# International Master of Public Health

***Master international de Santé Publique***

# ROLE OF DRINKING WATER CHLORINATION BY- PRODUCTS (CBPs) ON THE DEVELOPMENT OF CHILDHOOD AIRWAYS INFLAMMATORY CONDITIONS


**Presented by**

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**List of Acronyms**

| | |
|---|---|
| BDCM | Bromodichlormethane |
| CBPs | Chlorination by-products |
| $Cl_2$ | Chlorine |
| $CHCl_3$ | Chloroform |
| $CHBr_3$ | Bromoform |
| $CHCl_2Br$ | Bromodichlormethane |
| $CHClBr_2$ | Disbromochloromethane |
| DBPs | Disinfection by-products |
| DCP | 1,1 dichloropropanone |
| ERV | Expiratory reserve volume |
| ESRI | Environmental Systems Research Institute |
| FEV1 | Forced expired volume in 1 |
| $FEF_{25}$ | Forced expiratory flow at 25% |
| $FEF_{50}$ | Forced expiratory flow at 50% *(the rate of airflow recorded in measurements of forced vital opacity)* |
| FVC | Forced Vital Capacity |
| HAAs | Haloacetic acids |
| HANs | Haloacetonitriles |
| GIS | Geographical Information System |
| HKs | Haloketones |
| $NCl_3$ | Nitrogen Trichloride |
| INSERM | Institut national de la santé et de la recherche médicale |
| IARC | International Agency for Research on Cancer |
| RV | Residual volume |
| PEFR | Peak expiratory flow rate |
| ROS | Reactive Oxygen species |
| THMs | Trihalomethanes |
| TLC | Total Lung Capacity |
| TCP | 1,1,1-trichloropropanone |
| WHO | World Health Organisation |
| WGS | Wold Geographical System |
| WQM station | Water Quality Monitoring station |

## 1. GENERAL INTRODUCTION

Water chlorination has been successfully introduced in the early years of the 20$^{th}$ century as one of the methods to prevent waterborne diseases and many developed countries have adopted these means to provide “safe” drinking water. In the aspect of chemical reaction, during chlorination process, natural organic matters present in raw water supplies react and may produce chlorination by-products (CBPs) (Kim et al, 2002). Among the most widely occurring by-products are trihalomethanes (THMs), haloacetic acids (HAAs), haloacetonitriles (HANs), and haloketones (HKs) (WHO,2000; Krasner et al., 1989; Nieuwenhuijsen et al., 2000). THMs consist of four main substances, chloroform ($CHCl_3$), bromoform ($CHBr_3$), bromodichlormethane ($CHCl_2Br$), and disbromochloromethane ($CHClBr_2$) (WHO, 2000). Chloroform and bromodichloromethane are classified as possible carcinogenic to human while dibromochloromethane and bromoform could not be classified as carcigenicity (IARC, 1999). In 2000, the World Health Organization (WHO) has ratified a guideline to limit the maximum of the THMs in the treated water at 100µg/litre (WHO, 2000).

### 1.1 Chlorination by-products (CBPs) and Trihalomethanes (THMs) Exposure

Several exposure studies concluded that the main pathways of THMs exposures to general population are inhalation, ingestion, and skin absorption. These contacts were exposed mainly to drinking water during the household and leisure activities including showering, bathing, washing or at the pool setting (Gordon et al., 2006; Nuckol et al., 2005; Whitaker et al., 2003).

Clifford P et al. (1996) conducting an exposure assessment of ingestion, inhalation and dermal exposure to chloroform and trihalomethanes from tap water concluded that approximate equivalent amounts of volatile contaminants from water can enter the body by these three different routes typically from the activities of drinking and bathing.

In addition, CBPs exposures have been commonly examined by many epidemiological and toxicological studies to explore human health adverse effects. Most health adverse effects reported to be associated with cancers, pregnancy outcome, and birth untoward outcomes (Morris et al., 1992; Morris et al., 1995; Villanueva et al., 2007a; Jo et al., 1990; Reif et al., 1996; Hinckley et al., 2005).

Among those studies that concerned cancer association, addressed that CBPs exposure are associated with bladder, rectal and colon cancers (Cantor et al., 1999; Cantor et al., 1987). A review pooled of six case-control studies concluded the strength of the risk of bladder cancer is increased with long-term exposure to CBPs at critical levels and it is currently observed in many industrialized countries (Villanueva et al, 2004). However, other primary studies have not been consistent in indicating the association of THMs and colon cancers (Young et al., 1987; Lawrence et al., 1984).

Few epidemiological studies indicated a potential important relation between exposures to THMs and related later stage of pregnancy and birth outcome (Dodds et al., 1999; Gallagher et al., 1998).

Hence a critical review on weight of evidence for an association between adverse reproductive and developmental effects and exposure to CBPs addressed that the analysis were found inconsistent. This review recommended that in order to determine whether an association exists between adverse reproductive and developmental effects and exposures to DBP, studies must consider the THMs concentrations and the quantity of the water actually consumed (Carol et al., 2001).

1.2 Respiratory diseases and risk factors among children

The increase in prevalence of allergic and inflammation of respiratory tracts among children has been reported over the last few decades particularly in developed countries (Anderson et al., 2007; Aser et al., 2006). According to a WHO estimation (2005), 300 million people suffer from asthma and 255 000 people died of asthma. This disease considered as one of common diseases among infant and children.

The epidemiological and toxicological explanation of risk factor associations to those respiratory chronic diseases and asthma among infants and children are still complex. It has been suggested that both genetic predisposition and environmental risk factors might be involved. Regarding environmental exposures, studies suggested that respiratory chronic diseases, in particular to asthma, were associated with exposures to chemical substances such as particulate matter in air pollution, tobacco, or CBPs (Bougault et al., 2009; Uyan et al., 2009; Bernard et al, 2008; Bernard et al, 2007; Nystad et al., 2003).

A prospective study on early life risk factors for current wheeze, asthma, and bronchial hyper responsiveness illustrated that early exposure to allergenic factors of infants under four years-old was a risk factor for asthma in ten years-old (Hasan et al., 2005). It precisely indicated that the onset of asthma at ten years-old was associated with allergies already present at one-two years-old (eczema or food allergies) and at four years-old (eczema, food allergies or rhinitis).

A review conducted to investigate susceptibility factors linked to asthma indicated that changes in life style and environmental exposure might explain, in part, the increase in the prevalence of asthma (Karin et al., 2006). It also stated that duration of exposure, genetic or lifestyle should not be considered independently. Another review investigating the association for asthma and atopic diseases also suggested the important role and the interaction of environmental exposure and genetic predisposition (Hoffjan et al., 2003).

**1.3 Oxidative stress and airway mechanisms**

General explanation of oxidative stress is referred to *"an imbalance between the production of reactive oxygen and a biological system's ability to readily detoxify the reactive intermediates or easily repair the resulting damage"* (Wikipedia). Concerning to lung function, oxidizing agent or oxidants are compounds that transfer oxygen atoms or gain electron in a chemical reaction.

Prolonged oxidant exposure can lead to impaired anticrobial defenses and alter macrophage function in the lung. The reactive oxygen species (ROSs) which are small molecules that include oxygen ions, free radicals, and peroxides; ROSs form as a by-products oxygen metabolism and can increase dramatically in times of environmental stress (Ciencewicki et al., 2008). The reactive oxygen species cause inflammation of the airways which itself is a source of reactive oxygen species and self-perpetuates the cascade of inflammatory phenomena leading to the development of chronic respiratory pathologies (Cardoso et al., 2006).

A study concluded that oxidative stress is a feature of most airways diseases, particularly when inflammation is prominent (Bowler and James, 2002). Several studies stressed that oxidative stress increasingly play important role in triggering asthma (Ciencewicki et al., 2008; Smith et al., 1997; Calhoun et al., 1992; Kelly et al., 1987). In this respect, the airways of infants whose epithelium reaches maturity around six-eight years-old (Miller, 2004) seem to be particularly vulnerable to oxidative stress.

Recent observations on the relation between rhinitis and asthma support the hypothesis of a common psychopathological mechanism, an imbalance in the activation of the lymphocytes T helper 1 and 2 cells. This imbalance could be influenced by environmental exposure at a very early age (Karin et al., 2006). Oxidative stress could be a major part in these processes, especially in infants. However, little is known about the cellular and molecular mechanisms involved and the relative contribution of exposure to the various sources of reactive oxygen species, in particular CBPs from water treatment, needs to be clearly determined.

**1.4 Chorine, chlorination by-products (CBPs) inhalation and respiratory tracts**

High concentrations of chlorine exposures were well reported by many studies both in human and animal experiments as an irritant chemical to respiratory inflammation including asthma in the occupational or accidental exposures (Medina et al., 2004; Zock et al., 2002, Martin et al., 2002). It was additionally illustrated that repeated-low concentration of chlorine exposure was associated with the development of persistent airflow limitation (Henneberger et al., 1996; Gautrin et al., 1999).

Regarding CBPs exposures and respiratory tracts, many studies addressed the association and particularly focused on the chlorinated swimming pools setting. For example, several studies performed by Bernard et al. observed possible respiratory adverse effects in association to the CBPs in swimming pool setting mostly for children between four to ten years-old. One of his studies suggested that repeated irritation of the bronchial epithelium by CBPs, particularly Nitrogen Trichloride ($NCl_3$), encourages the penetration of allergens, which might explain the increase in the number of allergies and atopic diseases (Bernard A et al., 2003).

Besides, other studies stressed that prevalence of childhood asthma and chlorinated indoor and outdoor swimming pools are associated with airways changes, along with other factors, so that this source of exposure seems to predispose children to the development of asthma and recurrent bronchitis. The authors propose that the increasing exposure of children to CBPs in indoor pools might be an important cause of the rising incidence of childhood asthma and allergic diseases in industrialized countries (Bernard et al., 2007; Nickmilder et Bernard , 2007; Bernard et al., 2003).

A recent review conducted by Karin Yvonne et al in 2007 on the use of chlorine in swimming pool environment resulting chlorination by-products and potential effects on allergic and respiratory health, indicated that the main health effects stressed in the their evaluated studies resulted due to high dose or cumulative exposures to chlorination by-products. More particular, the review stated the primary studies posed the hypothesis that children who more frequently attend of chlorinated pools could be one important factor for rising frequencies of asthma and allergic diseases in industrialised countries (Karin et al., 2007).

Now Nitrogen Trichloride ($NCl_3$), one important CBP found in swimming pool air, is insoluble in water, highly volatile and is freely released. This situation is not likely equivalent for drinking water indoor environments such as home. Then it might be not be appropriate to generalize this swimming pool setting. At home, showering, bath taking, food making or dish washing in the sink seem to be the potential contacts to THMs, HAAs, haloacetonitriles, and haloketones that also need to be considered.
Furthermore, many studies stressed the inhalation exposure of THMs and other CBPs as a critical pathway compared to ingestion and skin absorption (Nuckols et al., 2005; Nieuwenhuijsen et al., 2000). These studies indicated that inhalation was a major route of exposure to this form of CBPs for indoor activities. An exposure risk assessment study revealed the exposure of THMs through inhalation as a critical pathway comparably with direct ingestion patterning to showering, pre- and post-cooking activities, and cooking processes (Tsair et Shih, 1999). A study compared the contribution of several activities involving the use of tap water and observed that taking a shower or a bath significantly increased the concentration of THM in the blood and the air exhaled (Nuckols et al., 2005).

In another study (Villanueva et al, 2004) indicating CBPs are related to airways inflammatory conditions both indoor and outdoor pools and indoor showing might be a second pathway of exposure. A very recent exposure study, which is in consistent with previous studies, stated that chloroform was the highest concentrations of THMs found in the air of both bathrooms and indoor swimming pools (Foos et al., 2008). It was also pointed out that continuous and point exposure were significantly correlated ($r_s = 0.69$ $p < 0.001$). These THMs could contaminate the inside of homes by spreading in the various places where tap water is used (toilet, kitchen, cleaning, etc.), whereas less volatile HAAs were found more commonly in the form of aerosols in bathrooms.

A study observed repeated exposure may play a role in the onset of acute respiratory diseases that could become chronic. This might depend on circumstances, time in the course of life and on the duration of exposure. In this aspect, the extent to which exposure to concentrations of CBPs in the home contributes to the subsequent onset of chronic respiratory diseases is questionable. Exposures to a moderate or even low concentrations that occur repeatedly at “critical moments” in life, in particular exposure during childhood, could have damaging effects on children’s airways. The question also arises of the role of CBPs other than $NCl_3$, not found in homes, particularly THM and HAA which also have irritant properties.

## 2. RATIONALE FOR THE PRESENT STUDY

We suspect that inhalation exposure of children to drinking water chlorination by-products (THMs, HAAs, HKs) in long-term even at low level during indoor activities such as showering, bathing or household activities may pose the hypothesis of experiencing airway inflammation that might end up in childhood asthma. Then this whole present study is not only designed as a dissertation fulfillment and practicum placement for master degree of public health, but this study is also meant to contribute to the initiation of environmental survey and epidemiological research program on risk factors of chlorination by-products (CBPs) on the childhood chronically airways inflammation of the Environmental and Occupational Health Department of Ecole des hautes etudes en santé publique (EHESP) later stage. The research program is divided into two main complementary components (exposure measurements and epidemiology study) prepared by an initial phase consisting the reconstitution of the population base, the Pélagie women cohort. Therefore, this present study concerns two main parts.

The first part of this present study is formed the systematic review carrying out to address the association of inhalation exposure to THMs and other by-products in drinking water and the respiratory inflammation development in infants and children. The review explores the association of THMs and other by-products in drinking water at home, schools and other leisure places.

The second part is formulated to estimate THMs concentrations in drinking water of concerned study population (PELAGIE cohorts) which will be later used in those two components, the environmental survey (exposure measurements) and epidemiology study. This second part study context is detailed in the second part.

# PART I

## SYSTEMATIC REVIEW

## ROLE OF DRINKING WATER CHORINATION BY-PRODUCTS (CBPs) ON THE DEVELOPMENT OF CHILDHOOD AIRWAYS INFLAMMATORY CONDITIONS

## 1. RESEARCH QUESTION AND OBJECTIVES:

**1.1. Research question:** Are water chlorination by-products (CBPs) found in the indoor air of residential settings associated with airways inflammations of infants and children?

**1.2 Objectives:** this review is aiming to provide structure summary to assess the association between the drinking water chlorination by-products (CBPs) and the infants and children airway inflammation conditions. Specific objective are following:

- To review epidemiological studies in infant, children and adult in relation to water chlorination by-products (CBPs) at home, school and other leisure places in order to assess the development of airways inflammation in particular in chronic bronchitis and asthma
- To review toxicological literatures that could be animal or human in relation to chlorination by-products with the view to assess the hazardous potency on the development of respiratory inflammation
- To review THMs and low chlorine inhalation exposure assessments in relation to chlorination by-products (CBPs) in order to infer how relevant to hazardous potency of DBP to illicit inflammatory disorders of the respiratory tract.

### 1.3 Key search terms

The search terms were developed based on the research question and were used to conduct the comprehensive search

- Drinking or tap water
- Chlorination by-products (CBPs): Trihalomethanes, Chloroform, Chlorine. Specific key words as haloacetic acids (HAAs), haloacetonitriles, and haloketones are less likely to yield findings but will be used
- Airway inflammations: Asthma, wheezing, acute and chronic bronchitis, respiratory system, airway inflammations
- Infants, children, adults, animals

## 2. METHODS AND METHODOLOGY

As a reviewer, I initially received a two-days training on how to conduct systematic review. I also received an-hour guidance how to search and use search term (MeSH) in e-database. Therefore, the methodology used for this review employs from systematic review methods which the systematic review guidance of York University and the Cochrane Collaboration Systematic Review handbook were used to be a backup support. Since this is the first experience I performed the review in a systematic approach, several pilot search scopes were undertaken with broad terms and followed by some modification on the search terms before the actual search scope conducted between the 5$^{th}$ January and 10$^{th}$ February 2010.

### 2.1 Identification of relevant reviews

To identify any relevant review to this proposed study topic, I conducted a literature search in Cochrane Database of Systematic Reviews to identify any relevant systematic review conducted in the past. Firstly, the search was done using the advance search in Cochrane search strategy by using the combined identified key search terms (See appendix 3 for search scope of Cochrane database). In addition, I conducted the free search for reviews in Google Scholar and other databases in order to identify more relevant reviews. There was no review found in the same topic. Given the absence of reviews on this particular initial topic, this review has focused on a primary studies according to the following protocol.

### 2.2 Developing inclusion and exclusion criteria

To review systematically, it is important to have clear inclusion and exclusion criteria. Based on the research question and discussion with supervisors, the inclusion and exclusion were developed, tested and modified after the pilot search. Table 1.1 and 1.2 give the criteria and definitions for inclusion and exclusion criteria.

**Table1.1: Inclusion criteria using in the review**

| Criteria | Definition |
|---|---|
| **Study designs** | All epidemiological, toxicological and exposure assessment studies |
| **Population** | • Infant and children 0 day- 12 years-old<br>• Adult – to be secondary population in order to document the hypothesis of a relation of CBPs and airway inflammatory conditions<br>• Animal- to be secondary population in order to document the hypothesis of a relation of CBPs and airway inflammatory conditions |
| **Exposure** | • Inhalation of THMs and other by-products from drinking water<br>• Inhalation of chlorine at extreme low concentration level (0.5ppm) |
| **Outcome** | studies which have reported : inhalation of THMs concentration, wheezing , chronic or repetitive bronchitis and asthma |
| **Measurement Analysis** | studies which use appropriate quantitative measurements of air concentration of by-products (CBPs) |
| **Setting** | Studies which addressed drinking water such as at home, school and leisure places, but not in swimming pool setting |
| **Language** | Only studies which published in English language |

**Table 1.2: Exclusion criteria using in the review**

| |
|---|
| Studies which not addressing directly to water chlorination by-products and low chlorine exposure |
| Studies which have no quantitative measurements of air concentrations of by-products (CBPs) |
| Studies which are addressing only Nitrogen Trichloride ($NCl_3$) and pool water setting. The reason for this exclusion due to Nitrogen Trichloride ($NCl_3$) has found only in swimming pool where could not find in indoor's air concentration and it is not in the purpose to be observed in this review. |
| Studies which are only published in languages other than English |

### 2.3 Primary research studies

A review was undertaken for published and unpublished papers concerning the association of the THMs inhalation in drinking water chlorination by-products and airway inflammation among infants and children. The relevant studies were considered for inclusion if the papers were conducted between 1950 and January 2010.

#### 2.3.1 Electronic database searching

As it was the first experience to conduct searching in systematic approach, I initially conducted several pilots focusing on the topic of THMs of drinking water chlorination by-products and the association of asthma, chronic bronchitis and repetitive among infants, children, adult and animal. To perform this, I used a combination of key words and Medical Subject Heading terms (MeSH) to map the subject heading from relevant primary study articles. Boolean of OR and AND were also used to combine the search terms. The first pilot search was developed for MEDLINE via OvidSP database and followed by and adapted for TOXILINE, EMBASE and other identified databases. The pilot searches were refined with the feedback and discussion with dissertation supervisors for key search terms before a final systematic search was developed. Then I performed the actual preliminary search between 5$^{th}$ January and 10$^{th}$ February 2010 using the defined MeSH terms. A list of 20-30 keywords was used during the search for all electronic databases: trihalomethanes; drinking water; chlorination by-products; chlorine; chloroform; haloacetic acids (HAAs); haloacetonitriles; haloketones; asthma; wheezing; acute; chronic bronchitis; respiratory system; airway inflammations; Infants; children; adults; animals. After obtaining a large number of papers, the two restrictions were apply to be limited to English language and full text only. Below electronic databases were systematically conducted for the preliminary search scope and details of search strategies developed for these databases are presented in Appendix 3.

- MEDLINE via Ovid SP 1950 to week 4 of Jan 2010
- EMBASE 1980 to week 4 of Jan 2010
- TOXILINE via SCA 1960 – 2010
- Environnemental Science and Pollution Management via SCA
- Web of Science

### 2.3.2 Search for other databases

In addition, general search using a broad phrase of the water chlorination by-products or THMs and asthma or respiratory tracts was run in the following databases:

- Health Protection Agency (HPA)
- European Respiratory Journal (ERJ)
- Environmental Health Perspective
- American Academy of Paediatrics

### 2.3.3 Grey search, references and hand searches

Based on the US interagency Grey literature working group (1995), grey search is an important source to search for unpublished reports, conference abstracts, dissertations, organization projects, consultation minutes and reports which have not been indexed in formal databases. Therefore, I conducted the grey search for Google Scholar, Opensingle Grey Literature, and Scopus websites for conference proceeding, or other unpublished articles or reports. But there was no article found to meet the inclusion criteria.

During the process of reading the full texts of the most potential papers (38 papers) to identify for final included studies, I carried out the scan for the references of each paper to find further relevant studies. There were eight (8) papers found from this references search and fully read. However, there were no paper found met the inclusion criteria.

According to UBC HealthLib, indicating hand search is seen to be useful for additional search to uncover relevant articles that maybe poorly or inaccurately indexed or un-indexed. This allows reviewer/researchers to scan content for relevant papers from top journals and ensures that relevant studies are not overseen. Yet for this review, resources were given in this timeframe was not sufficient to carry out the search manually. Then the hand search was not implemented.

## 2.4 Justification of data sources, search strategy and synthesis methods of the review

For the ideal systematic review, it would be trying all possibilities to utilize all the potential sources of data to ensure all the relevant studies would be included in the review. Yet this process extensively requires comprehensive resources, sufficient timeframe and proper systematic review team. Hence this goal is difficult to achieve in my context. Recognizing all sources of data are important to retrieve from all relevant existing evidences, MEDLINE database was primarily identified and followed by other particular relevant electronic databases and journal websites. Electronic databases search and references list search were decided to perform in this review. The grey literature and hand searching could be conducted in only few particular accessible websites.

On top of that, at the synthesis stage, we determined if the statistical synthesise for this review needed such as meta-analysis. However, the statistical data represented in each included study was not the same type of data from one study to another. Then this is not considerable to pool the data together for statistical synthesis. Therefore, this review was performed descriptively to present the finding.

## 3. RESULTS

The result of electronic search and details at each stage of the review's findings is reported in this section.

### 3.1 Electronic Database Search Scope

The result of systematic search of each e-database was imported to Reference Manager. There were seven hundreds and ninety three papers (793) identified for relevant papers from all e-databases. Of these numbers, there were three hundred and twenty six (326) retrieved from MEDLINE, three hundred and thirty (330) retrieved from EMBASE, one hundred (100) retrieved from TOXILINE and Environment Management and Pollution, and thirty seven (37) retrieved from Web of Science. All papers retrieved from MEDLINE were used as a basis to eliminate the duplicated papers from other e-databases. The first scan was performed for duplication and there were sixty five (65) papers found in duplication and eliminated at the first stage (the same paper that found more than one in all databases). The remained seven hundreds and twenty eight (728) papers were scanned for potential relevant titles. After scanning the titles, there were six hundred and thirty one (631) excluded due to the title were not related to the proposed review's topic. There were ninety seven (97) papers related titles and further read for the abstracts in order to assess for eligible full text reading and consider for inclusion criteria. After further review of abstracts, there were eighty (80) papers considered to be read for full text. However, papers which shown directly examined the high level of chlorine gas inhalations were not be considered to read for full text. Then there were fifty six (56) papers were found not relevant to the review (eight reviews and forty-one primary studies) and excluded.

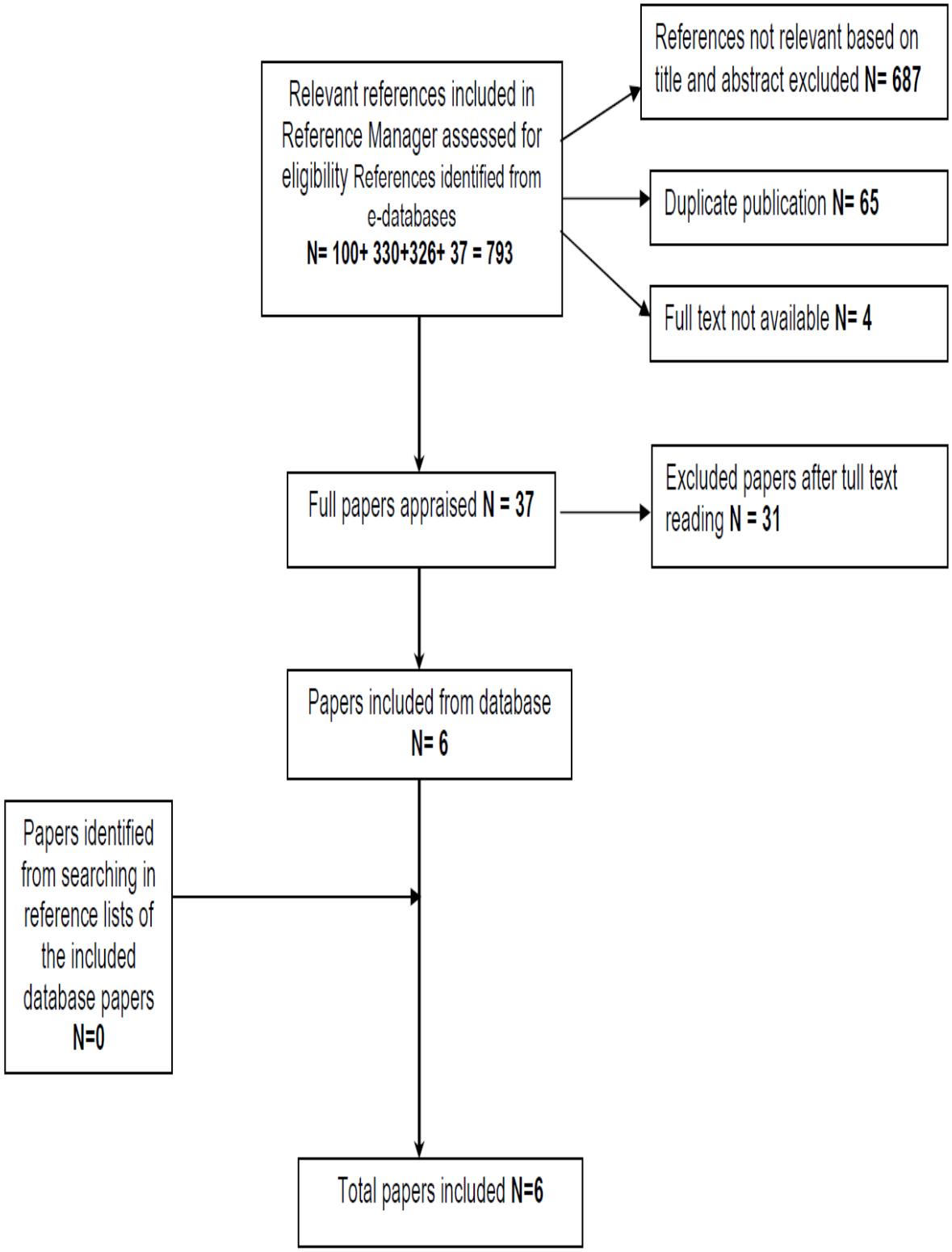
### 3.2 Total number of papers included in the review at the stage of evaluating full texts

At this last stage, there were forty one (41) remained papers were considered to obtain in full texts for reading in order to identify the potential for inclusion. But, there were only thirty seven (37) papers were able to obtain in full texts. After reading full text, thirty one (31) papers were excluded due to not meet the inclusion criteria. Figure1 highlights the flow chart for studies selection process. In total, there were six (6) studies were included in the review which the summary table of its basic characteristics is given in the table 1.3. Another detailed summary of each included studies attached in the appendix 1. A list of studies excluded from the final assessment and the reasons for their exclusion are presented in Appendix 2.

### 3.3 Grey literature and reference list search

Based on the result scanning for these literature's reports and other selected papers for reference searching, there was no paper found to meet the review criteria.

**Figure 1 Flowchart of study selection process**



### 3.4 Results of assessment against quality assessment criteria

All the six included papers had a clear objective, defined their study types, and clear statement of results. These included studies were mostly human exposure assessment study designs (Thiriat et al, 2009; Gordon et al, 2006; Xu and Weisel, 2005; Xu and Weisel, 2003; Nodelman and Ultman 1999; Rotman et al., 1983). Five studies were conducted in the United States which two studies conducted in New Jersey State (Xu and Weisel, 2005; Xu and Weisel, 2003); one study conducted in North Carolina and Texas (Gordon et al, 2006); one study conducted in Michigan State (Rotman et al., 1983), and one study conducted in Pennsylvania State (Nodelman and Ultman 1999). One study (1/6) was performed in France (Thiriat et al, 2009).

The study populations were primarily defined as infants and children, adult or animal (for toxicological papers). Only one study performed with children aged from four to ten years-old (Thiriat N. et al, 2009), one study performed in the laboratory with air sample (Xu and Weisel, 2003), while other four study participants were adults aged from 18-40 years-olds. Since the type of studies was human exposure assessments, the number of study participants was relatively small ranging between thirty and six subjects (Mean= 11.2).

Out of six studies, three were performed in experimental laboratories (Xu and Weisel, 2005; Xu and Weisel 2003; Nodelman and Ultman, 1999), two took place in participants' residential-based (Thiriat et al, 2009; Gordon et al, 2006). The duration of the all studies was between two weeks and two days and it was generally expressed in time of exposures.

The basic characteristics and research question of six included studies is presented in the below summary table 1.3.

**Table 1.3: Basic characteristics and research question of six included studies**

| N° | Rf ID | Author | Country | sample size | Age | Exposure | Evaluation Methods | Outcome | Research question |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 607 | Thiriat.N. et al. 2009. | Rennes, France. indoor air at children home and swimming pool | 30 | 4-10 yrs | THM exposure | A direct method with personal monitors assessing continuous exposure; and an indirect one with micro-environmental sampling and collection of time-activities data during the main events exposure: bathing, showering and swimming. | Inhalation exposures | The purpose of the study is to compare continuous exposure to inhaled THM with main event-specific exposure (bathing at home, and in indoor swimming pool). |
| 2 | 6 | Gordon S. M et al. 2006. | US: Texas and North Carolina 2 single private homes | 7 | 21-30 yrs | THM at indoor air: CHCl3 and BDCM | Air sample collected at baseline and during activities to evaluation inhalation exposure. Blood sample and water sample collected | Breath changes | The purpose of the study is to examine which common household water-use activities lead to an increase in the internal dose levels of CHCl3 and the other potentially harmful THMs in the human body through exhaled-breath measurements. |
| 3 | 742 | Xu. Xu et Weisel C 2005. | US | 6 | 24-39 yrs | Haloketones (HK) and chloroform exposure | Water samples collected after showering, and air and breath samples were collected for analysis | Respiratory uptake | The purpose of the study is to measure the HK concentration in exhaled breath of human subjects during and following inhalation exposure in a shower stall; and to estimate the magnitude of dose associated with the inhalation exposure route during showering for the HKs using linear compartmental pharmacokinetic models. |
| 4 | 13 | Xu. Xu and Weisel C. 2003. | New Jersey, US | N/A | N/A | Haloacetic Acids and Haloketones inhalation exposure | 1) Shower system: shower stall were used 2) Characterization of the aerosol size distribution: Lasair model 1002 optical counter was used. 3) Sampling and analysis of particulate DBP concentration: Whatman Glass Micro filters were used to collect aerosols generated by shower 4) Sampling and analysis of gas-phase HK concentration. 5) Determination of air exchange rate-breathing zone air sample | Inhalation exposure | The purpose of the study is 1) determine the temporal emission profile and the size distribution of the aerosol produced while shower water was on;2) measure the airborne particulate concentration of HAAs family;3) evaluate the transfer of semi volatile HKs from shower water to vapour phase by measuring the concentration of the volatilized HKs in the shower air; and 4) assessed the potential inhalation dose of DBPs during showering. |
| 5 | 709 | Nodelman and Ultma 1999. | Pennsylvania, US. Experimental laboratory | 10 | 18-40 yrs | Low chlorine inhalation exposure | Bolus inhalation system measuring clean air and chlorinated air and Cl2 concentration. | airway absorption | The purpose of the study is to observe the longitudinal distribution of Cl2 absorption in intact human airways during quiet breathing by employing the non-invasive bolus inhalation method that was previously developed for ozone. |
| 6 | 741 | Rotman et al. 1983. | Michigan, US. Chamber setting | 8 | 19-33 yrs | Chlorine gas at 0.5 or 1 ppm | Subject entered to the arranged chamber which chlorine gas were introduced at the concentration at 0.5 or 1 ppm | Respiratory effects | Examined the effect of low concentration of chlorine on pulmonary function in human. |

### 3.5 Summary of the main finding from six included studies

Among the six studies, four investigated inhalation exposures to THMs and other by-products concentrations (Thiriat et al, 2009; Gordon et al., 2006; Xu and Weisel, 2005; Xu and Weisel, 2003). The other two were focused on inhalation and absorption of low concentrations of chlorine and on effects on the pulmonary function in humans (Nodelman and Ultman 1999; Rotman et al., 1983). In this section, I summarized the main findings of these studies in three main points:

- Exposure assessment methods and setting used in included studies
- Inhalation exposure and human respiratory uptake to THMs and other by-products
- Low chlorine inhalation exposure and adverse effects on airways

#### 3.5.1 Exposure assessment methods and setting used in included studies

All six studies were exposure assessment study designs. However, the studies took place in different settings, either laboratories or in households. Five of six studies conducted human exposure assessment while one study conducted laboratory setting without human exposure (only experiment tools). The tools used to collect samples were also different between studies. Shower stalls in experiment laboratory were used in two studies (Xu and Weisel, 2005; and Xu and Weisel 2003). In other two studies, air was collected in the shower room of households and in swimming pools to assess human exposure (Thiriat et al, 2009; Gordon et al, 2006). In the other two studies that examined chlorine gas inhalation, the Bolus chlorine inhalation system and chlorine gas introduced chamber were used respectively in the laboratory experiments. Interestingly, a majority of the studies collected air samples and measured air breath concentration.

#### 3.5.2 Inhalation exposure and human respiratory uptake to THMs and other by-products

Four out of six studies informed the concentration outcomes of inhalation exposure and human respiratory uptake to THMs, Haloacetic Acids (HAAs), and Haloketones (KHs). Three included studies consistently found in their studies the present of chloroform in the air concentration at the experiment setting (Thiriat et al, 2009; Gordon M et al, 2006; Xu and Weisel, 2003). Based on the finding of Thiriat and his colleagues, the concentration of THMs in air was dominated by $CHCl_3$ (7.3µg/m³). It was also found that the continuous exposures was higher than the event exposure and it appears to be the most interesting THMs for observing association between THM exposure and respiratory effects because of its abundance (Thiriat et al, 2009).

Gordon M et al. identified that showering and bathing are two common household water-use activities that cause significant increases in exhaled breath concentrations of $CHCl_3$. Moreover, it was indicated that there were strong correlations for indoor air and exhaled breath, blood and exhaled breath, indoor air and blood, and tap water and blood during showering. On the other hand, for bathing, only water and breath, and blood and breath showed strong associations when exposed to $CHCl_3$ (Gordon et al. 2006).

In addition, Xu and Weisel confirmed their experiment that the human respiratory uptake of $CHCl_3$ and HKs presented in the air breath concentrations. The air breath concentration of HKs during exposure was higher than chloroform. Authors observed that the HKs were absorbed across the lungs more efficiently than $CHCl_3$. The lower breath concentrations for the HKs than for $CHCl_3$ were consistent with their greater solubility in water and blood than in air than $CHCl_3$. Based on the dose calculations, the respiratory uptake of HK s during showering is about 1/4 to 1/3 that of $CHCl_3$. The internal dose of the HKs from a typical shower was equivalent to ingesting about 0.1–0.3l of the drinking water. It was likely that inhalation absorption may be an important exposure route for the HKs. Then the suggested was made that these data can be used to evaluate total exposure and associated health risk of the DBPs in drinking water (Xu and Weisel, 2005).

Separately, Xu and Weisel (2003) found that the inhalation exposure to HAAs during showering stemmed predominantly through respiratory uptake of shower-generate aerosols, with an average daily dose of particulate HAA was approximately ranging 0.4-1.0 µg/day when the water concentration of HAAs was approximately 250µg/l. Moreover, this indicated that showering generated HAAs will be increased air concentration of HAA throughout the home because the dry particles of HAA will remain in the air even after the water evaporated from the aerosol. Regarding to HKs, the daily inhalation doses of vaporized DCP and TCP during showering were found to be 10.2 and 6.7 *µ*g/day respectively. However, KHs also occur after subject leaves the shower stall, then inhalation exposure to HKs is important to consider when estimating their risk in drinking water.

Interestingly, there was no study in this review reported the direct investigation the association of THMs and other by-products inhalation exposures and asthma or airways inflammation in either epidemiological or toxicological studies. Only one study from the included studies (Thiriat et al, 2009) suggested for further primary research on this particular subject.

### 3.5.3 Low chlorine inhalation exposure and adverse effects on airways

Two among the included studies addressed exposures to low chlorine ($Cl_2$) inhalation exposures and association of the effect of airway function (Nodelman and Ultman, 1999; Rotman et al., 1983). Rotman et al. reported that, from the experiment exposures at a low chlorine concentration at 0.5 and 1ppm exposures in both volume and flow rate, the result could adversely but transiently affect pulmonary function. The magnitude of the changes was apparently observed is related to the total dose received. From the experiment of bolus inhalation measurements (Nodelman and Ultman S.1999) indicated that nearly all of $Cl_2$ inhaled during quiet breathing was absorbed in the upper airways, whether the nose and mouth is the site of air access ($V_p$ of 80ml).This finding was not statistically different across gender of the study participants. Moreover, the authors addressed that the total absorption rate for the nose and mouth are similar, and reported that 95% or more of the continuously inhaled $Cl_2$ was absorbed in the upper airways. Then it suggested that high

absorptive of $Cl_2$ in the upper airways and domination of the gas-phase diffusion resistance were attributable to the rapid hydrolysis of Cl2 in the mucosa.

## 4. DISCUSSION AND CONCLUSION

### 4.1 Strengths and limitations of the review

This review was conducted for dissertation fulfilment of the master degree. While I did rigorously perform the search in e-databases and references searching from the included studies, I did not comprehensively perform grey literature. Besides, I did not perform the hand search for unpublished studies or contact study authors due to time constraints. On the other hand, this review was restricted to English publications; this restriction might result in the review missing some relevant publications. From the experience gained, I will be able to conduct systematic review in the future in an appropriate timeframe and completeness of resources for research study purpose. I will take these points into account and perform all required search strategies accordingly.

Another limitation of this review is the small number of the papers that examine the association between CBPs inhalation and airways inflammation in the household or school setting. The initial output during the scoping search indicated that there were plenty of studies in this related area. Nevertheless, on a closer investigation, most primary studies addressed the association of chlorination by-products at the swimming pool setting in association to asthma and respiratory inflammation; or by-products in association with cancers; or the studies that only addressed chlorine gas inhalation and asthma or respiratory inflammation in occupational setting.
Another issue, this review is dominated by primary studies conducted in the United State (5/6) and two papers were conducted by the same authors which might raise the concern of generability. For instance, chlorine doses in the US presented in the review studies were higher than that conducted in France, an observation which is consistent with the different water treatment approaches between the two countries.

### 4.2 Comparison with existing reviews

Based on my extensive literature search strategies I can state there is no other review performed on the same topic. Hence two reviews concerned, respectively, the uptake of chlorination disinfection by-products from different route of exposures and its implication for exposure assessment in epidemiological studies (Nieuwenhuijsen et al., 2000) and the allergic and respiratory health effects of chlorine and chlorination by-products in the swimming pool setting (Kolhammer and Heirnrich, 2007). In comparison to the two reviews, this current review illustrated the concern of THMs which addressing drinking water involved household activities which is considered to be an important route of inhalation exposure rather than looked at only swimming pool setting and other route of exposure. This review also concerns all types of existing primary studies including exposure assessment, toxicological and epidemiological evidences.

Nieuwenhuijsen et al. (2000) addressed the concern and challenges of exposure assessment models in relation to epidemiological studies and its cost-benefit. This review suggested that there are many different DBPs and uptake of DBPs occurs through various activities and exposure routes which should be taken into account in epidemiological studies. Also, it was stressed that THM data are generally available and modelling has been developed but there was limited information on personal exposure. Not employing personal estimates might lead to exposure misclassification because of personal activity variability. Another concern was the variability of exposure route across person in-term of ingestion, dermal absorption and inhalation routes, whose weigh may also vary across genders and ages. The author also indicated that personal exposure estimates is not likely to be able to measure DBP uptake of each subject in an epidemiological studies given of the time and cost incurred. It was suggested that the model could be considered for subset population using routine data, questionnaire, biomarker and PBPK modelling in order to use these to model the uptake in a wider population.

Another review conducted by Kolhammer and Heirnrich concluded that frequent exposures to chlorine and its by-products in the swimming pool setting is an important factor contributing to the development of respiratory and allergic diseases. This review also proposed prevention measures of adverse health effects in case of pool attendance, such as control of temperature, water quality and air quality, suggesting cost-benefit analysis should aid in defining safe exposure levels of pool attendees, especially for repeated, long-term exposure of the youngest population (Kolhammer and Heirnrich, 2007).

**4.3 Implications for future research**

This review finding informs that there is very limited research on THMs and other by-products inhalation in association with respiratory inflammation or asthma, either through epidemiological, toxicological studies or personal exposure estimates. This review confirms that inhalation is a significant route of exposure during household activities, specially showing and bathing with substantial concentrations of THMs found in the indoor air. It also observed that continuously exposed to considerably low chlorine concentration could have the adverse effects of respiratory tract. Further, very little is known about the cellular and molecular mechanisms involved and the relative contribution of exposure to the various CBPs sources to the formation of reactive oxygen species. A better understanding of those mechanisms and oxidative stress also calls for further studies such as toxicological approaches.

On the other hand, those by-products (THMs) were categorized by the International Agency for Research on Cancer (IARC) as substances cause and possibly cause cancers in human. This has been officially regulated for limiting the level of THMs usage in public health regulation. But this is

concerning only cancer risks. Nevertheless, THMs seem have not been seen as a factor associated with the adverse effects on the respiratory tract on daily exposures. This concern may have not been considered as an important issue if compare to cancers which it may have been overlooked, or there are limitation of scientific evidences to proof this association.

Given the above facts, there is a lack of evidence on the risk of airways inflammation to infants and children, segments of the population which are likely to be the most vulnerable group due to physical, biological and social interaction. This issue seem has been overlooked. Thus it can be questioned to explore further primary epidemiological or toxicological approaches to assess the association of the THMs and asthma or respiratory inflammation. Particular primary longitudinal observational studies should be potentially recommended, which a larger sample size (human subjects) should be taken into account to extrapolate these results to the general population. In addition, the oxidative stress and airway mechanisms involved and interacted exposure is limited known, thus toxicological approach could be also suggested to examine the action mechanisms in particular the role oxidative stress of CBPs and airways inflammation. The important of the further research on this field will be forming the evidence that can be informing the policy making to the concern of respiratory adverse effect and CBPs of the general population.

### 4.4 Conclusion

This review looked at the existing evidence regarding the association of chlorination by-products inhalation in indoor environments at home or similar settings and the onset of asthma and respiratory inflammation among infant and children. Through the systematic literature search, six studies were included and reviewed. The main finding from this review is the paucity of research on the topic and therefore a lack of evidence for or against the hazardous property of this exposure situation. However, the included studies indicated the important of inhalation route and exposure to by-products which showering and bathing consistently confirmed as important indoor exposure. In addition, the continuous exposure at low chlorine concentration pause the adverse effects of respiratory tract. Therefore, to inform the policy and decision making, further researches are needed in this field in particular to assess the inhalation by-products and the association of asthma and respiratory inflammation epidemiologically in the long-term continuous exposure to indoor activities. The toxicological approach should be recommended to response to the absence of evidence on the risk of airways inflammation that is possibly caused by the oxidative stress due to CBPs.

# PART II

# Comparing two different methods estimating THMs concentration levels in drinking water of Pélagie women locations in Ille-et-Villaine, Brittany Region

## 1. STUDY CONTEXT

As stated in the introduction part of this current study, the prevalence of inflammation of respiratory tracts in children (asthma, rhinitis, chronic bronchitis, etc) has increased considerably over the past thirty years in developed countries. From 1998 it seems to have stabilised in France and other developed countries at between 5 to 10% for children. The conditions for the onset of these respiratory diseases in children whether it caused by allergies or not, are complex. Several risk factors have been clearly indentified. The sex, the presence of animals and hereditary allergies are often reported. Also, the role of environmental exposure in the onset of certain chronic respiratory disease has been established. More recently, environmental exposure such as inhalation (chlorination by products, phthalates and biological contaminants) of indoor pollution have been reported in the literature but still further investigation.

This second part of the study is formulated to contribute to the research program of the Environmental and Occupational Health Department of EHESP on risk factors of chlorination by-products (CBPs) especially trihalomathanes (THMs) exposure and respiratory tract irritation and asthma association among children. The research program is divided into two main complementary components (exposure measurements and epidemiology study) prepared by an initial phase consisting the reconstitution of the population base, the Pélagie women cohort. The aim of the Pélagie cohort was to study the role of environmental pollutants on pregnancy course and outcome and on children's health and development. It is part of network of European cohorts (www.birthcohort.net) mobilized to respond to concerns about particular vulnerability of intrauterine development and its long-term consequences.

Being part of the research program, this second present study is initially performed the estimation of THMs concentration in drinking water in the area of Pélagie study population in Brittany which will be later used in those two components, the environmental survey (exposure measurements) and epidemiology study. The prospective research study population is children aged between 6-8 years-old which the mothers and children that were taken part in Pélagie cohort study in Brittany (2002-2005). The environmental survey aims to collect the data on a sub-sample of homes that can then be incorporated into a model to estimate the exposure of all children in a case-control study to risk factors for chronic inflammation of the airways. The research program concerns and correlates the children characteristics including children age, life style, and pollutants exposures in water quality.

Therefore, this current study is involved partly to perform the proximity of THMs concentration exposures of each woman location (homes) in the interest Pélagie geographical area. Results of this present study are given the mean of estimating THMs concentrations in the geographical area where Pélagie women located and exposed. Understanding the exposure level of THMs concentration of each women cohort location, therefore, is critical to predetermine the potential bias regarding level of THM exposure during the research program (environmental survey and epidemiology study) participant recruitment process. To do so, based on the data's availability and

resources of THMs concentrations from each water quality monitoring (WQM) station and distances between each woman location to the WQM stations, the THMs exposure estimation of each Pélagie women location is hypothesized. Knowing the water distribution networks of each woman location served by which water monitoring station in Pélagie geographical area was limited. Therefore, we formed hypothesis to construct and compare two methods, a simple method selecting the closest WQM stations comparing with another more sophisticated method (buffer method with different radiuses).

**2. OBJECTIVE:** to compare two different methods to estimate THMs concentration levels in drinking water at Pélagie women locations, Ille-et Villaine of Brittany Region, based on distances between the women locations (homes) and the water quality monitoring stations.

**Specific objectives:**

- Develop the spatial relative distribution map using ArcGIS software to formulate distances between Pélagie cohort location and water quality monitoring station;
- Construct and compare two different THMs concentration estimation methods, the first closest distance measurement method and the buffer methods, based on the distances between the Pélagie women location and water quality monitoring stations.

## 3. MATERIALS AND METHODS

### 3.1 Study population and site

Among four departments of Brittany region, Ille-et-Villaine was chosen to undertake this present study. Ille-et-Villaine is area where the majority of Pélagie cohorts are populated. About 3421 Pélagie women in Brittany, 2150 women data were reported their locations in Ille-et-Villaine, and Rennes (metropolitan) area is shown as the most populated area of all Pélagie women in Ille-et Villaine.

### 3.2 Sample size and data

The address dataset of Pélagie women were obtained from U625 INSERM Rennes. There were 2150 women in Ille-et-Villaine included in this study analyses. This women data were given in shape-files that could be read by the software we used to analyse the data. THMs concentrations data in 2009, from 161 water quality monitoring stations (WQM station) in Ille-et-Villaine, were obtained from the SIS' EAUX database of Direction régionale des Affaires sanitaires et sociale de Bretagne (DRASS).

### 3.3 Analysing methods

In this study, we used ArcView in ArcGIS 9.3 desktop, excel databases and STATA to compute and analysis the data. According to the Environmental Systems Research Institute, Inc. (ESRI), geographical information system (GIS) is a geographic information system integrates hardware, software, and data for capturing, managing, analyzing, and displaying all forms of geographically

referenced information. GIS allows us to view, understand, question, interpret, and visualize data in many ways that reveal relationships, patterns, and trends in the form of maps, globes, reports, and charts. In addition, ArcGIS is software products of geographic information system and the main concept of ArcGIS is producing geodata view, geovisulization view and geoprocessing view. In ArcVew, we developed maps representing Brittany region particular Ille-et-Villaine where the locations of Pélagie women and WQM stations were visualized on the maps with THMs concentration levels of each WQM station. The latitude and longitudes of both each WQM station and each cohort location were originally obtained in WGS 984 system and later converted into Lambert II étendu data type using the “Conversion de coordoneés” software in order to be read by ArcGIS.

We considered using the distance measurement function in ArcView to measure automatically distances between women location and WQM station. However, we were not able to perform this function due to ArcGIS license limitation. We finally used excel to compute the coordinate system data (latitudes and longitudes) of women locations and WQM stations employing the Pythagorean theorem (=RACINE (((X-X1)^2+ ((Y-Y1)^2))) to generate the distances. In this formula, X and Y represented latitude and longitude of woman location and X1 and Y1 represented latitude and longitude of WQM station.

The result of distance were calculated in metre and recorded in excel databases. After calculating distances of each cohort location and 161 WQM stations, we performed excel function to sort out the first closest distance between women location and WQM stations; and we did the same for buffer method which predefined radiuses at 1000, 2000 and 4000 metres circled around each woman location.

We used STATA to analyse data of distances and THMs concentrations. We calculated the mean and percentile of each first closest, 1000 and 2000, 4000 metres methods. Moreover, to understand our THMs concentration data in each method is normal distributed, we performed Shapiro-Wilk W test for normality. Based on Chen (1971) indicated that Shapiro-Wilks' W test is used in testing for normality. The Shapiro-Wilks' W test is the preferred test of normality because of its good power properties as compared to a wide range of alternative test.

Lastly, we used Wilcoxon signed-rank test to compare our two methods. Wilcoxon signed-rank test is a type of non-parametric test to test the difference between dependent groups (Stasoft). Using this test, we compare THMs concentrations of the first closest station with THMs concentrations of each radius buffer (1000, 2000, and 4000 metres). We tested the hypothesis if this two methods generate the same THMs concentrations estimation by observing the statistic significant of p-value for each comparison. Our hypotheses to compare these two methods were:

*Ho= THMs concentration estimations of the first closest method equal to THMs to concentration estimations of buffer method*

*$H_1$= THMs concentration estimation of the first closest method is not equal to THMs concentration estimations of buffer method*

### 3.4. Justification of the proposed methods

Knowing the water distribution system in the studied geographical area is an ideal to obtain direct distances between women location and its served water monitoring station. In Ille-et-Villaine, we learnt that Rennes, the area where most of Pélagie women located, was served by two water distribution systems (Villanueva et al., 2007b). However, we had limited information of water distribution networks of each woman location that served by which WQM station. For this reason, we were not able to estimate THMs concentrations of each woman location based on the direct distances. Yet we the data and information that we were able to generate the distances between each woman location to water monitoring station. Therefore, we considerably constructed two methods calculating distances between each woman location to each of 161 WQM stations and statistically compare these two methods to observe their significant results regarding THMs concentration estimations.

The first simple method, we considered and computed distances between each woman location and the first closest WQM station to illustrate the distribution trend of THMs concentrations of each women location based on distances.

The second method, we performed another more sophisticated method, the point buffer method, to estimate THMs concentrations of each woman location based on the distances between each woman location and WQM station within the radius at 1000, 2000, 4000 metres respectively. According to Sheppard (1999), buffer method uses to estimate the population or individual proximity within a definite distances of a given point, area or line. Among the three types of buffers, the point buffer method refers to the method using a predefined radius to understand the impacted population within a given point. Then we employed the concept of point buffer to cycle a defined point (women location) with three radius at 1000, 2000 and 4000 meters respectively.

Employing buffer methods, we initially piloted different radius of buffer starting from the 500 metres radius. Finally, we decided to set three radius of buffer method at 1000, 2000 and 4000 metres to be compared. The reason to suggest these three radiuses, we considered comparing the first closest method and the smaller, similar and larger radius at 1000, 2000 and 4000 metres respectively. Finally, the idea is to compare the first closest method and the buffer method at each radius.

## 4. RESULTS

### 4. 1 Spatial distribution Mapping

Initially, we developed the relative distribution map for the study area, Ille-et Villaine which visualized the concentrated location's trend of the WQM stations and the women location. Figure 1, 2 and 3 presented spatial distributional maps of women locations and WQM stations and attached in appendix 5. As seen in fig 1, 2 and 3, the spatial distribution maps indicated a large distribution of women locations which most of women locations were concentrated in the middle of Ille-et Villaine department (Rennes). Moreover, the 161 WQM stations were variably located across Ille-et Villaine. The WQM station colouring different level of THMs concentration where the women location likely to be exposed (the mean THMs concentration of all 161 WQM stations was 39.6µg/l).

### 4.2 The first closest distance method

The simple first closest distance method to estimate THMs concentrations at women formed the relationship of the first closest distance between every single woman location (2150) to each WQM station (161 stations).The first closest distance between women locations and WQM stations were computed the distances based on its latitudes and longitudes data. The mean of the first closest distance among all women location to WQM stations was 2233 metres, followed by the mean of THMs concentrations considering this first closest distance was 36.9µg/l and the standard deviation was 13.6. Summary statistic results reported in table 2.1 in appendix 6.

Looking at each 25 percents of frequency in table 2.2 and figure 2.4 (appendix 6 & 7), among 2150 women locations, 515 women locations reported by the first closest distances exposed to THMs concentrations between 2.3 to 27.8 µg/l; 669 women locations reported between 28.2-36.8µg/l; 616 women locations reported between 37.5µg/l to 48.4µg/l; and 350 women locations reported between 48.7-80.2 µg/l.

Observing the result in table 2.3, the percentile revealed that at 25%, 50%, 75% and 99%, based distances between the women location and WQM stations, THMs concentrations of the women locations were reported at 28.2, 36.1, 43.0 and 68.8µg/l. Only below 2%, the THMs concentrations were reported by the first closest distance method at 2.3 and 80.2 µg/l respectively.

The interest point to be observed from these results was the THMs concentrations were not considerably vary between 25-99 percentiles. Hence the first closest distances were reported quite vary from 25 to 99 quartiles. However, the result of Shapiro-Wilk W Test for normality test shown that choosing the closest stations, the THM concentration is not normal distributed (p=0.000). Table 2.3 presented the results of Shapiro-Wilk W Test for normality attached in appendix 6.

**4. 3.Buffer Methods**

As second method which was considered as a more sophisticated method to estimate THMs concentrations of each woman location using buffer concept, we set three radiuses at 1000, 2000 and 4000 metres. The THMs concentrations of these three radiuses were analysed using STATA for its means, percentiles, and normality distributions. Table 2.1, 2.3 and 2.4 presented statistical summary, percentile and normality test results of the three radiuses and attached in appendix 6. Figure 2.4 shown distributional graphs of THMs concentrations for each radius and attached in appendix7.

At 1000 metres buffer between women locations and WQM stations were reported by 848 women locations. The mean of THMs concentrations reported by this radius buffer was 37.2µg/l and the standard deviation was 10.9. The percentiles based on the distances, THMs concentrations were reported by WQM stations at 25, 50, 75 and 99 percentiles were at 32.0, 37.7, 45.2 and 68.8µg/l accordingly.

The second buffer, there were 1230 women locations reported having WQM stations within its 2000 metres radius. THMs concentrations mean reported by this radius distance was 36.1µg/l and the standard deviation was 11.3. By looking at percentile between women locations and WQM stations, the THMs concentrations reported at 30.1, 36.8, 44.2 and 68.8µg/l at 25, 50, 75 and 99 percentiles respectively.

The third radius was set at 4000 metres distance. At this distance, we observed that there were 1715 women locations reported having WQM stations within its cycle. THMs concentrations mean reported by this radius was 37.5µg/l and the standard deviation was 10.3. Considering of this distances, THMs concentrations reported by the 4000 metres distances was at 31.3, 35.8, 41.2, and 68.8µg/l at 25, and 50, 75 and 99 percentile respectively.

Interestingly, observing from these three radius distances, the mean of THMs concentrations of all three were relatively equal (37.2, 36.1 and 37.5µg/l). Also, within those distances, THMs concentrations variations were relatively similar for all three buffers between 28.2 to 68.8 µg/l. Observing distributions graphs (figure 2.4, appendix 7) indicated that the data distribution of each radius was likely normal distributed. Nevertheless, after running the statistical normality test (Shapiro-Wilk W test) for THMs concentration distributions reported by each radius, the result confirmed THMs concentrations reported by each radius was not normal distributed, the p-value for each radius was smaller than 0.05 (p=0.00). The summary result of Shapiro-Wilk W test presented in table 2.4 in appendix 6.

### 4.4. Comparison of the first closest method and buffer methods

After having generated the statistical results observing its distributions in each method, THMs concentrations reported by its distances in each method were compared using Wilcoxon signed-rank test. Using this sensitivity test, we hypothesised three comparisons between the THMs concentrations reported by the first closest station method and the buffer method at 1000, 2000 and 4000 metres respectively.

Observing the three comparisons, statistic results shown that by comparing the first closest distance method and the 1000 and 4000 metres radiuses, the result is statistic significant (p=0.00) which our hypothesis was rejected that the two methods were different if the THMs concentrations were estimated using the first closest distance and the smaller radius at 1000 metres and a larger radius at 4000 metre.

However, once we compared the first closest distance method with the radius at 2000 metres, the statistic results indicated that the two methods produced similarity of THMs concentration estimation. This confirmed by the p-value for this comparison was not statistically significant (p=0.08), which we accepted out null hypothesis that using the first closest method is equal to the buffer method considering 2000 metres radius. Table 2.5 given summary results of method comparisons for first closest method with each radius by sensitivity test (Wilcoxon signed-rank test) attached in appendix 6.

## 5. DISCUSSION AND CONCLUSION

### 5.1 Results interpretation

The comparison of two methods (a simple method choosing the first closest distance and a more sophisticated buffer method) were statistically performed to understand the estimations of THMs concentrations based on the first closest distance and distance buffer methods between women location and WQM stations. According to our statistical results to compare the first closest distance method and each radius buffer give two interesting indications.

First indication, based on our hypotheses, the comparison of the first closest method and buffer method at 2000 metres radius, our statistic results suggest that these two methods ( the first closest and 2000 metres radius) are likely similar to estimate THMs concentration exposure estimations (p=0.08). This could be interpreted that in order to estimate THMs concentration exposure in Pélagie women geographical area in Ille-et-Villaine using simple method (the first closest station) or buffer method within 2000 metres radius would give similar estimation results.

Second indication, the comparison of the first closest method and buffer method at 1000 metre and 4000 metres radiuses indicates that the two methods likely generate statistical significant different result regarding the estimations of THMs concentrations exposure in each woman location

(p=0.00). It could be noticed that if the THMs concentrations estimation using the first closest WQM stations or buffer methods at 1000 or 4000 metres radiuses, it would give different THMs concentration estimation results.

Considerably, these two different indications are concerned with radiuses set within buffer methods. If we observed our results, at a smaller radius 1000 metres gives only 848 women location reported having the WQM stations located within 1000 metres radius while the larger radius at 4000 metres generates 1715 women locations. Within these two radiuses, the 1000 metres seems not only obtaining small number of women reported having WQM stations, but also each woman location was limited to number of WQM stations located within their individual radius. On the other hand, once the radius increased to 4000 metres, larger number of women location reported having more water stations located in their radius. Then it seems indicate that at 1000 metre radius, each women location covers smaller number of WQM stations while the 4000 metres radius, each women location covers many WQM stations. This observation need to take into account for the statistical significant different from the first closest method. However, at 2000 metres radius, the total number of women location were 1230 reported having WQM stations located in their radius. Interestingly, this radius set at 2000 metres is relatively similar to the mean of the first closest method and the statistic result gives similar estimation to the first closest method.

### 5.2 Strengths and limitations of the study

The analysis appears that the two models generated interesting results in estimating THMs concentrations either the first closest method or buffer method. However, there was twofold of limitations that need to be taken into account.

Firstly, the concern may rise about the THMs concentrations variability between the observed stations. This might affect THMs concentration estimations which this current study trying to extrapolate calculating distances between women locations and WQM stations. Based on few studies observed variability of THMs concentrations addressed that THMs concentrations changes were depended on geographical location and season in the water distribution systems (Toroz and Uyak, 2004; Rodriguez et al., 2001; Williams et al., 1997). A study demonstrated the seasonal measurements of THMs concentrations indicated that THMs concentration variations significantly changes in water quality and temperature through the year (Toroz and Uyak, 2004). Therefore, our concern for this present study that THMs concentration data used in these two models were based on only one year data (2009) which each WQM stations were observed for THMs concentrations once in a year.

Another point, if compared to other previous studies, there were various evaluation methods to estimate THMs concentrations in water either at the raw water stations or water network systems where the chlorination process taken place. Nevertheless, common sampling methods to form the estimation of THMs concentrations were generally obtained water samples from chlorination stations and analysed in laboratory using biomarker and chemical procedure followed by statistic analytical test (Golfinopoulos et al., 2002; Williams et al., 1997; Rodriguez et al., 2001). According to a study conducted by Toroz and Uyak (2004) observing the seasonal variation of THMs concentrations used in water distribution networks, the water samples were used to analyze THMs concentrations. This study took the samples from chlorination water stations and from the representative points at the end utilities and moreover the distance between chlorinated water station and reprehensive points were clearly known. Therefore, observing at our methods used, another limitation could be associated with the limited understanding of water network system in the study geographical area. We could not identify which were the exact water networks or routes are served directly to each woman location. It limited us to compute the direct distances between each women location to each direct distributed water station. Thus, the two methods extrapolating THMs concentration estimation for each woman location were based on the first closest or buffer distances that probably was not the direct served WQM stations. The mean of distances of buffer or the closest distance measurements might limit to the accuracy of THMs concentration exposures of each woman location. Aware of this limitation, if the direct water networks/systems were known from WQM stations to each woman location, the direct distance from each woman location and WQM station would be more considerably useful to estimate THMs concentrations of each woman location more accurately.

**5.3 Conclusion:**

Spatial map illustrates a large distribution of women locations in the geographical area, which most of women locations are mainly concentrated in the middle of Ille-et Villaine department (Rennes); and WQM stations are variably located across Ille-et Villaine. After comparing two methods, a simple method (the first closest distance method) and a more sophisticated method ( buffer method at 1000, 2000, 4000 metres radiuses), extrapolating to estimate THMs concentrations in drinking water at Pélagie women locations in Ille et Villaine, our results appear to be two interesting indications. First, the result suggests that using the first closest distance method and the buffer method at 2000 metres radius to estimate THMs concentrations of each woman location is likely given similar estimation of THMs concentration. However, these two methods appear to be statistically significant different if the radius of buffer method set at the 1000 or 4000 metres. It does mean that to estimate the THMs concentrations considering the first closest and buffer method at 1000 or 4000metres, the result of THMs concentrations of each woman location gives different estimations.

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# Part I

## Appendix 1: Review of findings of six included studies

### 1. Thiriat N. et al, 2009

The purpose of this human exposure assessment study design was to compare continuous exposure to inhaled THM with main event-specific exposure (bathing at home, and in indoor swimming pool). There were two methods used to assess THMs inhalation which a direct method with personal monitors to assess continuous exposure and an indirect method with micro-environmental sampling and collection of time-activities data during the main events exposure bathing, showering and swimming were employed. 26 children aged from 4-10 years-old were recruited to participate and observe for seven days in Rennes, France. Bathroom air during the bathing or showering was sampled. The study participant who attended the swimming pool, the air was sample for 1 hour at the beach near the basin at 1 metre height. Specific stainless steel tubes were used. Time activity diaries reported the time spent in the bathroom and swimming pool during the study week was collected.

From the result section, this study reported that THMs concentrations in air were dominated by $CHCl_3$ in bathroom, median is 7.3µg/m for $CHCl_3$ while respectively 0.2, 1.7 and 0.5 for $CHBr_3$, $CHClBr_2$ and $CHCl_2Br$. Air concentration in bathrooms during shower or baths found lower than other previous studies estimation. But it was assumed that because previous studies mostly conducted in US where higher chlorine doses were used than in France. The same finding found as previous finding that chloroform concentration is higher during showering than bathing. The continuous exposure found lower than other studies (mean: 1.0, SD: 1.2µg/m3 for $CHCl_3$). No correlation was observed between shower, bath and swimming duration and ages of participants (rs: 0.08) or between ages and continuous exposure (rs: 0.04).

The study concluded that a significant correlation between continuous and event-specific exposure found for chloroform ($r_s=0.69$, $p<0.001$). The author suggested that chloroform shows to be the most relevant by-products compound to be assessed an association between THM exposure and respiratory effects due to its abundances. However, the study could not indicate and suggest the possibility of other THMs compound.

**2. Gordon et al, 2006**

This exposure experimental study design was aimed to examine which common household water activities lead to an increase in the internal dose levels of chloroform ($CHCl_3$) and other potentially harmful THMs in the human body through exhaled-breath measurements. Two single private houses were selected for experiment (one in Texas and another one in North Carolina) and seven young healthy subjects aged from 21-30 years-old were selected (4 males and 3 males). Indoor air, breath, tap water and blood samples were collected. Tap water and blood samples were collected at fix times before the next exposures started. Indoor air samples were collected before, during and after showering while breath samples were collected before and 5 minutes after showering. Standard and intensive protocols were used to evaluate the concentration of inhalation exposures which 13 air samples collected for standard protocol and 19 air samples were collected for intensive protocol. Integrated 13minutes air sample associated with showering activities were collected until the 3 minutes before the water turn off. For bathing, integrated 23 minutes air samples were collected at the 6 minutes bath filling period, through 14 minutes bathing and ended 3 minutes after the subject got out of the bathtub. Exhaled alveolar airs were directly collected into an evacuated 1-L Silco steel stainless steel canister at 5 min after completion of each activity.

The study reported the result of effects of tap water quality and water use activities on indoor air and exhaled-breath concentration. Mean water concentration of $CHCl_3$ and BDCM were high. The effect of water-use activities on the mean indoor air and exhaled-breath concentration of $CHCl_3$ normalised with respect to tap-water concentration. Showering and bathing activities are moderately higher in the breath BDCM measurement (2-fold increase in case). The result of Spearman correlation and coefficients for $CHCl_3$ and BDCM indicated that water-breath and blood air were significantly correlated. Data presented the mean air and exhaled-breath concentration, normalised with respect to the water concentration, were different from the showering and bathing activities. The normalised mean air concentrations were much greater fro the showering activity than for the bathing activities for both $CHCl_3$ and BDCM. The ratios of normalised mean breath to air concentration were much greater for bathing and showering activities (0.37 vs. 0.08 for $CHCl_3$; 0.40 vs. 0.11 for BDCM). In addition, the breath concentrations clearly increase with increasing air concentration for these two events. The breath concentration and blood concentrations correlated closely for the two activities.

The paper concluded the main finding that showering and bathing are two common household water use activities that cause significant increases in exhaled breath concentration of $CHCl_3$. The strong correlation of indoor air and exhaled breath, blood and tap water and blood with $CHCl_3$ while the strong association of $CHCl_3$ found only water and breath, and blood and breath in bathing activities. Further studies are suggested to explore change in these activities can affect exposure.

### 3. Xu and Weisel, 2005

This human exposure assessment study design was conducted in U.S to firstly evaluate the concentration of HK in human's exhaled breath during and following inhalation exposure and secondly to measure the magnitude of dose associated with the inhalation exposure route during showering using in a shower stall and linear compartmental pharmacokinetic models respectively.

Six subjects aged between 25-39 years-old were selected for experiment. The concentration of HKs and chloroform at 25 and 15µg/L in the water sample collected after the exposure began at 5 and 26 minutes. The air and breath sample were collected to isolatedly evaluate the respiratory uptake. Subjects were put on water-proof clothing and shoes throughout the experiment period to avoid dermal contact with water. The Tenax TA (60-80 mesh, Supelco, Inc.) was used to pack the alveolar breath which the breath samples were collected at 10, 15, 20 and 25 minutes during the exposure with sampling duration of 1mn.

The result shown that, during the sampling period, DBPs air concentration in the shower stall rapidly increased after the shower water was turned on and appeared to approach a steady state. The average transfer efficiency values were 0.56, 0.11, and 0.10 for chloroform, DCP and TCP respectively. These estimations are similar to previous studies. The background's mean of breath concentration of chloroform for all subjects was 1.33±0.42µg/m3. This was indicated that only DCP and TCP were detected in the pre-exposure. It was also found that HKs breath concentration decay curve shows to decline more rapidly than chloroform, this was possibly indicating a more rapid metabolism rate. The estimation between 85-90% of the inhaled DCP and TCP were absorbed through the lung barrier while the chloroform was absorbed between forty and eighty percent. Concerning for time, subject and compound effects, the p-value were 0.79, 0.16 and <0.001 respectively. During the vapour phase, DCP and TCP were absorbed through the lung barrier more efficiently than chloroform; this was consistent with their greater water solubility.

The study concluded that HKs are absorbed across the lungs more efficiently than chloroform due to air to breath concentration ratio during exposure was higher for HKs than for chloroform,. The respiratory uptake of HKs during showering is about 25% to 33% than of chloroform. The internal dose of the HKs from a typical shower was equivalent to ingesting about 0.1-0.3L of the drinking water. Thus this indicates that inhalation absorption may be an important exposure route for the HKs. It was suggested that these data could be used to measure DBPs and total exposure and health risk association in drinking waters. Further research involved a larger sample size should be considered to extrapolate these results to the general population.

**4. Xu and Weisel , 2003**

The aim of this exposure assessment were (1) determined the temporal emission profile and the size distribution of the aerosol produced while shower water was on;(2) measured the airborne particulate concentration of HAAs family;(3) evaluated the transfer of semi-volatile HKs from shower water to vapour phase by measuring the concentration of the volatilized HKs in the shower air; and (4) assessed the potential inhalation dose of DBPs during showering. There were 5 methods were employed to in this design: 1) Shower system: experiment shower stall were used; 2) Characterization of the Aerosol size distribution which the aerosols generated by the shower were collected by a typical glass micro-fibber filter; 3) Sampling and analysis of particulate DBPs concentration. Whatman Glass Micro-filters were used to collect aerosols generated by shower. 4) Sampling and analysis of Gas-Phase HK concentration 5) Determination of air exchange rate-breathing zone air sample.

The key finding from this study is concerned with emission rates and the composite decay constants of aerosols increased from 0.11 to 1.24 min-1 as the aerosol diameter increased while the showering was on. The emission rate in aerosol number decreased as the aerosol size decreased. The aerosol number emission rate in the size range of 0.1-0.2 μm was more than 1000 times greater that of the smallest aerosols. Aerosols with diameters greater than 1μm have longer half-lives than the smaller aerosols. The aerosols smaller than 2μm were approximately 0.1 min-1. However, aerosols larger than 2μm had lower decay constants than the smaller aerosols. Regarding to size distribution of aerosols, the majority of the shower-generated aerosols were in the smallest two size fraction ranges (0.1-0.2 and 0.2-0.3μm). The contribution of the smallest aerosols (0.3μm) to total aerosol mass was considerably less than the mass from the largest aerosols (90% for aerosols >1.0μm).The air exchange rate while showering was on and off were 0.14± 0.027 and 0.058 ± 0.023 min-1 respectively. The air exchange rate in the shower stall was approximately twice that when the shower water was off.

The study suggested that inhalation exposure to HAAs during showering will occur predominantly through respiratory uptake of shower-generated aerosols. The average daily dose of particulate HAA calculated for showering was approximately 0.4-1.0 *í*g/day when the HAA concentration in water is approximately 250*í*g/L.The inhalation dose of each HAA was much lower than the corresponding daily average ingestion dose of the compound (less than 0.5%), which indicates that the potential inhalation exposure to particulate HAAs during showering is not expected to contribute significantly to the total exposure. However, shower-generated airborne HAAs will also increase the air HAA concentration throughout the home since dry HAA particles will remain in the air after the water evaporates from the aerosol. The daily doses of particulate HKs were also an insignificant fraction of their daily ingestion doses. However, the daily inhalation doses of vaporized DCP and TCP during showering were found to be 10.2 and 6.7 *í*g/day, respectively, which represent 29% and 19% of the ingestion dose,

respectively. Additional inhalation exposure to HKs will also occur after an individual leaves the shower stall. It is therefore important to consider inhalation exposure to HKs when estimating their risk in drinking water.

**5. Nodelman V. and Ultman J, 1999**

This human exposure assessment study design aimed to observe the longitudinal distribution of chlorine ($Cl_2$) absorption in intact human airways during quiet breathing by employing the non-invasive bolus inhalation method. Ten healthy adult aged from 18-40 years old (Five males) were recruited. Bolus inhalation system measuring clean air and chlorinated air and $Cl_2$ concentration were collected. After the 2 minutes of clean air breathing, one expired breath sample was collected immediately, and at the last of a 2 minute exposure to 0.5ppm $Cl_2$, three replicate breath samples were obtained.

Among the five subjects, only two of the twenty expired breath samples collected were found in chlorinated vapours. In these cases, the concentration of the chlorinated compound in the breath sample was on the order of 0.002 ppm. Because the minimum detection limit of the thermionic ionization analyzer was 10 times larger than this, expired chlorinated compounds were unlikely to affect the $Cl_2$ bolus measurements. Bolus measurements were made during nasal and oral quiet breathing among the ten subjects participated in a 2- to 4-h session. At a predetermined time during inhalation, the data-acquisition system automatically injected a 10-ml $Cl_2$ bolus into the inspired airflow. The anatomy of the respiratory system of each subject was characterized by measurements of forced vital capacity (FVC) by using a forced spirometer, and dead space by using a previously described nitrogen-washout apparatus. Bolus inhalation data, compartmental and the overall mass transfer coefficient were analysis.

Results shown the inhaled $Cl_2$ boluses were completely absorbed immediately distal to the upper airways at a pharyngeal volume of 80 ml. The relationship of nasal and oral absorptions shown there was similar for both modes of breathing. However, the oral value is approximately larger than nasal values at volume that larger 10 ml. It was suggested that the mass transfer in the hypophrarynx was not markedly affected by modes of breathing or the inhaled $Cl_2$ in the nasal or oral compartments. Measurements of the $Cl_2$ during nasal and oral quiet breathing indicated that .95% of inspired $Cl_2$ was absorbed in the upper airways of all subjects, whereas the dose delivered to the respiratory air spaces was negligible. Although there were no statistically significant gender differences in the results, individual values of oral were inversely correlated with individual values of oral volume.

The study concluded that from the bolus inhalation measurements, it is clear that nearly all of the $Cl_2$ inhaled during quiet breathing is absorbed in the upper airways, whether the nose or the mouth is the site of air access. This suggested that diffusional resistance in the nasal mucosa was negligible relative to diffusional resistance in the respired gas. The high absorptivity of $Cl_2$ in

the upper airways and the domination of the gas-phase diffusion resistance were attributable to the rapid hydrolysis of $Cl_2$ in the mucosa.

**6. Rotman et al., 1983**

This human experimental exposure study design was aimed to examine the effect of low concentration of chlorine on pulmonary function in human. The experiment was conducted to expose to extreme low chlorine gas at 0.5 or 1 parts per million (ppm). Eight healthy volunteers without smoking history and completed test of pulmonary function before the experiment conducted. Samples entered the champers arranged to allow airflow pattern circulating fans. Chlorine gas was introduced into inlet ports at periphery of chamber. Air samples were taken for analyses of chlorine eight times a day. On the exposure day the measure chlorine concentrations throughout the day were 0.45 ± 0.12 (mean and SD) and 0.95 to 0.12 ppm for the 0.5 and 1-ppm exposures, respectively. The analysis method was conducted for pre-exposure, exposure and post-exposure at 0.5 and 1ppm.

Results shown that, for the 1-ppm exposure, there were many differences between the sham and exposure days. There was a greater change in FEV, PEFR, $FEF_{50}$, $FEF_{25}$, TLC, Raw, and ANZ after only 4 h of exposure. After the full 8-h exposure, there was a greater change in FVC, FEV1, FEV1%, PEFR, $FEF_{50}$, $FEF_{25}$, and Raw. Two hours after the full 8-h exposure, there was still a greater percent difference from base line in FVC and FEV1, and even the next day some changes were still present. The change in FEV1 from the base line was greater after 4h of the 1-ppm exposure than after 8 h of the 0.5-ppm exposure. There were no other significant differences observed. In the longitudinal analysis, after 8h of the 0.5-ppm exposure, there was a decrease in $FEF_{50}$ and ERV and an increase in Raw. After 8h there was a decrease in FVC, FEV1, FEV1%, $FEF_{50}$, and $FEF_{25}$. Two hours after the full 8-h sham exposure, there was a decrease in FVC, FEV1%, and DLco. The base-line values for some tests differed from each other on the experimental days. TLC was smaller before the 0.5ppm exposure than before the 1-ppm exposure; Raw was smaller before the 1-ppm exposure than before the 0.5ppm exposure.

In conclusion, changes were apparently dose related being more marked after eight hours of exposure than after four hours and after 1-ppm exposure than after 0.5-ppm exposure. The author concluded that the exposure even at low concentration can adversely but transiently affect pulmonary function and the observed change in magnitude is related to the total dose received.

**Appendix 2: Characteristics and main outcome of included studies**

| N° | Rf ID | Paper title, author, year of study | Location and setting | Study type, study aim and study design | Exposure | Population and age | Duration | Core outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | 6 | Changes in breath trihalomethane levels resulting from household water-use activities.S. M. Gordon, M. C. Brinkman, D. L. Ashley, B. C. Blount, C. Lyu, J. Masters, and P. C. Singer. Environ.Health Perspect. 114 (4):514-521, 2006. | US: Texas and North Carolina 2 single private homes | **Study type:** Experiential Exposure Assessment<br>**Study aim:** To examine exhaled breath measurements, which common household water-use activities lead to an increase in the internal dose levels of CHCl3 and other potentially harmful THMs in the human body.<br>**Study design:** Two homes selected from TX and NC based on assumption of different THMs in these 2 areas. 7 sujects selected. Air sample collected at baseline and during activities to evaluation inhalation exposure. Blood sample and water sample collected | THM at indoor air: CHCl3 and BDCM | 7 subjects (4 males & 3 females) aged from 21-30 yrs | 2 Week- 1 day in a week | Mean water concentration of TX for CHCl3 and BDCM were much higher than NC. CHCl3 exposure during showering was highly significant for breath and air, blood and breath, air and blood. For bathing, only water-breath, and blood-air correlation are significant. Showing and bathing is common household water-used that cause significant increase in exhale breath concentration of CHCl3. showering indicated strong correlation for indoor air and exhaled breath. Further studies should explore changes in these activities. |
| 2 | 607 | Exposure to inhaled THM: Comparison of continuous and event-specific exposure assessment for epidemiologic purposes. N. Thiriat, H. Paulus, Bot B. Le, and P. Glorennec. Environment International 35 (7):1086-1089, 2009. | Rennes, France. Indoor air at children home and swimming pool | **Study type:** Human Exposure Assessment.<br>**Study aim:** To compare continuous exposure to inhaled THM with main event-specific exposure ( bathing at home, and in indoor swimming pool).<br>**Study design:** Two methods for assessing THM inhalation: a direct method with personal monitors assessing continuous exposure and an indirect one with microenvironmental sampling and collection of time-activities data during the main events exposure: bathing, showering and swimming. | THMs exposure | 30 children aged 4-10 yrs selected from family of EHESP staff | 7 days | 26 children observed. Mean time in bath is 23mn and 30 in showering. THM concentration in air were dominated by CHCl3 in bathroom, median is 7.3µg/m3. this finding is consistent with previous study. Study suggested Chloroform appears to be the most interesting THM for testing an association between THM exposure and respiratory effects because of its abundance. but certainly can not rule out the possibility that other compound are hazardous. |

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| 3 | 741 | Effects of low concentrations of chlorine on pulmonary function in humans. H. H. Rotman, M. J. Fliegelman, T. Moore, and al et. Journal of Applied Physiology: Respiratory, Environmental & Exercise Physiology 54:1120-1124, 1983. | Michigan, US. Chamber setting | **Study type:** Human experimental exposure<br>**Study aim:** examined the effect of low concentration of chlorine on pulmonary function in human.<br>**Study design:** extremely low chlorine gas at 0.5 or 1 part per million (ppm).8 healthy volunteers without smoking history and completed test of pulmonary function before the experiment conducted. Sample entered the champers arranged to allow airflow pattern circulating fans. Chlorine gas introduced into inlet ports at periphery of champers. air sample taken for analyses of chlorine eight time a day. Mean of chlorine concentration 0.45-0.12 on the day exposure and 0.95-0.12ppm for the 0.5-1ppm exposures. Pre-exposure, exposure and post-exposure were analysed at 0.5 and 1ppm to observed FVC, FEV1FEV1%, PEFR, FEF50, FEF25, ERV, RV,TLC,FRC,TGV, Raw, Dlco, Slope phase III. | Low Cl2 gas concentration exposure at 0.5 or 1 part per million (ppm) in arranged champers | 8 healthy volunteers from 19-33 years-old | 1 week and 4 and 8 hours of exposure per day were observed at 0.5 and 1ppm. 2 hours and a day post exposures followed | The changes were apparently dose related. Raw values informed that changes in airway functions were found after exposure to 0.5ppm and consisted of decreased flow rate and increased airways resistance the dose and duration related after 4h and 8h; and 0.5 and 1 ppm exposures. TLC and FRC decreased at 0.5 exposures but increased at 1ppm. With 1ppm exposure, there were obvious changes in airway mechanics. Study concluded that in even low concentration can adversely affect pulmonary function and that the magnitude of the changes observed is related to the total dose received. The long term effects of such low concentration remain to be elucidated. |
| 4 | 13 | Inhalation exposure to haloacetic acids and haloketones during showering. X. Xu and C. P. Weisel. 37 (3):569-576, 2003. | New Jesrey, US | **Study type:** Risk Assessment<br>**Study aim:** were (1) determined the temporal emission profile and the size distribution of the aerosol produced while shower water was on;(2) measured the airborne particulate concentration of HAAs family;(3) evaluated the transfer of semi-volatile HKs from shower water to vapour phase by measuring the concentration of the volatilized HKs in the shower air; and (4) assessed the potential inhalation dose of DBPs during showering. | HAAs and HKs inhalation exposure | N/A | Not mentioned | Emission rates and the composite decay constants of aerosols increased from 0.11 to 1.24 min-1 as the aerosol diameter increased while the showering was on. The emission rate in aerosol number decreased as the aerosol size decreased. The air exchange rate in the shower stall was approximately twice that when the shower water was off. The average daily dose of particulate HAA calculated for |

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| | | | | **Study design:**1) Shower system: shower stall were used.2) Characterization of the Aerosol size distribution: Lasair model 1002 optical counter was used. 3) Sampling and analysis of particulate DBP concentration: Whatman Glass Micro filters were used to collect aerosols generated shower. 4) Sampling and analysis of Gas-Phase HK concentration<br>5) Determination of air exchange rate-breathing zone air sample. | | | | showering was approximately 0.4-1.0 íg/day when the HAA concentration in water is approximately 250íg/L.The daily inhalation doses of vaporized DCP and TCP during showering were found to be 10.2 and 6.7 íg/day, respectively. |
| 5 | 742 | Human respiratory uptake of chloroform and haloketones during showering. X. Xu and C. P. Weisel. Journal of Exposure Analysis and Environmental Epidemiology 15 (1):6-16, 2005. | New Jersey, US | **Study type:** Human exposure Assessment<br>**Study aim:** to measure the HK concentration in exhaled breath of human subjects during and following inhalation exposure in a shower stall; and to estimate the magnitude of dose associated with the inhalation exposure route during showering for the HKs using linear compartmental pharmacokinetic models.<br>**Study design:** 6 subjects selected. Water sample collected after showering. the air and breath were collected and analysis | HKs and CHCl3 exposures | 24-39 | Sample were collected between 5-25 minute | Air and breath concentration ratio during exposure was higher for HKs than chloroform, indicating that HKs are absorbed than chloroform. HKs respiratory uptake during showering is about 1/4-1/3 than chloroform. Inhalation absorption may be important exposure route for HKs. As small proportion of the absorbed dose was expired after exposure, indicating the majority of the dose is metabolised in human body. This can be used to evaluate total exposure and association health risk of DBPs and drinking water. Further extrapolation needed. |

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| 6 | 709 | Longitudinal distribution of chlorine absorption in human airways: comparison of nasal and oral quiet breathing. V. Nodelman and J. S. Ultman. Journal of applied physiology: respiratory, environmental and exercise physiology, 1999 Jun, 86(6):1984-93: environmental-9384, 1999. | Pennsylvania, US. Experimental laboratory | **Study type:** Human Exposure Assessment.<br>**Study aim:** The purpose of the study is to observe the longitudinal distribution of Cl2 absorption in intact human airways during quiet breathing by employing the non-invasive bolus inhalation method that was previously developed for Ozone.<br>**Study design:** 10 healthy adult (5male). Bolus inhalation system measuring clean air and chlorinated air and Cl2 concentration | low level Cl2 inhalation exposure | 10 healthy adult (5male) aged 18-40 yrs | 7 days | Distribution of Cl2 during nasal and oral quiet breathing indicated > 95% of inspired Cl2 was absorbed in the upper airways where the dose delivered to the respiratory air spaces was negligible. Study suggested that diffusional resistance in the nasal mucosa was negligible relative to diffusional resistance in the respired gas. Both high absorptivity of Cl2 in the upper airways and the domination of the gas-phase diffusion resistance were attributable to the rapid hydrolysis of Cl2 in the mucosa. |

**Appendix 3: Papers excluded and reasons for exclusion**

| N° | Paper ID | Article | Reason for exclusion |
|---|---|---|---|
| 1 | 779 | Acute lung injury induced by chlorine inhalation in C57BL/6 and FVB/N mice. 0 X. Tian, H. Tao, J. Brisolara, J. Chen, R. J. Rando, and G. W. Hoyle. Inhalation Toxicol. 20 (9):783-793, 2008. | This study examined only chlorine inhalation exposure which not consider for THMs and other by products |
| 2 | 815 | Assessment of airborne exposure to trihalomethanes from tap water in residential showers and baths.B. D. Kerger, C. E. Schmidt, and D. J. Paustenbach. Risk Analysis 20 (5):637-651, 2000. | This exposure assessment study was to measure the average airborne concentration of Chloroform (TCM) and other two THMs generated from showering and taking baths in chlorinated water. However, did not consider the inhalation exposure and respiratory tracts |
| 3 | 83 | Acute respiratory responses of the mouse to chlorine. J. B. Morris, W. S. Wilkie, and D. J. Shusterman. Toxicol.Sci. 83 (2):380-387, 2005. | This study examined only chlorine inhalation exposure which not consider for THMs and other by products |
| 4 | 819 | Asthma characteristics in cleaning workers, workers in other risk jobs and office workers.J. P. Zock, M. Kogevinas, J. Sunyer, D. Jarvis, K. Toren, J. M. Anto, and European Community. European Respiratory Journal 20 (3):679-685, 2002. | This study evaluated characteristics of asthma risk and of the clinical picture of asthma among cleaning worker which exposed to molecular weight (MW) agents |
| 5 | 507 | Asthma, chronic bronchitis, and exposure to irritant agents in occupational domestic cleaning: A nested case-control study.M. Medina-Ramon, J. P. Zock, M. Kogevinas, J. Sunyer, Y. Torralba, A. Borrell, F. Burgos, and J. M. Anto. Occup.Environ.Med. 62 (9):598-606, 2005. | Identified which agents in occupational domestics cleaning related to asthma and chronic bronchitis. The study examined the activities that might link to irritant exposure in occupational setting and home. But did not indicate the exposure of by products from tap or drinking water. |
| 6 | 161 | Chronic rhinitis in workers at risk of reactive airways dysfunction syndrome due to exposure to chlorine. C. Leroyer, J. L. Malo, D. Girard, J. G. Dufour, and D. Gautrin. Occupational & Environmental Medicine 56 (5):334-338, 1999. | This study addressed accidental chlorine exposure |
| 7 | 410 | Chlorine: State of the art.R. B. Evans. Lung 183 (3):151-167, 2005. | This study addressed only Chlorine gas toxicity |
| 8 | 698 | Chlorine-induced injury to the airways in mice. James G. Martin, Holly R. Campbell, Hiroaki Iijima, Denyse Gautrin, Jean Luc Malo, David H. Eidelman, Qutayba Hamid, and Karim MaghniAmerican journal of respiratory and critical care medicine, 2003 Sep 1, 168(5):568-74.Epub: 2003 Apr 30:2003-2074, 2003. | This study examined only chlorine inhalation exposure which not consider for THMs and other by products |
| 9 | 664 | Chlorination products: emerging links with allergic diseases. A. Bernard. Current medicinal chemistry, 2007, 14(16):1771-82:2007-2082, 2007. | This study is kind of review addressed chlorination products exposure including pool exposure. |
| 10 | 810 | Does chloroform exposure while showering pose a serious public health concern? D. Decker, S. R. DiNardi, and E. J. Calabrese. Medical Hypotheses 15 (2):119-123, 1984. | This paper is editorial paper and not focus on the particular subject for this reveiw |
| 11 | 801 | Dermal uptake of chloroform and haloketones during bathing.X. Xu and C. P. Weisel. Journal of Exposure Analysis and Environmental Epidemiology 15 (4):289-296, 2005. | This study assessed only the exposure, did not examine the respiratory effects outcome |
| 12 | 419 | Determinants of airway response to challenge with distilled water in a population sample of children aged 7 to 10 years old.T. Frischer, M. Studnicka, M. Neumann, and M. Gotz. Chest 102 (3):764-770, 1992. | This study examined only exposure of drinking distilled water. |

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| 13 | 808 | Exposure estimates to disinfection by-products of chlorinated drinking water. C. P. Weisel, H. Kim, P. Haltmeier, and J. B. Klotz. Environ.Health Perspect. 107 (2):103-110, 1999. | Study aim: evaluated how well drinking water concentrations measured within home correlated with biomarker concentration and weather an improvement in the association in achieved using exposure estimates based on the water concentrations combined questionnaire data about activities surrounding water uses. |
| 14 | 231 | Evaluation of dermal and respiratory chloroform exposure in humans. Levesque, P. Ayotte, A. LeBlanc, E. Dewailly, D. Prud'Homme, R. Lavoie, S. Allaire, and P. Levallois. .231. Environ.Health Perspect. 102 (12):1082-1087, 1994. | The study examined only the concentration of chloroform exposure and body burden and the outcome of the study was not related to the review |
| 15 | 820 | Exhaled human breath measurement method for assessing exposure to halogenated volatile organic compoundsJ. D. Pleil and A. B. Lindstrom. . Clinical Chemistry 43 (5):723-730, 1997. | This study assessed the concentration for halogenated volatile organic compound. Did not addressing respiratory health effect outcome |
| 16 | 15 | Exposure of pregnant women to tap water related activities. Occupational & Environmental Medicine.S. Kaur, M. J. Nieuwenhuijsen, H. Ferrier, and P. Steer. 61 (5):454-460, 2004. | This study determined the activities which exposure to tap water related water only among pregnant women. Did not consider DBP or THMs inhalation. |
| 17 | 806 | Eye and respiratory symptoms in poultry processing workers exposed to chlorine by-products.B. S. King, E. H. Page, C. A. Mueller, D. D. Dollberg, K. E. Gomez, and A. M. Warren. American Journal of Industrial Medicine 49 (2):119-126, 2006. | This paper has no clear statement of objective and research question |
| 18 | 811 | Health impacts of long-term exposure to disinfection by-products in drinking water in Europe: HIWATE.M. J. Nieuwenhuijsen, R. Smith, S. Golfinopoulos, N. Best, J. Bennett, G. Aggazzotti, E. Righi, G. Fantuzzi, L. Bucchini, S. Cordier, C. M. Villanueva, V. Moreno, Vecchia C. La, C. Bosetti, T. Vartiainen, R. Rautiu, M. Toledano, N. Iszatt, R. Grazuleviciene, and M. Kogevinas. Journal of Water & Health 7 (2):185-207, 2009. | The aim of the HIWATE study was to investigate potential human health risks (e.g. bladder and colorectal cancer, premature births, SGA, semen quality, stillbirth, congenital anomalies) associated with long-term exposure to low levels of disinfectants (such as chlorine) and DBPs occurring in water for human consumption and use in the food industry. Respiratory adverse effects were not considered. |
| 19 | 743 | House cleaning with chlorine bleach and the risks of allergic and respiratory diseases in children.M. Nickmilder, S. Carbonnelle, and A. Bernard. Pediatric Allergy and Immunology 18 (1):27-35, 2007. | Cross-sectional study to evaluate the potential health impact of house cleaning with bleach and not cleaned disinfectant and the respiratory health of children. The study were examined the disinfection by products inhalation. |
| 20 | 4 | Influence of tap water quality and household water use activities on indoor air and internal dose levels of trihalomethanes. J. R. Nuckols, D. L. Ashley, C. Lyu, S. M. Gordon, A. F. Hinckley, and P. Singer. Environ.Health Perspect. 113 (7):863-870, 2005. | The purpose of the study was to provide a description of the method used in this study and a summary of the result and the finding are relevant to the design and implementation of epidemiologic studies concerning exposure to volatile water supply contaminants. Did not examine inhalation exposure. |
| 21 | 336 | Inhalation exposure in the home to volatile organic contaminants of drinking water. J. B. Andelman. Science of the Total Environment VOL. 47 (pp 443-460):-460, 1985. | This study addressed Trichloroethylene concentration inhalation. Did not discuss the respiratory effect outcome |
| 22 | 11 | Ingestion, inhalation, and dermal exposures to chloroform and trichloroethene from tap water.C. P. Weisel and W. K. Jo. I Environ.Health Perspect. 104 (1):48-51, 1996. | This study assessed only human exposure to Trichloroethylene from the contaminated air and water in home. The result found that the air in the vicinity of the shower water was found to increase in TCE concentration with time. The air concentrations of TCE were dependent as expected on |

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| | | | several factors including water temperature and height of drop path. Do not reveal the outcome human respiratory health effects from this exposure |
| 23 | 34 | Indoor air quality and respiratory health of children. P. J. Franklin. Paediatric Respiratory Reviews 8 (4):281-286, 2007. | This paper is editorial-Mini symposium. By products was not addressed |
| 24 | 492 | Indoor risk factors for asthma and wheezing among Seattle school children.W. C. Maier, H. M. Arrighi, B. Morray, C. Llewellyn, and G. J. Redding. Environ.Health Perspect. 105 (2):208-214, 1997. | This study addressed other indoor air concentration rather than THMs. |
| 25 | 708 | Longitudinal distribution of chlorine absorption in human airways: a comparison to ozone absorption V. Nodelman and J. S. Ultman. Journal of applied physiology: respiratory, environmental and exercise physiology, 1999 Dec, 87(6):2073-80: environmental-8073, 1999. | The study addressed only chlorine gas inhalation |
| 26 | 812 | Longitudinal distribution of ozone and chlorine in the human respiratory tract: simulation of nasal and oral breathing with the single-path diffusion model.M. L. Bush, W. Zhang, A. Ben-Jebria, and J. S. Ultman. Toxicology & Applied Pharmacology 173 (3):137-145, 2001. | The study addressed only chlorine gas inhalation |
| 27 | 209 | Occupational asthma due to chloramine-T solution.V. M. Kujala, K. E. Reijula, E. M. Ruotsalainen, and K. Heikkinen. Respiratory Medicine 89 (10):693-695, 1995. | A case report which was not addressed THMs |
| 28 | 8 | Risk from exposure to trihalomethanes during shower: probabilistic assessment and control.S. Chowdhury and P. Champagne. Science of the Total Environment 407 (5):1570-1578, 2009. | This study addressed probabilistic approach on human health risk Assessment and risk characterization to predict cancer and non cancer risk from exposure to THMs. Predicted cancer risk were estimated is higher in Ottawa than Hamilton and Toronto. The cities with higher concentration of THMs likely to be higher risk from exposure to THMs. The outcome only considers cancer and non cancer risk. |
| 29 | 814 | Short-term respiratory effects of cleaning exposures in female domestic cleaners. M. Medina-Ramon, J. P. Zock, M. Kogevinas, J. Sunyer, X. Basagana, J. Schwartz, P. S. Burge, V. Moore, and J. M. Anto. European Respiratory Journal 27 (6):1196-1203, 2006. | The study evaluated only sort term effect of transient cleaning exposure. By-products or THMs were not considers. |
| 30 | 623 | The TEAM Study: Personal exposures to toxic substances in air, drinking water, and breath of 400 residents of New Jersey, North Carolina, and North Dakota.L. A. Wallace, E. D. Pellizzari, and T. D. Hartwell. Environ.Res. 43 (2):290-307, 1987. | The study only addressed concentration of chloroform and other toxic substances in indoors air. No related respiratory health effects were measured. |
| 31 | 14 | The relationship between water concentrations and individual uptake of chloroform: a simulation study. H. J. Whitaker, M. J. Nieuwenhuijsen, and N. G. Best. Environ.Health Perspect. 111 (5):688-694, 2003. | The pooling study examined only the concentration of chloroform exposure and uptake which pooled the statistical data from previous epidemiological study. |

## Appendix 4: Search strategies in electronic databases

### MEDLINE

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Molika Bou, Sheffield University

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| | # ▲ | Searches | Results | Search Type | Actions |
|---|---|---|---|---|---|
| | 1 | exp Trihalomethanes/ | 5366 | Advanced | Display More ≫ |
| | 2 | exp Halogenation/ | 393 | Advanced | Display More ≫ |
| | 3 | exp Water Supply/ or exp Chlorine/ or exp Water Purification/ or exp Disinfectants/ or exp Trihalomethanes/ | 91784 | Advanced | Display More ≫ |
| | 4 | Chloroform/ | 4956 | Advanced | Display More ≫ |
| | 5 | exp Asthma, Exercise-Induced/ or exp Asthma/ | 88743 | Advanced | Display More ≫ |
| | 6 | exp Respiratory Sounds/ | 7805 | Advanced | Display More ≫ |
| | 7 | exp Respiratory System/ | 328997 | Advanced | Display More ≫ |
| | 8 | exp Bronchitis, Chronic/ | 569 | Advanced | Display More ≫ |
| | 9 | exp Infant/ | 799343 | Advanced | Display More ≫ |
| | 10 | exp Child/ | 1300127 | Advanced | Display More ≫ |
| | 11 | exp Adult/ | 4494136 | Advanced | Display More ≫ |
| | 12 | Animals/ | 4470578 | Advanced | Display More ≫ |
| | 13 | 1 or 2 or 3 or 4 | 92080 | Advanced | Display More ≫ |
| | 14 | 5 or 6 or 7 or 8 | 411224 | Advanced | Display More ≫ |
| | 15 | 9 or 10 | 1703124 | Advanced | Display More ≫ |
| | 16 | 9 or 10 or 11 or 12 | 9961433 | Advanced | Display More ≫ |
| | 17 | 13 and 14 | 1492 | Advanced | Display More ≫ |
| | 18 | 16 and 17 | 1170 | Advanced | Display More ≫ |
| | **19** | **limit 18 to (full text and english language)** | **326** | **Advanced** | Display More ≫ |

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Saved Searches/Alerts

**Search History** (20 searches) (Click to close) View Saved

| | # ▲ | Searches | Results | Search Type | Actions |
|---|---|---|---|---|---|
| ☐ | 1 | exp water/ or exp drinking water/ or exp trihalomethane/ or exp chlorination/ or exp chlorine/ or exp water treatment/ or exp chloroform/ | 144013 | Advanced | Display More ≫ |
| ☐ | 2 | exp drinking water/ or exp haloacid/ | 27895 | Advanced | Display More ≫ |
| ☐ | 3 | exp asthma/ or exp allergic asthma/ or exp occupational asthma/ | 94258 | Advanced | Display More ≫ |
| ☐ | 4 | exp wheezing/ | 8010 | Advanced | Display More ≫ |
| ☐ | 5 | exp chronic bronchitis/ | 6092 | Advanced | Display More ≫ |
| ☐ | 6 | exp respiratory system/ | 278516 | Advanced | Display More ≫ |
| ☐ | 7 | infant/ | 183652 | Advanced | Display More ≫ |
| ☐ | 8 | child/ | 394487 | Advanced | Display More ≫ |
| ☐ | 9 | exp childhood disease/ or exp childhood/ | 75245 | Advanced | Display More ≫ |
| ☐ | 10 | adult/ | 2335002 | Advanced | Display More ≫ |
| ☐ | 11 | human/ | 6798939 | Advanced | Display More ≫ |
| ☐ | 12 | exp animal/ | 24378 | Advanced | Display More ≫ |
| ☐ | 13 | 1 or 2 | 152753 | Advanced | Display More ≫ |
| ☐ | 14 | 3 or 4 or 5 or 6 | 359976 | Advanced | Display More ≫ |
| ☐ | 15 | 7 or 8 or 9 or 10 or 11 or 12 | 6856709 | Advanced | Display |
| ☐ | 16 | 7 or 8 or 9 | 536093 | Advanced | Display More ≫ |
| ☐ | 17 | 13 and 14 | 1668 | Advanced | Display More ≫ |
| ☐ | 18 | 15 and 17 | 877 | Advanced | Display More ≫ |
| ☐ | 19 | 16 and 17 | 108 | Advanced | Display More ≫ |
| ☐ | 20 | limit 18 to (full text and english language) | 330 | Advanced | Display More ≫ |

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☐ Commented

(Choose one or more specific statuses above and use this option to limit these selections to commented articles.)

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**cochrane search 5 Jan 2010**

| ID | Search | Hits | Edit | Delete |
|---|---|---|---|---|
| #1 | (trihalomethanes) or (chlorination by-products):ti or (drinking water):au or (chloroform):ab or (chlorine):kw in Cochrane Reviews, Other Reviews and Clinical Trials | 115 | edit | delete |
| #2 | (haloacetic acids ) or (haloacetonitriles):ti or (haloketones):au or (tap water):ab in Cochrane Reviews, Other Reviews and Clinical Trials | 215 | edit | delete |
| #3 | (asthma) or (wheezing):ti or (chronic bronchitis):au or (respiratory sounds):ab or (respiratory system):kw in Cochrane Reviews, Other Reviews and Clinical Trials | 19260 | edit | delete |
| #4 | (infant) or (child):ti or (children):au or (childhood):ab in Cochrane Reviews, Other Reviews and Clinical Trials | 43427 | edit | delete |
| #5 | (adult) or (human):ti or (animal):au in Cochrane Reviews, Other Reviews and Clinical Trials | 255746 | edit | delete |
| #6 | (#1 OR #2) | 329 | edit | delete |
| #7 | (#6 AND #3) | 3 | edit | delete |
| #8 | (#7 AND #4) | 0 | edit | delete |
| #9 | (#4 OR #5) | 302319 | edit | delete |
| #10 | (#7 AND #9) | 3 | edit | delete |
| #11 | (#7 AND #9) | 3 | edit | delete |

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| AND / OR Combine | Search History |
|---|---|
| #7 | **Search Query #7** ((**infants** or **child** or **children**) or **childhood**) and(((**trihalomethanes** or **chloroform** or **chlorine**) or ((**chlorination by-products**) or (**drinking water**) or (**tap water**)) or ((**haloacetic acids**) or **haloacetonitriles** or **haloketones**)) and((**asthma** or **wheezing** or (**chronic bronchitis**)) or ((**respiratory sound**) or (**respiratory system**)))) (Copy Query)<br>43 Published Works results found in Multiple Databases +<br>1 Tables & Figures result found in ProQuest Deep Indexing: Environmental Sciences<br>3 Web Sites results found in Multiple Web Sites Databases +<br>Date Range: Earliest to Current<br>Limited to:<br>Edit \| Save OR Alert \| View Results \| Delete |
| #6 | **Search Query #6** ((**infants** or **child** or **children**) or (**childhood** or **adult** or **human**) or **animal**) and(((**trihalomethanes** or **chloroform** or **chlorine**) or ((**chlorination by-products**) or (**drinking water**) or (**tap water**)) or ((**haloacetic acids**) or **haloacetonitriles** or **haloketones**)) and ((**asthma** or **wheezing** or (**chronic bronchitis**)) or ((**respiratory sound**) or (**respiratory system**)))) (Copy Query)<br>112 Published Works results found in Multiple Databases +<br>1 Tables & Figures result found in ProQuest Deep Indexing: Environmental Sciences<br>3 Web Sites results found in Multiple Web Sites Databases +<br>Date Range: Earliest to Current<br>Limited to:<br>Edit \| Save OR Alert \| View Results \| Delete |
| #5 | **Search Query #5** ((**trihalomethanes** or **chloroform** or **chlorine**) or ((**chlorination by-products**) or (**drinking water**) or (**tap water**)) or ((**haloacetic acids**) or **haloacetonitriles** or **haloketones**)) and((**asthma** or **wheezing** or (**chronic bronchitis**)) or ((**respiratory sound**) or (**respiratory system**))) (Copy Query)<br>190 Published Works results found in Multiple Databases +<br>1 Tables & Figures result found in ProQuest Deep Indexing: Environmental Sciences<br>4 Web Sites results found in Multiple Web Sites Databases +<br>Date Range: Earliest to Current<br>Limited to:<br>Edit \| Save OR Alert \| View Results \| Delete |
| #4 | **Search Query #4** (**infants** or **child** or **children**) or **childhood** (Copy Query)<br>103046 Published Works results found in Multiple Databases +<br>0 Tables & Figures results found in ProQuest Deep Indexing: Environmental Sciences<br>2210 Web Sites results found in Multiple Web Sites Databases +<br>Date Range: Earliest to 2010<br>Limited to: English Only<br>Edit \| Save OR Alert \| View Results \| Delete |
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# Search Results

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for chlorine inhalation and a: Go

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| Publication date | Title | Author(s) |
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| 1997 | Asthma and asthmatiform dyspnea due to inhalation of simple chemicals | *Kabe, J.; Health and Safety Executive, Buxton (United Kingdom). Translation Services* |
| 1993 | Asthma - inhaled corticosteroid therapy | *Astra Pharmaceuticals Ltd., Kings Langley (United Kingdom)* |
| 1999 | The Self-Regulatory Model and its application to asthma and adherence to inhaled preventative medication | *Jessop, D.C.; Kent Univ., Canterbury (United Kingdom)* |
| 1995 | Audit of paediatric asthma morbidity and inhaler technique in the*school setting | *Austin, J.B; Scottish Office, Edinburgh (United Kingdom). Clinical Resource and Audit Group (CRAG)* |
| 1992 | Application of the country inhalation glucocorticoide, budesonide in treatment of patients with bronchial asthma | *Molotova Tatyana Nikolaevna* |
| 2002 | The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children A systematic review and economic evaluation | *Peters, J.; Stevenson, M.; Beverley, C. (and others); National Coordinating Centre for Health Technology Assessment, Southampton (United Kingdom); NHS R and D HTA Programme, Southampton (United Kingdom)* |
| 1995 | A prospective family study of the formation of allergic respiratory diseases A study of pupils' allergic diseases in southwest Germany. Final report | *Brandis, M.; Freiburg Univ. (Germany). Universitaets-Kinderklinik* |
| 2002 | The epidemiology and management of asthma and atopy in primary care | *Simpson, Colin Richard; University of Aberdeen (United Kingdom)* |
| 2000 | Are children's thoughts and feelings about illness related to medication use and symptom control? An examination of the self regulatory model | *Spong, A.J.; University of East Anglia, Norwich (United Kingdom)* |
| 2002 | Inhaler devices for routine treatment of chronic asthma in older children (aged 5-15 years) | *National Institute for Clinical Excellence (United Kingdom)* |

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# Part II

## Appendix 5: Spatial distribution maps

Figure2.1. Spatial distribution map of WQM stations in Ille-et-Villaine

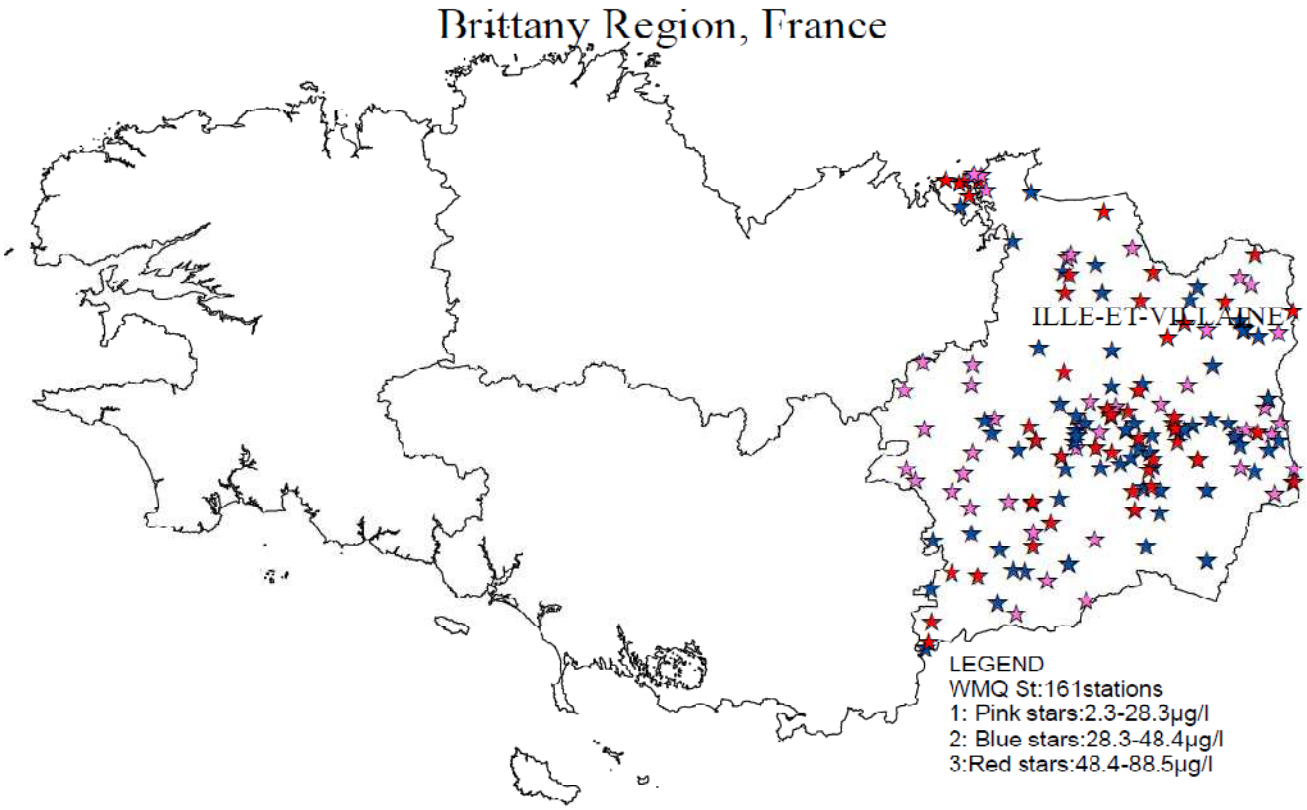



Figure2.2. Spatial distribution map of Pélagie women locations in Ille-et-Villaine

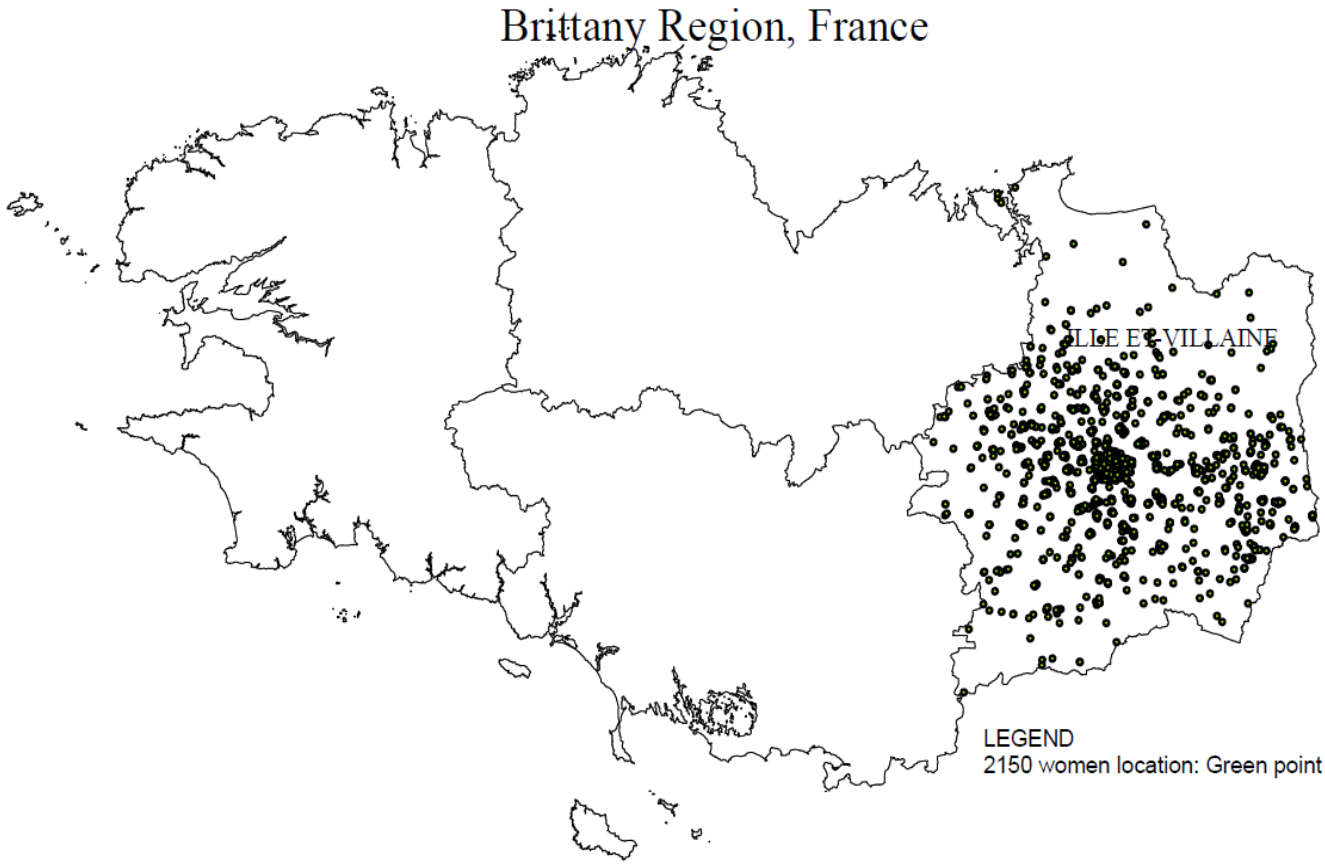
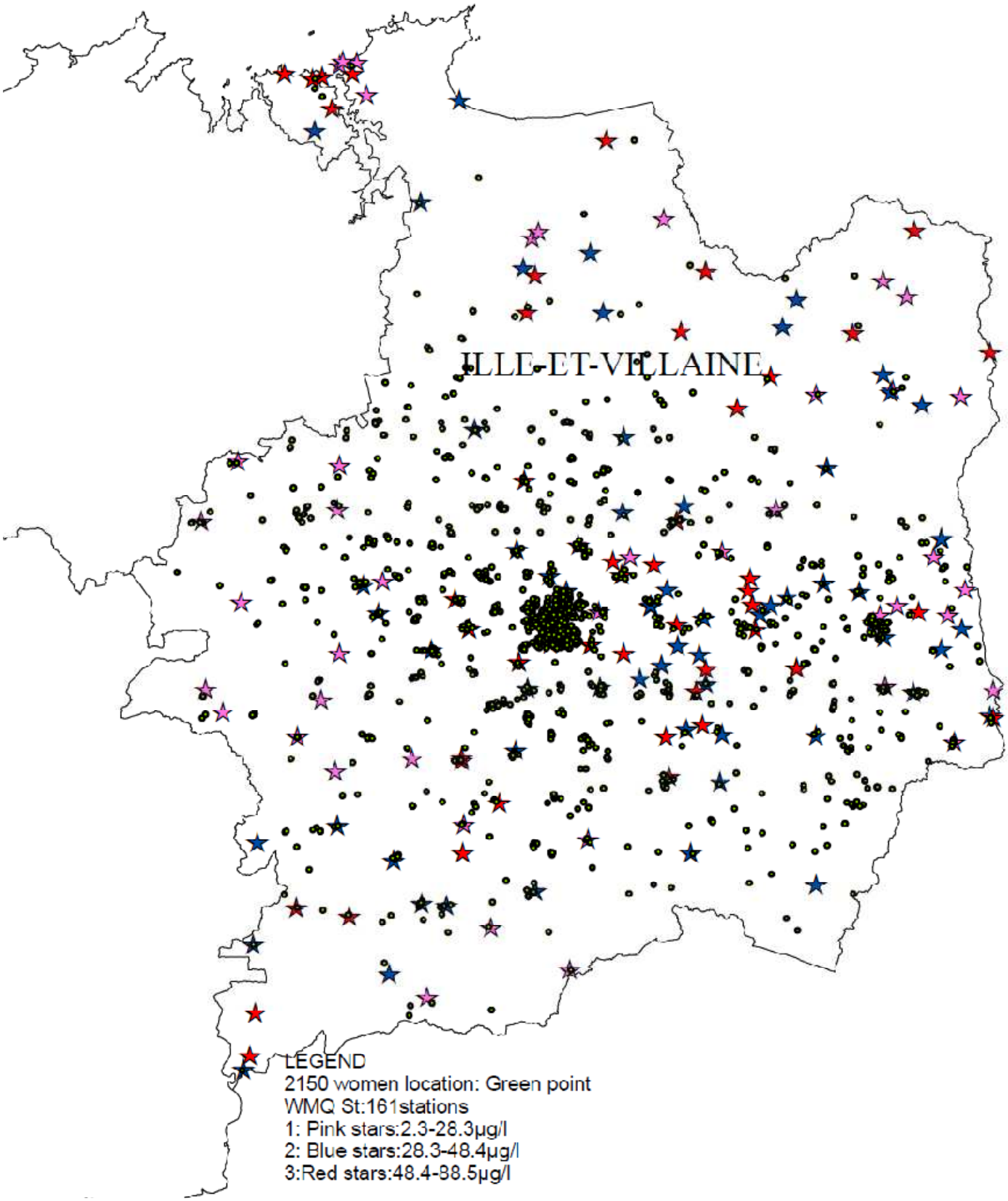


Figure2.3. Spatial distribution map of Pélagie women locations and WQM stations in Ille-et-Villaine



**Appendix 6: Statistic results**

**Table 2.1: Statistic summary of closest distance methods and three buffer radiuses between women cohort locations and WQM stations**

| Variables | Obs | Mean | Std. Dev. |
|---|---|---|---|
| **Closest station** | | | |
| WQM station (1) | 161 | | |
| Women location (2) | 2150 | | |
| Distances between (1)&(2) | | 2233 metres | 2031 |
| THMs concentration-WQM stations | | 36.9 µg/l | 13.6 |
| **Buffer- 1000 metres** | | | |
| Women location | 848 | | |
| THMs concentration of WQM station | | 37.2 µg/l | 10.9 |
| **Buffer-2000 metres** | | | |
| Women Location | 1230 | | |
| THMs concentration of WQM station | | 36.1 µg/l | 11.3 |
| **Buffer- 4000 metres** | | | |
| Women location | 1715 | | |
| THMs concentration of WQM station | | 37.5 µg/l | 10.3 |

**Table 2.2: Percentage of women locations and THMs concentrations reported by closest distance method**

| Percentages | # of women locations | THMs concentrations |
|---|---|---|
| 25% | 515 | 2.3 - 27.8 µg/l |
| 25% | 669 | 28.2 - 36.8 µg/l |
| 25% | 616 | 37.5 - 48.4 µg/l |
| 25% | 350 | 48.7 - 80.2 µg/l |
| 100% | 2150 | 2.3 - 80.2 µg/l |

**Table 2.3: Percentiles of THMs concentrations of the closest method and buffer at three radiuses**

| ***Methods\Percentiles*** | **25%** | **50%** | **75%** | **99%** |
|---|---|---|---|---|
| Closest station | 28.2µg/l | 36.1µg/l | 43.0µg/l | 68.8µg/l |
| Buffer at 1000 metres | 30.1µg/l | 36.8µg/l | 44.2µg/l | 68.8µg/l |
| Buffer at 2000 metres | 28.3µg/l | 34.1µg/l | 44.2µg/l | 68.8µg/l |
| Buffer at 4000 metres | 31.3µg/l | 35.8µg/l | 41.2µg/l | 68.8µg/l |

**Table 2.4. Summary result of Shapiro-Wilk W test for normality for each data set of first closest method and the three radiuses**

| Variable | Obs | W | V | z | Prob>z |
|---|---|---|---|---|---|
| THMs concentration-First closest | 2150 | 0.96204 | 48.074 | 9.877 | 0.00000 |
| THMs concentration- 1000M | 848 | 0.96748 | 17.653 | 7.061 | 0.00000 |
| THMs concentration- 200OM | 1230 | 0.95156 | 36.892 | 9.010 | 0.00000 |
| THMs concentration- 4000M | 1715 | 0.94067 | 61.172 | 10.405 | 0.00000 |

**Table 2.5. Wilcoxon signed-rank test results comparing THMs concentrations of first closest method and three radiuses**

**First closest method = 1000M radius**

| sign | Obs | Sum ranks | Expected |
|---|---|---|---|
| positive | 69 | 50450 | 79340.5 |
| negative | 145 | 108231 | 79340.5 |
| zero | 634 | 201295 | 201295 |
| all | 848 | 359976 | 359976 |
| unadjusted variance | | | 50906606 |
| adjustment for ties | | | -1436.5 |
| adjustment for zeros | | | -21286946 |
| adjusted variance | | | 29618223 |
| Ho: conclosest = con1000m | | | |
| z = -5.309 | **Prob > \|z\| = 0.0000** | | |

**First closest method = 2000M radius**

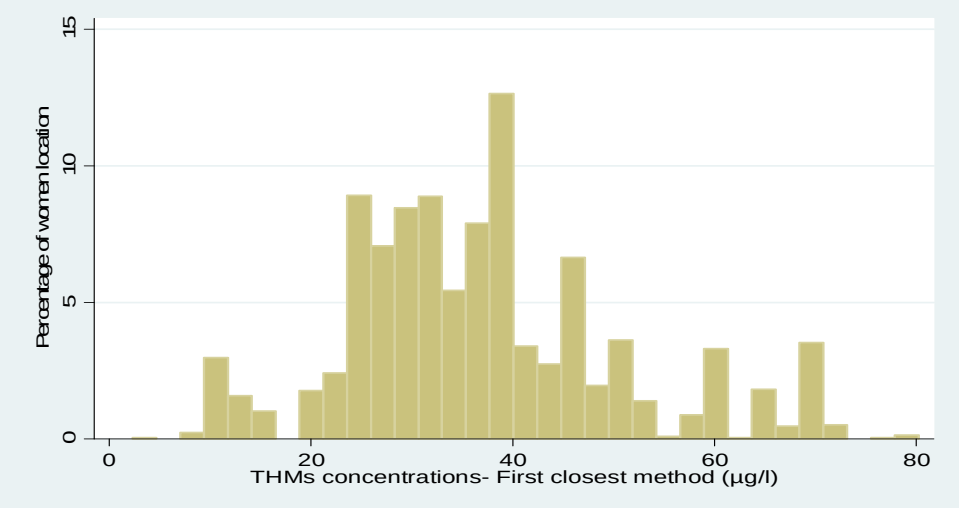
| sign | Obs | Sum ranks | Expected |
|---|---|---|---|
| positive | 304 | 279514 | 299712 |
| negative | 365 | 319910 | 299712 |
| zero | 561 | 157641 | 157641 |
| all | 1230 | 757065 | 757065 |
| unadjusted variance | | | 1.553e+08 |
| adjustment for ties | | | -49941.875 |
| adjustment for zeros | | | -14752570 |
| adjusted variance | | | 1.405e+08 |
| Ho: conclosest = con2000m | | | |
| z = -1.704 | **Prob > \|z\| = 0.0883** | | |

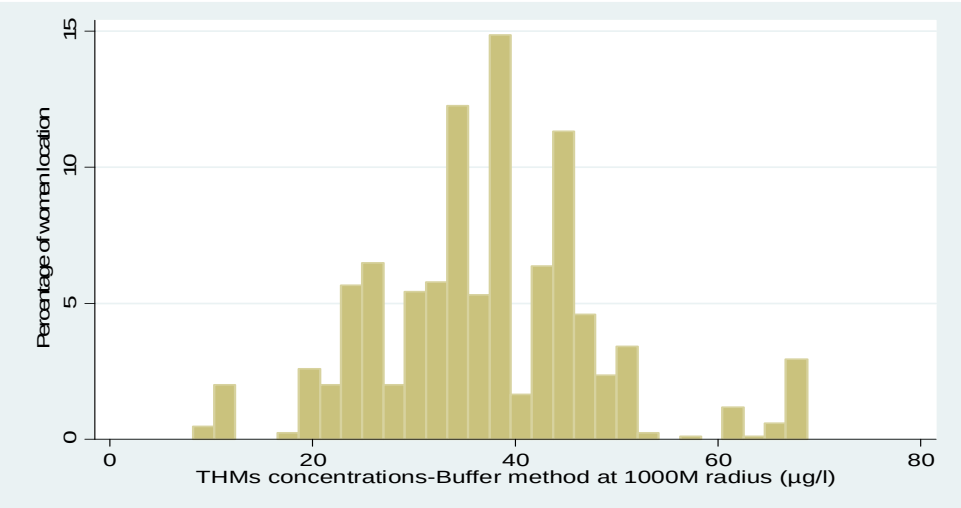
**First closest method = 4000M radius**

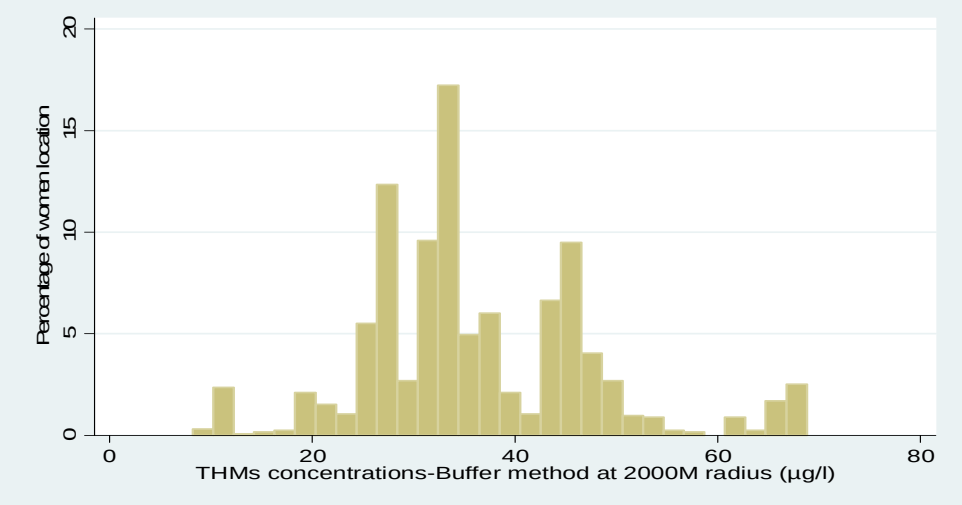
| sign | Obs | Sum ranks | Expected |
|---|---|---|---|
| positive | 482 | 550173.5 | 677050 |
| negative | 749 | 803926.5 | 677050 |
| zero | 484 | 117370 | 117370 |
| all | 1715 | 1471470 | 1471470 |
| unadjusted variance | | | 4.207e+08 |
| adjustment for ties | | | -36183 |
| adjustment for zeros | | | -9477627.5 |
| adjusted variance | | | 4.112e+08 |
| Ho: conclosest = con4000m | | | |
| z = -6.257 | **Prob > \|z\| = 0.0000** | | |

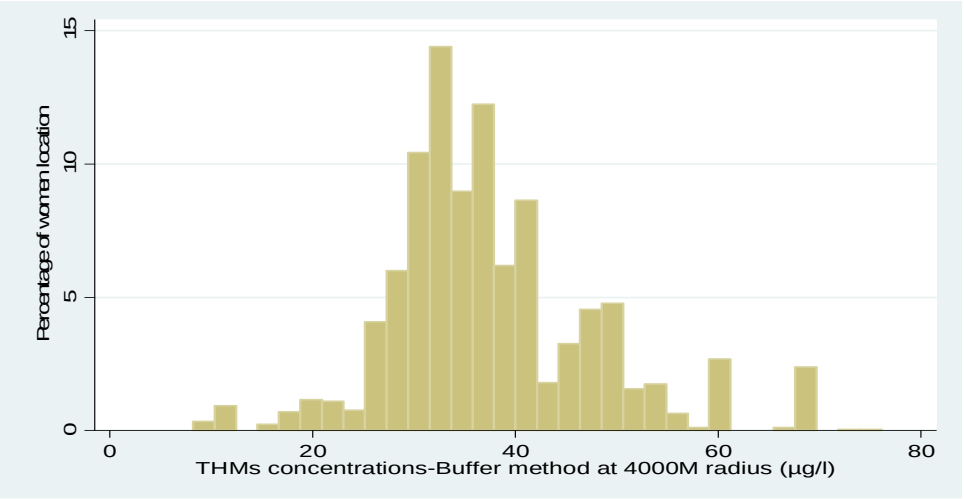
**Appendix 7: Distribution graphs**

Figure 2.4. Distributional graphs of THMs concentrations (µg/l) based on closest distance and three radiuses



# Abstract

**Background:** During water chlorination process, natural organic matters present in raw water supplies react and may produce chlorination by-products (CBPs) which the common CBPs is trihalomethanes (THMs). Studies stressed inhalation is a major pathway of THMs exposures. Respiratory chronic diseases, in particular asthma, might be associated with exposures to CBPs in occupational or pool settings. Low level and long run inhalation exposure to CBPs exists indoor due to their presence in drinking water in association with activities such as showering, bathing or household activities. This might cause airways inflammation eventually yielding asthma.

**Objective:** to assess the association between exposure to CBPs and airway inflammation conditions among infants and children; and to compare two different methods estimating THMs concentrations in Pélagie cohort area in Ille-et Villaine, Brittany region.

**Method:** Systematic review and constructing two different methods, the closest distance method and buffer method, to be compared using statistical.

**Results**: First, eighty papers were considered. Six studies fully met the selection criteria and could be selected, forming the material of the review. There is no finding directly indicates THMs inhalation yields asthma or respiratory inflammation among children. However, chloroform is the most present by-product in the air with showering and bathing as the main exposure activities leading to inhalation. Very low concentration of chlorine with continuous exposure was shown to elicit adverse effects on respiratory tracts. Second, comparing two methods, result suggests two indications. Using the closest method and buffer method, the 2000 metre radius is likely given similar THMs concentration estimations ($p=0.08$); while comparing the closest method and buffer at 1000 or 4000 metres radius, it indicates statistically significant different in estimating THMs concentrations ($p=0.00$).

**Conclusion:** Our review finding shown a lack of evidence to inform the association between inhalation of CBPs and asthma or respiratory inflammation among infant and children. Further research needed to assess possible respiratory effects of long-term continuous exposure during indoor activities. Toxicological approach recommended to response to the absence of evidence on the risk of airways inflammation that is possibly caused by oxidative stress due to CBPs. The two methods (closest and buffer methods) found similar THMs concentration estimation if the buffer is 2000 metres radius. Nevertheless, the smaller or larger radiuses, the two methods are given different THMs concentration estimations.



**Key words:** drinking water, chlorination by-products, trihalomethanes, airways inflammation, asthma, infants, children

**Résumé**

**Rôle des produits dérivés chlorés (DC) dans le développement des conditions inflammation voies respiratoires chez nourrissons et les enfants**

**Contexte:** Pendant le processus de chloration, les matières organiques naturelles présentes dans l'eau brute peuvent former des **produits dérivés chlorés** (DC). Les plus connus sont les trihalométhanes (THM). Différentes études ont souligné que l'inhalation pouvait être une voie majeure d'exposition aux THM et autres sous-produits. Certaines études ont suggéré que les maladies respiratoires chroniques, en particulier l'asthme, pouvaient être associées à l'exposition à certains DC en milieu professionnel ou lors de la baignade en piscine. L'exposition chronique au DC dans l'environnement intérieur est liée à leur présence dans l'eau potable lors des activités telles que la douche, le bain ou les activités domestiques. Ce type d'exposition est susceptible d'entrainer une inflammation des voies respiratoires.

**Objectif :** évaluer l'association entre l'exposition aux produits dérivés chlorés et la survenue de l'inflammation des voies respiratoires chez les nourrissons et les enfants en réalisant une revue bibliographique sur les données d'exposition, les études toxicologiques et épidémiologiques. Par ailleurs, deux méthodes différentes visant à estimer les concentrations de THM au sein de la cohorte Pélagie à partir des concentrations mesurées sur le réseau de distribution ont été développées et comparées, ce travail vise à préparer une étude sur l'exposition environnementale au sein de cette cohorte.

**Méthode :** Revue systématique de la littérature scientifique et construction et comparaison de deux méthodes différentes visant à estimer les concentrations d'exposition aux THM (distance la plus proche et différents buffers).

**Résultats :** quatre-vingts documents ont été examinés. Six études répondent pleinement aux critères de sélection et ont été retenues. Aucun résultat n'indique directement une association entre l'inhalation aux THM et l'asthme ou une inflammation des voies respiratoires chez les enfants dans les études toxicologiques ou dans les études épidémiologiques. Le chloroforme est le plus présent des produits dérivés chlorés dans l'air lors de la douche et le bain. Il a été montré qu'une très faible concentration de chlore en lien avec une exposition chronique pouvait conduire à des effets néfastes sur les voies respiratoires. La comparaison de deux méthodes pour estimer l'exposition aux THM au sein de la cohorte Pélagie montre que la méthode fondée sur la plus courte distance entre le domicile et la station de surveillance sur le réseau de distribution et la méthode de type « buffer » avec un rayon de 2000 mètres conduisent statistiquement aux mêmes résultats ($p = 0.08$).

**Conclusion:** il n'y a pas assez d'évidence pour éclairer le lien entre l'inhalation de produits dérivés chlorés et l'asthme ou une inflammation des voies respiratoires chez les nourrissons et les enfants. D'autres recherches sont nécessaires pour évaluer les éventuels effets respiratoires de l'exposition chroniques au cours des activités dans l'environnement intérieur. Des études toxicologiques sont recommandées à la réponse à l'absence de preuve sur le risque d'inflammation de voies aériennes qui est probablement causée par le stress oxydatif dû aux produits dérivés chlorés. Enfin, les deux méthodes (plus proche distance et la méthode de type « buffer ») conduisent à des résultats similaires pour un rayon mètres 2000.

**Mots clés:** produits dérivés chlorés, trihalométhanes, inflammation des voies respiratoires, l'asthme, nourrissons, l'enfant