models are based on the conceptualization of an organism with typically five- or six-tissue compartments linked by systemic blood circulation (Figure 3). These compartments commonly include (1) the skin for cutaneous absorption; (2) the liver as organ responsible for biotransformation (or metabolism), which also serves as input for oral absorption; (3) adipose tissue, which is storage tissue for lipophilic compounds; (4) slowly perfused tissues, which basically represent the muscles; and (5) rapidly perfused tissues, which mainly represent the brain, glands, and visceral organs. The kidneys are sometimes chosen as a compartment because of their contribution to biotransformation. Any description of the gas exchange in the lungs is invariably included for volatile chemicals in order to account for

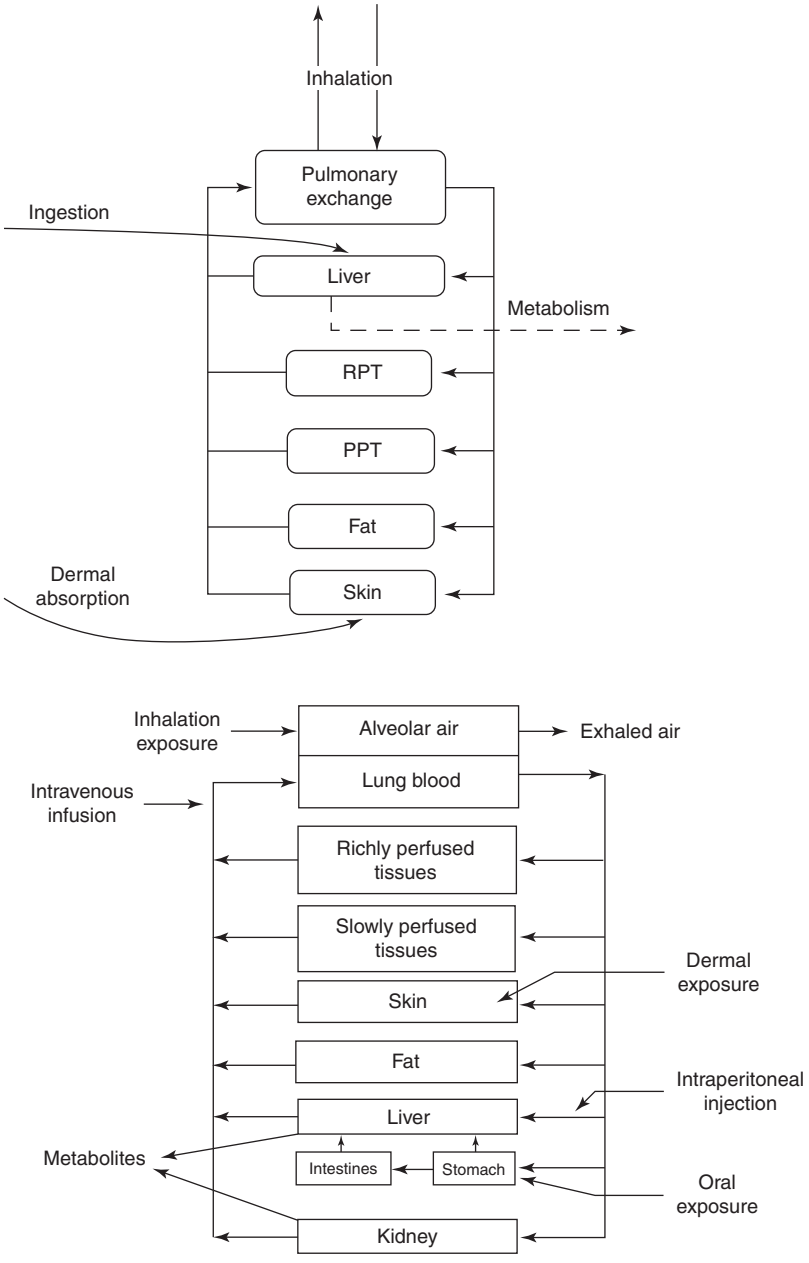

Figure 3 Schematic representation of PBTK models for multiroute exposure.

absorption through inhalation and elimination through exhalation.

Absorption: Absorption through skin when exposed to contaminated water is basically described as a first-order process dependent on the permeability constant (K_p). Oral absorption has been described either by (1) a first-order rate process, governed by an oral absorption constant (K_o), occurring in the gut where the absorbed chemical is released in the liver via portal vein or (2) a two-step process where the ingested chemical goes to the stomach. Finally, absorption by inhalation is described by a steady-state pulmonary gas exchange equation that is driven by the blood–air partition coefficient and the cardiac output and the alveolar ventilation rates.

Distribution: Once absorbed, the chemical enters the blood circulation and distributes into the tissue compartments. This process is assumed to be perfusion limited, i.e., the chemical is assumed to distribute homogeneously in the compartment. The accumulation in the compartment depends on the tissue–blood partition coefficient and the blood flow to the compartment.

Elimination: THMs are eliminated mainly through biotransformation and exhalation. Their biotransformation occurs almost exclusively in the liver, although a small portion also occurs in the kidneys. The process is described as a saturable one with a maximal rate (V_{max}) and an affinity constant (K_m). Excretion occurs essentially through exhalation, which is described by the steady-state pulmonary gas exchange used for inhalation.

Parameterization (Physiological, Biochemical, and Physicochemical)

Parameters used in these PBTK models fall into three categories: physiological (**Table 2**), physicochemical, and biochemical parameters (**Table 3**). Values for the parameters are generally very similar between PBTK modeling publications for THM, but uncertainties remain, especially regarding the latter two categories.

Physiological parameters used in the published PBTK models for THMs are tissue volumes, tissue blood flows, cardiac output, alveolar ventilation rate, and body surface. The values for these parameters are similar from one publication to another. Some authors have added information on the distribution of the parameter values or equations relating to gender age, body weight, and body height to account for the variability in these parameters. Blood flows can also be adjusted according to workload/activity or even temperature.

Reported physicochemical parameters included the blood–air and tissue–air partition coefficients of a compound as well as the effective skin permeability coefficients (K_p). The reported blood–air values were experimentally determined using human blood, whereas the values for other tissue–air partition coefficients were

Table 2 Physiological parameter values for a standard adult human

Parameters	*Symbol*	*Value*[a]	*Value*[b]
Body weight (kg)	BW	70	–
Body surface area ($cm^2\,kg^{-1}$)	S	257.14	286
Cardiac output ($l\,min^{-1}$)	Qc	14.6	16.5 (1.5)
Alveolar ventilation rate ($l\,min^{-1}$)	Qalv	14.6	24 (3.8)
Compartment volume (%BW)			
Adipose tissue	Vf	19	21.4 (6.42)
Liver	Vl	2.6	2.57 (0.77)
Richly perfused tissues	Vr	5	5.39 (1.62)
Kidneys	Vk	–	0.44 (0.13)
Poorly perfused tissues	Vp	52	56.1 (16.8)
Skin	Vs	10[b]	5.1 (1.53)
Blood flow to tissue compartment (%Qc)			
Adipose tissue	Qf	5	5 (1.5)
Liver	Ql	26	25 (7.5)
Richly perfused tissues	Qr	44	25.4 (7.62)
Kidneys	Qk	–	19 (5.7)
Poorly perfused tissues	Qp	21.6	17 (5.1)
Skin	Qs	3.4[b]	8.6 (2.6)

[a]Values taken from Haddad S, Tardif GC, and Tardif R (2006) Development of physiologically based toxicokinetic models for improving the human indoor exposure assessment to water contaminants: Trichloroethylene and trihalomethanes. *Journal of Toxicology and Environmental Health Part A* 69(23): 2095–2136.

[b]Values taken from Tan YM, Liao KH, and Clewell III, HJ (2007) Reverse dosimetry: Interpreting trihalomethanes biomonitoring data using physiologically based pharmacokinetic modeling. *Journal of Exposure Science and Environmental Epidemiology* 17: 591–603. Values in parentheses are values used as standard deviations in Monte Carlo simulations.

Table 3 Chemical specific parameters[a]

Parameters	*Symbol*	*TCM*	*DBCM*	*BDCM*	*TBM*
TRANSFER EFFICIENCY					
Shower	Φs	0.534	0.534	0.513	0.495
House	Φh	0.503	0.495	0.484	0.466
ABSORPTION CONSTANTS					
Oral (min-1 kg^{-1})	KoC	0.032	0.0303	0.0224	0.023
Dermal (cm min^{-1})	Kp	0.00267	0.003	0.00333	0.0035
PARTITION COEFFICIENTS					
Blood:air	Pb	10.7	49.2	26.6	102.3
Liver:air	Pla	17	126	30.6	210.3
Adipose tissue:air	Pfa	280	1917	526	4129
Richly perfused tissues:air	Pra	17	126	30.6	210.3
Poorly perfused tissues:air	Ppa	12	55.6	12.4	115.1
Skin:air	Psa	19.7	97.21	46.45	238.23
Water:air	Pwa	3.66	11.83	7.43	24.71
METABOLIC CONSTANTS					
Maximal rate (μg min^{-1} kg^{-1})	VMAXc	211.33	228.33	133.50	173.33
Affinity constant (μg l^{-1})	Km	448	720	302	420

[a]From Haddad S, Tardif GC, and Tardif R (2006) Development of physiologically based toxicokinetic models for improving the human indoor exposure assessment to water contaminants: Trichloroethylene and trihalomethanes. *Journal of Toxicology and Environmental Health Part A* 69(23):2095–2136.

BDCM, bromodichloromethane, DBCM, dichlorobromomethane; TBM, tribromomethane (bromoform); TCM, trichloromethance (chloroform).

determined from rat tissues assuming they were similar. Mechanistically based algorithms were applied to estimate the reported skin–air partition coefficients. Values of K_p have been measured in *in vitro* studies using human skin samples or estimated with an algorithm. In the particular case of chloroform (TCM), the most investigated THM, the dermal absorption constants come either from (1) models fitting to measured levels in blood concentrations or exhaled concentrations following *in vivo* cutaneous exposures or (2) *in vitro* experimentation on human skin. Reported values for this parameter can be separated into two groups that differ by at least one order of magnitude. However, some authors have reported that K_p is dependent on temperature (level of variation between 25 and 40°C is estimated to be from one- to sixfold).

Two sets of oral absorption parameter values exist for humans. One set was extrapolated from rat values by assuming a similar mechanism of absorption in human species and scaled according to body surface differences. The source of the other set was unspecified. The first set of values uses the unicompartmental model for gastrointestinal absorption, whereas the other uses a bicompartmental one and therefore uses three parameter values: (1) absorption into blood from the stomach, (2) transfer from the stomach to the gut, and (3) absorption into the blood from the gut.

Regarding biochemical parameters, the only reported metabolic rate constants (V_{max} and K_m) for humans are for TCM. Values for other THMs were derived from PBTK model optimization to rat kinetics data. The V_{max} values were allometrically scaled and K_m was assumed to be the same.

Simulations and Validations

Human PBTK models were first developed and used to simulate THM kinetics under controlled exposure conditions for model validation purposes and in later stages to estimate/predict real life exposure conditions. Many of the later models were based on and constructed from the earlier validated models. TCM is the only THM for which model validation (comparison of predictions with experimental/actual data) has been undertaken in humans. Human models for the other main THMs (i.e., dichlorobromomethane, chlorodibromomethane, and bromoform) were constructed assuming similar mechanisms of ADME and by simply changing compound-specific parameters. PBTK models developed in rats support such inter-compound extrapolations.

PBTK models have been used in various ways. The following section proposes some examples.

Simulating In-House Exposures

Current PBTK modeling-based studies have estimated daily internal exposures to THMs from in-house exposures accounting for ingestion of tap water, dermal exposure via skin contact in showering/bathing, and inhalation exposure to ambient air contaminated by volatilized THMs. These PBTK models were linked to an exposure module, based on previous work, describing how the chemicals are distributed from tap water to the air of different compartments of a house. Calculations are based on the chemical's water-to-air transfer efficiency, water use (e.g., dishwashing and showering), in-house ventilation, and house compartment sizes.

Using this approach, the proportional contribution of different routes of exposure (inhalation, dermal, and ingestion) for a daily in-house exposure was estimated. Assuming a person takes a 10-min shower in the morning, it was estimated that an average male who drinks 1.5 l additionally absorbs a dose equivalent to ~1.5 l of ingested water by other routes (inhalation and dermal). However, when internal doses typically approximated by the area under the curve (AUC) of a THM biological concentration versus time or the peak of concentration (C_{max}) are the considered endpoints, exposure from other routes of absorption is equivalent to ingesting ~10 l or 64.8 l to 101.5 l of water, respectively. Showering was shown to have a major impact, contributing to more than 61% or 97% of the daily internal exposure for AUC or C_{max}, respectively. The impact of age, gender physiological parameter values, and physicochemical parameter values on internal exposure was also investigated. The simulations showed children under 12 presented higher AUC than older people, but overall variability within age groups seems greater than between age groups. The variability in partition coefficients was found to be an important factor in the determination of chemical internal dose range in populations of the same age, whereas variability in physiological parameters showed a significant impact only on AUC in the same age groups.

Other modeling studies estimated the absorbed dose distribution from inhalation, dermal exposure, and ingestion of several DBPs The distribution of absorbed dose was estimated in adults and 6-year-old children according to reported exposure distribution patterns. However, the results are not easily comparable because doses from each exposure route are independently reported as distributions, and their sum does not amount to 100% of the total dose. Nevertheless, a difference appears regarding the magnitude of dermal absorption for BDCM, which is much lower than what is estimated in the first mentioned study (3% and 17%, respectively). This can be explained in that a much lower value of K_p was used in the study.

In-house TCM exposures were simulated based on information on US distributions of THM concentrations in tap water and household air, shower durations, shower stall dimensions, and water use. Variability to all physiological, biochemical, and physicochemical parameters was considered assuming a coefficient of variance of 20% or 30% of the parameter values. This study showed that metabolic interactions are not likely to occur with the blood THM concentrations observed in the US population. Interestingly Monte Carlo simulations adequately simulated the blood concentration distributions observed in the 1996 National Health and Nutrition Examination Survey (NHANES) III study. Two different approaches for reverse dosimetry with the PBTK model for THMs were proposed. The aim of this reverse dosimetry is to estimate daily THM intakes in a given population based on blood concentration distribution data. One approach consisted of establishing a blood level distribution unit per $\mu g\,l^{-1}$ of THM in tap water with Monte Carlo simulation of the PBTK model. Using this unit distribution per $\mu g\,l^{-1}$ in water and the blood concentration distribution in the population, a distribution of the water concentrations to which the population is exposed could then be estimated. The second approach consisted of using the PBTK model with a Bayes probability formula (i.e., a matrix with rows being the input water concentration and the columns being the blood concentration units) to estimate the probability distribution of water concentrations. Both approaches gave values that differed by about 20% for the 50th percentile.

Simulating Bathing Exposures

PBTK modeling and simulation studies with TCM have been used to assess human exposures from bathing and swimming. Exhaled breath was measured in swimmers following different levels of activities, and these values were simulated after optimizing effective K_p values. The model was then used to estimate metabolite binding to macromolecules in the kidney and liver. The simulations showed that competitive swimmers were more internally exposed to TCM and its metabolites than leisure swimmers but were still at relatively safe levels. Finally the kinetics of TCM in humans following skin-only exposure was examined during bathing at different water temperatures. This modeling study assumed that skin blood flow increased with temperature. To adequately simulate exhaled TCM in human subjects bathing in water with the temperature rising from 30 °C to 40 °C, it was necessary to increase the effective K_p values by 5 × (males) or 20 × (females). It was estimated that a 30-min bath was equivalent to 1–28% of an ingestion of 2 l of the same water, depending on temperature.

Conclusions and Perspectives

The previous sections described the difficulties encountered in both external and internal DBP exposure assessment and illustrated some available methods for coping with the deficiencies inherent in typical exposure measurements (environmental or biological monitoring) widely used in epidemiological studies.

Environmental occurrence modeling allows the drinking water concentrations of a preselected DBP to be output from a set of operational data and quality parameters. These concentrations can be estimated/predicted: (1) weekly or monthly (depending on the availability of data relative to checking frequency) and

(2) in various areas of a distribution, taking into account the important spatial end temporal variability affecting drinking water levels.

PBTK modeling is particularly useful for multiroute-absorbed DBPs such as THMs. These models enable us to predict internal exposure (expressed either as blood levels, total internal dose, and amount metabolized) from ingestion of tap water, inhalation of volatilized THMs, in-house exposure, and dermal exposure through bathing/showering in a given population, taking into account the specific physiological characteristics of exposed individuals (children, pregnant women, etc.).

Modeling has greatly improved DBP exposure assessment and still is promising for further exploration and use, especially through previously established multidisciplinary perspectives, such as integrating environmental and biological modeling into epidemiological contexts. Therefore, the availability of such tools represents a clear progress for human exposure assessment of DBPs and would certainly benefit the assessment of other water contaminants including new DBPs that have been identified more recently (e.g., haloacetonitrile and haloaldehydes).

However, additional work needs to be done to deal with two important issues: (1) the still inadequately understood and therefore predictable influence of various factors/conditions that are known to affect (increase/decrease) the concentration of DBPs water levels, such as those related particularly to water handling (boiling, filtering, and duration and temperature of storage) and (2) the influence of within-day and day-to-day variations in water levels of DBPs. The relevant, suitable, and best way to cope with these influences (e.g., by applying corrective factors) in exposure assessment is particularly challenging.

Further Reading

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ANNEXE II

L'annexe II reproduit avec l'autorisation de l'éditeur et des autres coauteurs l'article suivant, actuellement sous presse :

Levallois P, Gingras S, Marcoux S, Legay C, Catto C, Rodriguez MJ and Tardif R (2012). **Small-for-gestational Age Neonates and Maternal Exposure to Drinking Water Chlorination By-products**. *Epidemiology*, *23*(2), 267-276.

Le lecteur y trouvera un exemple concret d'application de la stratégie conceptuelle d'estimation d'exposition que cette thèse contribue à développer.

Relativement à ce document, ma contribution a notamment tenu, avec l'aide de Suzanne Gingras et sous la supervision de Robert Tardif, à l'adaptation du modèle PBPK utilisé dans l'étude, à son développement sous SAS, à la traduction des conditions d'exposition du questionnaire aux entrant du modèle, ainsi que, après discussion avec Patrick Levallois, à la définition des facteurs correctifs pour ajuster les concentrations d'exposition environnementale… et finalement à la rédaction des parties concernant ses aspects méthodologiques de l'étude.

Maternal Exposure to Drinking-water Chlorination By-products and Small-for-gestational-age Neonates

Patrick Levallois,[a,b,c] *Suzanne Gingras,*[a] *Sylvie Marcoux,*[b] *Christelle Legay,*[d] *Cyril Catto,*[e] *Manuel Rodriguez,*[d] *and Robert Tardif*[e]

Background: There is concern about possible effects of disinfection by-products on reproductive outcomes. The purpose of this study was to evaluate the association between maternal exposure to chlorination by-products and the risk of delivering a small for-gestational-age (SGA) neonate.

Methods: We conducted a population-based case-control study in the Québec City (Canada) area. Term newborn cases with birth weights <10th percentile (n = 571) were compared with 1925 term controls with birth weights ≥10th percentile. Concentrations of trihalomethanes and haloacetic acids in the water-distribution systems of participants were monitored during the study period, and a phone interview on maternal habits was completed within 3 months after childbirth. We estimated chlorination by-products ingestion during the last trimester of pregnancy and trihalomethanes doses resulting from inhalation and dermal exposure. We evaluated associations between chlorination by-products in utero exposure and SGA by means of unconditional logistic regression with control of potential confounders.

Results: When total trihalomethanes and the 5 regulated haloacetic acids concentrations were divided into quartiles, no clear dose-response relationship was found with SGA. However, increased risk was observed when haloacetic concentrations were above the fourth quartile and when either trihalomethanes or haloacetic acids concentrations were above current water standards (adjusted OR= 1.5 [95% confidence interval = 1.1–1.9] and 1.4 [1.1–1.9], respectively). Inhalation and dermal absorption of trihalomethanes did not contribute to this risk, but a monotonic dose-response was found with haloacetic acids ingestion.

Conclusion: Oral exposure to high levels of chlorination by-products in drinking water could be a risk factor for term SGA.

(*Epidemiology* 2012;23: 267–276)

Chlorine is widely used as a drinking water disinfectant due to its efficacy and cost-effectiveness. However, it also reacts with natural organic matter present in water and leads to the formation of potentially toxic chemicals known as chlorination by-products.[1] Trihalomethanes and haloacetic acids are the 2 most prevalent chlorination by-products found in chlorinated drinking water.[2] Because of their potential carcinogenic properties,[3,4] these chemicals are now regulated in North America and in several countries elsewhere, based on an annual mean of quarterly samples.[5,6]

Interest in the possible adverse reproductive effects of disinfection by-products is more recent. The first epidemiologic study on the topic was published in 1992.[7] Thereafter, several studies raised the specter of possible effects on fetal development.[8–12] Although the results of epidemiologic studies conducted primarily on reproductive outcomes are rather inconsistent, the available evidence suggests a positive association between exposure to chlorination by-products and intrauterine growth restriction.[11,12] However, because of severe limitations regarding exposure assessment in particular, the epidemiologic data remain inconclusive, and further studies with improved personal exposure assessment have been recommended.[11–13]

Due to important spatial and seasonal variations of chlorination by-products within and between distribution systems, the use of regulatory measurements of these compounds in drinking water is not considered adequate to assess exposure within a short-time window.[14–16] Consideration of personal water consumption is also important, as are the frequency and duration of showers and baths, because volatile trihalomethanes (unlike haloacetic acids) are easily absorbed by inhalation and dermal contact.[17,18]

The possible effect of chlorination by-products on reproductive outcomes is supported by laboratory studies on animals.[8,9,19] Trihalomethanes have not been found to be

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teratogenic, but severe maternal and fetotoxic effects have been observed at high doses with reduction of fetal body weight and survival.[8] Retarded fetal development and reduced fetal weight, length, and size have been found in pregnant rats, mice, and rabbits subjected to high-dose exposure to chloroform,[9] normally the most abundant trihalomethane. Haloacetic acids have been linked to several fetal malformations; in utero exposure to dichloroacetic acid and trichloroacetic acid (the main haloacetic acids) has also been associated with reduced weight of pups.[9]

Fetal growth is an important public health concern because of its strong relationship to infant morbidity and mortality.[20] Moreover, mounting evidence suggests that babies with growth restriction at birth might be more prone to developing important diseases during adulthood, such as type 2 diabetes, hypertension, metabolic syndrome, and coronary heart disease.[21] Although smoking is a well-recognized risk factor, few other environmental risk factors for fetal growth have been studied.[22,23] Considering the prevalent exposure to chlorination by-products and their toxic potential, we focus here on this possible effect.

The purpose of this study conducted in the Québec City area was to evaluate the association between residential exposure to chlorination by-products (eg, trihalomethanes and haloacetic acids) and fetal growth restriction. The design of the study considered temporal and spatial variations of chlorination by-products in water distribution systems and the multiple pathways of maternal exposure to trihalomethanes during pregnancy.

METHODS

Study Design and Population

We conducted a population-based case-control study in the greater Québec City area (covering some 650,000 inhabitants). It includes the 16 water distribution systems serving the populations of Québec City and the city of Lévis. Among these systems, 9 are supplied by surface water sources and 7 by groundwater sources. All use free chlorine for primary or secondary disinfection, but differ in water source, water treatment processes, population served, system size, and hydraulic conditions.

The study population includes all singleton infants born between August 2006 and April 2008 to women residing in the areas served by the selected facilities. The Commission d'accès à l'information du Québec (the Quebec office for access to information) gave permission to access selected nominal information from the birth certificates of children born to mothers living in the study area shortly after their birth. Cases and controls were selected using information recorded on these birth certificates. To be eligible for the study, the women had to be aged 16 years or older and have resided in no more than 2 residences in the study area during their entire pregnancy. Additionally, they should not have resided away from their residence for more than a month during their pregnancy.

Definition of Cases and Controls

Cases were term small-for-gestational-age (SGA) singletons born at 37 completed weeks or more of pregnancy to women living in the targeted study area during the 23-month recruitment period. A case of SGA corresponds to a neonate weighting less than the sex-specific 10th percentile of weight for gestational age, according to the Canadian sex-specific standards of birth weight for gestational age.[24]

Three controls per case were randomly selected from the live birth database with frequency matching on period of birth. We defined a control as a singleton term infant born the same calendar week as the case with a birth weight at or above the 10th percentile sex-specific weight for gestational age.[24] Because participation was slightly higher for controls, the ratio of controls to cases was 3.4.

Interview of Cases and Controls

An interviewer contacted potential participants by telephone to verify their eligibility and seek their participation. A computer-assisted telephone interview of participants lasting approximately 30 minutes gathered detailed information on all independent variables (water-use behavior and risk factors for SGA), as well as information on the birth outcome (infant weight, duration of pregnancy). In the event of any discrepancies in case status between a mother's interview and a birth certificate, medical records were checked, and corrections were made based on medical records (this was necessary for 3 cases). The participation rates were 91% for eligible cases and 93% for eligible controls. The median time lag for completing an interview after birth was 9.1 weeks for cases and 9.3 for controls. Interview data were available for a total of 571 cases and 1925 controls.

Exposure Assessment

The chlorination by-products exposure of participants was based on assessment of the chlorination by-products concentration in the tap water at the participant's residence, ingestion of trihalomethanes and haloacetic acids, and multiroute exposure to trihalomethanes expressed as total absorbed dose (μg/d). Because the last trimester is usually considered to be the critical period of exposure for intrauterine growth retardation,[7,25–28] it was the main focus of our exposure assessment. However, exposure during the other trimesters of pregnancy was also evaluated.

Chlorination By-products Data Collection

Sampling campaigns tailor-made for the study were conducted from April 2006 to April 2008. We carried out monthly sampling campaigns for trihalomethanes and haloacetic acids measurements at 46 sites distributed in the 9 surface water systems and 7 sites for the 7 systems supplied by groundwater (one site per system). The strategy used to

select the sampling sites in the surface-water systems was based on system characteristics influencing the spatial variability of chlorination by-products. Each system was divided into subsystems according to water supply infrastructure (supplied directly by the treatment plant or through a rechlorination station or a tank). Then, at least one sampling site was located in each subsystem. Details on sampling and analytic procedures are provided elsewhere.[29] Briefly, water samples were collected according to standard procedures after 5 minutes of flushing and were stored at 4°C. Analyses of the 4 trihalomethanes (chloroform, bromodichloromethane, chlorodibromomethane, and bromoform) and 9 haloacetic acids (monochloroacetic, dichloroacetic, trichloroacetic, monobromoacetic dibromoacetic, tribromoacetic, bromochloroacetic, dibromochloroacetic, and bromodichloroacetic acids) were carried out in accordance with EPA method 524.2[30] and EPA method 552.2,[31] respectively. Internal and external quality controls were conducted during the study.

Chlorination By-products Concentration in Tap Water of Participants' Residences

The strategy to estimate the concentration of chlorination by-products at each participant's residence for each trimester of pregnancy considered the spatial and temporal variability of these compounds. For the spatial aspects, the closest sampling sites located in the participant's subsystem were selected. For the temporal aspect, samples taken within or close to the trimester under study were selected. We estimated chlorination by-product concentration by calculating the mean of all these samples with specific weighting factors (see eAppendix 1 http://links.lww.com/EDE/A560 for details). A validation study was conducted on a subsample of participants (n = 115) during the summer of 2008 to validate the strategy used to spatially assign trihalomethanes and haloacetic acids data (from the sampling campaign) to a participant's residence. For each system included in the validation study, no statistical difference ($P < 0.05$) was found between total trihalomethanes and total of the 9 haloacetic acids levels measured on samples taken at the tap of the residences compared with those estimated with our strategy (data not shown).

Ingestion of Chlorination By-products

The doses (expressed in μg/day) of chlorination by-products absorbed by each participant via ingestion during a typical day of the last trimester of pregnancy were calculated for each trihalomethane and haloacetic acid by multiplying the daily ingested volume from various water sources (ie, cold and hot beverages) with the estimated chlorination by-products concentrations in the ingested water during this trimester. We used information reported by the participants during the interview regarding sources of water consumed (ie, bottled water from private source, cold or hot water from public distribution system) and particular water handling (ie, filtering, boiling, storage in fridge) to adjust the chlorination by-products concentration in water actually ingested. The chlorination by-products concentration in water serving the participant's residence was corrected by applying factors (see factors in eAppendices 2 and 3, http://links.lww.com/EDE/A560) derived from a literature review and researchers' experience.

Assessment of Multiroute Exposure to Trihalomethanes

Intakes from inhalation and dermal absorption (expressed as μg/d) during one typical 24-hour day of the last trimester were calculated and added to the previous estimated ingested dose using a physiologically based toxicokinetic model. The details of this model are described in a previous paper published by our team.[18] This model was adapted for SAS, for each trihalomethane, and took into account the increase of body weight and body surface during pregnancy. Such modeling considers simultaneous multiroute exposure and also allows estimating the specific contribution of each pathway (dermal, ingestion, and inhalation) to total absorbed dose of trihalomethanes. More specifically, simulations accounted for dermal exposure during showering or bathing, and 24-hour inhalation of ambient air (from the bathroom during showering or bathing and from the rest of the house otherwise). Self-reported information on duration and frequency of showering and bathing was used to estimate the average time spent in the bathroom per day. Showering and bathing were regarded as equivalent activities by the model. We used trihalomethanes concentrations in water serving the participant's residence as input for the models. From these water concentrations, volatilization models (based on the work of McKone and Knezovich[32] and integrated into the toxicokinetic modeling) served to predict trihalomethanes concentrations in the air in the bathroom and in the rest of the house. Given uncertainty about reported information on room sizes, the standard parameters fixed by Haddad et al[18] were used for all simulations. Finally, exposure of each participant was expressed as total (ingestion + inhalation + dermal) absorbed dose (μg/day).

Potential Confounders

The following variables documented during the interview were considered: maternal age, maternal ethnicity, maternal education, annual household income, working status, marital status, prepregnancy body mass index, parity, history of chronic disease, medical problem during pregnancy, active and passive maternal smoking throughout the pregnancy, coffee and alcohol consumption, and risky occupational exposure.

Statistical Analysis

We analyzed the data using the SAS software package, version 9.1 (SAS Institute Inc., Cary, NC).[33] Exposure was categorized primarily by quartiles of exposure of the

control groups. Other categorizations were based on current chlorination by-products drinking water standards.[5,6] Most of the analyses considered the effect of total trihalomethanes and total haloacetic acids (sum of the 5 regulated haloacetic acids or sum of the 9 measured haloacetic acids). The sum of brominated trihalomethanes was considered as an index of exposure, as well as the concentration of important species (chloroform, bromodichloromethane, dichloroacetic, and trichloroacetic acids). Separate models were constructed for each family of chlorination by-products (trihalomethanes and haloacetic acids) and for the different routes of exposure to trihalomethanes (ingestion vs. inhalation plus dermal absorption). Odds ratios (ORs) and their 95% confidence intervals (CIs) for association with the various indexes of exposure to chlorination by-products were determined using unconditional logistic regression models while controlling for possible covariates and for the calendar week of birth. All variables associated in univariate analysis with SGA (with $P < 0.15$) were included in the multivariate analyses. Tests for trend were based on a Wald χ^2 test conducted by assigning the median value to each level of a categorical variable and treating the variable on a continuous scale in a logistic regression model.

RESULTS

Characteristics of Participants

Most mothers were white and 25 to 34 years of age (Table 1). Case mothers tended to be nulliparous, poorer, and less educated and had a lower body mass index. Chronic diseases were also more prevalent among case mothers than control mothers. Moreover, occurrence of preeclampsia or hypertension during the pregnancy was more frequent among case mothers. Active as well as passive smoking at home was reported about twice as often by case mothers as by control mothers. Consumption of coffee and alcohol during pregnancy was also more frequent among case mothers. For those who worked or studied, we asked about various occupational risk factors for SGA; these were reported with the same frequency by case and control mothers. Of the 571 case infants, 111 (19%) were low birth weight (<2500 g).

Water Exposure and Chlorination By-products Concentrations

Types of water consumption were very similar between case and control mothers (Table 1) as was the quantity consumed for each type (eAppendix 4, http://links.lww.com/EDE/A560). Shower and bath frequencies were also similar between the 2 groups. Swimming pool attendance, especially indoors, was reported slightly more often by the control mothers (Table 1). Modeled mean concentrations of chloroform, total trihalomethanes, and various species of haloacetic acids at the tap water

TABLE 1. Maternal Characteristics and Environmental Exposures of 571 Cases and 1925 Controls Participating in the Québec City Area Study on Exposure to Chlorination By-products and Term SGA, 2006–2008

	Cases No. (%)	Controls No. (%)
Maternal age (years)		
<25	77 (14)	212 (11)
25–29	222 (39)	811 (42)
30–34	191 (34)	673 (35)
≥35	80 (14)	225 (12)
Missing	1	4
Maternal ethnicity		
White	547 (96)	1859 (97)
Other	24 (4)	66 (3)
Highest education level (years)		
≤12	159 (28)	399 (21)
>12	412 (72)	1523 (79)
Missing	0	3
Annual household income ($Canadian)		
<35,000	133 (23)	288 (15)
35,000–69,999	226 (40)	811 (42)
≥70,000	212 (37)	826 (43)
Marital status		
Married	123 (22)	458 (24)
Not married	448 (78)	1467 (76)
Parity and history of low birth weight (LBW)		
Nulliparous	372 (65)	953 (50)
Parous without history of LBW	168 (29)	909 (47)
Parous with history of LBW	31 (5)	62 (3)
Missing	0	1
Body mass index (kg/m^2)		
<19.8	161 (29)	296 (16)
19.8–25.9	308 (55)	1152 (61)
26.0–29.9	51 (9)	239 (13)
>29.9	41 (7)	202 (11)
Missing	10	36
History of chronic disease		
Yes	59 (10)	144 (7)
No	512 (90)	1781 (93)
Medical problem during pregnancy		
Gestational diabetes	25 (4)	96 (5)
Preeclampsia or hypertension	45 (8)	82 (4)
Uterine bleeding in first trimester	94 (16)	286 (15)
Uterine bleeding in last trimester	28 (5)	74 (4)
Missing	0	1
Coffee consumption during pregnancy		
Yes	304 (53)	909 (47)
No	267 (47)	1016 (53)
Fish consumption during last trimester		
Yes	481 (84)	1612 (84)
No	90 (16)	313 (16)
Mean consumption of portion by week (SD)	0.94 (0.80)	0.91 (0.81)

(*Continued*)

TABLE 1. (*Continued*)

	Cases No. (%)	Controls No. (%)
Maternal smoking (active smoking) during pregnancy		
Never	430 (75)	1644 (85)
Only before the third trimester	22 (4)	91 (5)
Ever	119 (21)	190 (10)
Passive maternal smoking at home		
Yes	95 (17)	134 (7)
No	476 (83)	1791 (93)
Alcohol consumption during pregnancy		
Yes	240 (42)	716 (37)
No	331 (58)	1209 (63)
Employed or studying during pregnancy		
Yes	487 (85)	1674 (87)
No	84 (15)	251 (13)
Occupational exposure[a]		
Stand up >6 hours/day	115 (24)	400 (24)
Work >40 hours/week	76 (16)	254 (15)
Carry heavy loads	97 (20)	339 (20)
Rotating working hours	58 (12)	209 (13)
Exposed to passive smoking	11 (2)	40 (2)
Exposed to chemicals	104 (21)	332 (20)
Water consumption during last trimester		
Plain tap water	191 (34)	700 (37)
Filtered tap water	94 (16)	279 (15)
Let water stand in the fridge	45 (8)	144 (8)
Bottled water	208 (37)	707 (37)
Boiled tap water	3 (1)	6 (0)
Other	13 (2)	55 (3)
Do not drink water	2 (0)	4 (0)
Missing	15	30
Bath frequency (baths per day)[b]		
<1	466 (82)	1591 (83)
1	86 (15)	287 (15)
>1	19 (3)	46 (2)
Shower frequency (showers per day)[c]		
<1	167 (30)	535 (28)
1	361 (64)	1282 (67)
>1	38 (7)	102 (5)
Swimming during last trimester		
Indoor pool	115 (20)	473 (25)
Outdoor pool	149 (26)	543 (28)

[a]For women who worked during pregnancy. 1 to 2 missing values for cases and 8 to 14 for controls.
[b]1 missing value for controls.
[c]5 missing values for cases and 6 for controls.

at participants' residences during last trimester were slightly higher for cases than controls (Table 2). Correlations between chloroform or total trihalomethanes and total haloacetic acid (5 or 9 species) were high (≥0.8). In particular, the Spearman correlation coefficient between total trihalomethanes and total haloacetic acids (5 species) was 0.86 (eAppendix 5, http://links.lww.com/EDE/A560).

TABLE 2. Estimation of Third Trimester CBP Concentrations (μg/L) in Tap Water at Participating Residences of SGA Cases and Controls, Québec City Area, 2006–2008

	Chlorination By-products Concentrations (μg/L)	
	Cases Mean (SD)	Controls Mean (SD)
Trihalomethanes[a]		
Chloroform	43.3 (40.7)	41.1 (39.2)
Bromodichloromethane	4.7 (3.1)	4.7 (2.9)
Chlorodibromomethane	1.3 (1.4)	1.3 (1.4)
Bromoform	0.1 (0.3)	0.1 (0.3)
Brominated trihalomethanes	6.1 (4.1)	6.1 (3.9)
Total trihalomethanes	49.3 (39.8)	47.2 (38.3)
Haloacetic acids		
Monochloroacetic acid[a]	2.4 (1.8)	2.3 (1.7)
Dichloroacetic acid[a]	15.8 (15.6)	14.8 (14.6)
Trichloroacetic acid[a]	18.2 (22.2)	16.4 (20.5)
Bromochloroacetic acid[b]	0.9 (0.8)	0.9 (0.7)
Total Haloacetic acids (5 species)[a]	37.0 (38.3)	34.2 (35.7)
Total Haloacetic acids (9 species)[b]	45.2 (38.7)	42.5 (36.1)

[a]7 missing values for cases and 11 for controls.
[b]10 missing values for cases and 18 for controls.

Risk of Small Size for Gestational Age

No clear dose-response relationship was found between quartiles of chlorination by-products concentrations in tap water of the residences during the last trimester of pregnancy and term SGA (Table 3). However, we found an increase of risk for the highest quartile concentration for trichloroacetic acids and total haloacetic acids (5 or 9 species), as well as when chlorination by-products concentrations were dichotomized using either the current total trihalomethanes standard of 80 μg/L (adjusted OR = 1.5 [95% CI = 1.1–1.9]) or the current total haloacetic acids standard of 60 μg/L (1.4 [1.1–1.9]) (Table 3). The associations with exposure to total trihalomethanes and total haloacetic acids were slightly lower when the 2 families of compounds were included in the same model and adjusted for each other. For example, for total trihalomethanes and total haloacetic acids concentrations above current standards, the ORs were: 1.3 (0.8–1.9) and 1.2 (0.8–1.8), respectively. When adjustment was provided for exposure during the previous 2 trimesters, the association with exposure to total trihalomethanes or total haloacetic acids during the last trimester was similar but with wider confidence intervals (data not shown).

The evaluation of the association accounting for multiroute exposure showed that most of the excess risks were explained by oral ingestion (Table 4). We found a slight excess risk for participants in the fourth quartiles of exposure for ingestion of chloroform, total trihalomethanes, and dichloroacetic and trichloroacetic acids. The highest ORs for the fourth quartile of exposure (in comparison with the first

TABLE 3. Association Between Estimations of Third Trimester CBP Concentrations (μg/L) in Tap Water at Participating Residences and Term SGA, Québec City Area, 2006–2008[a]

	Cases No. (%)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Trihalomethanes (μg/L)[2]			
Chloroform			
Quartile 1 (<15.96)[c]	138 (24)	1.0	1.0
Quartile 2 (15.96–27.26)	133 (24)	1.0 (0.7–1.3)	0.9 (0.7–1.3)
Quartile 3 (27.27–51.07)	141 (25)	1.0 (0.8–1.3)	1.0 (0.8–1.4)
Quartile 4 (>51.06)	152 (27)	1.1 (0.8–1.4)	1.2 (0.9–1.7)
Test for trend			$P = 0.10$
Bromodichloromethane			
Quartile 1 (<2.67)[c]	148 (26)	1.0	1.0
Quartile 2 (2.67–3.94)	150 (27)	1.0 (0.8–1.3)	0.9 (0.7–1.2)
Quartile 3 (3.95–5.89)	124 (22)	0.8 (0.6–1.1)	0.8 (0.6–1.1)
Quartile 4 (>5.89)	142 (25)	1.0 (0.7–1.2)	0.9 (0.7–1.2)
Test for trend			$P = 0.70$
Brominated trihalomethanes			
Quartile 1 (<3.11)[c]	142 (25)	1.0	1.0
Quartile 2 (3.12–5.00)	153 (27)	1.1 (0.8–1.4)	1.0 (0.7–1.3)
Quartile 3 (5.01–9.02)	137 (24)	1.0 (0.7–1.3)	0.9 (0.6–1.2)
Quartile 4 (>9.02)	132 (23)	0.9 (0.7–1.2)	0.9 (0.7–1.2)
Test for trend			$P = 0.46$
Total trihalomethanes			
Quartile 1 (<21.57)[c]	142 (25)	1.0	1.0
Quartile 2 (21.57–34.61)	134 (24)	0.9 (0.7–1.2)	0.9 (0.7–1.3)
Quartile 3 (34.62–57.50)	129 (23)	0.9 (0.7–1.2)	0.9 (0.7–1.3)
Quartile 4 (>57.50)	159 (28)	1.1 (0.9–1.5)	1.2 (0.9–1.7)
Test for trend			$P = 0.07$
>80 μg/L vs. <80 mg/L	105/459	1.2 (1.0–1.6)	1.5 (1.1–1.9)
Haloacetic acids (μg/L)[2]			
Dichloroacetic acids			
Quartile 1 (<5.41)[c]	143 (25)	1.0	1.0
Quartile 2 (5.41–9.71)	142 (25)	1.0 (0.8–1.3)	1.0 (0.7–1.3)
Quartile 3 (9.72–18.18)	120 (21)	0.8 (0.6–1.1)	0.9 (0.7–1.2)
Quartile 4 (>18.18)	159 (28)	1.1 (0.9–1.4)	1.2 (0.9–1.6)
Test for trend			$P = 0.11$
Trichloroacetic acids			
Quartile 1 (<5.03)[c]	136 (24)	1.0	1.0
Quartile 2 (5.03–8.98)	148 (26)	1.1 (0.8–1.4)	1.1 (0.8–1.5)
Quartile 3 (8.99–17.78)	113 (20)	0.8 (0.6–1.1)	0.8 (0.6–1.1)
Quartile 4 (>17.78)	167 (30)	1.2 (0.9–1.6)	1.4 (1.0–1.8)
Test for trend			$P = 0.01$
Total haloacetic acids (5 species)			
Quartile 1 (<12.72)[c]	133 (24)	1.0	1.0
Quartile 2 (12.72–21.35)	150 (27)	1.1 (0.9–1.5)	1.2 (0.9–1.6)
Quartile 3 (21.36–39.59)	119 (21)	0.9 (0.7–1.2)	1.0 (0.7–1.3)
Quartile 4 (>39.59)	162 (29)	1.2 (0.9–1.6)	1.4 (1.0–1.8)
Test for trend			$P = 0.03$
>60 μg/L vs. <60 mg/L	110/454	1.3 (1.0–1.7)	1.4 (1.1–1.9)
Total haloacetic acids (9 species)			
Quartile 1 (<21.35)[c]	137 (24)	1.0	1.0
Quartile 2 (21.35–30.02)	147 (26)	1.1 (0.8–1.4)	1.1 (0.8–1.5)
Quartile 3 (30.03–48.47)	117 (21)	0.9 (0.6–1.1)	0.9 (0.7–1.2)
Quartile 4 (>48.47)	163 (29)	1.2 (0.9–1.5)	1.4 (1.0–1.8)
Test for trend			$P = 0.02$

[a]7 missing values for cases and 11 for controls.
[b]Adjusted for maternal age, calendar week, highest education level obtained, annual household income, body mass index, parity and history of LBW, maternal smoking during pregnancy and passive smoking at home, coffee consumption during pregnancy, alcohol consumption during pregnancy, history of chronic disease, and preeclampsia.
[c]Reference category.

quartile) were found for total trihalomethanes (OR = 1.4 [95% CI = 1.0–9 1.9]), dichloroacetic acid (1.4 [1.1–1.9]), total haloacetic acids (5 species) (1.4 [1.0–1.9]), and total haloacetic acids (9 species) (1.4 [1.1–1.9]). Also, we observed a monotonic dose-response for ingested total haloacetic acids.

DISCUSSION

This study did not find a clear dose-response relationship between exposure to chlorination by-products during last trimester of pregnancy and the risk of SGA, using quartiles of concentrations as exposure categories. However, a slight excess risk was found for exposure above the fourth quartiles of concentrations and above the current drinking water standards. Moreover, using a multiroute exposure assessment, we found an increased risk of SGA for women at the highest quartile of ingestion of various chlorination by-product species, and a small dose-response associated with total haloacetic acids ingestion.

Our results are in line with those of the recent prospective study by Hoffman et al,[34] which found a risk ratio of 2.0 (95% CI = 1.1–3.6) for total trihalomethanes levels >80 μg/L in the third trimester and no clear risk using the quartiles categorization. Other published studies on intrauterine growth retardation and chlorination by-products exposure were summarized recently by Grellier et al (2010).[12] Some very limited evidence was found for exposure to total trihalomethanes, with a small increase when levels were above 80 μg/L (meta-OR = 1.1 [95% CI = 1.0–1.2]). However, important limitations of the reviewed studies were acknowledged by the authors, who recommended large and well-designed epidemiologic studies with improved exposure assessment and control of relevant confounders.[12]

Our study was initiated to address these limitations. In particular, our study used a population-based design and had a high rate of participation that precludes important selection bias in our case and control identification. Sample size was

TABLE 4. Association Between Third Trimester Average Exposure to Chlorination By-products and Term SGA According to Route of Exposure, Québec City Area, 2006–2008[a]

	Route of Exposure	Dose (μg/Day)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Chloroform[2]	Ingestion	Quartile 1 (<1.72)[c]	1.00	1.00
		Quartile 2 (1.72–11.88)	1.1 (0.9–1.6)	1.2 (0.9–1.6)
		Quartile 3 (11.89–34.30)	1.1 (0.9–1.5)	1.1 (0.8–1.5)
		Quartile 4 (>34.30)	1.4 (1.1–1.9)	1.3 (1.0–1.8)
		Test for trend		$P = 0.10$
	Inhalation/dermal	Quartile 1 (<31.89)[c]	1.00	1.00
		Quartile 2 (31.89–60.82)	0.8 (0.6–1.1)	0.8 (0.6–1.1)
		Quartile 3 (60.83–131.19)	1.0 (0.8–1.3)	1.0 (0.8–1.4)
		Quartile 4 (>131.19)	0.9 (0.7–1.2)	0.9 (0.7–1.2)
		Test for trend		$P = 0.81$
	Total pathway	Quartile 1 (<42.24)[c]	1.00	1.00
		Quartile 2 (42.24–80.21)	1.0 (0.7–1.3)	0.9 (0.7–1.2)
		Quartile 3 (80.22–169.81)	1.0 (0.8–1.4)	1.0 (0.7–1.3)
		Quartile 4 (>169.81)	1.1 (0.8–1.4)	1.0 (0.8–1.4)
		Test for trend		$P = 0.67$
Brominated trihalomethanes	Ingestion	Quartile 1 (<0.36)[c]	1.00	1.00
		Quartile 2 (0.36–2.19)	1.3 (1.0–1.7)	1.3 (0.9–1.7)
		Quartile 3 (2.20–6.14)	1.4 (1.1–1.9)	1.3 (1.0–1.8)
		Quartile 4 (>6.14)	1.2 (0.9–1.6)	1.1 (0.8–1.5)
		Test for trend		$P = 0.96$
	Inhalation/dermal	Quartile 1 (<5.85)[c]	1.00	1.00
		Quartile 2 (5.85–10.72)	0.9 (0.6–1.2)	0.8 (0.6–1.1)
		Quartile 3 (10.73–19.60)	0.9 (0.7–1.2)	0.8 (0.6–1.1)
		Quartile 4 (>19.60)	0.9 (0.6–1.1)	0.8 (0.6–1.0)
		Test for trend		$P = 0.18$
	Total pathway	Quartile 1 (<7.55)[c]	1.00	1.00
		Quartile 2 (7.55–14.62)	1.0 (0.8–1.4)	0.9 (0.7–1.3)
		Quartile 3 (14.63–26.08)	1.0 (0.8–1.3)	0.9 (0.7–1.3)
		Quartile 4 (>26.08)	0.9 (0.7–1.2)	0.8 (0.6–1.1)
		Test for trend		$P = 0.11$
Total trihalomethanes	Ingestion	Quartile 1 (<2.72)[c]	1.00	1.00
		Quartile 2 (2.72–16.46)	1.2 (0.9–1.6)	1.2 (0.9–1.7)
		Quartile 3 (16.47–41.18)	1.0 (0.8–1.4)	1.0 (0.7–1.3)
		Quartile 4 (>41.18)	1.5 (1.1–1.9)	1.4 (1.0–1.9)
		Test for trend		$P = 0.05$
	Inhalation/dermal	Quartile 1 (<42.88)[c]	1.00	1.00
		Quartile 2 (42.88–76.88)	0.9 (0.7–1.2)	0.9 (0.7–1.2)
		Quartile 3 (76.89–152.65)	1.0 (0.8–1.3)	1.0 (0.7–1.3)
		Quartile 4 (>152.65)	1.0 (0.7–1.3)	0.9 (0.7–1.3)
		Test for trend		$P = 0.89$
	Total pathway	Quartile 1 (<58.02)[c]	1.00	1.00
		Quartile 2 (58.02–102.44)	1.0 (0.7–1.3)	0.9 (0.7–1.2)
		Quartile 3 (102.45–195.73)	1.0 (0.8–1.3)	1.0 (0.7–1.3)
		Quartile 4 (>195.73)	1.0 (0.8–1.4)	1.0 (0.7–1.4)
		Test for trend		$P = 0.76$
Dichloroacetic acid	Ingestion	Quartile 1 (<1.09)[c]	1.00	1.00
		Quartile 2 (1.09–5.61)	1.1 (0.9–1.5)	1.1 (0.8–1.5)
		Quartile 3 (5.62–14.80)	1.1 (0.8–1.5)	1.0 (0.8–1.4)
		Quartile 4 (>14.80)	1.5 (1.1–1.9)	1.4 (1.1–1.9)
		Test for trend		$P = 0.01$

(*Continued*)

TABLE 4. (*Continued*)

	Route of Exposure	Dose (μg/Day)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Trichloroacetic acid	Ingestion	Quartile 1 (<0.98)[c]	1.00	1.00
		Quartile 2 (0.98–5.11)	1.2 (0.9–1.5)	1.1 (0.8–1.5)
		Quartile 3 (5.12–14.13)	1.2 (0.9–1.5)	1.1 (0.8–1.5)
		Quartile 4 (>14.13)	1.4 (1.1–1.8)	1.3 (1.0–1.8)
		Test for trend		$P = 0.06$
Total haloacetic acids (5 species)	Ingestion	Quartile 1 (<2.61)[c]	1.00	1.00
		Quartile 2 (2.61–13.02)	1.2 (0.9–1.5)	1.1 (0.8–1.5)
		Quartile 3 (13.03–33.40)	1.3 (1.0–1.7)	1.2 (0.9–1.6)
		Quartile 4 (>33.40)	1.5 (1.1–1.9)	1.4 (1.0–1.9)
		Test for trend		$P = 0.02$
Total haloacetic acids (9 species)	Ingestion	Quartile 1 (<4.29)[c]	1.00	1.00
		Quartile 2 (4.29–19.35)	1.2 (0.9–1.5)	1.1 (0.8–1.5)
		Quartile 3 (19.36–43.74)	1.1 (0.8–1.5)	1.1 (0.8–1.4)
		Quartile 4 (>43.74)	1.5 (1.2–2.0)	1.4 (1.1–1.9)
		Test for trend		$P = 0.01$

[a]7 missing values for cases and 11 for controls.
[b]Adjusted for maternal age, calendar week, highest education level obtained, annual household income, body mass index, parity and history of LBW, maternal smoking during pregnancy and passive smoking at home, coffee consumption during pregnancy, alcohol consumption during pregnancy, history of chronic disease, and preeclampsia.
[c]Reference category.

large, with statistical power to detect moderate effects. The best available science was applied to improve exposure assessment. Specifically, the temporal and spatial variability of chlorination by-products, important in the distribution systems under study, were taken into consideration using prospective water-quality monitoring and a strategy to assign chlorination by-products data to participants implemented especially for this study. Also, unlike previous studies addressing multiple pathways of exposure,[34,35] we did not apply the same absorption coefficients for all subjects and instead used a pharmacokinetic model developed to predict the absorbed dose based on the physiological characteristics of our subjects. Likewise, we modeled the air concentration of trihalomethanes within participants' residences according to realistic hypotheses,[18] and our analyses considered all important risk factors for growth retardation, including active and passive smoking.

Nevertheless, despite these improvements, there are study limitations that could have led us to underestimate the possible risk associated with in utero chlorination by-products exposure. Exposure habits were assessed through a questionnaire administered retrospectively, which may have introduced some exposure misclassification when evaluating multiple routes of exposure. The corrective factors used to account for particular water-handling habits were derived from limited studies. Moreover, despite improvements to the internal exposure assessment, our ability to model exposure to various trihalomethanes species remained limited due to the uncertainties associated with the model, especially for trihalomethanes other than chloroform.[18] All these measurement errors could partially explain why the multiple-routes-exposure assessment did not provide higher ORs than the use of the simple concentration of chlorination by-products as a measure of exposure. Also, while SGA assessment is a method for evaluating growth retardation in epidemiologic studies, it is well known that SGA is a proxy for intrauterine growth retardation[36] and can lead to misclassifications of growth-retardation status.

Despite improvements in the study design and exposure assessment in particular, our study did not find a higher odds ratios for chlorination by-products exposure compared with previous studies.[12] Indeed, no increased risk was observed for chlorination by-products concentrations under the current US Environmental Protection Agency guidelines, with the exception of total haloacetic acids (5 species) above the fourth quartile (OR = 1.4 [95% CI = 1.0–1.8]). Laboratory studies on rodents found reproductive effects at high doses, but no studies had evaluated such low levels of exposure. Nevertheless, because more than 600 disinfection by-products have been identified[37] and very few have been evaluated for their reproductive toxicity, it is difficult to exclude possible biologic plausibility based on laboratory studies. Consistency of results among epidemiologic studies and increased relative risks at the highest exposure levels are the most robust arguments for a possible causal link. However, we found some discrepancies in comparison with previous studies. In particular, in comparison with the Hoffman et al study,[34] we did not find any increased risk related to absorbed doses of trihalomethanes with inhalation or dermal absorption. Also, despite some suspicion of a possible increase in risk for

exposure to brominated trihalomethanes in previous studies,[34,38] we did not find such a relationship. Unlike Hoffman et al,[34] our results for trihalomethanes and haloacetic acids were similar to each other. However, the 2 families of compounds were correlated in our own study, and we were not able to separate their individual effect. Nevertheless, in light of the consistent association with the oral route and a monotonic dose-response with haloacetic acids ingestion, our study provides some support regarding the effects of nonvolatile haloacetic acids. A few studies have evaluated the effects of haloacetic acids on SGA, but their results are not consistent.[39,40]

Our results support the hypothesis of a possible effect of chlorination by-products on fetal growth and their effect via the oral route during the last trimester. Present guidelines for chlorination by-products in drinking water are based primarily on their potential carcinogenic risk, and use an annual mean to monitor water concentrations. The results of the present study suggest the importance of taking into account the short-term exposure to chlorination by-products during pregnancy in evaluating and managing the potential public health impact of these exposures.

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eAppendix 1

Exposure assessment

Assessment of the chlorination by-products (CBP) concentration in tap water at the participant's residence: The strategy applied to assign CBP data (from sampling campaigns) to each participant's residence for each pregnancy trimester under study was based on spatial and temporal aspects. For each participant, this assignment was carried out as follows:

Spatial aspect: the participant's residence was positioned geographically in the appropriate system and sub-system using a geographical information system (MapBasic version 8.0 with Platinum Postal Suite$_{TM}$ 2008.3). Thereafter, the two closest sampling sites located in the same residence sub-system were selected. A spatial weighted factor was applied to these two sampling sites according to their distance from the participant's residence:

$$WF_{P1} = 1 - \left(\frac{d_{P1}}{d_{P1} + d_{P2}}\right) \quad (1)$$

$$WF_{P2} = 1 - \left(\frac{d_{P2}}{d_{P1} + d_{P2}}\right) \quad (2)$$

where WF represents the spatial weighted factor, P_1 and P_2 are the sampling sites selected to represent participant exposure to CBPs, and d denotes the distance between each sampling site and the participant's residence (without units: distances were standardized from coordinates).

In the case where a sub-system included a single sampling site, CBP data from the site were used directly to assess the CBP concentration in tap water at the participant's residence located in this sub-system.

Temporal aspect: for each selected sampling site (following the spatial aspect), the CBP concentration measured on each sampling date was considered as representative of the CBP concentration in tap water during a temporal window (denoted TW). The TW of each specific sampling date was calculated considering ± 15 days (for systems with a monthly sampling frequency) or ± 30 days (for systems with a bimonthly sampling frequency) from the date. CBP data from sampling dates for which the TW was included within each participant's pregnancy period were averaged according to the number of days of each TW included in the pregnancy trimester under study. For each selected sampling site, the CBP concentration in tap water during the pregnancy trimester under study was estimated as follows:

$$\left(C_P\right)_{it} = \left(\left(Cm_{D1}\right)_P * \left(\frac{n_{D1}}{n_{TOT}}\right)\right)_{it} + \ldots + \left(\left(Cm_{Dx}\right)_P * \left(\frac{n_{Dx}}{n_{TOT}}\right)\right)_{it} \qquad (3)$$

where *C* is the concentration (μg/L) of the CBP compound *i* estimated for each sampling site *P* (P1 or P2) selected to represent the exposure of the participant to CBPs during the pregnancy trimester *t*, *Cm* is the concentration (μg/L) of the CBP compound *i* measured at each sampling site *P* for each sampling date *D* selected (1 to x), *n* is the number of days of the TW of each sampling date *D* included in the pregnancy trimester *t* and n_{TOT} is the total number of days in the pregnancy trimester *t*.

Finally, the CBP concentration in tap water at the participant's residence during the pregnancy trimester under study was assessed by combining the two aspects (spatial and temporal) and was calculated as follows:

$$E_{it} = \left(C_{P1} * WF_{P1}\right)_{it} + \left(C_{P2} * WF_{P2}\right)_{it} \qquad (4)$$

where *E* is the concentration (μg/L) of the CBP compound *i* estimated during the pregnancy trimester *t* at the tap of the participant's residence and *C* is the concentration (μg/L) of the CBP compound *i* estimated for each sampling site *P1* and *P2* selected to represent the exposure of the participant to CBPs during the pregnancy trimester *t*.

eAppendix 2

Corrective factors applied to concentrations of trihalomethanes (THM) to estimate their ingestion according to type of water handling or devices

Devices/Handling	Percentages of elimination				References
	Chloroform	DCBM	CDBM	Bromoform	
Filtration at home					
Point of Entry					
	86.8	86.8[a]	86.8[a]	86.8[a]	Egorov et al.[1]
Water Source					
Bottled water	100[b]	100[b]	100[b]	100[b]	Savitz et al.[2]

Hot tap water	-160[c]	-70 [c d]	-70 [c d]	-70 [c d]	Dion-Fortier et al.[3]
Filtration at home					
Point of Use					
Not used – RO [1]	48.0[b]	48.0[b]	48.0[b]	48.0[b]	Weinberg et al.[4]*
Used – RO [1]	86.8	86.8[a]	86.8[a]	86.8[a]	Egorov et al.[1]
Not used – AC [2]	99[b]	99[b]	99[b]	99[b]	Weinberg et al.[4]*
Used – AC [2]	86.8	86.8[a]	86.8[a]	86.8[a]	Egorov et al.[1]
Additional handling					
Storage in fridge	13.0	9.6	12.7[e]	12.7[e]	Levesque et al.[5]
Filtering pitcher	85.7	80.3	85.7[e]	85.7[e]	Levesque et al.[5]
Boiling	81.6	84.9	81.8[e]	81.8[e]	Levesque et al.[5]

[a] Percentages were assumed to be the same as in the sole informed case of TCM.

[b] Percentages were assumed to be the same as in the sole informed case of TTHMs.

[c] Negative values indicate an increase rather than a decrease in contamination.

[d] Percentages were assumed to be the same as in the informed case of brominated THMs.

[e] Percentages assumed to be the same as the calculated average for TTHMs.

[1] RO=Reverse osmosis.

[2] AC=Activated carbon.

[*] Only one datum was available for RO and three for AC.

eAppendix 3

Correction factors applied to estimate haloacetic acids (HAA) ingestion according to type of water handling or devices

Devices/Handling	Percentages of elimination						References
	MCAA	**DCAA**	**TCAA**	**BCAA**	**HAA5**	**Other HAAs**[a]	Levesque et al.[5]
Water Source							
Bottled water	100	100	100	100	100	100	
Hot tap water	0	0	0	0	0	0	
Filtration at home							

Point of Use						
RO and AC [1]	8	45	64	59	30	60
Additional handling						
Storage in fridge	0	0	0	0	0	0
Filtering pitcher	2	30	35	33	30	60
Boiling	0	0	0	0	0	0

[a] Difference between HAA9 and HAA5

[1] RO=Reverse osmosis, AC=Activated carbon.

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eAppendix 4

Mean water consumption (l/day) among women during pregnancy by type of water

	Cases n (%)	Water consumption (95%CI)	Controls n (%)	Water consumption (95%CI)
Water consumption during last trimester				
Plain tap water	191 (34)	0.93 (0.83-1.03)	700 (37)	0.94 (0.89-0.99)
Filtered tap water	94 (16)	1.11 (0.94-1.27)	279 (15)	0.96 (0.87-1.05)
Water stand in the fridge	45 (8)	1.05 (0.77-1.32)	144 (8)	1.03 (0.85-1.20)
Bottled water	208 (37)	1.06 (0.95-1.16)	707 (37)	1.01 (0.95-1.07)
Boiled tap water	3 (1)	0.52 (0-1.69)	6 (0)	0.96 (0.09-1.83)
Other	13 (2)	1.25 (0.42-2.09)	55 (3)	0.93 (0.68-1.17)

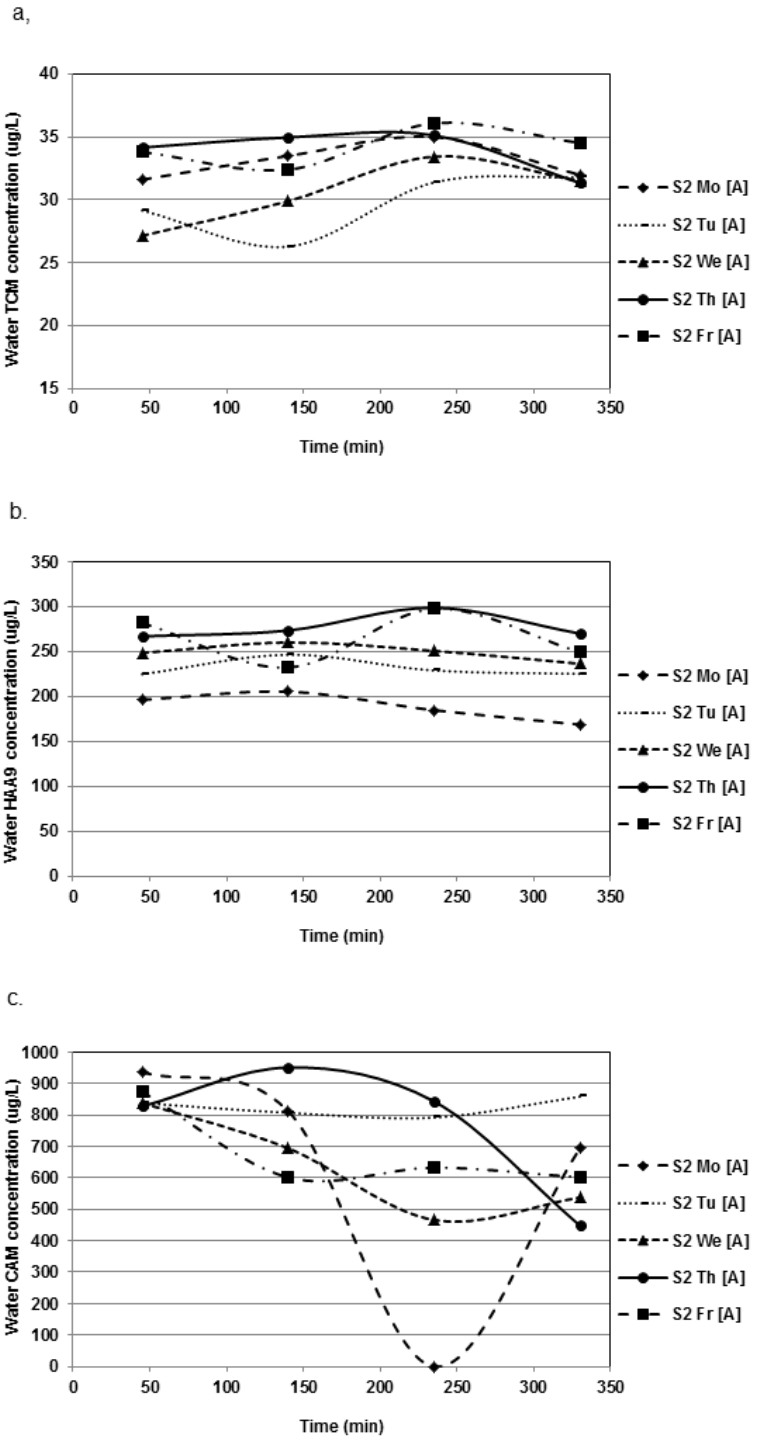
eAppendix 5

Spearman Correlation between different concentrations of chlorination by-products species at the tap of participants' residence

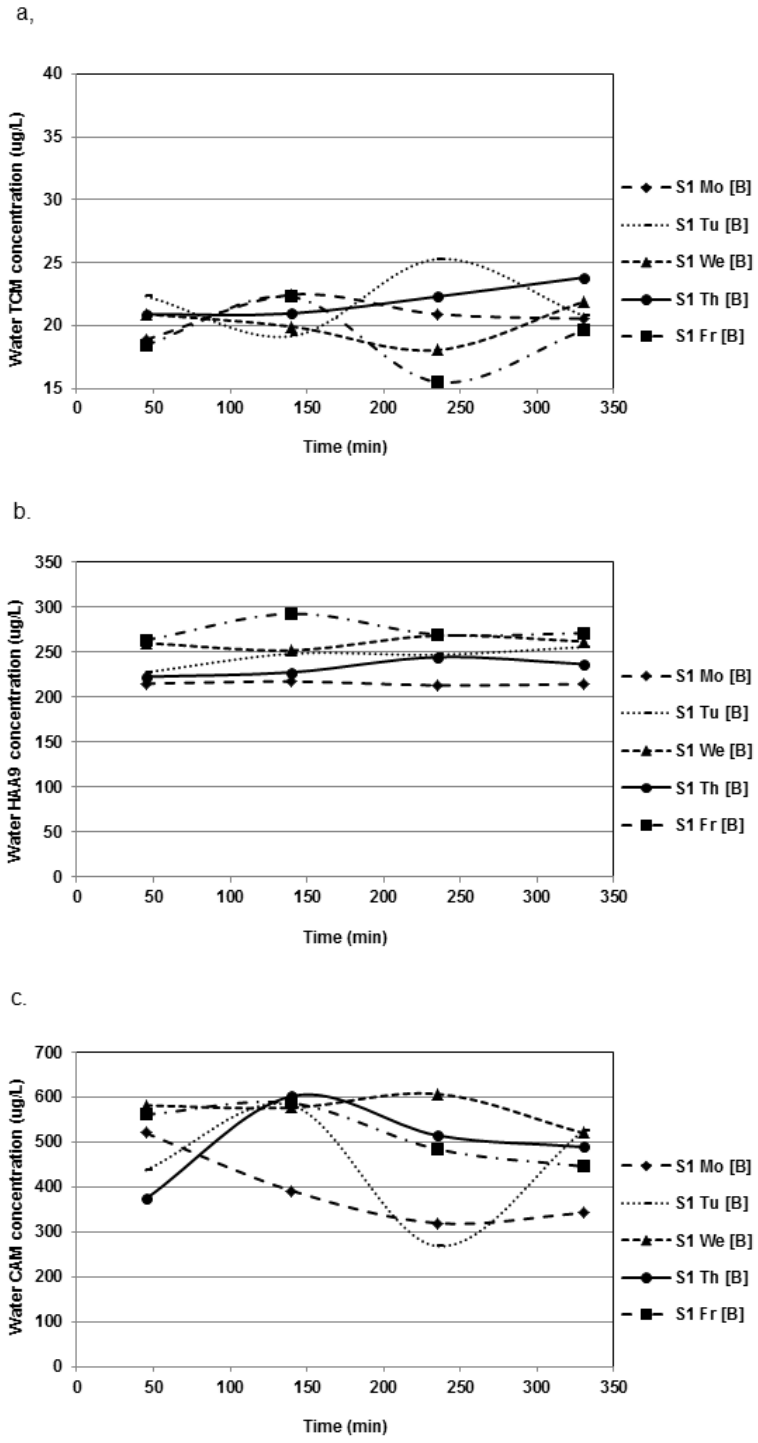
	Bromodichloro-methane	Brominated Trihalomethanes	Total Trihalomethanes	Dichloro-Acetic acid	Trichloro Acetic acid	Total haloacetic acids (5 species)	Total haloacetic acids (9species)
Trihalomethanes							
Chloroform	-0.06	-0.22	0.99	0.84	0.91	0.89	0.87
Bromodichloromethane	-	0.96	0.04	-0.29	-0.20	-0.22	-0.21
Brominated trihalomethanes	-	-	-0.11	-0.43	-0.35	-0.36	-0.34
Total Trihalomethanes	-	-	-	0.91	0.88	0.86	0.85
Haloacetic acids							
Dichloro acetic acid	-	-	-	-	0.9	0.98	0.97
Trichloro acetic acid	-	-	-	-	-	0.98	0.97
Total Haloacetic acids (5 species)	-	-	-	-	-	-	0.99
Total Haloacetic acids (9 species)	-	-	-	-	-	-	-

ANNEXE III

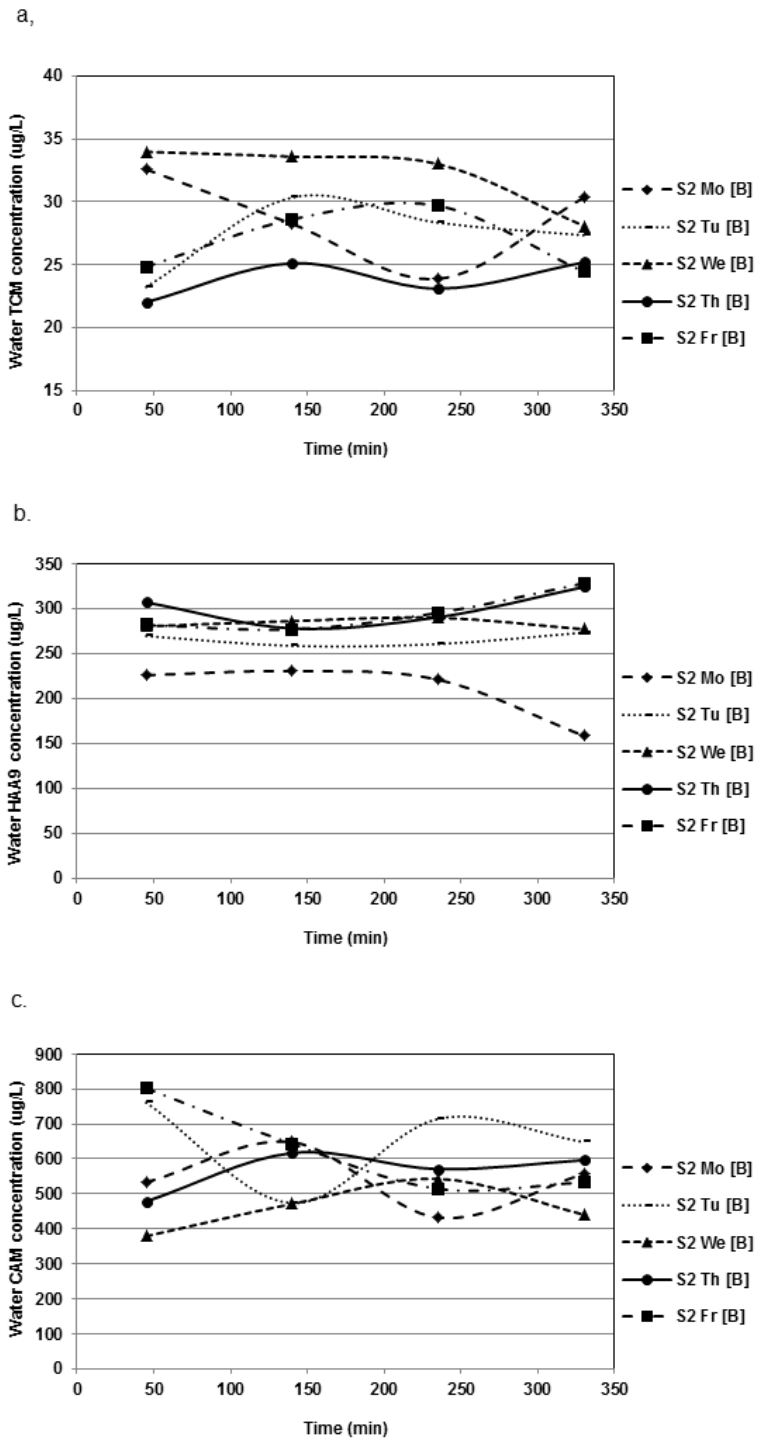
L'annexe III complète la figure 1 de l'article III (cas de la piscine [A] pour la session 2 et de la piscine [B] pour les sessions 1 et 2).



Article III- Figure 1. (Supplementary) Mean DBP water concentrations (µg/L) in the swimming pool [A] during the four sampling periods of each day of the campaign S2 (Time = 0 min → 9a.m). **(a)** TCM; **(b)** HAA9; **(c)** CAM



Article III- Figure 1. (Supplementary) (Continued) Mean DBP water concentrations (µg/L) in the swimming pool [B] during the four sampling periods of each day of the campaign S1 (Time = 0 min → 9a.m). **(a)** TCM; **(b)** HAA9; **(c)** CAM



Article III- Figure 1. (Supplementary) (Continued) Mean DBP water concentrations (µg/L) in the swimming pool [B] during the four sampling periods of each day of the campaign S2 (Time = 0 min → 9a.m). **(a)** TCM; **(b)** HAA9; **(c)** CAM

ANNEXE IV

L'annexe IV, en supplément du tableau 6 de l'Article III, présente le détail des corrélations (coefficient de Pearson) entre les concentrations des différents SPD mesurés dans l'air et dans l'eau des piscines [A] et [B] au cours des deux sessions d'échantillonnage (S1 et S2)

Les tableaux suivant présentent les corrélations entre les concentrations des différents composés (ou groupes de composés) dans l'eau.

A-S1	DCAA	TCAA	BCAA	BDCAA	HAA9	TTHM	MCAM	DCAM	TCAM	CAM
Mean	73.34	95.45	2.59	21.61	193.00	25.42	311.34	14.68	315.04	641.07
SD	12.83	14.19	0.10	1.08	26.31	4.48	56.12	28.59	171.85	166.90
n	60	60	60	60	60	60	20	20	20	20
DCAA	1.0000									
TCAA	* 0.8973	1.0000								
BCAA	0.0207	0.0474	1.0000							
BDCAA	-0.0825	0.0154	0.0462	1.0000						
HAA9	* 0.9683	* 0.9777	0.0413	0.0091	1.0000					
TTHM	0.1209	0.1113	0.0188	-0.2418	0.1092	1.0000				
MCAM	-0.2993	-0.2281	0.1299	-0.0752	-0.2728	0.2502	1.0000			
DCAM	0.1716	0.3817	0.1290	0.2989	0.3054	-0.2887	-0.1919	1.0000		
TCAM	0.1613	-0.0518	0.1136	-0.1201	0.0448	0.4328	0.0617	* -0.6327	1.0000	
CAM	0.0948	-0.0647	0.1828	-0.0977	0.0067	* 0.4803	0.3669	-0.5447	* 0.9420	1.0000

* $p < 0.05$

A-S2	DCAA	TCAA	BCAA	BDCAA	HAA9	TTHM	MCAM	DCAM	TCAM	CAM
Mean	113.25	119.54	1.02	8.41	242.22	32.24	335.13	35.61	368.75	739.49
SD	25.96	23.88	0.15	1.32	49.33	4.81	51.85	136.32	194.23	152.67
n	60	60	60	60	60	59	19	19	19	19
DCAA	1.0000									
TCAA	* 0.9190	1.0000								
BCAA	-0.0881	-0.1029	1.0000							
BDCAA	* 0.3634	* 0.3854	-0.2059	1.0000						
HAA9	* 0.9807	* 0.9778	-0.0986	* 0.4040	1.0000					
TTHM	* 0.0365	-0.0649	* 0.1596	0.0516	-0.0101	1.0000				
MCAM	0.2174	0.2882	0.3037	0.1006	0.2603	0.2005	1.0000			
DCAM	-0.3161	-0.3466	-0.0278	-0.0311	-0.3417	0.2771	0.0440	1.0000		
TCAM	0.0103	-0.0492	-0.3470	-0.3104	-0.0229	* -0.5400	-0.4436	* -0.5170	1.0000	
CAM	-0.1953	-0.2741	-0.3631	-0.3885	-0.2458	-0.3823	-0.1855	0.2501	* 0.6600	1.0000

* $p < 0.05$

B-S1	DCAA	TCAA	BCAA	BDCAA	HAA9	TTHM	MCAM	DCAM	TCAM	CAM
Mean	97.12	124.14	2.72	21.16	245.14	20.72	256.93	9.86	219.25	486.04
SD	12.81	16.79	0.06	1.03	27.49	3.95	55.05	22.50	121.25	101.57
n	60	60	60	60	60	58	20	20	20	20
DCAA	1.0000									
TCAA	* 0.7889	1.0000								
BCAA	* 0.3301	* 0.4478	1.0000							
BDCAA	* -0.7499	* -0.3734	-0.1007	1.0000						
HAA9	* 0.9208	* 0.9657	* 0.4260	* -0.5406	1.0000					
TTHM	0.0759	0.1742	0.2419	0.1502	0.1478	1.0000				
MCAM	-0.1708	-0.0035	0.3279	0.3916	-0.0689	0.1594	1.0000			
DCAM	0.1689	-0.0003	-0.2043	-0.1953	0.0742	0.3612	-0.0059	1.0000		
TCAM	0.2681	0.2234	-0.0489	* -0.4899	0.2419	* -0.6094	-0.3665	* -0.5528	1.0000	
CAM	0.2649	0.2647	0.0740	-0.4158	0.2678	* -0.5534	0.1032	-0.4416	* 0.8727	1.0000

* $p < 0.05$

B-S2	DCAA	TCAA	BCAA	BDCAA	HAA9	TTHM	MCAM	DCAM	TCAM	CAM
Mean	126.95	133.57	0.94	9.05	270.51	27.96	310.68	13.04	244.05	567.76
SD	18.48	25.86	0.26	1.15	43.83	4.37	95.21	20.09	168.96	111.87
n	60	60	60	60	60	58	20	20	20	20
DCAA	1.0000									
TCAA	* 0.9279	1.0000								
BCAA	* -0.6161	* -0.5274	1.0000							
BDCAA	* 0.4027	* 0.3156	* -0.4794	1.0000						
HAA9	* 0.9760	* 0.9864	* -0.5777	* 0.3794	1.0000					
TTHM	-0.1739	-0.2295	0.1238	0.1796	-0.2033	1.0000				
MCAM	0.3643	0.3857	* -0.5951	0.0119	0.3803	-0.3953	1.0000			
DCAM	0.1334	0.0146	-0.0826	0.2385	0.0725	0.1027	0.3326	1.0000		
TCAM	-0.2975	-0.2695	0.3292	-0.2902	-0.2926	0.1099	* -0.6661	* -0.7869	1.0000	
CAM	-0.1153	-0.0761	-0.0241	-0.3852	-0.1052	-0.1516	-0.0952	* -0.7258	* 0.8021	1.0000

* $p < 0.05$

Les tableaux suivant présentent les corrélations entre les concentrations des différents composés (ou groupes de composés) dans l'air. (Les indices _L et _H indiquent respectivement les valeurs correspondant à des mesures effectuées à 30 cm et 150 cm au dessus de la surface de l'eau)

A-S1	**TCAM**	**TCM**	**DCBM**	**TTHM**	**TCM_L**	**DCBM_L**	**TTHM_L**	**TCM_H**	**DCBM_H**	**TTHM_H**
Mean	243.33	112.43	1.38	113.81	113.47	1.38	114.85	111.40	1.37	112.77
SD	46.90	13.00	0.34	13.16	14.47	0.37	14.70	14.65	0.44	14.77
n	9	20	20	20	20	20	20	20	20	20
TCAM	1									
TCM	0.6197	1								
DCBM	0.5198	* 0.4720	1							
TTHM	0.6252	* 0.9997	* 0.4917	1						
TCM_L	* 0.7366	* 0.8917	* 0.4778	* 0.8929	1					
DCBM_L	* 0.7087	* 0.5252	* 0.7940	* 0.5390	* 0.5927	1				
TTHM_L	* 0.7410	* 0.8914	* 0.4905	* 0.8929	* 0.9998	* 0.6089	1			
TCM_H	0.3590	* 0.8943	0.3658	* 0.8927	* 0.5949	0.3467	* 0.5946	1		
DCBM_H	0.2959	0.2804	* 0.8608	0.2989	0.2327	0.3741	0.2386	0.2679	1	
TTHM_H	0.3650	* 0.8952	0.3884	* 0.8941	* 0.5968	0.3549	* 0.5967	* 0.9996	0.2954	1

* $p < 0.05$

A-S2	**TCAM**	**TCM**	**DCBM**	**TTHM**	**TCM_L**	**DCBM_L**	**TTHM_L**	**TCM_H**	**DCBM_H**	**TTHM_H**
Mean	199.00	145.52	1.74	147.26	182.19	2.23	184.42	113.24	1.29	114.53
SD	79.37	42.35	0.57	42.84	64.07	0.98	64.93	43.74	0.57	44.22
n	10	20	20	20	18	18	18	20	20	20
TCAM	1									
TCM	0.5517	1								
DCBM	* 0.6322	* 0.8592	1							
TTHM	0.5537	* 0.9999	* 0.8627	1						
TCM_L	0.3643	* 0.8763	* 0.8279	* 0.8771	1					
DCBM_L	0.3795	* 0.7222	* 0.8870	* 0.7256	* 0.8667	1				
TTHM_L	0.3651	* 0.8757	* 0.8304	* 0.8766	* 0.9999	* 0.8705	1			
TCM_H	* 0.7803	* 0.7058	* 0.5570	* 0.7051	0.3141	0.1986	0.3129	1		
DCBM_H	* 0.8955	* 0.5382	* 0.5845	* 0.5398	0.2577	0.1513	0.2566	* 0.8284	1	
TTHM_H	* 0.7833	* 0.7052	* 0.5586	* 0.7045	0.3140	0.1984	0.3129	* 0.9999	* 0.8325	1

* $p < 0.05$

B-S1	TCAM	TCM	DCBM	TTHM	TCM_L	DCBM_L	TTHM_L	TCM_H	DCBM_H	TTHM_H
Mean	145.00	110.26	1.25	111.51	111.61	1.28	112.89	110.86	1.23	112.08
SD	52.76	25.53	0.42	25.93	25.32	0.44	25.72	28.01	0.48	28.46
n	10	19	19	19	19	19	19	18	18	18
TCAM	1									
TCM	0.4053	1								
DCBM	0.5567	* 0.9456	1							
TTHM	0.4080	* 0.9999	* 0.9473	1						
TCM_L	0.3201	* 0.9424	* 0.9002	* 0.9425	1					
DCBM_L	0.5136	* 0.8523	* 0.9240	* 0.8543	* 0.9104	1				
TTHM_L	0.3239	* 0.9423	* 0.9019	* 0.9424	* 0.9999	* 0.9133	1			
TCM_H	* 0.7500	* 0.9510	* 0.8931	* 0.9508	* 0.7786	* 0.7029	* 0.7785	1		
DCBM_H	* 0.7189	* 0.9141	* 0.9315	* 0.9151	* 0.7689	* 0.7159	* 0.7691	* 0.9434	1	
TTHM_H	* 0.7499	* 0.9513	* 0.8946	* 0.9511	* 0.7792	* 0.7038	* 0.7790	* 0.9999	* 0.9452	1

* p < 0.05

B-S2	TCAM	TCM	DCBM	TTHM	TCM_L	DCBM_L	TTHM_L	TCM_H	DCBM_H	TTHM_H
Mean	132.50	67.97	0.83	68.80	71.90	0.92	72.82	64.19	0.73	64.92
SD	25.50	19.35	0.30	19.50	24.39	0.47	24.55	21.66	0.37	21.96
n	8	20	20	20	20	20	20	19	19	19
TCAM	1									
TCM	* 0.8927	1								
DCBM	0.4751	* 0.5005	1							
TTHM	* 0.8896	* 0.9999	* 0.5119	1						
TCM_L	* 0.9273	* 0.8729	0.3321	* 0.8712	1					
DCBM_L	* 0.8026	0.2314	* 0.8039	0.2420	0.3122	1				
TTHM_L	* 0.9269	* 0.8719	0.3456	* 0.8704	* 0.9998	0.3296	1			
TCM_H	0.4758	* 0.8261	* 0.5348	* 0.8279	* 0.4444	0.0623	0.4429	1		
DCBM_H	0.0688	* 0.5425	* 0.6125	* 0.5476	0.1513	0.0241	0.1509	* 0.8183	1	
TTHM_H	0.4695	* 0.8239	* 0.5377	* 0.8257	0.4408	0.0618	0.4393	* 0.9999	* 0.8238	1

* p < 0.05

ALL	TCAM	TCM	DCBM	TTHM	TCM_L	DCBM_L	TTHM_L	TCM_H	DCBM_H	TTHM_H
Mean	180.81	109.03	1.30	110.33	118.28	1.44	119.71	100.10	1.16	101.26
SD	69.50	38.69	0.53	39.15	53.12	0.76	53.78	35.32	0.53	35.74
n	37.00	79	79	79	77	77	77	77	77	77
TCAM	1									
TCM	* 0.5435	1								
DCBM	* 0.6124	* 0.8695	1							
TTHM	* 0.5451	* 0.9999	* 0.8728	1						
TCM_L	* 0.4218	* 0.9243	* 0.8142	* 0.9244	1					
DCBM_L	* 0.4697	* 0.7777	* 0.8890	* 0.7805	* 0.8646	1				
TTHM_L	* 0.4228	* 0.9240	* 0.8168	* 0.9241	* 0.9999	* 0.8681	1			
TCM_H	* 0.6540	* 0.8148	* 0.6971	* 0.8147	* 0.5237	* 0.4042	* 0.5230	1		
DCBM_H	* 0.6725	* 0.6341	* 0.7445	* 0.6367	* 0.3835	* 0.3370	* 0.3835	* 0.8125	1	
TTHM_H	* 0.6558	* 0.8144	* 0.6997	* 0.8143	* 0.5231	* 0.4044	* 0.5224	* 0.9999	* 0.8175	1

* p < 0.05

Les tableaux suivant présentent les corrélations entre les concentrations des différents groupes de composés dans l'air et celles dans l'eau. (L'indice « a » - chaque ligne - indique les concentrations dans l'air)

A-S1		TTHM	HAA9	CAM
	Mean	25.42	193.00	641.07
	SD	1.98	23.27	100.25
	n	10	10	10
TCAMa				
Mean	243.33	-0.6026	* -0.7193	0.4075
SD	46.90			.
n	9			
	Mean	25.42	193.00	641.07
	SD	3.04	24.69	166.90
	n	20	20	20
TCMa				
Mean	112.43	* -0.4623	-0.1460	0.1898
SD	13.00			
n	20			
DCBMa				
Mean	1.38	* -0.4591	-0.4859	-0.2431
SD	0.34			
n	20			
TTHMa				
Mean	113.81	* -0.4683	-0.1566	0.1813
SD	13.16			
n	20			

* $p < 0.05$

A-S2		TTHM	HAA9	CAM
	Mean	32.25	242.22	737.22
	SD	2.42	33.60	123.62
	n	10	10	10
TCAMa				
Mean	199.00	0.3296	-0.6020	0.5200
SD	79.37			.
n	10			
	Mean	32.25	242.22	739.49
	SD	2.63	35.34	152.67
	n	20	20	19
TCMa				
Mean	145.52	0.1943	0.0043	0.1491
SD	42.35			
n	20			
DCBMa				
Mean	1.74	0.2688	-0.1519	0.0469
SD	0.57			
n	20			
TTHMa				
Mean	147.26	0.1956	0.0022	0.1480
SD	42.84			
n	20			

* $p < 0.05$

B-S1		TTHM	HAA9	CAM
	Mean	20.47	245.14	486.04
	SD	1.75	22.46	79.26
	n	10	10	10
TCAMa				
Mean	145.00	0.1310	-0.4690	-0.6003
SD	52.76			.
n	10			
	Mean	20.75	245.14	486.04
	SD	2.17	22.79	101.57
	n	20	20	20
TCMa				
Mean	110.26	-0.2060	0.1054	0.1418
SD	25.53			
n	19			
DCBMa				
Mean	1.25	-0.0038	-0.0151	-0.0259
SD	0.42			
n	19			
TTHMa				
Mean	111.51	-0.2028	0.1035	0.1392
SD	25.93			
n	19			

* $p < 0.05$

B-S2		TTHM	HAA9	CAM
	Mean	27.80	270.51	567.76
	SD	3.06	36.98	90.52
	n	10	10	10
TCAMa				
Mean	132.50	-0.2652	-0.1267	0.1664
SD	25.50			.
n	8			
	Mean	27.80	270.51	567.76
	SD	3.73	38.64	111.87
	n	20	20	20
TCMa				
Mean	67.97	-0.1721	0.2295	-0.0110
SD	19.35			
n	20			
DCBMa				
Mean	0.83	-0.0132	0.0803	-0.1237
SD	0.30			
n	20			
TTHMa				
Mean	68.80	-0.1710	0.2290	-0.0128
SD	19.50			
n	20			

* $p < 0.05$

ANNEXE V

L’annexe V dresse la liste des principales communications qui ont contribué à la valorisation scientifique de ces travaux de doctorat.

COMMUNICATIONS ORALES

• **Ier colloque printanier du RRSE.** *Apports de la modélisation PBPK à l'étude de l'exposition aux sous-produits de désinfection : étude comparative de la contribution de différentes sources à l'exposition au chloroforme.* Catto Cyril, Charest-Tardif Ginette, Tardif Robert. Mai 2006 **[Abstract primé]**

• **ISEE/ISEA. International conference on environmental epidemiology and exposure. AFSSET Paris 2006.** *Modeling exposure to THMs : a multidisciplinary approach integrating environmental occurrence and toxicokinetic profile.* Catto Cyril, Haddad Sami, Levallois Patrick, Marcoux Sylvie, Rodriguez Manuel et Tardif Robert. 2 au 6 Septembre 2006. **[Mention d'honneur catégorie étudiant]**

• **Association pour la Recherche En Toxicologie. Colloque 2007.** « Toxicocinétique des xénobiotiques dans l'évaluation des risques pour l'homme et l'environnement ». *Reconstruction et analyse de l'exposition en piscine au chloroforme par utilisation de la modélisation toxicocinétique à base physiologique.* Catto Cyril, Charest-Tardif Ginette, Rodriguez Manuel, Tardif Robert. Paris, 4 et 5 Juin 2007.

• **X2009 - 6th International Conference on Innovations in Exposure Assessment.** *Improving exposure assessment for disinfection by-products by integrating environmental and toxicokinetics modeling for epidemiological purposes: accounting for short-term variations in drinking water concentrations?.* Catto Cyril, Charest-Tardif Ginette, Rodriguez Manuel, Tardif Robert. Boston, M.A. Aout 2009**.**

• **Rencontres Scientifiques de l'ANSES - "Exposition aux contaminants de l'environnement".** L'*exposition aux sous-produits de désinfection en piscine : Perspectives pour l'intégration de modèles d'occurrence environnementale à des modèles toxicocinétiques.* Tardif Robert, Catto Cyril et Rodriguez Manuel. Cité internationale Paris 14 (France), 6 Décembre 2010.

COMMUNICATIONS PAR AFFICHES

• **Société de Toxicologie du Canada. 38eme Colloque annuel « impact des substances toxiques sur la santé des enfants ».** *Modélisation de l'exposition aux trihalométhanes par intégration de données d'occurrence environnementale à une approche PBPK. Conceptualisation.* Catto Cyril, Haddad Sami, Levallois Patrick, Marcoux Sylvie, Rodriguez Manuel et Tardif Robert. 5 et 6 décembre 2005.

• **Colloque annuel Centre TOXEN 2005.** *Modélisation de l'exposition aux trihalométhanes par intégration de données d'occurrence environnementale à une approche PBPK. Conceptualisation.* Catto Cyril, Haddad Sami, Levallois Patrick, Marcoux Sylvie, Rodriguez Manuel et Tardif Robert. 9 décembre 2005. **[Affiche primée]**

• **Gordon Research Conference "Drinking Water Disinfection By-Pproducts : Integrating Occurrence and Formation , Exposure, Toxicity and Epidemiology".** *Modeling exposure to THMs : a multidisciplinary approach integrating environmental occurrence and toxicokinetic profile.* Catto Cyril, Ginette Charest-Tardif Haddad Sami, Levallois Patrick, Marcoux Sylvie, Rodriguez Manuel et Tardif Robert. 13 au18 Août 2006.

• **Canadian Society for Epidemiology and Biostatistics 2007 Conference "Epidemiology in a changing world".** *Chlorination By-products and intra-uterine growth retardation.* Levallois Patrick, Marcoux Sylvie, Gingras Suzanne, Legay Christelle, Rodriguez Manuel, Catto Cyril et Tardif Robert. Calgary, 28 au 31 Mai 2007.

• **Rencontres Scientifiques de l'AFSSET - "Eaux et Santé".** *Exposition aux sous-produits de désinfection en piscine et modélisation TCBP : Analyse des contributions des voies respiratoire et percutanée à l'exposition au chloroforme.* Tardif Robert, Catto Cyril et Rodriguez Manuel.. Lyon (France), 10 et 11 Décembre 2008.

• **IVeme colloque printanier du RRSE.** *Improving exposure assessment for disinfection by-products by integrating environmental and toxicokinetics modeling for epidemiological purposes: accounting for short-term variations in drinking water concentrations ?.* Catto Cyril, Charest-Tardif Ginette, Rodriguez Manuel, Tardif Robert. Juin 2009 **[Abstract primé]**

• **ISES 2009 Conference: "Transforming exposure science in the 21st century".** *Exposure assessment to chlorination cy-products in a case-control study on reproductive outcomes.* Levallois Patrick, Marcoux Sylvie, Gingras Suzanne, Legay Christelle, Catto Cyril, Charest-Tardif Ginette, Rodriguez Manuel, Tardif Robert et Marcoux Sylvie. Minneapolis, 2 au 5 Novembre 2009.

• **IUTOX 2010 – XII International Congress of Toxicology.** *Modeling the impact of short-term variations in trihalomethane drinking water levels on internal exposure*. Catto Cyril, Rodriguez Manuel, Lavoué Jérôme, Charest-Tardif Ginette et Tardif Robert. Barcelone, 19 au 23 juillet 2010.

• **ISES/ISEE 2010 Joint Conference: "Technology, Environmental sustainability and Health".** *Contributions of dermal and pulmonary routes to chloroform exposure in swimming pools: a comparison between three estimation approaches*. Catto Cyril, Charest-Tardif Ginette et Tardif Robert. Seoul, 28 aout au 1 septembre 2010. **[ISES Student travel award – Bourse d'aide à la diffusion des résultats IRSPUM]**

RAPPORT DE FIN DE CONTRAT

• **2010.** Rapport scientifique final pour le projet intitulé « *Développement d'une méthodologie pour l'évaluation de l'exposition des populations en piscine aux sous-produits de désinfection de l'eau par intégration des données d'occurrence environnementale à des modèles toxicocinétiques à base physiologique* ». **AFSSET** / **EST-2007-79** (Programme : Environnement-Santé-Travail). Tardif Robert, Catto Cyril et Rodriguez Manuel.