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CHLORINATION DISINFECTION BY-PRODUCTS IN DRINKING WATER AND RISK OF PANCREATIC CANCER

by

MINH T. DO

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the School of Graduate Studies and Research
in partial fulfilment of the requirements for the
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CHLORINATION DISINFECTION BY-PRODUCTS IN DRINKING WATER AND RISK OF PANCREATIC CANCER

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ABSTRACT

This thesis studied the effect of chlorination disinfection by-products (CDBPs) in drinking water on the risk of developing pancreatic cancer. The study was based on the case-control component of the National Enhanced Cancer Surveillance System. Incident cases and frequency-matched population controls recruited between 1994 and 1997 from six Canadian provinces were used to estimate pancreatic cancer risks associated with exposure to CDBPs.

Residence history collected from subjects was linked to two sources of water quality data to estimate historical exposure. The first source provided a lifetime average estimate of known exposure to trihalomethane (THM), bromodichloromethane (BDCM), and chloroform (TCM), while the second provided residence-specific estimates of THM exposure. Adjusted risk estimates were based on the most recent 30 years of exposure with missing data imputed using Observed Control Mean Imputation.

Overall, no consistent significant increase (or decrease) in pancreatic cancer risks was observed with 30-year exposure to THM, BDCM, and TCM after adjusting for potential confounders.

Key words: pancreatic cancer, chlorinated disinfection by-products, trihalomethane, chloroform, bromodichloromethane, drinking water, case-control, and risk assessment.

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LIST OF ACRONYMS

BDCM	Bromodichloromethane
DBCM	Dibromochloromethane
CI	Confidence Interval
(C)DBP	(Chlorination) Disinfection Byproducts
DOC	Dissolved Organic Carbon
ETW	Exposure Time Window
HAA(s)	Haloacetic acid(s)
HAN(s)	Haloacetonitrile(s)
KWQD	Kingston Water Quality Data
MAC	Maximum Acceptable Concentration
MUD	Municipal Water Use Database
MX	Mutagen X, 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone
NECSS	National Enhanced Cancer Surveillance System
NOM	Natural Organic Material
OCMI	Observed Control Mean Imputation
OR	Odds Ratio
THM(s)	Trihalomethane(s)
SD	Standard Deviation
TCM	Chloroform
TOC	Total Organic Carbon
USEPA	United States Environmental Protection Agency
VOC	Volatile Organic Carbon

CHAPTER 1 - INTRODUCTION

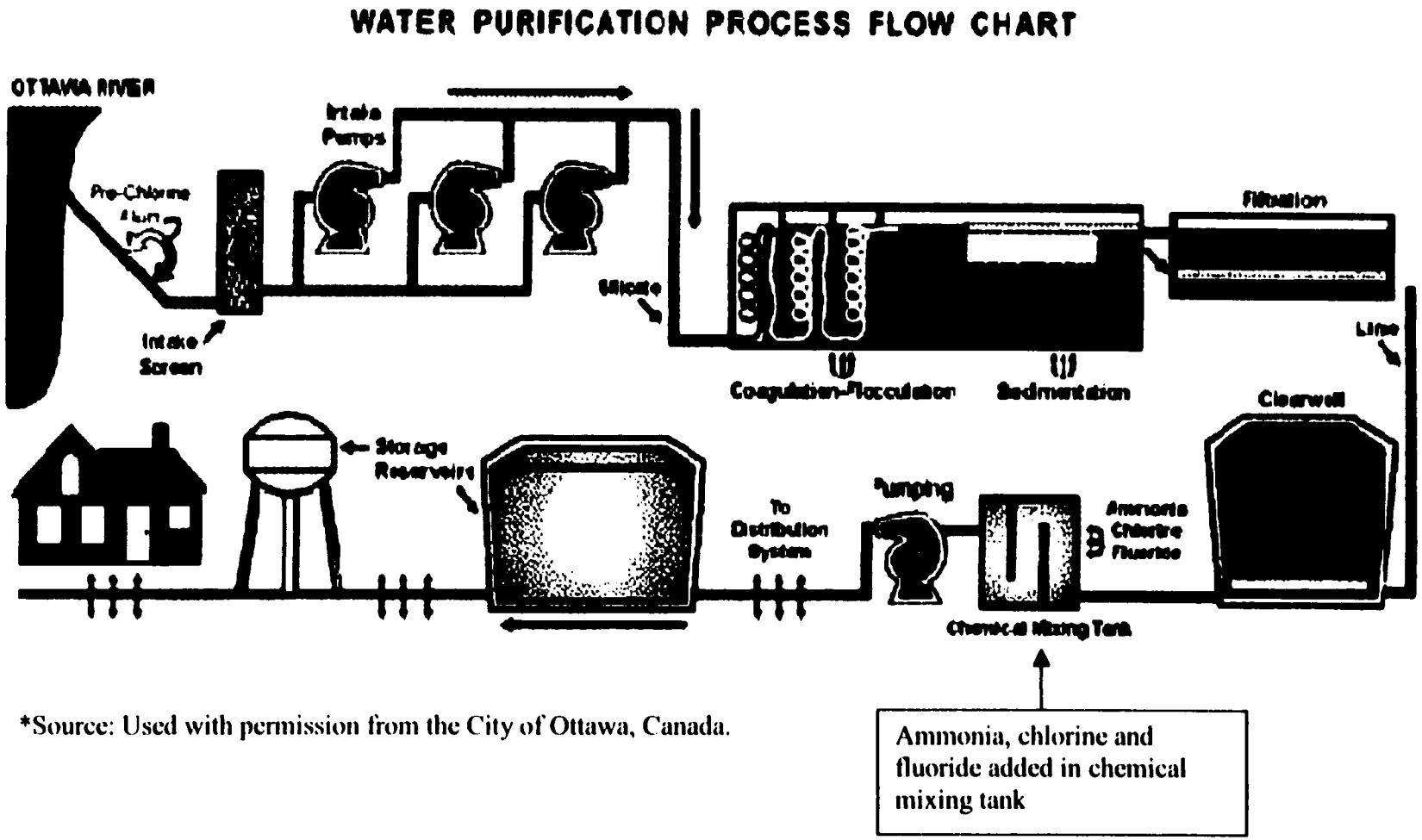
Providing safe drinking water is a major public health challenge [1]. One of the most famous examples that demonstrates the importance of providing drinking water free of contaminants dates back to the mid-1800s with John Snow's landmark investigation of a cholera outbreak. His investigation of the transmission of cholera led him to one particular part of London, where the concentration of cholera was so great that as much as over 500 people had died within a span of 10 days [2]. The result of the investigation showed that higher risk of contracting cholera was associated with household that used water supplied by the Southwark and Vauxhall company where the water intake source was taken downstream of city sewage disposal. The cross contamination city sewage and water supplies resulted in the cholera outbreak. Today, the quest to provide clean drinking water remains a major public health challenge in population health risk management [3]. Although waterborne disease outbreaks are not as common as in the time of John Snow, microbial contamination of public drinking water remains problematic. A recent example was observed in the small Ontario town of Walkerton where the bacteria *E. coli* O157:H7 contaminated the public water supply, killing seven people and making another 2300 people ill [4, 5].

There are three main methods to control water born pathogens in raw water supplies: boiling, filtration, and chemical treatment [6]. While boiling is an effective method for disinfecting small quantities of water, filtration and chemical treatment remain the methods of choice of most water utilities worldwide. Conventional water treatment facilities typically employ a multi-step process to treat raw water, similar to

that used at the Britannia and the Lemieux Island water treatment plants in Ottawa, Canada. As shown in Figure 1, the treatment process involves a sequence of steps that include: primary disinfection (chlorine), coagulation, flocculation, sedimentation, filtration, pH correction, and secondary disinfection (chloramine) [7]. The treatment process employed by the Britannia water treatment plant is a two-stage disinfection process (i.e. chlorine-chloramine). Other plants may use some other variations or combination of this process [8].

Water is a solvent, and as a result, it contains more than just elemental hydrogen and oxygen. Water dissolves many chemicals including: arsenic, aluminum, benzene, antimony, nickel, selenium, radon, and lead [9, 10]. In Canada, the Federal-Provincial Subcommittee on Drinking Water provides recommended maximum acceptable concentration (MAC) for over 30 chemicals found in drinking water [11]. Untreated surface water also contains organic (carbon containing) materials that can react with chemicals such as the chlorine used in the treatment process. Chemical treatment using chlorine is the common practice among many water utilities worldwide as it is relatively inexpensive yet provides effective protection of water supplies against waterborne infectious diseases [12]. Despite its effectiveness, concerns have been raised over the last 20 years about the possibility of adverse health effects as a result of chlorinating raw water. In particular, chlorine's ability to react with organic materials in raw water supplies, producing chlorination disinfection byproducts (CDBPs), has generated interest among toxicologists and epidemiologists alike with respect to the potential health risks of these byproducts.

Figure 1: **Water treatment process of the Britannia water treatment plant.**



*Source: Used with permission from the City of Ottawa, Canada.

In Canada, each province, in conjunction with its municipalities, has the responsibility of providing drinking water free of harmful contaminants. The federal government, specifically Health Canada, works in collaboration with the provincial health and environment ministries to develop guidelines for drinking water quality. The *Guidelines for Canadian Drinking Water Quality* (1993) identifies substances found in drinking water that may pose risks to human health. The guidelines also establish maximum acceptable concentrations (MAC) of substances in drinking water. Currently, the guidelines suggest that a MAC for trihalomethanes (THMs), a surrogate measurement of CDBPs, be 100 ug per liter of drinking water. This recommendation is currently under review as more toxicological and epidemiological evidence is being accumulated regarding the associations between CDBPs and possible adverse effects on human health.

With the use of chemical treatment processes, health concerns relating to public drinking water supplies have shifted from microbiological to chemical contaminants. In recent reviews and meta-analyses, CDBPs have been shown to be associated with increased cancer risks [13], and more recently, with adverse reproductive outcomes [14]. Epidemiological studies of cancer have focused primarily on three tissues: bladder, colon, and rectum [15]. Although pancreatic cancer is the fourth leading cause of death due to cancer in Canada [16], the link between pancreatic cancer and the wide spread use of chlorinated drinking water has yet to be examined in detail.

In response to increased public concerns regarding exposure to environmental pollutants in the late 1980s, the Government of Canada initiated a program called the "Action Plan on Health and the Environment" [17]. The goal of this program was to promote research addressing the issue of health in the population in relation to the

environment. One of the initiatives under this program was the creation of the National Enhanced Cancer Surveillance System (NECSS) [18]. The NECSS was a collaborative effort between Health Canada and eight of the ten Provincial Cancer Registries. One of the main components of the NECSS initiative was a case-control surveillance infrastructure capable of collecting risk factor information from a population-based sample of newly-diagnosed cancer cases of various cancer sites and from population controls. Cancer sites included: bladder, brain, breast, colon, kidney, liver, lung, non-Hodgkin's lymphoma, pancreas, rectum, and stomach. Individual data collected from the cases and controls could be linked to environmental databases in order to assess the relationship between environmental exposures and health outcomes. The environmental databases contain information about a number of potential environmental hazards including the concentration of CDBPs in drinking water supplies of municipalities across Canada. The NECSS and associated water quality information form the basis of this thesis.

Research Objectives

The primary objective of this thesis is to investigate the role that chlorination disinfection byproducts may play in the etiology of pancreatic cancer. The specific objectives of the thesis are as follows:

1. To critically review and assess the utility and validity of using selected pre-existing exposure data sources to assess the relationship between CDBPs and the risk of pancreatic cancer using the NECSS;

2. To evaluate the association between exposure to chlorinated disinfection byproducts and the risk of pancreatic cancer; and,
3. To examine the association between different types of disinfection by-products (THM, TCM, and BDCM) and the risk of pancreatic cancer.

Outline of Thesis

This thesis is divided into six chapters beginning with the Introduction. Chapter 2 reviews the literature on disinfection byproducts, and their association with different health outcomes. Chapter 3 provides a brief background of the NECSS, and outlines the methodology that was used to recruit cases and controls for the study. Chapter 4 discusses the methodology used in this dissertation. Chapter 5 contains the primary analyses, and Chapter 6 discusses the results and provides conclusions and recommendations for further research.

CHAPTER 2 - LITERATURE REVIEW

The literature review begins with a brief overview of the formation of CDBPs and a general discussion of some of the different CDBPs discovered to date. This will be followed by a critical review of published studies that have examined the relationship between CDBPs and adverse health outcomes, particularly cancer. Based on the literature, the review will suggest a plausible biological mechanism whereby CDBPs could potentially induce neoplasms of the pancreas. Although some toxicological studies will be discussed, the review will focus on epidemiological studies, particularly those relating to cancer. Reports of cancer risks for the most frequently researched cancer sites (i.e., bladder, colon, and rectum) will be discussed. The literature review will then focus on pancreatic cancer as a candidate site for investigation. It summarizes the epidemiological studies conducted to date where pancreatic cancer was one of the anatomical sites examined. The review will also discuss other risk factors that may be important as potential confounders.

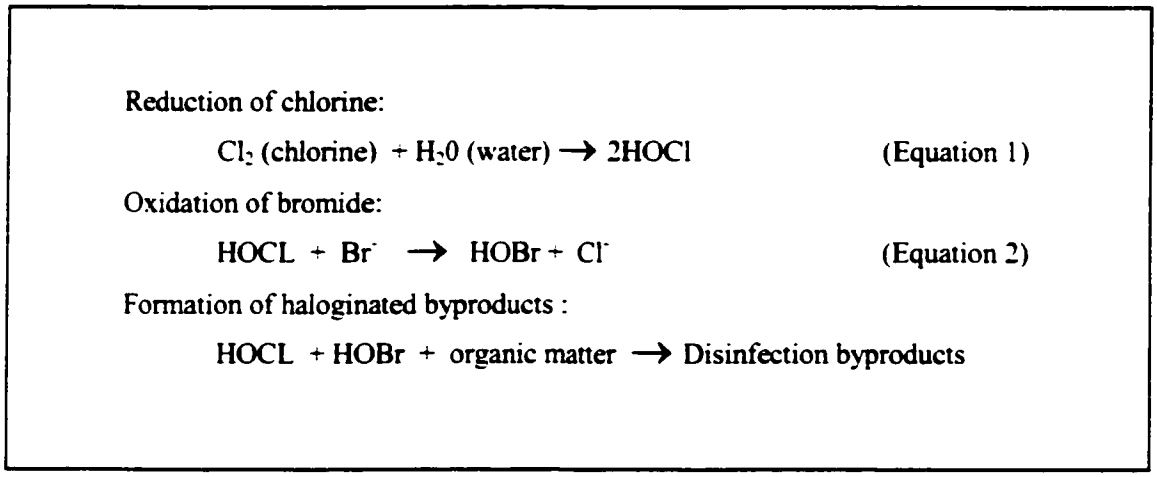
Chlorination Disinfection Byproducts

The first documented use of chlorine to treat raw water supplies dates back to the early 1900s [1]. Since its introduction, chlorine has been largely responsible for the significant decrease in disease outbreaks due to water borne pathogens and is considered to be one of the major public health advances of the 20th century [19]. However, in the mid 1970s, advances in analytical techniques led researchers to the discovery of chemical compounds produced in treated water as a result of an oxidative reaction between chlorine and organic material in raw water supplies [20, 21]. These compounds later became collectively known as chlorination disinfection byproducts.

Morris [22], as shown in Equation 1 of Figure 2, demonstrated that when chlorine is added to water, it produces a weak acid called hypochlorous acid (HOCl). In the presence of bromine, a common constituent of natural water, some of the hypochlorous acid reacts with the bromide ion shown in Equation 2 of Figure 2 to form another weak acid, HOBr. Both HOCl and HOBr can act as electrophiles and react with organic material in natural water supplies to produce halogenated DBPs. The detailed mechanisms involved in the formation of other DBPs are more complex and will not be discussed further in this thesis. The reader is referred elsewhere for a more detailed treatise of this material [22].

The formation of CDBPs is dependent on a number of factors. The rate of CDBPs formation is directly proportional to the water temperature and chlorine dose, while inversely related to pH levels [8, 23]. Another major determinant of the concentration of CDBPs is the level of natural organic material (NOM) in the water supply. The higher the concentration of NOM, the higher the concentration of CDBPs will be once the water is chlorinated. In surface water such as lakes and rivers, the concentration of NOM is much higher than in ground water sources such as wells and springs. Surface water will therefore produce higher levels of CDBPs as compared to in ground water supplies. The source of water supplies has been used previously in epidemiological studies as a surrogate for exposure to CDBPs [10].

Figure 2: Formation of chlorinated disinfection byproducts.



To date, almost a hundred different CDBPs have been identified and many more remain to be identified [24-26]. CDBPs are often grouped together based on the similarities of their chemical structure. As depicted in Figure 3, there are three distinct groups of CDBPs: trihalomethanes (THMs), haloacetic acids (HAAs), and haloacetonitriles (HANs). Each group in turn comprises a number of species of CDBPs. For example, the THMs comprise of four chemicals: chloroform (TCM), bromodichloromethane (BDCM), dichlorobromomethane (DCBM), and bromoform (BCM). The most commonly occurring of the known CDBPs are THMs followed by the HAAs and HANs [26]. In addition to the THMs, HAAs, and HANs, other halogenated and non-halogenated compounds have also been discovered. Examples of these chemicals include the haloaldehydes, haloketones, carboxylic acids, aldehydes, and ketones. Chemical structures of these compounds are shown in Figure 4.

Figure 3: Families of chlorination disinfection byproducts.

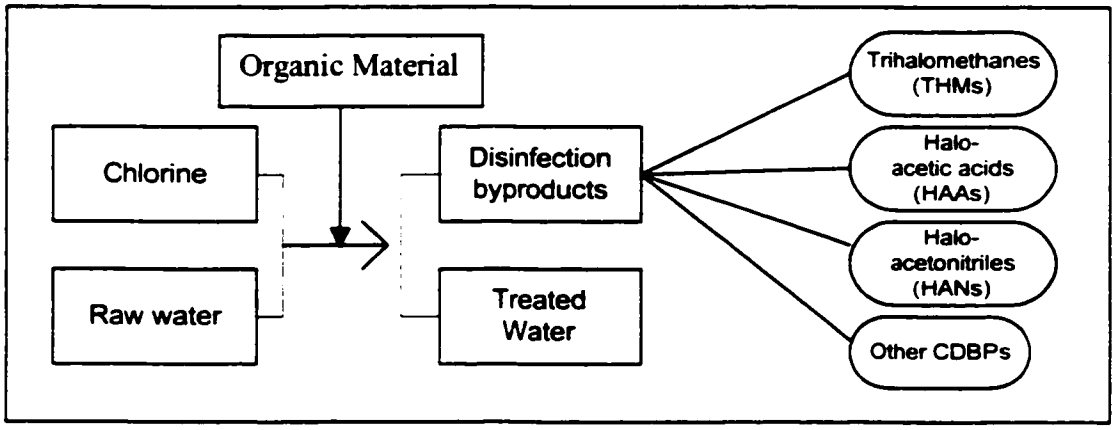
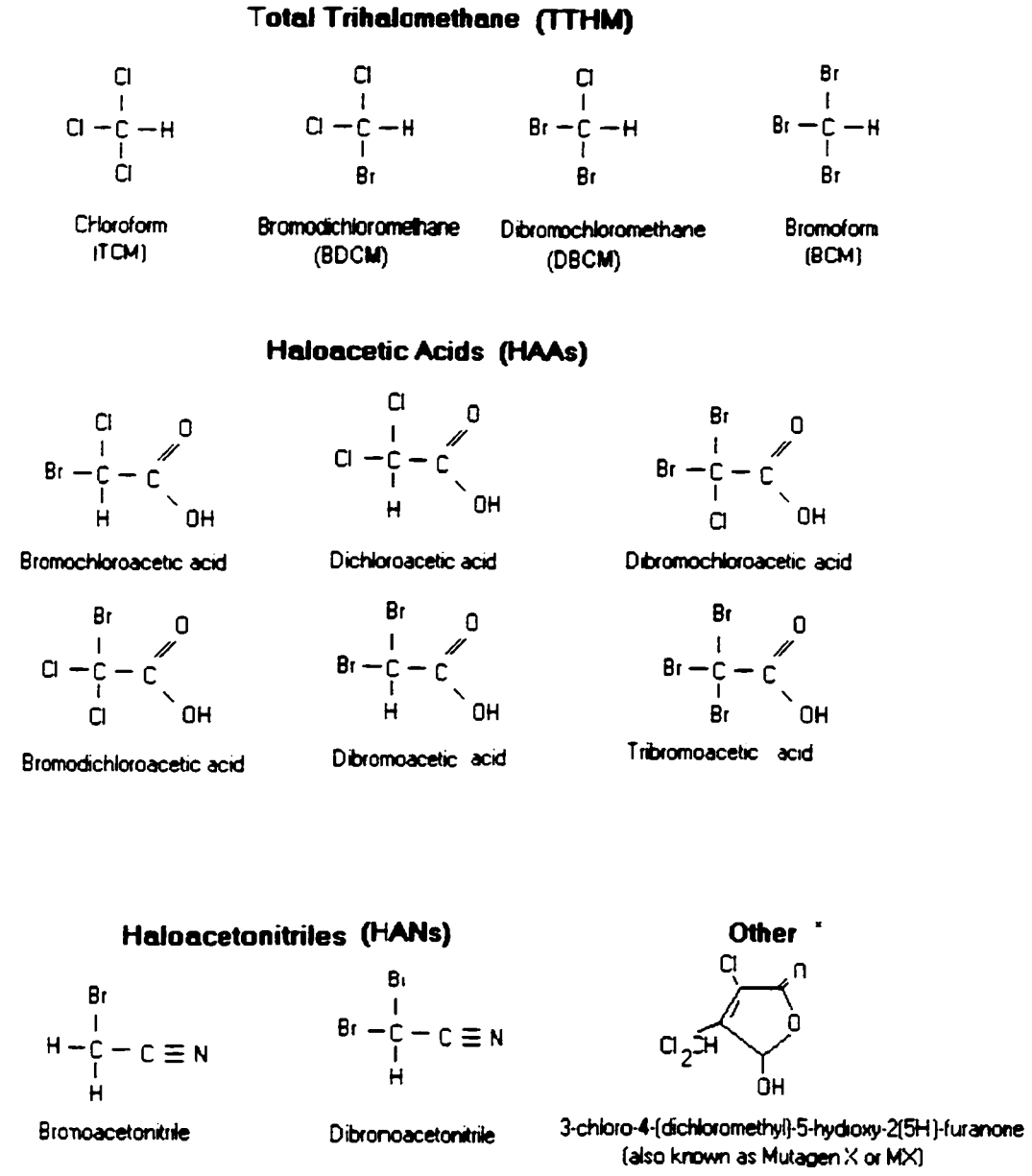


Figure 4: Chemical structures of chlorination disinfection byproducts.



Trihalomethanes

Trihalomethanes (THMs) are one of the most common groups of CDBPs formed when chlorine reacts with naturally occurring organic matter in raw water. These volatile compounds make up an estimated 20 percent of total CDBPs [27]. THMs have been used as surrogates of total exposure to CDBPs. The most common THMs are: chloroform (TCM), bromodichloromethane (BDCM), chlorodibromomethane (CDBM), and bromoform (BCM) [27]. Typical concentrations of THMs range from less than 10μg/L during the winter months to 100 μg/L during the mid summer months. The current recommended MAC according the *Guidelines for Canadian Drinking Water Quality* is 100 ug/L.

Haloacetic Acids

Examples of haloacetic acids (HAAs) include the family of mono, di, and tri-carboxylic acids. These compounds are present in drinking water at average levels of 50 ug/L. Currently, Health Canada does not have a recommended MAC for HAAs. However, the World Health Organization (WHO) has a provisional guideline of 50 ug/L for dichloroacetic acid [28]. This guideline was based on the no-observable-adverse-effect-level (NOEL) for liver toxicity in mice. For trichloroacetic acid, the WHO provisional guideline was set at 100 ug/L based on the lowest-observed-adverse-effect (LOAEL) liver toxicity in mice [28].

Haloacetonitriles

Examples of haloacetonitriles (HANs) include dichloroacetonitrile and dibromoacetonitrile. These compounds are present in drinking water at average concentrations of between 1 and 40 ug/L. The *Guidelines for Canadian Drinking Water Quality* does not have a recommended MAC for HANs. However, the WHO has a provisional guideline for dichloroacetonitrile and dibromoacetonitrile at 90 ug/L and 100 ug/L respectively. Both provisional guidelines were based on NOEL in animal studies [28].

Other disinfection byproducts

While hundreds of chlorinated hydrocarbons including chlorinated ketones, aldehydes, and carboxylic acids have been discovered, these represent less than 50 percent of the estimated pool of organically bound halogens [27, 29]. Other compounds such as the "Mutagen X" family of disinfection byproducts (e.g., 3-chloro-4-(dichloromethyl)-5-hydroxy-2-(5H)-furanone) have also been examined recently due to their high toxicity. MX has been shown to be carcinogenic in rats [30]. MX has also been shown to be associated with bladder, rectal, esophageal, and breast cancer in population-based studies in Finland [31].

Assessing Human Exposure to Chlorinated Disinfection Byproducts

The assessment of exposure to CDBPs in humans is a topic of some debate. We will limit this review to consideration of issues relevant to assessing exposure in case-control studies where retrospective estimation of exposure is required. Three major issues need to be considered:

1) routes of exposure;

2) sources of information about exposure; and,

3) conversion of self-report information into estimated CDBP exposures.

Routes of Exposure

There are three primary routes by which humans can be exposed to CDBPs:

1) ingestion;

2) dermal contact; and,

3) inhalation.

Backer and colleagues [32] have demonstrated that the quantity of CDBPs absorbed into the blood stream can differ depending on the route of exposure. The researchers recruited 31 volunteers and divided them into three groups: drinkers (ingestion), bathers and showerers (exposed to a combination of inhalation and dermal contact). One group of adult volunteers (n=11) was asked to shower for ten minutes, a second group (n=10) was asked to bathe for 10 minutes, while the third group (n=10) drank one litre of tap water (from the same water source) within a 10 minute period. Blood samples were taken from participants at baseline, 10 minutes, and 60 minutes post-intervention. Blood samples were then analyzed for THMs. The results showed the highest level of THMs were found in blood samples taken from subjects who took 10-

minute showers while subjects who drank 1 liter of water within a period of 10 minutes had the lowest blood level of THMs.

Based on this information, it should be possible for epidemiological studies to estimate CDBP exposure from multiple sources (e.g., drinking water, cooking water, showers, swimming pool use). However, to date, no study has assessed long-term exposure to DBPs from all routes exposure. We are not aware of any attempts to develop exposure assessment instruments that have included multiple routes of exposures. Therefore, in the absence of a validated questionnaire, we will focus on surrogate information to estimate CDBP exposure.

Source of Information about Exposures

The most common surrogate measure is residence. Information on residence can be obtained either from administrative sources or by direct interview of the subjects. The residence information is then linked to administrative datasets based on the source of water for that individual (e.g., data from local water utilities). The CDBP level at the water source is then used to estimate exposure (see next section).

Three main sources of residence information have been used to link with administrative date to estimate exposure:

- Death certificates;
- Census information; and,
- Personal interviews.

Since death certificates only report the last place of residence, this information may provide a poor surrogate for lifetime CDBP exposure. In addition, if people move following their diagnosis of cancer (perhaps to be closer to family members), the place of

residence might actually reflect exposure after disease onset. These factors can result in misclassification of exposure.

Similar problems can exist when using census information to determine place of residence. If one uses a single census to provide the residence information, then one can not account for people who move. One might be able to use information from multiple census data files to track residence changes over time although this would involve a complex record linkage process. One advantage to using census information is that, unlike death certificates, information collected from cases reflect actual place of residence prior to diagnosis or death.

Of the three sources of residence information, personal interviews are most desirable. Lifetime residence information can be collected directly from subjects (or proxies). This information can be used to estimate lifetime and annual CDBP exposure, taking into account variation in place of residence and water source. Self-report residence information would be subject to reporting error, which could produce some misclassification in exposure status, but this would likely be a smaller bias than using single place of residence to estimate lifetime exposure.

Personal interview information has been used in studies of CDBPs and bladder cancer [33, 34]. However, studies of CDBP and pancreatic cancer have all used either death certificate[35, 36] or census information [37, 38] as the basis for estimating exposure. This is a potential serious limitation that will be addressed in our study.

Determining CDBP levels from residence information

Estimation of the daily CDBP ingestion requires knowledge of both the CDBP levels in water and the amount of water ingested. In the absence of personal water intake

information, it is not possible to determine the daily CDBP intake. Therefore, CDBP exposure must be represented by the concentration levels in the water source. This will limit the validity of CDBP assessment since people with the same water source will have the same CDBP concentrations in their water but might be exposed to different daily intakes.

Studies in the past have used a number of different approaches to estimated CDBP exposure based on different places of residence(s). These have included:

- Surface vs. ground water sources;
- Chlorinated vs. non-chlorinated water supplies;
- Duration of time exposed to chlorinated water supplies;
- Administrative records reporting CDBP levels in the water supply to the residence; and
- Different degrees of water mutagenicity (e.g., MX).

The first three approaches are essentially dichotomous classifications (exposed/not exposed) while the last two attempted to estimate the actual concentration in water supplied to the residence. All of these methods are subject to measurement error. For example, different sources of surface water (e.g., river vs. lakes) may contain different concentration of organic precursors resulting in different levels of CDBPs. The amount of chlorine added to treated water varies among water treatment plants and through-out the year, resulting in different quantities of chlorination byproducts being formed. This variability can result in misclassification of exposure if DBPs are not quantified.

No studies have been reported which have assessed the validity of the various

approaches to estimating CDBP levels. Prior studies of CDBPs and pancreatic cancer have relied on one of the first three approaches. The dichotomous classification limits the variation in exposure and constrains analysis options. Linkage of place of residence to measured CDBP levels would be expected to improve exposure estimation and the potential to detect adverse effects.

Summary and Recommendations

With current technology, a method to measure individual exposure does not exist. Direct measurement of CDBP levels using personal monitoring devices (such as dosimeter to measure radiation exposure) might theoretically provide the best estimates. However, this would require a cohort study approach. The long latency period for cancer development would make this impractical. For these reasons, exposure to CDBPs using historical water treatment records to reconstruct individual exposure profiles remains the best option to estimate exposure to CDBPs.

The best practical approach to CDBP exposure estimation involves:

1) Personal interview to obtain a detailed history of all residences where a person has lived, covering at least the 30 years prior to cancer diagnosis. This information should also indicate if the water source was from a private well or from a municipal supply as well as individual characteristics such as average quantity of water consumed;
2) Linkage of each residence to administrative records from water supply facilities where CDBP concentrations have been measured. Ideally, these measurements would be available for 30 years in order to account for variation in levels due to changes in water treatment practices or similar factors;

3) Create a summary measure of exposure by combining the residence-specific levels of exposure.

Chlorination Disinfection Byproducts and Adverse Health Effects

Chlorination is by far the most commonly used chemical for disinfection of water supplies. In Canada, it has been estimated that 87 percent of the population depends on public water that has been treated with chlorine [39]. With the wide spread use of, and dependence on, chlorination as the primary means of water disinfection, the discovery of the mutagenic and carcinogenic effects in chlorinated drinking water has generated considerable concern. Over the past 20 years, a number of toxicological and epidemiological investigations have been undertaken to determine the effects of CDBPs on health outcomes.

Plausible Biological Mechanisms of CDBPs Induced Pancreatic Cancer

In a simple multistage model of carcinogenesis, prolonged and repeated exposure to carcinogenic agents could ultimately compromise a host cell's defense mechanisms. An imbalance resulting from the constant exposure to a carcinogenic agent could result in the alteration of host cells' genetic composition leading to tumour growth. As discussed earlier, host cells could come in contact with carcinogenic agents such as CDBPs in one of three ways: ingestion, inhalation, and dermal contact.

The specific mechanisms involved in uncontrolled host cell growth as a result of the interaction of CDBPs and host cells remain unclear. The difficulty in delineating the mechanisms is in part due to the wide variety of CDBPs. Furthermore, the effects of CDBPs on cancer sites seem to be species-specific [15].

Physiologically-based pharmacokinetic (PBPK) models have been developed to assess animal toxicity [40]. However, they have not been used in epidemiological studies [41]. Evidence from animal PBPK models suggests that the rates of metabolism (in rats) are different for different types of CDBPs. Different rates of metabolism are in part due to different rates of absorption. Lilly and colleagues [40] demonstrated that DCBM administered in an aqueous medium resulted in higher blood concentration than using a corn oil vehicle. The rate of absorption by tissue in turn depends on the specific species of CDBPs. DCBM is absorbed into tissues and metabolized more rapidly than chloroform [30].

Within the human body, many organs could be potentially exposed to CDBPs via the blood supply. Like every organ in the human body, the pancreas maintains constant contact with the blood supply. The persistent and prolonged interaction of CDBPs in the circulatory system with pancreatic cells could initiate the carcinogenic process. The reaction of a specific tissue to a given toxic agent can depend on the sensitivity of the tissue. Less sensitive tissue will require higher dose of CDBPs before an observable effect can be detected. Conversely, highly sensitive tissues will require a lower dose of CDBPs before changes in the morphology of the cells of the tissues occur. The sensitivity of pancreatic cells to CDBPs is not known. However, if pancreatic cells are sensitive to CDBPs, then it is possible that exposure of these cells to CDBPs could induce tumourous cell growth.

Toxicological Investigations.

Animal studies have historically been instrumental in identifying potential human

health hazards. A recent review conducted by an Expert Working Group [15] evaluated the toxicological evidence regarding CDBPs, and their ability to induce tumour growth. The Group observed that the most frequently implicated cancer sites in animal studies were the liver and the kidney. However, the Group acknowledged that the level of toxicity and the mechanism of tumour induction vary considerably among CDBPs and animal species.

Of the different types of CDBPs, THMs occur in the greatest concentration and therefore were the first to be evaluated [19]. Two years after the discovery of CDBPs in 1974, chloroform (a principal THM), was shown to be carcinogenic in rodents [19]. Dunnick and Melnick [42] observed that chloroform has different effects on different species. When male rats were administered 180 mg/kg/day of chloroform, 24 percent (n=12) of the male rats developed neoplasms of the kidney tubular cells while no kidney tubular cell neoplasms were observed in mice. However, an increased incidence of hepatocellular neoplasms was observed among treated mice but not in rats. When 138 mg/kg/day and 238 mg/kg/day of chloroform was administered to male and female mice respectively, 36 percent (n=18) of male mice and 80 percent (n=36) of female mice developed hepatocellular neoplasms.

In addition to chloroform, carcinogenic potential has also been shown for other types of THMs. Boorman and colleagues [19] reviewed the findings of toxicological studies of other CDBPs. Chlorodibromomethane (CDBM) was associated with a small increase in liver tumour in female mice but not in rats. Bromodichloromethane (BDCM) caused an increase in colon cancer in male and female rats while bromoform was associated with a low incidence of colon tumours in female rats. In fact, there is evidence

demonstrating that 'brominated by-products often have greater genotoxic activity than chlorinated compounds' [30].

Given the variability in the effects of CDBPs between species, there are several limitations of animal studies that make extrapolation of the findings to the human species difficult. These limitations include the following:

1. exposures in animals (in laboratories) are typically several orders of magnitude higher than exposed human populations:
2. inter-species differences (e.g., differences in mechanism/rate of metabolism); and,
3. human populations are simultaneously exposed to a mixture of different CDBPs rather than a single chemical as in the case of animal studies.

Epidemiological Investigations (Non-pancreatic cancer)

Over the past 20 years, concerns about the potential health effects of the CDBPs have prompted a number of epidemiological studies to examine their association with cancers. A number of cancer sites have been examined. Some of these sites include: brain [43, 44], esophagus [43], stomach [43, 45, 46], liver [31, 47], colon [31, 43, 45, 48], rectum [31, 33, 43, 45, 48], kidney [31, 43, 45], bladder [34, 49, 50], prostate [31], testis [31], ovaries [31, 45], uterus [31, 45], and pancreas[37, 38].

These studies vary considerably with respect to design, method of assessing health outcomes, and approach to evaluating exposure. Some studies employed an ecological design while others used analytical designs (e.g., cohort and case-control). While ecological designs can be valuable to identify potential associations of exposed groups, the lack of individual data makes interpretations difficult due to biases inherent within the design (e.g., ecological fallacy). Furthermore, some of the above analytical studies were unable to adequately control for the effects of potential confounding

variables. Many of the earlier studies also relied on information obtained on death certificates to estimate exposure. For example, the level of exposure to CDBPs has been determined based on the address that appeared on an individual's death certificate. Exposure assessments based on death certificates will result in exposure misclassification since an individual typically resides in a number of different places prior to the one appearing on the death certificate. Overall, the inability of many studies to control for potential confounders, uncertainty (non-confirmed) in health outcomes, and relatively crude approaches to exposure assessment make it difficult to determine whether CDBPs found in chlorinated public drinking water supplies truly pose a risk on human health.

In 1992, Morris and colleagues [13] conducted a meta-analysis of the early epidemiology literature to derive an overall estimate of the risk of CDBPs on various cancer sites. They evaluated analytical studies with data for 12 anatomic sites; bladder, brain, breast, colon, colorectal, esophagus, kidney, liver, lung, pancreas, rectum, and stomach. The results of the meta-analysis showed that all 12 sites produced an overall relative risk estimate (RR) greater than 1.00, suggesting an increased risk of cancer of these sites when exposed to CDBPs. These RRs ranged from 1.01 for lung to 1.38 for rectal. However, only bladder and rectal cancers had a 95 percent confidence interval that was greater than unity, indicating that the overall risk estimate for these two cancer sites achieved statistical significance.

The results of the meta-analysis were criticized on several grounds. In an editorial, Cantor [51] indicated that the meta-analysis conducted by Morris and colleagues was premature. In addition to poor exposure estimates, Cantor [51] noted that some of the studies in the meta-analysis did not have adequate control for confounders. For example,

some of the studies evaluated relied on information appearing on death certificates as the primary source of information in determining outcome and assessing exposure to chlorinated treated water supplies. Poole, who also reviewed the meta-analysis on behalf of the United States Environmental Protection Agency, concluded that there was significant heterogeneity in the way in which studies assessed exposure and outcome, which could render the overall risk estimate invalid [52].

Since the publication of this meta-analysis, a number of studies have reported their findings. Unlike earlier work, the recent studies use health outcomes where diagnoses have been histologically confirmed and/or assigned ICD codes. Furthermore, some of the recent studies also used incident cases rather than decedent cases. One of the main advantages of using incident cases is that it allows for information to be collected directly from the individual. Recall of past events in personal histories should be more accurate in cases diagnosed close to the inception of an investigation than recall in the distant past [53]. In addition, incident cases avoid treatment bias. Recent studies have also enhanced the assessment of exposure by constructing individual exposure profiles by combining different places of residence with quantitative measurements of CDBPs of water treatment plants [49]. Finally, individual data was collected to control for potential confounders.

These more recent studies have mainly focused on bladder, colon and rectal cancer. These studies were conducted by research groups in Iowa [34, 48], Colorado [50], and Ontario [33, 49]. These studies are summarized below.

Bladder Cancer

In 1993, McGeehin and colleagues [50] conducted a population-based case-control study of bladder cancer and water disinfection methods. The study consisted of 327 histologically confirmed incident cases of bladder cancer and 261 controls living in the Colorado area. Exposure profiles of each individual were constructed using residence information collected from personal interviews and combined with data obtained from a survey of water treatment plants. After adjusting for cigarette smoking, tap water and coffee consumption, using an unconditional logistic regression model, years of exposure to chlorinated surface water were found to be significantly associated with bladder cancer. The OR for those exposed to more than 30 years of chlorinated water was 1.8 (95% CI, 1.1-2.9) relative to those with no known exposure.

King and Marrett [33] also examined the association between bladder cancer and CDBPs by conducting a population-based case control study in Ontario that included 696 histologically confirmed cases identified from pathology reports and 1,545 population controls. Exposure to CDBPs was estimated by linking individual information to historical treatment practices of corresponding water utilities. An unconditional logistic regression analysis adjusting for potential confounders (age, gender, cigarette smoke, education, and caloric intake) yielded an OR of 1.41 (95% CI, 1.10-1.81) for those exposed to chlorinated surface water for 35 or more years compared to those exposed for less than 10 years. King and Marrett also observed that those exposed to a THM level in excess of 50 ug/L for 35 or more years had a 63% increased risk compared to those exposed for less than 10 years (OR=1.63; 95% CI, 1.08-2.46).

Cantor and colleagues [34] conducted a population-based case-control study of

1,123 cases of bladder cancer and 1,983 controls that had exposure data for at least 70 percent of their lifetimes. An unconditional logistic regression analysis showed an increased risk with increased duration of chlorinated water use. The logistic regression model included sex, age, study period, education, high-risk occupation, and cigarette smoking (6 strata). Those with more than 60 years of chlorinated water use had an OR of 1.6 (95% CI, 1.2-2.3) relative to those with less than 20 years (referent) of exposure to chlorinated water.

Overall, the weight of evidence seems to support the view that prolonged exposure to CDBPs is associated with a modest increase in the risk of developing bladder cancer. The three studies cited here [33, 34, 50] are considered to be of high quality since they are characterized by large sample sizes, good definition of outcome (i.e. histologically confirmed diagnosis), relatively good exposure assessments, and individual data that controlled for potential confounders.

Colorectal Cancer

Hildesheim and colleagues [48] used a case-control design to examine the association between chlorination byproducts and colon and rectal cancer in residents of Iowa. Odds ratios were calculated using an unconditional logistic regression model to adjust for potential confounders. The results showed a modest increase in risk with rectal cancer, but none for colon cancer. For rectal cancer, increases in years of exposure to chlorinated water corresponded to an increased risk of rectal cancer. Odds ratios of 1.1 (95% CI 0.8-1.4), 1.6 (95% CI 1.1-2.2), 1.6 (95% CI 1.0-2.6), and 2.6 (95% CI 1.4-5.0) were observed for exposures of 1-19, 20-39, 40-59, and at least 60 years of exposure to chlorinated water as compared to "no exposure" respectively. The OR was adjusted for

age, sex, and average population size.

In contrast, King et al. [49] observed a significant association with colon cancer and CDBPs but not with rectal cancer. Specifically, King and colleagues observed that males who have been exposed to chlorinated surface water for at least 35 years had an increased risk of 1.53 (95% CI, 1.13-2.09) for colon cancer compared with those exposed for less than 10 years. Furthermore, males exposed to an estimated THM level of 75 ug/L for at least 35 years had a two-fold increase in risk of colon cancer as compared to those with less than 10 years of exposure (OR =2.10, 95% CI = 1.21-3.66). The observed ORs were based on an unconditional logistic regression and adjusted for age, sex, education, BMI, energy intake, cholesterol, calcium, alcohol, and coffee. A significant relationship was observed in men but not in women. No significant relationship was observed between rectal cancer risk and exposure to CDBPs in either men or women. For men, exposure of at least 35 years to chlorinated water yielded an adjusted OR for rectal cancer of 0.97 (95% CI 0.72-1.32) as compared to those with less than 10 years of exposure to chlorinated water (referent). For women, exposure to at least 35 years of chlorinated water yielded an OR for rectal cancer of 1.04 (95% CI 0.71-1.53) as compared to those with less than 10 years of exposure to chlorinated water.

While both studies are of similar design, the results obtained are somewhat contradictory. One possible explanation for the differences in the results observed could be attributed to exposure to different watershed. Different watersheds may have different composition of precursors to DBPs and therefore could result in different concentrations of disinfection byproduct formation. Furthermore, the two studies adjusted for different risk factors that may have influenced the ORs.

Summary

Epidemiological investigations to date have focused mostly on bladder, rectal, and colon cancers. However, based on the traditional approach for assessing causality [54], the information presented remains inconclusive. Current evidence seems to support a modestly elevated risk of bladder cancer with prolonged exposure to chlorinated water while evidence regarding the association between colorectal cancer and exposure to chlorinated water remains inconclusive.

The Pancreas and Pancreatic Cancer

The pancreas is a small but highly perfused organ located in the abdomen posterior to the stomach and adjacent to the upper part of the small intestine. The pancreas has two primary functions: production of exocrine enzymes and endocrine hormones. Exocrine enzymes are involved in the digestion process while the endocrine hormones are involved in the regulation of energy metabolism: insulin and glucagon [55].

Pancreatic cancer is one of the most lethal neoplasms. The incidence is highest in North America, intermediate in Europe and Japan, and lowest in Africa and Asia [56]. In Canada, the age standardized incidence rate for pancreatic cancer among Canadians is approximately 9 cases per 100,000 [16]. Pancreatic cancer is the fourth leading cause of cancer mortality among both males and females in Canada [16]. The survival rate for pancreatic cancer patients is poor since its symptoms are non-specific and are often disregarded, resulting in late diagnosis. Furthermore, there are no reliable screening tests for detecting pancreatic cancer in asymptomatic individuals. As such, pancreatic cancer usually goes undetected until it is in the advanced stages and by then, it is no longer resectable [57]. The death to incidence ratio worldwide was approximately 0.99 in 1985

[58] and the median survival time for pancreatic cancer patients is only 3 months [59]. The five-year survival rate for pancreatic cancer is less than one percent [16]. According to the Surveillance, Epidemiology, End Results (SEER) Summary Staging method [60], eight percent of pancreatic cancers at the time of diagnosis were localized to the pancreas [61] while 23 percent were regional [61]. The majority of the pancreatic cancers (51 percent) at the time of diagnosis were considered to be distant [61] and the remaining cancers (19 percent) were unstaged.

Risk Factors for Pancreatic Cancer

As with most other forms of cancer, the etiology of pancreatic cancer is poorly understood [62]. However, a number of risk factors have been identified. Some of the risk factors are biologically based while others are potentially modifiable risk factors such as smoking, diet and level of physical activity. A search of the literature in the CANCERLIT and MEDLINE databases identified four recent review papers that summarize the epidemiology of, and risk factors for, pancreatic cancer [56, 58, 59, 63]. The information presented below is largely drawn from these review articles.

Biological-based Risk Factors for Pancreatic Cancer

Age

Like most cancers, there is a strong positive association between age and pancreatic cancer [56]. Registry data have consistently shown that as age increases, the incidence of pancreatic cancer also increases. The highest incidence of pancreatic cancer occurs among those between the age of 60 and 80 [59, 64]. For those with a chronic history of pancreatitis, however, the age of onset of pancreatic cancer is usually 10 to 20

years earlier [56].

Gender

Pancreatic cancer seems to be more common in men than women [58, 59]. In the United States, the incidence ratio between male and female is approximately 1.35 [58]. However, incidence and mortality rates have declined slightly over last couple of decades, particularly for men [59, 63]. Tominaga and colleagues [63] postulated that the reason for a more rapid decrease in men is associated with the corresponding declining trend in smoking being more evident in men as compared to women. A study [65] cited in both reviews [58, 59] showed that men have carcinoma more often in the head of the pancreas, whereas women more often have carcinoma of the body and tail. No other studies to date (to our knowledge) confirm or disprove this observation [66].

Diabetes Mellitus

Diabetes mellitus has been frequently associated with pancreatic cancer. However, it is not clear whether diabetes is an etiologic factor or if it is simply an early manifestation of pancreatic cancer [56]. Many patients present with symptoms similar to those of diabetics prior to diagnosis of pancreatic cancer [56]. However other studies suggest that the symptoms of diabetes may be due to insufficient endocrine pancreatic function resulting from the cancer [58].

In a study reviewed by Ahlgren [58] comparing 760 patients with pancreatic cancer with 720 controls, 164 patients had diabetes compared to 60 controls (OR = 3.04, 95% CI, 2.2-4.2). However, this relationship was insignificant when restricting the analysis to those having diabetes for more than 3 years (OR = 1.43, 95% CI 0.98-2.07).

Chronic Pancreatitis

A history of chronic pancreatitis (inflammation of the pancreas) has been linked to pancreatic cancer. For individuals with a chronic history of pancreatitis, the age of onset of pancreatic cancer is usually 10 to 20 years earlier [56]. Simon and Printz [56] have observed that the duration of the history of pancreatitis is associated with risk of pancreatic cancer. For every decade the patient has pancreatitis, the risk of pancreatic cancer is increased by 2 percent above baseline. This increased risk is independent of country, sex, and type of pancreatitis.

As in the case of diabetes, it is not clear whether pancreatitis is a true etiologic factor or if it is simply an early manifestation of pancreatic cancer. The expanding mass due to tumour cell growth in patients with pancreatic cancer could lead to ductal obstruction and consequently inflammation [58]. Conversely, chronic inflammation of the pancreas could lead to genetic mutation that may result in tumour cell growth.

Body Mass Index

A number of studies have examined the relationship between body mass index (BMI) and the risk of pancreatic cancer. BMI is defined as the ratio of the mass of the individual (in kilograms) to the square of the individual's height (in metres). Recent evidence seems to support a positive association between BMI and elevated risk of pancreatic cancer.

In an analysis of two prospective cohort studies (the Health Professional Follow-up Study and Nurses' Health Study), Michaud and colleagues [67] observed a relative risk of 1.72 (95% CI, 1.19-2.48) for those having a BMI of at least 30 kg/m^2 as compared to those have a BMI of less than 23 kg/m^2.

Similar results were observed in a large Canadian case-control study [68], a study based on the same study population (except for Ontario) as this thesis. Men with a BMI of at least 28.3 kg/m^2 had an estimated risk of 1.90 (95% CI, 1.08-3.35) as compared to those having a BMI of less than 23.7 kg/m^2 after adjusting for age, province of residence, percent weight change, caloric intake and composite index of physical activity. Increased risk was also observed in women, but the estimated risk was not statistically significant (OR=1.21; 95%CI, 0.70-2.06).

Environmental and Lifestyle Risk Factors

Cigarette Smoking

Smoking is considered as the main preventable risk factor for the development of pancreatic cancer. Reviews of a large number of studies have consistently shown a positive association between smoking and pancreatic cancer [56, 58, 59, 63]. In 1985, the International Agency for Research on Cancer (IARC) concluded that cigarette smoking is a risk factor for pancreatic cancer [56]. Among other chemicals, tobacco smoke contains nitrosamines that could be activated metabolically to induce a carcinogenic effect in the pancreas [59]. Changes in the morphology of pancreatic duct cells have been observed in autopsies of subjects with a history of smoking. These changes appear to increase with the amount of tobacco smoked [59].

Numerous studies have shown an increase of approximately 1.5 to 3.0 fold in the risk of pancreatic cancer in smokers. The risk increases with the intensity and duration of tobacco smoking [56]. In a recent analysis of the population-based case-control component of the NECSS data (same data used in this study) [69] comparing 583

histologically confirmed cases of pancreatic cancer with 4813 controls, the results showed a significant increase in risk for both men (OR=1.46; 95% CI, 1.0-2.1) and women (OR=1.8; 95% CI, 1.2-2.7) who smoked at least than 35 cigarette pack-years as compared to those who do not smoke (i.e., 0 pack-years).

Alcohol Consumption

It has been suggested that alcohol consumption is associated with pancreatic cancer. Unlike cigarette smoking, however, the association is not as strong and the weight of evidence is not as consistent. A cohort study reviewed by Ahlgren [58] of 16,713 individuals with 63 cases of pancreatic cancer showed an elevated risk of 5.4 (95% CI, 1.9-15.2) for frequent consumers of alcoholic beverages as compared to abstainers. While this result is statistically significant, the relatively small number of cases (and the correspondingly wide confidence interval) provides little reassurance of this observation as generalisable to all pancreatic cancer cases. Furthermore, different types of alcoholic beverages may have different effects on health outcomes. For example, red wine contains antioxidants which may reduce the risk of pancreatic cancer by preventing free radical damage [70]. Some types of beer on the other hand contain nitrosamines [56], a chemical linked to carcinogenic effects. To further complicate the situation, tobacco smoking and alcoholic consumption are social behaviors that tend to occur together. Therefore, one behavior may modify the effect of the other. Villeneuve and colleagues [69] conducted a study examining various risk factors for pancreatic cancer including consumption of alcoholic beverages. The results of that study show that among non-smokers, consumption of 1 beer per day yields a 3-fold increase in risk compared to consuming less than 4 beers per month (OR=3.15; 95% CI, 1.6-6.3). Consumption of one

glass of wine per day, however, yielded a protective (although not significant) effect (OR=0.63; 95% CI, 0.3-1.4) as compared to those consuming less than four glasses of wine per month.

Dietary Factors

Although the role of nutritional intake as a risk factor for pancreatic cancer has been examined in a number of case-control and cohort studies, direct evidence linking specific dietary carcinogens has been difficult to establish. Currently there is a body of evidence supporting the view that diets containing high intake of fruits and vegetables reduce the risk for pancreatic cancer [56]. The protective properties of fruits and vegetables is likely due to substances such as caroteinoids, vitamin C and E, flavonoids, and selenium which are known to have anticancer properties [56]. Conversely, diets high in carbohydrates and fats are suspected of contributing to increased risk of pancreatic cancer [56]. A multi-national case-control study conducted by Howe and colleagues [71] showed a positive association between total carbohydrate intake and pancreatic cancer. The estimated relative risk for a comparison of the highest against the lowest quintile of carbohydrate intake was 2.57 (95% CI, 1.64-4.03). In a review conducted by Gold and Goldin [59], the authors grouped different types of food into one of three levels of risk: possible risk, unproven risk, and decreased risk. The category of "possible risk" consists of foods that contain carbohydrates, cholesterol, meat, salt dehydrated food, fried food, refined sugar, soybeans, and nitrosamines [59]. The "unproven risk" category consists of foods such as coffee, beta-carotene, and fat [59]. Finally, foods associated with decreased risks are those containing fibre, vitamin C, fruits, and vegetables [59].

Coffee Consumption

Coffee consumption has been suggested as a risk factor for pancreatic cancer. MacMahon and colleagues [72] reported an increased risk for those consuming three or more cups of coffee per day. A number of studies have been published since this initial paper with conflicting findings. Some have supported the association [64, 73], while other studies have found no significant association [74], and still others have found a decreased risk of pancreatic cancer among coffee drinkers [75] [76].

A recent case-control study conducted by Villeneuve and colleagues [69] comprising of 583 histologically confirmed cases and 4813 controls recruited between 1994 to 1997 examined the association between the number of cups of coffee consumed per day and the risk of pancreatic cancer. This study was based on the same study population as this thesis. The results showed no statistically significant association between consumption of coffee and risk of pancreatic cancer (OR=1.23; 95% CI, 0.78-1.97 when comparing those consuming at least 4 cups per day to those consuming less than 3 cups per month).

The overall weight of evidence appears to be inconclusive. Should an association between consumption of coffee and pancreatic cancer exist, the association is expected to be weak.

Occupation

In a review conducted by Gold and Goldin [59], a number of studies that examined the relationship between occupational exposure and pancreatic cancer was evaluated. A summary list of occupations was grouped in a table under the following headings: "possible risk", "unproven risks", and "no risks". Among those with possible

risk of developing pancreatic cancer were those working in the metal industry, leather tanning, textile industry, building trades, textile industry and those exposed to chemicals such as DDT.

A recent meta-analysis was conducted examining the relationship between exposure to cadmium and pancreatic cancer [77]. The analysis combined three studies published between 1985 and 1998 that provided the numerical data used to derived the overall estimate. The standardized mortality ratio was 166 (95% CI, 98-280, p=0.059). The authors concluded that cadmium is a plausible pancreatic carcinogen citing that cadmium is a nonessential metal that is known to accumulate in the pancreas and that it "can cause the transdifferentiation [a change from one differentiated cell type into another] of pancreatic cells, increases in the synthesis of pancreatic DNA, and increases in oncogene activation" [77].

Physical Activity

The relationship between the level of physical activity and pancreatic cancer is inconclusive. Some studies observed an inverse relationship between level of physical activity and risk of pancreatic cancer while others did not observe any association.

A recent study examined the relationship between the level of physical activity and pancreatic cancer using data collected in two prospective cohorts: the Health Professional Follow-up Study and the Nurses' Health Study [67]. The results showed a relative risk of 0.45 (95% CI, 0.29-0.70) for those exerting the highest level of activity as compared to those with the lowest level of physical activity. This relationship was only observed among those with a BMI of at least 25 kg/m^2. For those with a BMI less than 25 kg/m^2, no significant differences were observed.

Lee and colleagues [78] examined the relationship between the level of physical activity and cancer risks in a prospective study of college alumni. Of the 17,607 subjects followed, 88 cases of pancreatic cancer were observed. The authors did not observe a significant association between level of physical activity and pancreatic cancer.

Summary

The etiology of pancreatic cancer largely remains unknown. Except for age and tobacco smoke, other risk factors identified (both biological and environmental and lifestyle) so far are largely inconclusive.

Chlorination Disinfection Byproducts and Pancreatic Cancer

Despite the seriousness of pancreatic cancer and the wide spread use of chlorinated drinking water, the relationship between chlorinated drinking water and pancreatic cancer has not been well examined. Since 1978, there have been 11 studies published in the peer-reviewed literature looking at the effects of chlorinated drinking water and pancreatic cancer.

Ecological Studies of Pancreatic Cancer

Of these 11 studies, two were ecological in nature [47, 79]. Flaten [79] used nation-wide incidence data from the Cancer Registry of Norway to examine the relationship between chlorination of drinking water and cancer incidence of 15 anatomical sites collected between 1975 and 1984, one of which was the pancreas. In total, 1,111 male and 882 female pancreatic cancer cases were collected during this period. The municipalities within Norway were grouped into one of three categories depending on the source of drinking water: 1) at least 60 percent of the population of a

given municipality received chlorinated water supplies, 2) less than 60% of the population of a given municipality received chlorinated water, and 3) non-chlorinated water. Flaten found a weak negative correlation (r=-0.16) for men and a weak positive correlation (r=0.21) for women with respect to the rate of pancreatic cancer and chlorinated water treatment. Neither correlation achieved statistical significance ($p>0.05$). Due to the study design, no adjustments could be made for other risk factors at the individual level.

Koivusalo and colleagues [47] assessed the level of mutagenicity in chlorinated drinking water and cancer in Finland. Chlorination byproducts have been shown to contain a highly mutagenic and stable compound called [3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furamone], more commonly known simply as MX. This compound has been detected in drinking water in several countries and the concentration of MX has been shown to be highly correlated with the degree of mutagenicity according to the Ames test. Incident cases of pancreatic cancer were derived from Finnish Cancer Registries from 1966 to 1989. In all, 6,654 cases of pancreatic cancer were identified. Historical information on water quality was used in an additive relative risk model based on a Poisson regression to assess the association between mutagenicity of chlorinated water and a number of cancers. It was observed that exposure to water with high mutagenicity was associated with a modest increased risk of pancreatic cancer (RR=1.13, 95% CI, 1.07-1.39). Again, no adjustments could be made for potential confounders.

Although ecological studies are useful in generating hypotheses, they are limited in their ability to delineate causality [80]. This limitation is a result of the reliance on data that describes the overall population rather than the characteristics of the individuals

within that population. As such, ecological studies are typically susceptible to a variety of limitations including: within-group misclassification, lack of confounder control, temporal ambiguity, collinearity, and cross-migration [80] [81]. The authors of both ecological studies discussed these limitations and suggested exercising caution when interpreting the results.

Analytical Studies of Pancreatic Cancer

The remaining nine studies that examined the association between pancreatic cancer and exposure to chlorination disinfection byproducts are analytical in nature. Two of these studies were of a cohort design while the remaining 7 studies were of a case-control design. Summaries of these studies are shown in Table 1 (starting on page 48). The results from these studies show that the estimated relative risk associated with exposure to chlorinated water ranged from 0.66 to 2.2. Of the nine studies, only three studies found a positive statistically significant association while one study found a statistically significant negative association between exposure to chlorinated water and pancreatic cancer. The remaining five studies had a 95% confidence interval that included 1.00 suggesting that there is no difference in the risk of developing pancreatic based on exposure to DBPs.

One of the first analytical studies to examine the association between CDBPs and adverse health outcomes was conducted by Alavanja and colleagues [82]. This case-control study examined the relationship between gastrointestinal (GI) and urinary tract cancer deaths of residents from the state of New York occurring within the period between 1968 and 1970. The pancreas was among one of the 13 GI cancer sites examined

in the study, although the number of pancreatic cancer cases was not indicated. In total, 3,446 GI and urinary tract cancer mortalities were identified from computer tapes of New York State death certificates. Non-cancer deaths occurring within the same year were used as controls. Controls were also matched (1:1 matching) for sex, age, race, and country of birth. Exposure was defined using the type of residential water source at the time of death. The results showed that those living in area with chlorinated water had an increased risk of pancreatic cancer (OR = 1.97, 95% CI, 1.23-3.16) relative to those who did not.

In 1980, Brenniman and colleagues [83] conducted a case-control study examining the effects of CDBPs on GI and urinary tract cancer deaths in the state of Illinois. Cases and controls for this study were identified from death certificates, and exposure was determined based on the type of residential water source at the time of death (i.e., chlorinated vs. non-chlorinated). Pancreatic cancer was among the cancer sites examined. Controls were non-cancer deaths matched for sex, age, and geographic region. In all, 504 cases of pancreatic cancer were identified. The results of this study show no increased risk of developing pancreatic cancer when exposed to chlorinated water supplies (OR = 1.02, 95% CI, 0.85-1.52).

One year later, Willkins and Comstock (1981) published results from a cohort study that assessed the effects of the chlorination of drinking water on cancer incidence in Washington County, Maryland. Vital status records and census data on 31,000 study subjects were used to compute incidence rates, and relative risk for those exposed to chlorinated water supplies as compared to deep well users (non-chlorinated water supplies). Sources of drinking water and personal information such as sex, age, marital

status, cigarette smoking, education, and church attendance were collected in 1963. The source of water of study subjects was compared based on a 12-year follow up. In exposed populations (chlorinated water), the annual mortality rate from pancreatic cancer was 17.8 per 10^5 residents. Surprisingly, the annual mortality rate due to pancreatic cancer for deep well users (non-chlorinated) was higher (22.2 per 10^5 residents). Results of a multiple logistic regression analysis adjusted for age, marital status, education, smoking history, frequency of church attendance, adequate housing, and persons per room suggest a decreased risk when exposed to chlorinated water supplies (RR= 0.80, 95%CI, 0.44-1.52). However, this relationship was not statistically significant.

Young and colleagues [35] examined the relationship between chlorinated drinking water and cancer mortality of Wisconsin women using a case-control design. Like the previous studies, this study relied on death certificates to estimate CDBP exposure. It was assumed that the address appearing on the death certificates represented the "usual place of residence", and that daily water consumption was also from the address appearing on the death certificate. Results of a logistic regression analysis adjusted for urbanicity, marital status, and high-risk occupation yielded odds ratios of 1.06 (95% CI, 0.16-1.82), 1.05 (95% CI, 0.62-1.80), and 1.26 (95% CI, 0.77-2.08) for high, medium, and low chlorine levels respectively relative to non-chlorinated water sources.

Gottlieb and colleagues [36] conducted a case-control study looking at the relationship between cancer mortality of residents living in Louisiana and their source of drinking water. The study assessed 17 cancer sites including pancreatic cancer. Using death certificates, 806 pancreatic cancer deaths and controls matched for a 5-year age

group, sex, race, and year of death were identified. The results showed that, when compared to ground water (non-chlorinated), there was a small but insignificant increased risk for males who used surface water (OR = 1.11, 95% CI, 0.74-1.68) and a small but insignificant lower risk in women based on the same comparison (OR =0.94, (95% CI, 0.64-1.40).

Zierler and colleagues [84] conducted a large case-control study examining the mortality patterns of residents living in Massachusetts and drinking water. Again, information from cases and controls was captured from death certificates. In all, 4,548 pancreatic cases were included in the study. Controls were selected if they satisfied two of the following principles: 1) the primary cause of death was not known to be associated with disinfectants in drinking water, and 2) the primary cause of death was known to be associated with smoking in the event that the case group comprised cancer associated with smoking. In all, 214,988 controls were selected for the study. The result showed no risk associated with use of chlorinated drinking water (OR = 0.94, 95% CI, 0.89-1.00) as compared to chloraminated (a treatment process that appears to have less potent carcinogenic effect than chlorination) drinking water.

The IJsselmuiden et al. study [37] was based on 101 cases of pancreatic cancer identified through the Washington Cancer Registry. Population-based controls (n=206) were used as the comparison group. Both cases and controls were residents of Washington County in Maryland and were restricted to those who took part in a private 1975 census. The census collected the following individual data: age, sex, race, education, employment status, smoking history, marital status, years of residence in present address, and source of drinking water. An unconditional logistic regression

analysis, adjusted for confounders, yielded an OR of 2.23 (95% CI, 1.20-3.95) for those using municipal (chlorinated) as compared to those using non-municipal (non-chlorinated) water. There were two primary limitations associated with IJsselmuiden et al.'s [37] study. First the exposure estimate was based on the place of residence at the time of the census. Therefore, misclassification of exposure would have occurred if subjects had subsequently lived in different residences with different sources of drinking water users. Secondly, quantitative measurements of CDBPs were not available, and therefore, exposure was based on the crude comparison of chlorinated and unchlorinated water.

In a historical cohort study (1971-1993), Koivusalo and colleagues [31], examined the association between mutagenicity of drinking water resulting from chlorination and cancer. The study consisted of a cohort of 621,431 persons living in 56 towns in Finland with cancer subjects identified through the Finnish Cancer Registry. Individual data was collected by Statistics Finland. In total, 24 cancer sites including pancreatic cancer were examined in the study. A Poisson regression model, after adjusting for gender, age, time-period, and urbanization, and social status (derived from occupation), showed no excessive risk of pancreatic cancer when exposed to water with high mutagenicity (OR=1.01; 95% CI, 0.70-1.20) compared to those using non-chlorinated drinking water.

Kukkula and Lofroth [38] also conducted a case-control study examining the relationship between chlorinated drinking water and pancreatic cancer. The study consisted of 183 cases of pancreatic cancer recruited from eight municipalities in Finland. Approximately, two population controls (n=360) were also randomly selected for each

case matched for sex and year of birth. Estimated exposure was assessed based on the type and duration of water source used at the residence of the participant. The exposed group was those who have "chlorinated municipal drinking water from a surface source available at home", while the non-exposed group were those who were "without this kind of water available at home". The results of the study showed a protective effect for those who were exposed to chlorinated municipal drinking water. The highest odds ratio 0.66 (95% CI, 0.33-1.33) was observed for those who were exposed for 5 years to chlorinated water supply. The lowest OR was observed for those who were exposed to a chlorinated water supply for 20 years or more (OR=0.20; 95% CI, 0.04-0.94). There are two important limitations associated with the Kukkula and Lofroth study [38]. First, no breakdown was given of duration of exposure beyond 20 years. Given the latency of appearance of most cancers, comparisons with longer exposure period may be needed. In addition, the study did not control for known risk factors of pancreatic cancer such as cigarette smoking, diet, and lifestyle.

Summary of Pancreatic Cancer Studies

The evidence accumulated to date does not provide clear evidence of the direction of the association between CDBPs on pancreatic cancer. Some studies suggest a significant increase in risk when exposed to CDBPs, while one study suggests a significant protective effect. The estimate of the relative risk associated with pancreatic cancer when exposed to chlorinated disinfection byproducts ranged from 0.20 [38] to 2.20 [37]. Interestingly, different results were observed in independent studies conducted within the same population and even within the same research group. A comparison of

study results grouped by study population and research group is summarized in Table 1.

Wilkins et al. [85] and IJsselmuiden [37] examined the association between chlorinated drinking water and pancreatic cancer. Both studies were based on the same population: Washington County, Maryland. While both studies used the unconditional logistic regression to derive risk estimates, the results obtained were contradictory. Wilkins et al. observed a small (but insignificant) decrease in the risk of pancreatic cancer when exposed to chlorinated drinking water. However, IJsselmuiden et al. (1992) observed a significant increase in risk in pancreatic cancer when exposed to chlorinated drinking water. The discrepancies in the results may be due to a couple of factors. Although both studies relied on census data to assess exposure based on place of residence and individual data to control for confounders, the Wilkins study used information collected during the 1963 census while the IJsselmuiden study used information collected during the 1975 census. The increased in risk may be a result of better recording and tracking of pancreatic cancer cases resulting in an increase in the number of diagnosed cases.

Koivusalo and colleagues published 2 studies examining the association between exposure to CDBPs and pancreatic cancer. In an ecological study, Koivusalo et al. [47], found a significant increase in risk of pancreatic cancer among those exposed to water with high mutagenicity. However, a historical cohort study conducted two years later by the same group [31] did not observe an increase in the risk associated with pancreatic cancer when exposed to chlorinated drinking water with high mutagenicity. Perhaps the discrepancy can be attributed to the fact that the cohort design could control for potential confounders that were not addressed in the ecological study.

Other factors could contribute to inconsistent results. The disparities may be due to the heterogeneity in approaches to assessing exposure, outcome, and controlling of confounders. To resolve the disparity, a study of high quality is needed to clarify the discrepancies. The study should not only consider sources of drinking water, but also measure THM levels (and other byproducts) and require histologically confirmed end results. Finally, the study should contain individual data in order to adequately control for potential confounders.

Table 1 : Summary of case-control studies of chlorinated drinking water and pancreatic cancer.

Reference	Population	Subject Status	Exposure Assessment	Analysis	Outcome (CI)*
Alavanja, Golstein, Susser (1978)	New York State residents. **Cases:** 3446 gastrointestinal and urinary cancer deaths (number of pancreatic cases not given) **Controls**: Noncancer and lung cancer deaths matched 1:1 for age, sex, and county on death certificates.	Decedent cases Decedent controls (non cancer)	Chlorinated vs unchlorinated water source according to address on death certificate.	Stratified odds ratio with chi-square test. Controlled for urbanicity and occupation.	1.97 (1.23-3.16)
Brenniman, Lagos, Amsel, Namekata, Wolff (1980)	Illinois State residents (Caucasians only). **Cases:** 504 cases of pancreatic cancer (294 males and 210 females). **Control:** Noncancer and lung cancer deaths matched 14:1 for age, sex, and county on death certificates.	Decedent cases Decedent controls (non cancer)	Chlorinated vs unchlorinated water source according to address on death certificate	Mantel Haenszel with adjustment. Controlled for urbanicity, population density.	1.02 (0.85-1.23)

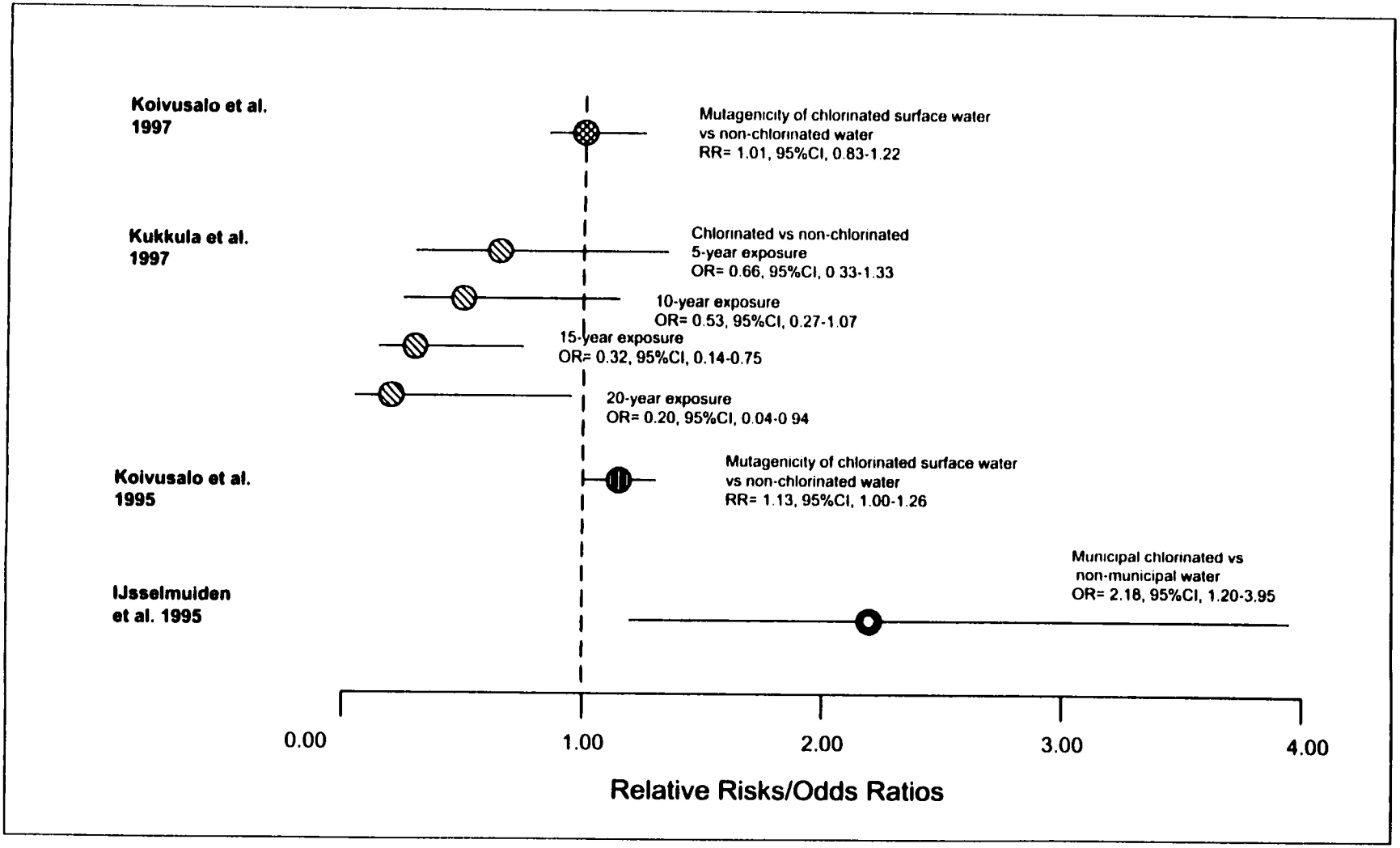
Reference	Population	Subject Status	Exposure Assessment	Analysis	Outcome (CI)*
Wilkins, Comstock (1981) (Cohort Study)	Residents of Washington County, Maryland. **Cancer subjects:** 63 cases of pancreatic cancer were recruited through death certificates, cancer registries, and medical records.	NA	Chlorinated vs unchlorinated water (deep well) according to residence data from past census.	Logistic regression. Controlled for age, marital status, education, smoking history, frequency of church attendance, adequacy of housing, persons per room.	0.80 (0.44-1.52)
Young, Kanarek, Tsiatis (1981)	Wisconsin State residents (White female only). **Cases:** 701 pancreatic cancer deaths between 1972 - 1977. **Controls:** Noncancer and lung cancer deaths matched 1:1 for age, sex, race, and county on death certificates.	Decedent cases Decedent controls	Chlorine dose used to treat water source according to address on death certificate	Logistic regression Controlled for population density, occupational risk, marital status	High:1.06 (0.16-1.82), Medium: 1.05 (0.62-1.80), Low: 1.26 (0.77-2.08)

Reference	Population	Subject Status	Exposure Assessment	Analysis	Outcome (CI)*
Gottlieb, Carr, Clarkson (1982)	Louisiana State residents. **Cases:** 806 pancreatic cancer deaths between 1960-1975. **Controls:** non-cancer deaths frequency 1:1 matched for age, sex, race, and geographic region.	Decedent cases Decedent controls (non cancer)	Chlorinated vs unchlorinated water source according to address on death certificate	Stratified odds ratio with chi-square test	Male: 1.11 (0.74-1.68) Female: 0.94 (0.60-1.49)
Zierler, Danley, Feingold (1986)	Massachusetts State residents between 1969 1983. **Cases:** 4,548 pancreatic cancer deaths **Controls:** 214,988 controls were identified.	Decedent cases Decedent controls (other cancer)	Chlorination/Chloramination on death certificates	Odds ratios with Mantel Haenszel adjustment. Controlled for age.	0.94 (0.89-1.00)
IJsselmuiden, Gaydos, Feighner et.al. (1992)	Washington County (Maryland) residents. **Cases:** 101 pancreatic cancer cases **Controls:** 206 controls	Incident cases with individual information collected from census data. Non-decedent controls.	Chlorination/unchlorinated water source according to residence history.	Logistic regression. Controlled for sex and smoking.	2.18 (1.20-3.95)

Reference	Population	Subject Status	Exposure Assessment	Analysis	Outcome (CI)*
Koivusalo, Pukkala, Vartiainen et al. (1997)	Residents of 56 towns in Finland No controls identified, internal comparison. 825 cases of pancreatic cancer	NA	Mutagenicity of Drinking water	Poison Regression model Controlled for age, gender, social class, urbanicity,	OR=1.01, (0.70-1.20) Comparing no exposure to mutagenicity at 3000+ net rev/l.
Kukkula, Lofroth (1997)	Residents of the District of Turku, Findland **Cases:** 183 cases of pancreatic cancer identified through Finnish Cancer Registry. Diagnosis was histologically confirmed for 63% of cases. **Controls:** 360 controls identified through the National Population Registry and matched by sex, age, and geographical region.	Incident cases with individual information collected from census data. Non Decedent controls.	Cummulative Chlorination/unchlorinated water source according to residence history.	Logistic regression. Did not control for confounders (e.g age, smoking, etc.)	Highest OR = 5 years of exposure 0.66 (0.33-1.33) 20 years exposure 0.20 (0.04-0.94)

* CI - Confidence interval, 95% otherwise noted.

Figure 5: **Results of recent (1992-1997) studies of chlorination disinfection byproducts and pancreatic cancer.**



Summary of Literature Review

The process of chlorinating public water supplies to control water borne pathogens has been hailed as one of public health's major achievements of the 20th century. While the effectiveness of chlorine in controlling water borne outbreaks is not in dispute, the byproducts produced as a result of chlorination and the adverse health effects associated with these byproducts have been the focus of much research in the last 25 years. Adding chlorine to raw water supplies initiates a cascade of reactions resulting in a host of chemical compounds known collectively as chlorination disinfection byproducts. Most CDBPs discovered to date fall within three groups: THMs, HAAs, and HANs. Of these three groups, the THMs are the most common and are often used as a surrogate measure of CDBPs. A body of evidence is accumulating regarding the association between CDBPs and cancer.

Within the cancer literature, three cancer sites have been well examined: bladder, rectal, and colon. Early studies had some important limitations, namely, poor exposure assessment, outcome, and inadequate controlling of potential confounders, but in general found modest elevated risks.

Pancreatic cancer risks associated with exposure to DBPs has also received some attention in the last 25 years, although not as much as the aforementioned cancer sites. A meta-analysis conducted in 1992 showed a small increase in risk in relation to CDBPs. However, the increase was not significant. Since the meta-analysis, results of two case-control and one cohort study have been published. One study showed a statistically significant increase in risk [37] while the other showed statistically significant decrease in risk [38]. The cohort study showed no change in risk [31]. The limitations associated with these three studies have been discussed.

The proposed study differs from previous studies based on the combined characteristics:

- Use of incident cases;
- Use of non-decedent controls;
- Population-based study design;
- Large sample size (both cases and controls);
- Individual information used to control for confounders;
- Individual information collected directly from participants (or proxies);
- Individual exposure profile constructed based on different places of residence using THM levels; and,
- Outcomes were based on histologically confirmed diagnosis.

CHAPTER 3 - METHODS I: The National Enhanced Cancer Surveillance System

This study is a secondary analysis of existing data collected through the case-control component of the Canadian National Enhanced Cancer Surveillance System (NECSS). Access to the databases was approved by the Cancer Bureau of the Population and Public Health Branch of Health Canada. Four SAS datasets were provided in Zipped formats: 1) Main Data, 2) Residence Data, 3) Supplemental Data on Ontario Subjects, and 4) Occupational Data. Dr. Will King of Queen's University also provided water quality collated from the provincial and municipal water monitoring databases.

The National Enhanced Cancer Surveillance System (NECSS) is part of an initiative by the Action Plan on Health and the Environment, a collaborative effort of Health Canada and the Provincial Cancer Registries [18]. The goal of this collaboration is to address issues of health as it relates to the surrounding environment. To effectively address this goal, the NECSS developed a case-control component aimed at collecting individual risk factor information from newly diagnosed cancer patients and from population controls frequency-matched for age, sex and province of residence. Environmental databases were also developed to link to residence history of cases and controls in order to assess cancer risks as a function of various environmental exposures. In total, eight provinces participated in this initiative: Newfoundland, Prince Edward Island, Nova Scotia, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia.

Ascertainment of Cases

The NECSS, through the Provincial Cancer Registries, identified and collected risk factor information on newly diagnosed cancers of concern. Case subjects were recruited for 18 cancer sites: prostate, breast, colon, leukemia, bladder, kidney, rectum, Non-Hodgkin's lymphoma, liver, testis, pancreas, lung, brain, stomach, and other rare

cancer sites (bone/cartilage, salivary, multiple myeloma, mesothelioma) [18]. These sites were recommended by a Steering Committee on site selection based on literature reviews and other environmental concerns [86].

The specific approaches used for recruitment of cancer cases were left to the discretion of the participating Provincial Cancer Registries and the characteristics of cancer sites of interest. For pancreatic cancer, the goal was to recruit every eligible pancreatic cancer case reported to the Registries [87] within the 3-year study period (1994-1997). Arrangements to contact cancer cases in order to collect individual information were made as soon as the Registries received notification of a case in order to minimize loss of subjects due to severe illness or death. Once identified, attending physicians of the cases were contacted in order to obtain consent to contact the patient. A questionnaire was then mailed to the cases inquiring about residential and occupational history among other relevant risk factors. For the most part, questionnaires were sent to the patient within four months of diagnosis. In Ontario, Nova Scotia, and Alberta, proxies were used when cancer patients were too ill or had already died. Cases were eligible for inclusion in the study if it was their first primary neoplasm of concern reported between January 1994 and March 1997 [87].

Ascertainment of Controls

Provincial Cancer Registries were also involved in the recruitment of population controls. Since different registries operated under different provincial constraints, the recruitment process was left to the individual registries to use their own experience and expertise in developing and implementing an optimal control selection strategy. Prior to starting control selection, the sampling strategies were discussed with and approved by LCDC. Three different strategies were used to recruit population controls for the NECSS:

1) Health Insurance Plan, 2) Property Assessment Database, and 3) Random Digit Dialling.

In British Columbia, Saskatchewan, Manitoba, Prince Edward Island (PEI), and Nova Scotia, a random sample was obtained through a database of the provincial health insurance plan [87]. In British Columbia, Manitoba, and PEI, the survey instruments were mailed directly from the Provincial Registries. In Saskatchewan and Nova Scotia, the survey instruments were prepared by the respective Registry and mailed out by its Department of Health. While this strategy is an efficient approach to obtain names and addresses of the targeted population, it could not be applied to all provinces as these types of databases were either not available or not easily accessible. In Ontario, a random sample of controls was selected from the Property Assessment Database of the Ontario Ministry of Finance [87]. Access to this information was possible under the Freedom of Information and Protection of Privacy Act [87]. Alberta used random digit dialing to obtain population controls.

Controls were first recruited in 1996 [18]. The sampling was structured such that the controls were of similar age (5-year interval) and sex distribution as anticipated in the overall case group. Mail-out questionnaires with follow-up telephone interviews were used to obtain information on individual residence histories.

Survey Instrument

Individual information was collected using a questionnaire developed by the LCDC in collaboration of the Provincial Cancer Registries. The self-administered questionnaire was developed using questions from standard and previously validated questionnaires. The topics covered by the questionnaire included the following:

- General information (e.g., sex, age, height, weight, education);

- Smoking (e.g., age first smoked, duration, type of tobacco products, years smoked, average number of cigarettes smoked per day/week);
- Residence history (e.g., time period (year from and to), street, city, county/district, province, postal code, main sources of drinking water for each place of residence (town, dug well, drilled well, bottled, other), type of heating);
- Employment history (e.g. industry, job duties/title, job status (full-time, part-time), presence of dust/odour, chemicals of concern);
- Diet (vitamins/minerals, beverages, fruits, vegetables, bread/cereals, meat, sweets, fats, salts); and,
- Questions relating to women (menstruation, pregnancy, and breast feeding).

A complete copy of the self-administered questionnaire is contained in Appendix A.

Water Quality Information

Two sources of water quality information were used in the current study to estimate individual exposure to CDBPs. The first source was obtained from the Environmental Health Directorate (EHD) 1993 National Water Sampling Data while the second source was from Provincial and Municipal Water Monitoring (PMW) Data 1990-1996. The data for these two sources of water quality data were in turn obtained by collating water quality information previously collected from a number of different surveys of municipal water treatment plants.

EHD 1993 National Water Sampling Data

The EHD water quality information was derived from two independent Canada-wide water quality surveys: 1) National Survey of Chlorination Disinfection By-products (NSCDB), and 2) water monitoring data of DBPs in municipal water supplies.

The NSCDB (1993) was a survey of water treatment plants from 53 major cities across Canada. The cities were selected since they represented a major water source used

by a significant portion of the Canadian population [88]. A questionnaire was sent out to water treatment plants of these cities requesting detailed information about treatment processes and operating practices. Furthermore, samples of treated water were collected from each of the 53 municipal sites and analyzed for chemicals of concern, including THM, BDCM, and TCM. The method used in the sample collection and analysis was described in a publication by Health Canada [88]. While the NSCDB provided comprehensive cross-sectional measurements of CDBPs in treated water, it did not adequately cover many smaller communities in which cases and controls participating in the NECSS had previously lived.

Monitoring of CDBPs is also conducted on a regular basis by Ministry of the Environment or by individual water treatment plants. For example, the City of Ottawa analyzes treated water samples on a regular basis, and the results of various CDBPs levels are publicly available via quarterly and annual reports. Four cross-Canada surveys of water treatment plants have been conducted: 1962, 1975, 1986, and 1995. Water treatment plants were asked to provide the names of the municipality(ies) which they serviced. Each municipality was then assigned a municipality identification number. The numbering scheme allowed for different spellings (e.g., Macleod vs. MacLeod) or mis-edits (e.g., Toronto vs. Torotno) to link to the appropriate municipal water services. In total, monitoring data for approximately 650 cities were obtained through these surveys.[1]

The EHD water quality data was derived by the staff at Health Canada. It combined information obtained from the NSCDB and the municipal surveys. Linear regression models were developed to estimate CDBPs levels for years without water

[1] Much of the work involved in the collection and collation of water quality information was conducted by Dr. W. King and his research team from Queen's University.

quality data. The estimates took into account imbalances in sampling by season and treatment plant effect. All households within the water distribution system of a given treatment plant were assumed to have the same CDBPs level as the treatment plant. Senior epidemiologists at Health Canada linked CDBPs levels with participants of the NECSS. Single estimates for THM, BDCM, and TCM for each participant were provided with the dataset. It was not possible for me to obtain access to residence specific EHD exposure information.

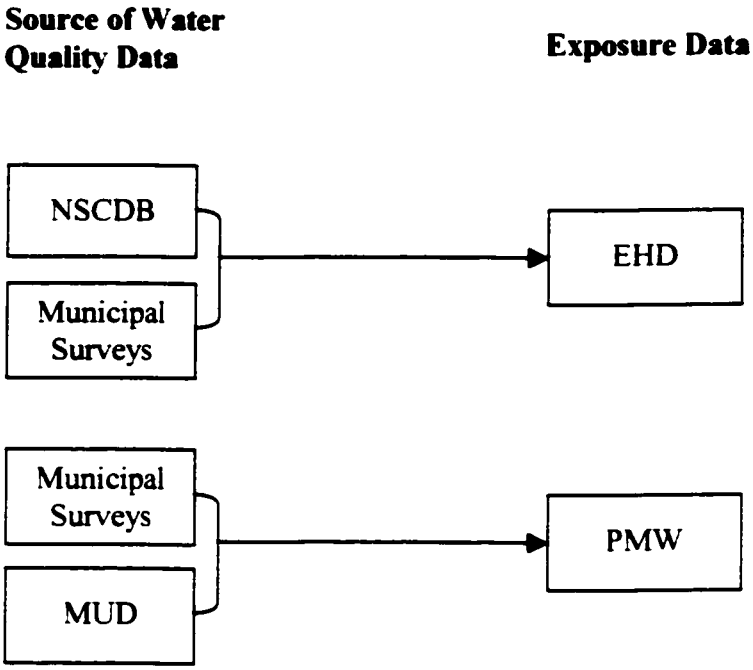
Provincial and Municipal Water Monitoring (PMW) Data 1990-1996

The Provincial and Municipal Water Monitoring (PMW) Data 1990-1996 were based on sampling data of CDBPs that are regularly monitored by provincial/municipal authorities. Sampling data between 1990 and 1993 was used to estimate THM exposure. The data was also adjusted for seasonal variation and the organic content of water source. Where sampling data was not available, information from the 1996 Municipal Water Use Database (MUD) was used to estimate water quality information. MUD contains information on water source, treatment practices and population (over 1000) served by the water facility. A linear regression model was developed to predict THM levels in drinking water. The model regressed THM levels on water source (ground vs. surface), treatment practices, and hydrometric area. As was the case with the EHD data, all households living within the distribution system were assumed to have the same CDBP level as that of the source water treatment plant.

Summary of Water Quality Data

In the current study, two sets of water quality data were used to estimate exposure to CDBPs: EHD National Water Sampling Data and PMW monitoring data. Figure 6 below shows that these two sources of water quality data were based on various surveys of water treatment plants. For the EHD data, the data was derived from NSCDB and Municipal surveys. The PMW was also based on municipal surveys supplemented with information from the MUD database.

Figure 6: Sources of water quality information used to derive exposure data.



Abbreviations: EHD-Environment Health Directorate 1993 National Water Sampling Data; PMW- provincial and Municipal Water Monitoring (PMW) Data 1990-1996; NSCDB- national Survey of Chlorination Disinfection By-products, and MUD- Municipal Water Use Database

CHAPTER 4 - METHODS II: Thesis

The current study is a secondary analysis of existing data collected through the case-control component of the Canadian National Enhanced Cancer Surveillance System (NECSS). Incident cases were identified through cancer registries with population controls frequency-matched for sex and age (matched for all 18 cancer sites of the NECSS). However, only pancreatic cancer was examined in this study. Individual information was collected through self-administered questionnaire. In addition to individual risk factor information, residence history was also collected. Exposure was estimated by linking residence information collected from the self-administered questionnaire with matching water quality information.

Case and Control Definition

The NECSS collected information from 628 pancreatic cancer cases from 8 different provinces. To be included in the current study, cases had to meet the following criteria:

1. Age at diagnosis between 30 and 74 years of age;
2. Diagnosis of first primary cancer of the pancreas (ICDO/2: C25, ICD9:157); and,
3. Diagnoses were histologically confirmed;

Cases from Newfoundland and Prince Edward Island were excluded from the main analyses due to very few numbers of recruited cases in these provinces (n= 13 and 3 respectively).

The NECSS also collected information from 5,039 population controls between the ages of 30 and 74 from all participating provinces. Controls from Newfoundland and

Prince Edward Island were excluded. Controls with a history of cancer (of any type) were excluded from the analysis.

Exposure Information

In generally, the average DBP levels measured at a particular treatment plant or within its distribution system were assigned to all households serviced by that treatment plant. This practice has been used previously in studies looking the association between CDBPs and bladder and colorectal cancer [34, 49, 89].

In this study, two sources of water quality information were used to independently estimate/assign historical exposure to DBPs. As indicated in the previous chapter, the two sources of water quality information are:

1) Environmental Health Directorate (EHD) 1993 National Water Sampling Data, and;
2) Provincial and Municipal Water Monitoring (PMW) Data 1990-1996.

The EHD water quality data provides a single estimate of exposure to THM, BDCM, and TCM expressed as cumulative lifetime averages of known exposure information. For the PMW data, disaggregated THM information by residence was provided for each subject. Information regarding BDCM and TCM was not available in the PMW water quality data.

Exposure Time Window

Individual exposure assignment was based on a predetermined exposure time window (ETW) of 30 years. This *a priori* criterion was used since it was felt that 30 years was an adequate exposure window for cancer induction. The 30-year ETW ends at the year of interview. In most instances, the ETW is between 1966 and 1996.

Individual Exposure Assignment

In the current study, a 30-year exposure time window ending with the year of interview was used to assign historical exposure to DBP. To derive this estimate, residence information collected from respondents was merged with the EHD and PMW water quality data. For each subject, we disaggregated the exposure measures into 30 annual records, one for each year of the 30 year ETW. The information in the annual records was based on the 30-year ETW, the residence history, and the appropriate CDBPs exposure.

For the analyses using the EHD water quality data, only the lifetime averages of known THM, BDCM, and TCM exposure estimates were available for each subject. These estimates were assigned to each of the annual records reported by the study participants. The average cumulative CDBPs concentration for each subject was assigned to all annual records with known residence information within the 30-year ETW.

For the analyses using the PMW monitoring data, we were provided with THM information at a level that permitted us to link each residence to a THM value. The THM information for a specific residence was used to directly represent THM exposure for all years within the corresponding residence period. In addition, information regarding the main source of drinking water as reported by respondents was also taken into account. In some instance, subjects may have lived within the distribution network of the water treatment plant, but they did not use the treated water. Instead, some subjects may have relied on private wells where the water was untreated. If the respondent indicated that their main source of water was "city water" then the entire residence period was assigned the corresponding THM concentration. If the respondent indicated that their main source

of drinking water was "well water" (dug or drilled) then their level of exposure was assigned 0 ug/L of THM since well water is not usually treated with chlorine and therefore, very little or no CDBPs could be formed.

Some problems arose in creating the annual disaggregated records, largely because subjects were not always consistent in reporting residence information. In some instances, the residence histories provided were incomplete or they were not chronologically coherent. Treatment of these irregularities were as follows:

- Those who reported living in a given residence after the date of interview were assumed to be living only up to year in which the interview was conducted;
- Those who reported living in a given residence before their year of birth were assumed to have begun at their year of birth;
- Those with overlapping residences (living at 2 or more places at the same time) were removed from the main analyses; and,
- Those with gaps in their residence history were included in the analyses but the exposure to DBPs during the residence history gap was treated as missing and was imputed
- Those who moved in the middle of the year (i.e., the end date in one residence is the same as the start date at the next residence) were given a DBP level for that year which was an average of the THM levels for the two residences. This problem only arose as an issue for the PMW analysis.

Table 2 provides an example of the approach used to estimate exposure for a 30-year exposure time window using both water quality data sources. The sample calculation

was based on a hypothetical subject who had lived in three cities within the last 30 years (Ottawa, Toronto, and Vancouver). For the EHD exposure data, a single estimate of 100 ug/L of THM was available. Therefore, for each of the last 30 years (1966 to 1996), annual average exposure was estimated to be 100 ug/L. For the same subject, the PMW exposure data provided three exposure estimates for THM, each corresponding with a place of residence (city). For this subject, average exposure to THM while living in Ottawa between 1986 and 1995 was 100 ug/L. While living in Toronto (1976-85), this subject, on average, was exposed to 50 ug/L of THM. Finally, while living in Vancouver (1966-75), the subject was exposed to an average of 150 ug/L of THM. The overall average exposure for this subject, based on the most recent 30-years of exposure was 100 ug/L.

Table 2: **Example of derived estimates for 30-year exposure time window using two sources of exposure data; Environment Health Directorate (EHD) 1993 water quality data and the Provincial Municipal Water (PMW) water monitoring data for hypothetical subject with 3 places of residence.**

Place of Residence	Period of Residence	Year of Exposure Time Window	EHD Exposure data (THM, ug/L)	PWM Exposure Data (THM, ug/L)
Ottawa	1986 to 1995	1	100	100
		2	100	100
		3	100	100
		4	100	100
		5	100	100
		6	100	100
		7	100	100
		8	100	100
		9	100	100
		10	100	100
Toronto	1976 to 1985	11	100	50
		12	100	50
		13	100	50
		14	100	50
		15	100	50
		16	100	50
		17	100	50
		18	100	50
		19	100	50
		20	100	50
Vancouver	1966 to 1975	21	100	150
		22	100	150
		23	100	150
		24	100	150
		25	100	150
		26	100	150
		27	100	150
		28	100	150
		29	100	150
		30	100	150
		Average	**100 ug/L**	**100 ug/L**

Observed Control Mean Imputation

Missing DBP values were imputed using the mean of the control group, an imputation method referred to as Observed Control Mean Imputation (OCMI) [90]. OCMI uses the mean of the control group to impute for missing exposure information gaps for both case and control subjects. For EHD water quality data, the mean for THM, BDCM and TCM for controls were 22.48 ug/L, 2.86 ug/L and 17.81 ug/L respectively. For the PMW monitoring data, the average of the THM concentration among controls was 23.28 ug/L.

Imputation with the EHD water quality data was used when subjects were missing residence information. The appropriate control group mean was inserted into the annualized records for residences which were missing. Imputation in the PMW occurred for subjects who were missing residence information but also for subject for whom we were unable to establish a link of their residence to a THM value. Again, the appropriate control group mean was inserted into the annualized records.

Comparison of Water Quality Data

Tables 3 and 4 compares the means of the THM levels from the EHD and PMW water quality data bases. Table 3 compares the means for the entire reported residence history while Table 4 reports the means for the 30-year ETW. On average, the mean concentration of THM was slightly higher in the PMW water monitoring data than the EHD water quality data. The correlation between the two water quality datasets was fairly high. However, correlation decreased slightly when only a 30-year ETW was considered. Based on the full residence history, the Pearson correlation was 0.966. With the 30-ETW, the correlation was reduced to 0.903.

Table 3: **Derived mean annual exposure to THMs from the Environmental Health Directorate (EHD) and the National and Provincial (PMW) water quality data bases for *full residential history*.**

THM characteristics	Water Quality Database	
	EHD	PMW
Mean (cases and controls)	22.51 ug/L	23.79 ug/L
Range	0 – 290.67 ug/L	0 – 227.98 ug/L
Pearson Correlation	0.966	

Table 4: **Derived mean annual exposure to THMs from the Environmental Health Directorate (EHD) and the National and Provincial (PMW) water quality data bases for *30-year exposure time window*.**

THM characteristics	Water Quality Database	
	EHD	PMW
Mean (cases and controls)	22.72 ug/L	24.58 ug/L
Range	0 – 290.67 ug/L	0 – 227.98 ug/L
Pearson Correlation	0.903	

Data Analysis

An overview of the analytic strategy is shown in Figure 6. Two sources of water quality information were used to assess for pancreatic cancer risks: 1) Environmental Health Directorate 1993 National Water Sampling Data and 2) National and Provincial Water Monitoring data. These sources of water quality information were in turn used to estimate exposure in three different ways:

1. *Complete Exposure Information*: This category requires that subjects have valid exposure information for the entire 30 years ETW with no exposure information gaps;
2. *At least 20 years of Exposure Information*: This category requires that subjects have valid exposure information for at least 20 years within the 30 year ETW. The missing information was imputed using OCMI; and,
3. *Full Imputation of missing exposures*: This category does not require subjects to have any minimum exposure information within the 30-year ETW. Missing exposure information was imputed using OCMI.

For each of the above categories, unconditional logistic regression analysis was performed on the entire sample, as well as stratified by sex. For the EHD data, analyses were conducted for THM, BDCM, and TCM while only THM was available from the PMW monitoring data.

The effects of latency on pancreatic cancer risks as a result of exposure to DBPs were also considered. For the EHD water quality data, the 3-years immediately prior to diagnosis had been excluded from the overall exposure estimate (3-year latency model).

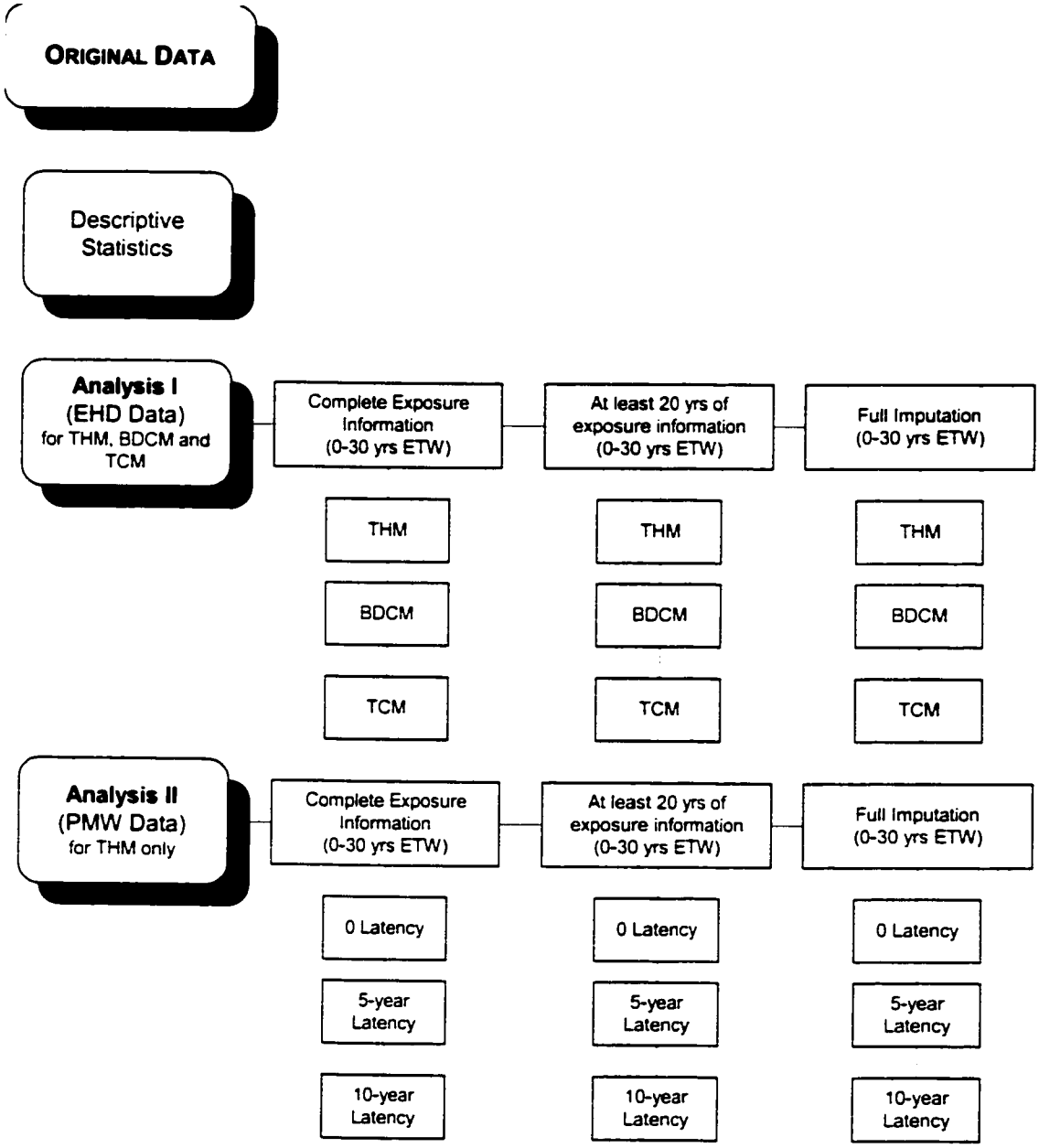
For the PMW monitoring exposure data, three latencies were assessed: no latency (0-year), 5-year and 10-year latency.

Imputation increases the availability of sample but might introduce a bias. The analytical strategy shown in Figure 7 permits examination of this effect. In the 'Complete Exposure' category, the number of cases and controls were greatly reduced since all subjects in this analysis required complete exposure information. Conversely, the 'Full Imputation' exposure model contained almost the entire database since missing information was imputed with the mean of the control group. Therefore, when going from left to right (Figure 7), the number of subjects in the analysis increased as did the extent of imputation.

For the analyses using the PMW monitoring data, 0-year to 10-year latency effects were considered (Figure 7). The number of subjects does not change since the same subjects are included in the analyses: only the number of years prior to the year of interview which were excluded from exposure estimation changed. At 0-year latency, 30 years were used to derive the average exposure. At 10-year latency, only 20 years of exposure information were used (year-10 to year-30).

Analyses were conducted using the SAS System for Windows Release 8.2 (TS2M0). The analysis began with the exploration of the datasets provided to identify irregularities and potential coding errors. This was followed by descriptive analysis examining the distribution of subject status (cases and controls), age, province as well as other potential confounders.

Figure 7: Summary of the analytical process.



Abbreviations: ETW - Exposure Time Window, THM-Trihalomethane, BDCM-Bromodichloromethane, TCM-Chlorofrom, EHD-Environmental Health Directorate 1993 Water Sampling data, and PMW- Provincial Municipality Water Monitoring Data, 1990-1996.

Frequency Matched Variables

Age, and sex were frequency-matched variables. As such, it was also determined *a priori* that all analyses were to be adjusted for province of recruitment given that different provinces used different methods of recruiting subjects. Therefore, the *minimally adjusted model* included these three variables. Age was re-coded into 5-year age groups with the lowest age group (less than 50 years of age) being the referent group. For sex, females served as the referent group. For province, Ontario was the referent group.

Model Building Strategy

Potential confounders were determined from the literature review, and through an exploratory univariate analysis. A p-value of 0.25 was used for entry into the fully adjusted model, a value suggested by Hosmer and Lemeshow [91]. The Type III Chi square was also reported. It is a likelihood ratio statistic that tests the hypothesis that the betas for all categories of a variable are simultaneously '0' while adjusting for the other variables in the model.

Below are the covariates included in the minimally adjusted models, and fully adjusted models for males and females combined as well as analyses stratified by sex. All analyses were adjusted for matching variables: sex, age, and province.

1. *Minimally Adjusted Model*: Age + Sex + Province+ Covariate;
2. *Combined Fully Adjusted Model*: Age + Sex + Province+ BMI+Weight Change (from current to maximum weight) + Education + Total Fat Consumption + Total Energy Consumption + Smoking (pack years) + Coffee + Beer;

3. *Male Fully Adjusted Model*: Age + Province+ Weight Change (from current to maximum lifetime weight) + Total Fat Consumption + Total Energy Consumption + Smoking (pack years) + Coffee + Beer + liquor; and,
4. *Female Fully Adjusted Model*: Age + Province+ BMI+Weight Change (from current to maximum weight) + Education + Total Fat Consumption + Smoking (pack years) + Coffee + Age at First Menstruation + Number of Pregnancies;

Variable Specification

The data set obtained from Health Canada contained 576 variables describing 5,667 subjects (628 cases and 5,039 controls). Some of the variables were used directly as collected from the subjects (e.g., sex, province), some were derived using simple calculations (e.g., body mass index (BMI)), and others were derived using a compilation of variables to construct an index (e.g., energy intake). Furthermore, some variables were re-coded from continuous to categorical variables. One advantage of using categorical variables is that it avoids having outliers. The categories selected were either based on previously published literature in order to facilitate comparison or individual observations were grouped together to avoid small/empty cell situations. Most of the variables in the data set were not used in the model building process since they were either not supported or discussed in the literature or no plausible rationale for the association could be determined. Since the NECSS collected information for 18 cancer sites, some information collected may have been more relevant to other cancer sites. The variables considered in the analyses are described below.

Trihalomathanes

Since THMs are the most abundant type of disinfection byproduct, modeling for exposure to CDBPs was based on the surrogate-measured levels of THMs. These values were used to reconstruct defined cumulative individual exposures by linking known residence data with corresponding THM data. These continuous values were then grouped into four categories. Since no consistent cut-points for different THM categories have been used in the literature, the cut points selected for use in this thesis were chosen to ensure that adequate numbers of subjects were present in each cell to provide stable point estimates with relatively small standard error. The *a priori* determined cut-points were: less than 10 ug/L, 10 to 20 ug/L, 20 to 50 ug/L and greater than 50 ug/L. The first category (< 10 ug/L) was used as the referent category.

Bromodichloromethane

Like the previous models, individual exposure to bromodichloromethane (BDCM) was assessed by linking water quality data with known residence data. Merging of these two data sets provided an estimate of cumulative exposure of known exposure periods. This information was then grouped into four categories. The *a priori* determined cut-points were less than 1 ug/L, 1-3 ug/L, 3-5 ug/L, and greater than 5 ug/L. The first category (< 1 ug/L) was the referent group.

Chloroform

Like the THM model, individual exposure to chloroform (TCM) was assessed by linking water quality data with known residence data. Merging of these two data sets provided an estimate of cumulative exposure of known exposure periods. This information was then grouped into four categories. The *a priori* determined cut-points were less than 3 ug/L, 3-10 ug/L, 10-30 ug/L and greater than 30 ug/L. The first category (<3 ug/L) is the referent category.

Sex

The sex of every subject was known, and therefore, none of the cases or controls were removed from the analysis because they were missing this characteristic. Females were used as the referent group. Sex was included in the minimally adjusted model.

Age

The age of the subject at interview was calculated by using the subject's date of birth and date of the interview. It was a continuous variable re-coded into 5-year age categories. Three coding errors were observed. The errors resulted in an invalid age of zero (n=2) and –11 (n=1). All three subjects were controls. These subjects were removed from further analysis. The age of participants was categorized into 5-year age groups but those under age 50 were combined into one group. This group (< 50 years old) was also the referent group. Age was included in the minimally adjusted model.

Province

Since each of the participating provinces had their own method of selecting cases and controls and, it was determined *a priori* that the variable 'province' was to be adjusted in all models. However, in Prince Edward Island (PEI), only three pancreatic

cancer cases were identified during the study period although there were 220 controls. Furthermore, as PEI is a small island surrounded by ocean water, its primary source of drinking water is from underground sources that contain less organic material to form CDBPs as compared to surface water (i.e., lakes and rivers). Given the low number of cases combined and the homogenous sources of drinking water, PEI was excluded from the main analyses. Cases and controls from Newfoundland were also excluded due to low number of cases. For the remaining provinces, Nova Scotia was grouped with Ontario. British Columbia, Alberta, Saskatchewan, and Manitoba were grouped together. Grouping of provinces was necessary since some provinces contained very few cases (e.g., n=35 cases for Saskatchewan) that could yield unstable risk estimates.

Education

Subjects reported their level of education by reporting the number of years of primary, secondary (elementary and high school) and post-secondary schooling completed. These values were added to provide an overall estimate of level of education. The combined years of schooling was re-coded into three categories: 0-8 years (less than high school), 9-12 years (some or all high school), and more than 12 years of schooling.

Body Mass Index

BMI is a ratio of body weight (kg) and the square of the height (meters) of the individual. Information about self-reported weight and height was used to calculate the BMI of the individual. The calculated BMI was collapsed into four categories: 1) less than 23 kg/m^2, 2) 23-27 kg/m^2, 3) 27-30 kg/m^2, and 4) greater than 30 kg/m^2, with the lowest category being the referent group.

Smoking

Participating subjects' level of tobacco consumption was assessed using a number of variables. The subjects were asked if they had smoked at least 100 cigarettes in their entire life. If they responded yes, information regarding smoking period and average number of cigarettes smoked were inquired. A continuous composite smoking index (i.e. pack-years) was constructed based on the average number of cigarettes smoked per day (divided by 25 cigarettes to give packs per day) and the duration of smoking. This continuous variable was then re-coded as a categorical variable with cut-off points based on previously published literature [68].

Energy and Fat Intake

Diet information was collected using questionnaires modeled on the reduced Block questionnaire [92] and the Nurses Health Study cohort [93]. Fat consumption and caloric intake were assessed based on a composite of subjects' responses to the diet related questions. The type and frequency of consumption of each food item were multiplied by a factor calibrated for fat and caloric content. The calibration factor was obtained from the *Canadian Nutrient Guide.* Total fat and caloric intake were derived by adding individual fat caloric contributions of all food items. The matrix used to derive energy and fat intake was previously developed by Villeneuve et al. [68].

For fat intake, the cut points used in the current study are the same ones as in other published studies [68]. The referent group is those with weekly consumption of less than 236 grams. The other three groups are those consuming 237-323 g/week, 324-420 g/week, and > 420 g/week.

For energy intake, the cut points were based on quartiles. The referent group is those with daily intake of less than 1,370 calories. The other three groups are those consuming 1,370-1,710 Cal/day, 1,710-2,050 Cal/day, and > 2,052 Cal/day.

Alcohol Consumption

Participants were asked about their usual consumption of alcoholic beverages. Specifically, questions were asked about the frequency of beer, wine and liquor consumption. The responses were grouped into three categories: 0-3 times per month (referent group), 1-6 times per week, and at least once per day.

Tap water

Information regarding consumption of tap water was also requested. The responses were categorized into four groups based on a daily consumption: 1) less than 3.57 glasses per day (referent group), 3.57-5.00, 5.00-7.86, and > 7.86 glasses per day.

Coffee consumption

Respondents were asked to report their regular coffee consumption. The responses were grouped into 4 different categories: 1) <4 cups per week (referent group), 2) 5-7 cups per week, 2-3 cups per day, and 4) more than 3 cups per day.

Female Reproductive History

For female respondents, questions regarding their reproductive history were also requested, particularly those relating to age at first menstruation and number of pregnancies.

For age at first menstruation, the responses were categorized into three groups with cut points obtained from previous published literature [68]. The referent group was

those with age at first menstruation of less than 12 compared to those between the ages of 12-14 years, and those with age at first menstruation of at least 15 years old.

With respect to the number of pregnancies, responses were grouped into five categories with those with zero pregnancies serving as the referent group. The highest group was those with at least 4 pregnancies.

Percent Weight Change

Percent weight change is defined as the difference between the maximum lifetime and the weight at 2 years prior to interview divided by the weight 2 years prior to interview. The continuous variable was re-coded into four categories: < 2.9 %, 2.9-5.7%, 5.7 -10.2% and > 10.2%. The referent group became those with percent weight change of less then 2.9%. The cut-point was obtained from previously published literature [68].

Comparison of Analytical Strategies for EHD and PMW Water Data

Table 5 compares the differences between EHD (Analyses I) and PMW (Analysis II). There are 3 differences between the two main analyses: 1) source of exposure data, 2) specific DBPs assessed, and 3) latency effect. In Analysis I, the EHD water sampling data was used while the second analysis, Analysis II, the PMW monitoring water was used to assess exposure. In Analysis I, risk estimates were obtained for THM, BDCM, and TCM while Analysis II, only THM was assessed. Information regarding BDCM and TCM was not available. Finally, latency effects were assessed for Analysis II due to availability of disaggregated data.

Table 5: Comparison of the two main analyses, Analysis I and II.

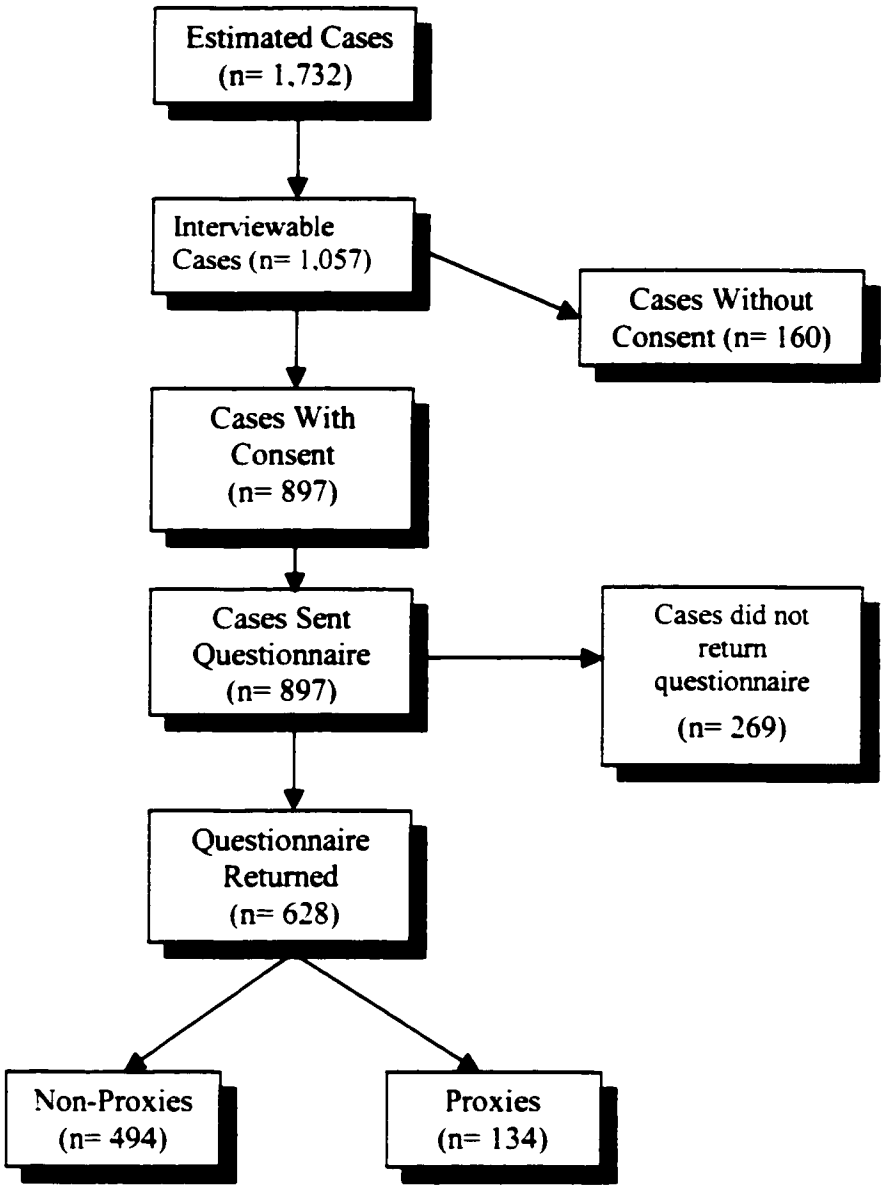
Characteristic	Analysis I	Analysis II
Study Population	Participants of NECSS (incidence pancreatic cancer cases and population controls)	Participants of NECSS (incidence pancreatic cancer cases and population controls)
Analytical Strategy	Logistic Regression	Logistic Regression
Sources of Water Quality Information	Environmental Health Directorate Water Sampling Data	Provincial Municipal Water Monitoring Data
Type of CDBPs	THM, BDCM, and TCM (average estimates for each CDBPs were provided by Health Canada)	THM (average estimates were derived by re-constructing individual exposure profile using residence specific THM information from PMW)
Evaluate different latency effects	No	Yes

Response Rate

The overall response rate for the case-control component of the NECSS was 70 percent for men and 68 percent for women for both cases (of all cancer sites) and controls. However, like other fatal cancers with low survivor rates and a short survival period, the percentage of information collected directly from pancreatic cancer cases was lower.

As shown in Figure 8, within the 3-year study period, 1,732 cases of pancreatic cancer were expected [87]. However, during the study period, only 1,057 pancreatic cancer cases were identified (61 percent of expected cases). Figure 8 also shows that physicians provided consent to contact 897 subjects (85%). Of this group, interviews were completed in 628 cases for a completion rate of 70%. Overall, based on the estimated number of cases occurring during the case recruitment period, the study completed interviews on 36 percent (0.61 x 0.85 x 0.70).

Figure 8: **Breakdown of outcome of case recruitment.**



Proxy Interviews

With the exception of Ontario, information from proxy subjects was not intentionally collected from cases or controls. Table 6 describes the number of proxy subjects with respect to participating provinces prior to the application of inclusion and exclusion criteria. In Ontario, information was collected from proxies for 134 case subjects and 3 controls. Most of these proxies were spouses of case subjects (74 percent). Another six percent of case information was collected from daughters of subjects while five percent was collected from the sons of subjects. Other relationships of proxies to case subjects include common-law partner, and friend.

Unsolicited proxy responses were also accepted for the provinces of Alberta and Nova Scotia, although the participating Registries did not request these responses. In Alberta, personal information for 6 case subjects was collected. In Nova Scotia, personal information for 13 case subjects and two controls was collected.

Overall, the proxy case subjects comprised 24 percent of all case subjects.

Table 6: Proxy respondents by province.

Province	Proxy Respondents	
	Cases (% of n_{Total} = 628)	**Controls (% of n_{Total} = 5039)**
Newfoundland	0	0
Prince Edward Island	0	0
Nova Scotia	13 (2)	2 (0)
Ontario	134 (21)	3 (0)
Manitoba	0	0
Saskatchewan	0	0
Alberta	6 (1)	0
British Colombia	0	0
Total Proxy Subjects	153 (24)	5 (0)

CHAPTER 5 – RESULTS

Descriptive Statistics

Figure 9 shows the distribution of the entire sample of study participants according to province. The total sample consisted of 628 cases and 5030 controls. A large percentage of subjects (40 percent) were recruited from Ontario. This is followed by British Columbia (17 percent) and Alberta (13 percent). The smallest number of subjects came from Newfoundland (4 percent) and Prince Edward Island (4 percent). Table 7 shows the distribution of cases and controls according to province. In total, there were 628 pancreatic cancer cases and 5026 controls recruited for the study. Four controls did not have provincial identification information. The largest percentage of cases (44 percent) and controls (38 percent) were recruited from Ontario. Conversely, Table 7 also shows very few cases were from Newfoundland (2 percent) and PEI (0.5 percent).

Table 8 shows that there were slightly more males (51 percent) than females (49 percent). Among cases, 44 percent of cases were female while 56 percent of cases were male. Among controls, 49 percent of subjects were female and 51 percent were male.

Figure 10 shows the distribution of participants by 10-year age groups. Most of the participants were 50 years of age or older (73 percent). Only four percent of participants were less than 29 years of age. Table 9 compares the distribution of cases and controls by province of recruitment. Overall, the percent distribution of cases and controls within respective provinces was similar. In some provinces (Alberta, Saskatchewan, Manitoba and Ontario), the percent distribution for cases was slightly higher among cases than controls. Figure 11 compares the 10-year age distribution of cases and controls. On average, cases were older than controls. The average age of cases were 61.6 years while the average age of controls were 56.7 years.

Figure 9: **Percent distribution of subjects by province.**

Table 7: **Distribution of subjects status (case vs. control) by province.**

Province	Subject Status		
	Cases (%)	**Controls (%)**	**Total (%)**
British Columbia	92 (15)	869 (17)	961 (17)
Alberta	107 (17)	618 (12)	725 (13)
Saskatchewan	35 (6)	270 (5)	305 (5)
Manitoba	53 (8)	307 (6)	360 (6)
Ontario	275 (44)	1932 (38)	2207 (39)
Nova Scotia	50 (8)	569 (11)	619 (11)
Prince Edward Island (PEI)	3 (0.5)	220 (4)	223 (4)
Newfoundland	13 (2)	241 (5)	254 (4)
Total	**628**	**5026**	**5654***

* 4 controls with missing province information.

Table 8: Distribution of participants by gender by subject status (case vs. control).

Gender	Subject Status		Total (%)
	Case (%)	Control (%)	
Male	353 (56)	2540 (51)	2,893 (51)
Female	275 (44)	2490 (49)	2,765 (49)
Total	**628**	**5030**	**5,658**

Figure 10: Distribution of participants by 10-year age groups.

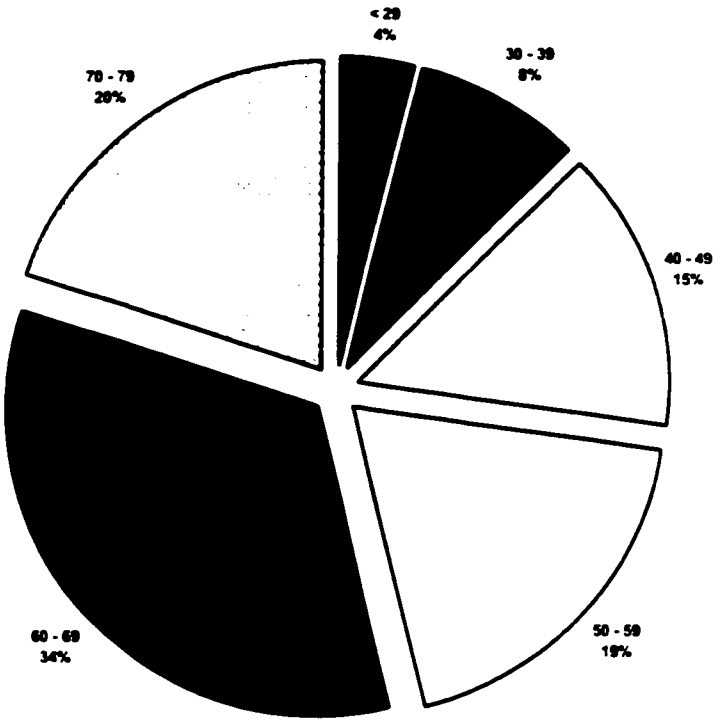
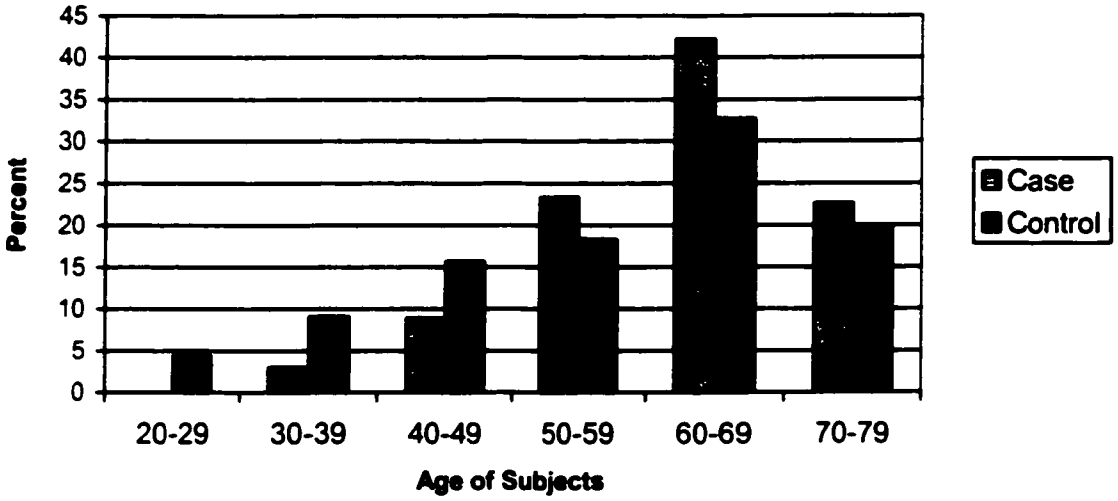


Table 9: Distribution of 10-year age groups by province.

Province	Age Groups					
	< 29	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**
British Columbia (%)	53 (6)	91 (9)	135 (14)	167 (17)	344 (36)	171 (18)
Alberta (%)	25 (3)	67 (9)	108 (15)	144 (20)	240 (33)	141 (19)
Saskatchewan (%)	18 (6)	21 (7)	35 (11)	57 (19)	107 (35)	67 (22)
Manitoba (%)	14 (4)	30 (8)	49 (14)	78 (22)	122 (34)	67 (19)
Ontario (%)	85 (4)	194 (9)	384 (17)	379 (17)	710 (32)	454 (21)
Nova Scotia (%)	8 (1)	35 (6)	61 (10)	130 (21)	243 (39)	142 (23)
PEI (%)	11 (5)	19 (8)	33 (15)	63 (28)	61 (27)	36 (16)
Newfoundland (%)	12 (5)	19 (7)	39 (15)	51 (20)	82 (32)	51 (20)
Total (%)	**221 (4)**	**404 (8)**	**724 (15)**	**896 (19)**	**1632 (34)**	**962 (20)**

Figure 11: Distribution of cases and controls according to 10-year age groups.



Association of Pancreatic Cancer with Potential Confounders (Partially Adjusted Model)

The associations between potential confounders and pancreatic cancer are presented in Table 10 to 12. Table 10 presents the results of the combined analysis of male and female while Tables 11 and 12 present results for males and females respectively. The analyses were based on the entire study population and all analyses were adjusted only for sex, age, and province of recruitment.

Body Mass Index

The male and female combined univariate analysis showed a decreased risk among those having a BMI between 23 kg/m^2 and 30 kg/m^2. However, a modest increase in pancreatic cancer risk was observed for those with BMI above 30 kg/m^2 as compared to the referent group (OR=1.36; 95% CI=1.05-1.77). Among male subjects, a similar trend was observed, although none of the comparisons achieved statistical significance. Among female subjects, those with BMI above 30 kg/m^2 had a significant increased risk (OR=1.52; 95% CI 1.06-2.19) compared to those with BMI of 23 kg/m^2 or less. The Type III Chi square (likelihood ratio statistic) supports including BMI as a potential confounder in the combined (p=0.003) and female (p=0.002) analyses, but not for males (p=0.340).

Weight Change

Percent weight change from maximum lifetime weight appears to have a protective effect for pancreatic cancer in all three types of analyses (combined, male and female separately). The protective effect is particularly strong for those with weight change (from maximum lifetime weight and reported weight 2 years prior to interview) of 2.9 to 5.7 percent as compared to those with less than 2.9 percent (referent group). For

the male and female combined analysis as well as those stratified by sex, weight change had ORs ranging from 0.52 to 0.53 with the 95% CI ranging from 0.35 to 0.79.

Education

The association between education (pre and post secondary) and cancer risk was assessed. For males, no significant association was observed between education and cancer risk. For females, education appeared to be associated with pancreatic cancer. When compared to those with less than 9 years of schooling, females with 9 to 12 years of schooling had higher odds ratio (OR=1.53; 95% CI, 1.01-2.31).

Total Fat Intake

A modest increase in pancreatic cancer risk in relation to total fat intake was observed for women. When comparing individuals consuming the equivalent of 237-323 grams of fat per week to those consuming less than 236 grams per week, the odds ratio was 1.51 (95% CI, 1.04-2.29). In the combined analysis, those consuming more than 420 equivalent grams of fat also had a small increase in pancreatic cancer risk (OR=1.29; 95% CI, 1.00-1.67). No significant increase in pancreatic cancer risk was observed for males.

Total Energy Intake

No significant association was observed in the separate analyses of males and females. A small increase in risk was observed for the combined analysis when comparing those consuming an equivalent of 1,710 to 2,050 Cal/day to the referent group (<1,370 Cal/day), with the odds ratio estimated to be 1.33 (95% CI, 1.02-1.72).

Smoking

Cigarette smoking is an important risk factor for pancreatic cancer. In the combined analysis, participants with 15 to 35 pack-years of cigarette smoking had a significantly increased risk of pancreatic cancer (OR=1.51; 95% CI 1.20-1.90) as compared to non-smokers (0 pack-years). The risk was slightly higher among those with more than 35 pack-years of cigarette smoking; the odds ratio was 1.53 (95% CI, 1.15-2.03). Although pancreatic cancer risks were numerically elevated in relation to pack-years of cigarette smoke among male subjects, the association did not achieve statistical significance. However, the association was highly significant among female participants. When comparing with those who did not smoke (0 pack-years), pancreatic cancer risk was increased by two-fold among female subjects who had more than 35 pack-years of cigarette smoking (OR=2.00; 95% CI, 1.23-3.28).

Consumption of Tap Water

No statistical significant associations were observed with the consumption of tap water and pancreatic cancer for any of the analyses.

Coffee Consumption

Coffee may be an important risk factor for pancreatic cancer. All associations were significant when comparing the highest group (consuming more than 3 cups per day) to those consuming less than 4 cups per week for all three analyses. The increased risk ranged from 56 percent for males (OR=1.56; 95% CI, 1.01-2.47) to 61 percent among females (OR=1.61; 95% CI, 1.02-2.54).

Beer Consumption

Pancreatic cancer risk increased with the amount of beer consumed. The highest significant increased was observed in the combined analysis when comparing those

consuming in excess of one beer per day to those consuming a maximum of 3 beers per month (OR=1.41; 95% CI, 1.09-1.81). For the same comparison, analyses with male subjects showed an odds ratio of 1.32 (95% CI, 1.00-1.75). Increased pancreatic cancer risk with increased beer consumption was also observed among women, although the increase was not significant (OR=1.47; 95% CI, 0.82-2.65).

Wine Consumption

No significant increase (or decrease) in pancreatic cancer risk associated with wine consumption was observed. A decreased risk was observed for those who reported consuming at least 1 glass of wine per day as compared to those who reported consuming at most 3 glasses per month among female subjects. However, this association was not statistically significant (OR=0.87; 95% CI, 0.51-1.49).

Liquor Consumption

Increased pancreatic cancer risks were associated with liquor consumption among male subjects and the combined analysis when comparing at least one drink of liquor per day as compared to at most 3 drinks per month. The odds ratios were 1.63 (95% CI, 1.22-2.18) and 1.43 (95% CI, 1.12-1.84) for the males only and combined analyses. Analysis with female subjects only did not show any significant association between pancreatic cancer and liquor consumption.

Female Reproductive Characteristics

The associations between age at first menstruation and number of pregnancies and pancreatic cancer risks were examined. Although no significant associations were observed for these reproductive characteristics and cancer risks, the type III Chi square is suggestive of a role for age of menarche (p=0.177) and number of pregnancies (p=0.178).

Table 10: Estimated risk of pancreatic cancer by selected characteristics of study subjects.

- ***Males and Females***

Characteristics	No. of Cases (%)	No. of Controls (%)	OR[a] (95% CI)	Wald X^2 P Value	Type III X^2 *P* value
BMI (kg/m^2)					
≤ 23	151 (25)	1349 (28)	1.00*		
23 – 27	212 (36)	1889 (40)	0.86 (0.68 – 1.07)	0.174	0.003[b]
27 – 30	113 (19)	873 (18)	0.96 (0.74 – 1.25)	0.765	
> 30	119 (20)	653 (14)	1.36 (1.05 – 1.77)	0.021	
n	595	4764			
% Weight Change[T]					
< 2.9	193 (33)	1042 (22)	1.00*		<0.001[b]
2.9 - < 5.7	100 (17)	1050 (22)	0.52 (0.40 – 0.67)	<0.001	
5.7 - <10.2	143 (24)	1303 (28)	0.64 (0.51 – 0.81)	<0.001	
≥ 10.2	155 (26)	1344 (28)	0.67 (0.54 – 0.85)	<0.001	
n	591	4739			
Education (Total yrs)					
< 9	98 (17)	725 (15)	1.00*		0.082[b]
9 – 12	293 (50)	2059 (44)	1.23 (0.96 – 1.57)	0.108	
> 12	197 (33)	1939 (41)	1.01 (0.77 – 1.31)	0.957	
n	588	4723			
Total Fat Intake (g/wk)					
< 236	111 (21)	1017 (23)	1.00*		0.219[b]
237 – 323	122 (23)	1062 (24)	1.07 (0.81 – 1.40)	0.644	
324 – 420	134 (24)	1053 (24)	1.18 (0.81 – 1.40)	0.240	
> 420	173 (32)	1243 (29)	1.29 (1.00 – 1.67)	0.053	
n	540	4375			
Total Energy Intake (Cal day)					
< 1,370	137 (25)	1286 (29)	1.00*		0.053[b]
1,370 – 1,710	124 (23)	1123 (26)	0.98 (0.76 – 1.27)	0.886	
1,710 – 2,050	128 (24)	886 (20)	1.33 (1.02 – 1.72)	0.032	
≥ 2,050	151 (28)	1080 (25)	1.23 (0.96 – 1.58)	0.105	
n	540	4375			
Smoking (pack years)					
0	187 (32)	1823 (39)	1.00*		<0.001[b]
1 - 15	119 (21)	1404 (30)	0.84 (0.66 – 1.07)	0.164	
15 – 35	176 (30)	989 (21)	1.51 (1.20 – 1.90)	<0.001	
> 35	97 (17)	479 (10)	1.53 (1.15 – 2.03)	0.003	
n	579	4695			

Characteristics	No. of Cases (%)	No. of Controls (%)	OR[a] (95% CI)	Wald X^2 P Value	Type III X^2 *P* value
Tap Water (glasses per week)					
< 3.57	147 (25)	1313 (28)	1.00*		0.907
3.57 – 5.00	139 (23)	1074 (22)	1.08 (0.84 – 1.38)	0.554	
5.00 – 7.86	216 (36)	1633 (34)	1.21 (0.86 – 1.36)	0.461	
> 7.86	97 (16)	766 (16)	0.99 (0.80 – 1.38)	0.733	
n	599	4786			
Coffee					
≤ 4 cups/wk	65 (11)	704 (15)	1.00*		0.004[b]
5 – 7 cups/wk	157 (27)	1363 (29)	1.06 (0.78 – 1.44)	0.698	
2 – 3 cups/day	214 (36)	1692 (36)	1.16 (0.87 – 1.57)	0.309	
> 3 cups/day	156 (26)	956 (20)	1.57 (1.15 – 2.15)	0.004	
n	592	4715			
Beer					
0 – 3 times per month	415 (73)	3595 (78)	1.00*		0.017[b]
1 – 6 times per week	57 (10)	405 (8)	1.28 (0.94 – 1.73)	0.118	
≥ 1 per day	99 (17)	632 (14)	1.41 (1.09 – 1.81)	0.008	
n	571	4632			
Wine					
0 – 3 times per month	468 (81)	3903 (84)	1.00*		0.375
1 – 6 times per week	51 (9)	348 (8)	1.25 (0.91 – 1.71)	0.164	
≥ 1 per day	55 (10)	387 (8)	1.05 (0.77 – 1.42)	0.755	
n	574	4638			
Liquor					
0 – 3 times per month	443 (76)	3799 (80)	1.00*		0.013[b]
1 – 6 times per week	45 (8)	394 (8)	0.93 (0.67 – 1.29)	0.666	
≥ 1 per day	92 (16)	475 (10)	1.43 (1.12 – 1.84)	0.005	
n	580	4668			

* Referent group.

[a] Adjusted for sex, age, and province of recruitment.

[b] Potential confounder to be included in fully adjusted model.

[T] Percent weight change from maximum lifetime weight.

Table 11: Estimated risk of pancreatic cancer by selected characteristics of study subjects.

- **Male subjects**

Characteristics	No. of Cases (%)	No. of Controls (%)	OR[a] (95% CI)	Wald X^2 P Value	Type III X^2 *P* value
BMI (kg/m^2)					
≤ 23	61 (18)	472 (20)	1.00*		0.340
23 – 27	137 (41)	1058 (44)	0.92 (0.66 – 1.27)	0.610	
27 – 30	76 (22)	510 (22)	1.02 (0.71 – 1.46)	0.931	
> 30	63 (19)	338 (14)	1.24 (0.84 – 1.82)	0.277	
n	337	2378			
% Weight Change[T]					
< 2.9	115 (34)	579 (25)	1.00*		0.012[b]
2.9 - < 5.7	59 (18)	585 (25)	0.52 (0.37 – 0.73)	<0.001	
5.7 - <10.2	78 (23)	623 (26)	0.67 (0.49 – 0.91)	0.012	
≥ 10.2	84 (25)	576 (24)	0.75 (0.55 – 1.02)	0.067	
n	336	2363			
Education (Total yrs)					
< 9	67 (20)	423 (18)	1.00*		0.422
9 – 12	152 (45)	964 (41)	1.04 (0.76 – 1.43)	0.784	
> 12	116 (35)	968 (41)	1.01 (0.63 – 1.23)	0.444	
n	335	2355			
Total Fat Intake (g/wk)					
< 236	58 (19)	396 (18)	1.00*		0.068[b]
237 – 323	52 (17)	483 (22)	0.73 (0.49 – 1.09.)	0.124	
324 – 420	83 (27)	528 (25)	1.13 (0.78 – 1.62)	0.517	
> 420	116 (37)	746 (35)	1.14 (0.81 – 1.61)	0.449	
n	309	2153			
Total Energy Intake (Cal day)					
< 1,370	67 (22)	519 (24)	1.00*		0.017[b]
1,370 – 1,710	57 (18)	539 (25)	0.81 (0.55 – 1.18)	0.265	
1,710 – 2,050	75 (24)	430 (20)	1.35 (0.95 – 1.93)	0.099	
≥ 2,050	110 (36)	665 (31)	1.29 (0.93 – 1.79)	0.131	
n	309	2153			
Smoking (pack years)					
0	76 (23)	630 (27)	1.00*		<0.001[b]
1 - 15	62 (20)	727 (31)	0.69 (0.49 – 0.99)	0.042	
15 – 35	116 (35)	604 (26)	1.36 (0.99 – 1.87)	0.057	
> 35	73 (22)	378 (16)	1.39 (0.97 – 2.00)	0.070	
n	327	2339			

Characteristics	No. of Cases (%)	No. of Controls (%)	OR[a] (95% CI)	Wald X^2 P Value	Type III X^2 *P* value
Tap Water (glasses per week)					
< 3.57	78 (23)	708 (30)	1.00*		0.311
3.57 – 5.00	84 (24)	530 (22)	1.32 (0.95 – 1.85)	0.098	
5.00 – 7.86	125 (37)	810 (34)	1.29 (0.95 – 1.75)	0.102	
> 7.86	53 (16)	342 (14)	1.27 (0.88 – 1.86)	0.205	
n	340	2390			
Coffee					
≤ 4 cups/ wk	31 (9)	297 (13)	1.00*		0.018[b]
5 – 7 cups/ wk	79 (23)	691 (29)	0.95 (0.61 – 1.48)	0.829	
2 – 3 cups/ day	128 (38)	846 (36)	1.22 (0.80 – 1.86)	0.346	
> 3 cups/ day	99 (29)	523 (22)	1.56 (1.01 – 2.47)	0.045	
n	337	2357			
Beer					
0 – 3 times per month	196 (60)	1506 (65)	1.00*		0.107[b]
1 – 6 times per week	45 (14)	286 (12)	1.26 (0.89 – 1.80)	0.197	
≥ 1 per day	85 (26)	537 (23)	1.32 (1.00 – 1.75)	0.052	
n	326	2329			
Wine					
0 – 3 times per month	256 (79)	1920 (83)	1.00*		0.568
1 – 6 times per week	28 (9)	165 (7)	1.16 (0.76 – 1.78)	0.485	
≥ 1 per day	39 (12)	219 (10)	1.18 (0.81 – 1.71)	0.381	
n	323	2304			
Liquor					
0 – 3 times per month	222 (68)	1724 (74)	1.00*		0.001[b]
1 – 6 times per week	29 (9)	275 (12)	0.80 (0.53 – 1.20)	0.273	
≥ 1 per day	76 (23)	333 (14)	1.63 (1.22 – 2.18)	0.001	
n	327	2332			

* Referent group.
[a] Adjusted for age and province of recruitment.
[b] Potential confounder to be included in fully adjusted model.
[T] Percent weight change from maximum lifetime weight.

Table 12: Estimated risk of pancreatic cancer by selected characteristics of study subjects.

- **Female subjects**

Characteristics	No. of Cases (%)	No. of Controls (%)	OR[a] (95% CI)	Wald X^2 P Value	Type III X^2 *P* value
BMI (kg/m^2)					0.002[b]
≤ 23	90 (35)	877 (37)	1.00*		
23 – 27	75 (29)	831 (35)	0.76 (0.55 – 1.05)	0.513	
27 – 30	37 (14)	363 (15)	0.82 (0.54 – 1.23)	0.094	
> 30	56 (22)	315 (13)	1.52 (1.06 – 2.19)	0.336	
n	258	2386			
% Weight Change[T]					
< 2.9	78 (31)	463 (19)	1.00*		0.004[b]
2.9 - < 5.7	41 (16)	465 (20)	0.53 (0.35 – 0.79)	0.002	
5.7 - <10.2	65 (25)	680 (29)	0.62 (0.44 – 0.88)	0.008	
≥ 10.2	71 (28)	768 (32)	0.61 (0.43 – 0.86)	0.005	
n	255	2376			
Education (Total yrs)					
< 9	31 (12)	302 (13)	1.00*		0.083[b]
9 – 12	141 (56)	1095 (46)	1.53 (1.01 – 2.31)	0.045	
> 12	81 (32)	971 (41)	1.23 (0.79 – 1.92)	0.367	
n	253	2368			
Total Fat Intake (g/wk)					
< 236	53 (23)	621 (28)	1.00*		0.141[b]
237 – 323	70 (30)	579 (26)	1.51 (1.04 – 2.22)	0.031	
324 – 420	51 (22)	525 (24)	1.35 (0.78 – 1.75)	0.456	
> 420	57 (25)	497 (22)	1.29 (0.94 – 2.09)	0.096	
n	231	2222			
Total Energy Intake (Cal/day)					
< 1,370	70 (22)	767 (34)	1.00*		0.593
1,370 – 1,710	67 (18)	584 (26)	1.17 (0.82 – 1.67)	0.383	
1,710 – 2,050	53 (24)	456 (21)	1.27 (0.87 – 1.87)	0.213	
≥ 2,050	41 (36)	415 (19)	1.03 (0.69 – 1.56)	0.869	
n	231	2222			
Smoking (pack years)					
0	111 (44)	1193 (51)	1.00*		0.002[b]
1 - 15	57 (23)	677 (29)	1.03 (0.74 – 1.45)	0.853	
15 – 35	60 (24)	385 (16)	1.69 (1.20 – 2.38)	0.002	
> 35	24 (9)	101 (4)	2.00 (1.23 – 3.28)	0.005	
n	252	2356			

Characteristics	No. of Cases (%)	No. of Controls (%)	OR[a] (95% CI)	Wald X^2 P Value	Type III X^2 *P* value
Tap Water (glasses per week)					
< 3.57	69 (27)	605 (25)	1.00*		0.693
3.57 – 5.00	55 (21)	544 (23)	0.84 (0.58 – 1.22)	0.365	
5.00 – 7.86	91 (35)	823 (34)	0.86 (0.61 – 1.21)	0.383	
> 7.86	44 (17)	424 (18)	0.80 (0.53 – 1.20)	0.284	
n	259	2396			
Coffee					
≤ 4 cups/wk	34 (13)	407 (13)	1.00*		0.130[b]
5 – 7 cups/wk	78 (31)	672 (29)	1.22 (0.80 – 1.88)	0.363	
2 – 3 cups/day	86 (34)	846 (36)	1.11 (0.73 – 1.68)	0.636	
> 3 cups/day	57 (22)	433 (22)	1.61 (1.02 – 2.54)	0.039	
n	255	2358			
Beer					
0 – 3 times per month	219 (89)	2089 (91)	1.00*		0.346
1 – 6 times per week	12 (5)	119 (5)	1.27 (0.68 – 2.37)	0.447	
≥ 1 per day	14 (6)	95 (4)	1.47 (0.82 – 2.65)	0.200	
n	245	2303			
Wine					
0 – 3 times per month	212 (79)	1983 (83)	1.00*		0.344
1 – 6 times per week	23 (9)	183 (7)	1.37 (0.86 – 2.18)	0.186	
≥ 1 per day	16 (12)	168 (10)	0.87 (0.51 – 1.49)	0.610	
n	251	2334			
Liquor					
0 – 3 times per month	221 (87)	2075 (89)	1.00*		0.479
1 – 6 times per week	16 (6)	119 (5)	1.37 (0.80 – 2.38)	0.254	
≥ 1 per day	16 (6)	142 (6)	0.94 (0.55 – 1.61)	0.814	
n	253	2336			
Age at first menstruation (yrs)					
< 12	36 (18)	389 (17)	1.00*		0.177[b]
12 – < 15	143 (70)	1490 (68)	1.00 (0.68 – 1.47)	0.989	
≥ 15	24 (12)	335 (15)	0.65 (0.38 – 1.12)	0.124	
	203	2214			
No. of pregnancies					
0	29 (11)	284 (12)	1.00*		0.178[b]
1	21 (8)	197 (8)	1.06 (0.58 – 1.93)	0.841	
2	61 (23)	564 (24)	1.07 (0.67 – 1.72)	0.768	
3	56 (22)	466 (19)	1.06 (0.66 – 1.72)	0.800	
≥ 4	92 (36)	880 (37)	0.74 (0.47 – 1.16)	0.193	
	259	2391			

* Referent group.

[a] Adjusted for age and province of recruitment.

[b] Potential confounder to be included in fully adjusted model.

[T] Percent weight change from maximum lifetime weight.

Exposure Levels to Disinfection By Products (EHD Water Quality Data)

Figures 12 to 15 describe the characteristics of DBPs (THM, BDCM, and TCM) from the EHD water quality data as a function of subject status, province, gender, and age respectively. Cases had lifetime average THM, BDCM, and TCM levels of 22.8 ug/L, 2.93 ug/L, 18.2 ug/L while controls were exposed to estimated lifetime averages of 22.5 ug/L. 2.86 ug/L, 17.8 ug/L of the respective CDBPs.

Among the different provinces, Figure 13 shows that participants recruited from Manitoba (MB) had an average exposure to THM (72 ug/L) while residents living in Prince Edward Island at the time of the study had an average THM exposure of 6 ug/L. Residents living in Manitoba at the time of the study had a lifetime average exposure to BDCM of 5.5 ug/L. Participants from PEI had low average exposure to BDCM. Participants from Manitoba also had high average exposure to TCM (65 ug/L) while participants from Newfoundland had the lowest average exposure to TCM (5 ug/L).

Male participants on average had higher average levels of THM (23.1 ug/L) than female participants (21.8 ug/L). Average exposure to BDCM was the same for both males and females (2.9 ug/L). Male had an average exposure to TCM of 18 ug/L while females had an average exposure of TCM of 17 ug/L.

Figure 12: **Average exposure to trihalomethane (THM), bromodichloromethane (BDCM, and chloroform (TCM) by subject status.**

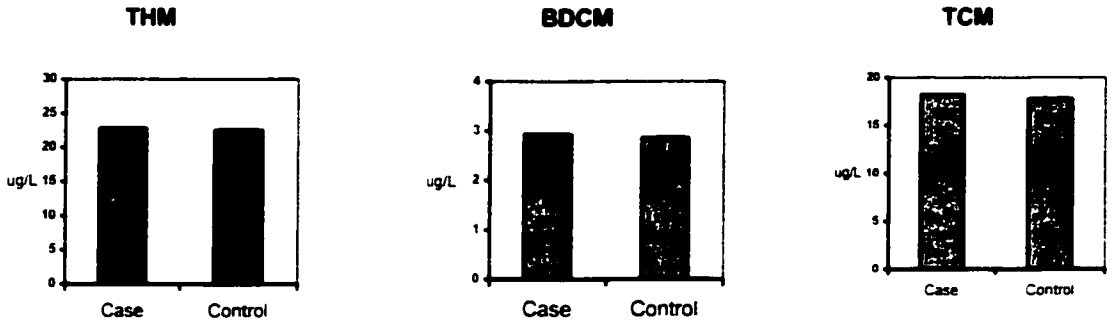


Figure 13: **Average exposure to trihalomethane (THM), bromodichloromethane (BDCM), and chloroform (TCM) by province of residence.**

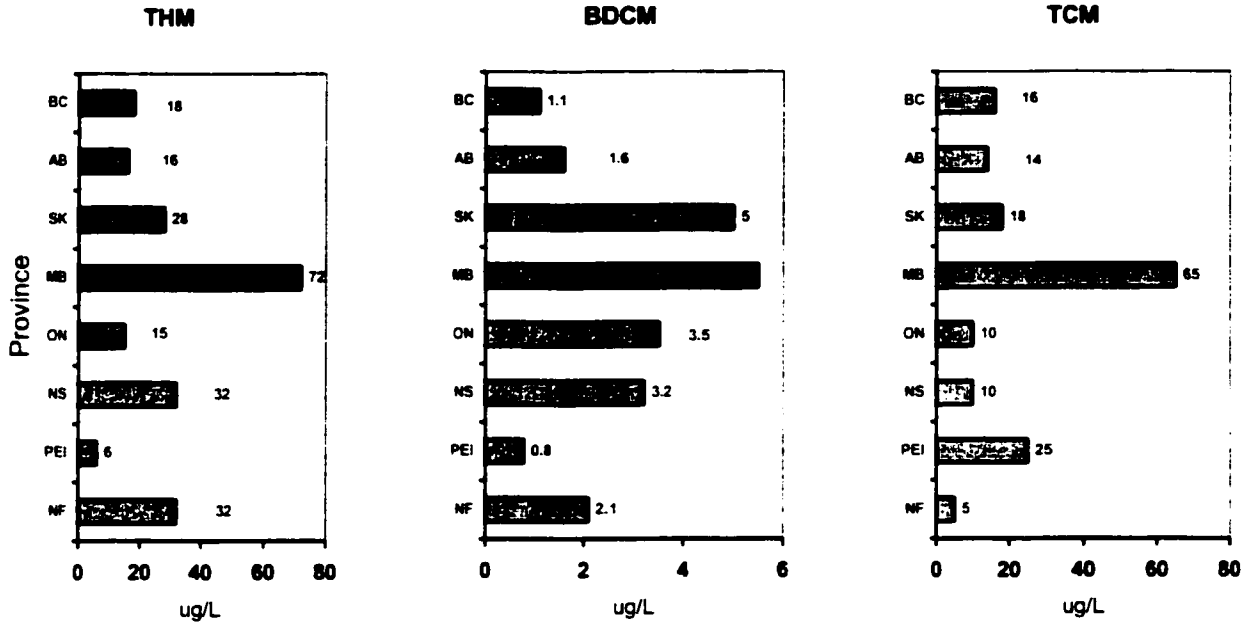


Figure 14: **Average exposure to trihalomethane (THM), bromodichloromethane (BDCM), and chloroform (TCM) by gender.**

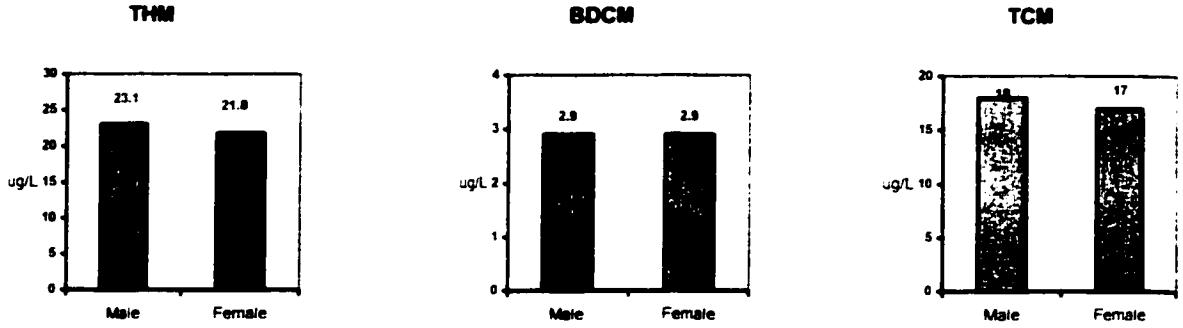
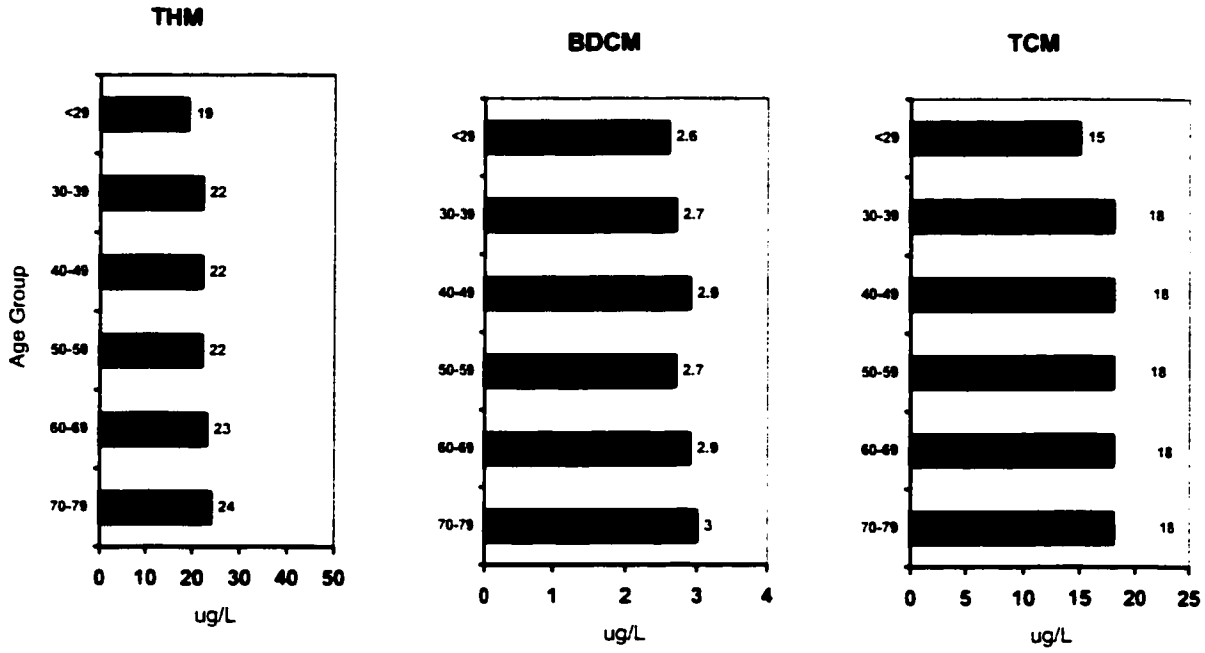


Figure 15: **Average exposure to trihalomethane (THM), bromodichloromethane (BDCM), and chloroform (TCM) by 10-year age groups.**



Pancreatic Cancer Risk According to DBPs (EHD Water Quality Data)

Exposure to DBPs within the most recent 30-year exposure time window were estimated using three different approaches. The first approach, complete exposure within the most recent 30 years, did not require imputation. The second approach included only those with at least 20 of years of exposure information. The missing exposure was imputed using the mean of the control groups. Finally, the third approach, the full imputation of all missing exposure information, did not require minimum number of years with exposure information. Any missing information within the 30-year window was imputed using OCMI.

Table 13 shows the percentages of imputed data for the different approaches. Since the first approach used only subjects with complete exposure information, imputation was not needed and therefore not shown in Table 13. In the second approach, approximately 13 percent of the exposure information was imputed. In the third approach, the proportion of exposure that was imputed increased to approximately 20 percent. The increase in frequency of imputation for the analyses with full imputation was expected given that there was no limitation on the number of years that could be imputed.

Table 13: **Comparison of percent of imputation for two exposure models (at least 20 years of exposure information and full imputation) using the Environmental Health Directorate 1993 water quality data.**

Subject Status	Total Person Years *without* Imputation	Total Person Years *with* Imputation	Percent Imputation
At Least 20 yrs of Exposure Information			
Cases	13,447	15,450	12.96
Controls	94,837	109,320	13.25
Total	108,284	124,770	13.21
Full Imputation Model			
Cases	13,801	17,280	20.13
Controls	98,203	123,150	20.26
Total	112,004	140,430	20.24

Tables 14 to 16 show the results for pancreatic cancer risk estimates for exposure to THM, BDCM, and TCM for those with complete exposure information. In total, 445 cases and 3,092 controls met the exposure requirement to be included in this part of the analysis. All subjects had 30 years of exposure information (i.e. no imputation).

Overall, the results did not demonstrate any significant increase (or decrease) in pancreatic cancer risk for THM, BDCM or TCM in the combined analyses or analyses stratified for sex. Among males, increase in pancreatic cancer risk was observed with increased exposure to BDCM. When comparing those with less than 1 ug/L of BDCM, those with average exposure of more than 5 ug/L had a 31 percent increase in pancreatic cancer risk (95%CI, 0.85-2.02) after adjusted for potential confounders. However, the increase was not statistically significant. Furthermore, the risk estimates did not exhibit an exposure-response pattern.

Table 14: **Estimated risk of pancreatic cancer and exposure to DBPs with 30-year exposure time window, Environmental Health Directorate 1993 water quality data.**

- ***Males and Females***
- ***Complete Exposure Information***

DBPs[c] (ug/L)	Minimally Adjusted [a]				Fully Adjusted [b]			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR [b] (95% CI)	Type III X^2 *P* value
THM								
< 10	146 (33)	976 (32)	1.00*	0.330	129 (34)	845 (34)	1.00*	0.493
10 – 20	112 (25)	877 (28)	0.86 (0.65-1.13)		94 (25)	779 (29)	0.84 (0.62-1.14)	
20 – 50	127 (29)	795 (26)	1.08 (0.83-1.39)		107 (28)	720 (24)	1.01 (0.76-1.35)	
> 50	60 (13)	444 (14)	0.83 (0.57-1.23)		51 (13)	379 (13)	0.81 (0.53-1.24)	
n	445	3092			381	2723		
BDCM								
< 1	142 (32)	970 (31)	1.00*	0.912	126 (33)	862 (32)	1.00*	0.783
1 – 3	95 (21)	692 (23)	0.93 (0.74-1.36)		80 (21)	617 (23)	0.89 (0.65-1.21)	
3 – 5	94 (21)	647 (21)	1.03 (0.91-1.71)		74 (19)	562 (21)	0.95 (0.67-1.34)	
> 5	114 (27)	783 (25)	1.04 (0.64-1.22)		101 (27)	682 (25)	1.05 (0.75-1.46)	
n	445	3092			381	2723		
TCM								
< 3	115 (26)	765 (25)	1.00*	0.853	104 (27)	657 (24)	1.00*	0.490
3 – 10	116 (26)	856 (28)	0.93 (0.70-1.25)		94 (25)	751 (27)	0.85 (0.61-1.17)	
10 – 30	121 (27)	861 (27)	0.92 (0.69-1.23)		103 (27)	779 (29)	0.82 (0.60-1.13)	
> 30	93 (21)	610 (20)	1.05 (0.76-1.45)		80 (21)	536 (20)	1.02 (0.71-1.46)	
n	445	3092			381	2723		

* Referent group.

[a] Adjusted for sex, age, and province of recruitment.

[b] Adjusted for sex, age, province of recruitment, BMI, percent weight change, education, smoking, coffee, beer, liquor, total fat and energy intake.

[c] Average DBPs were based on an arithmetic mean of 30 years of exposure information from date of interview.

Acronyms: DBPs: Disinfection Byproducts, THM: Trihalomethanes, BDCM: Bromodichloromethane, and TCM: Chloroform.

Table 15: Estimated risk of pancreatic cancer and exposure to DBPs with 30-year exposure time window, Environmental Health Directorate 1993 water quality data.

- ***Males***
- ***Complete Exposure Information***

DBPs[c] (ug/L)	Minimally Adjusted [a]				Fully Adjusted [b]			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR [b] (95% CI)	Type III X^2 *P* value
THM								
< 10	88 (37)	505 (35)	1.00*	0.852	75 (37)	427 (33)	1.00*	0.845
10 – 20	63 (26)	401 (27)	0.86 (0.60-1.24)		55 (26)	356 (27)	0.86 (0.57-1.30)	
20 – 50	63 (21)	389 (25)	0.90 (0.63-1.28)		55 (21)	345 (25)	0.85 (0.57-1.27)	
> 50	41 (16)	237 (14)	0.89 (0.55-1.42)		36 (16)	202 (15)	0.90 (0.53-1.53)	
n	255	1532			221	1330		
BDCM								
< 1	80 (32)	513 (33)	1.00*	0.203	67 (30)	446 (33)	1.00*	0.136
1 – 3	44 (17)	324 (21)	0.80 (0.53-1.19)		39 (18)	291 (22)	0.74 (0.45-1.16)	
3 – 5	54 (21)	310 (20)	1.09 (0.72-1.64)		44 (20)	267 (20)	1.01 (0.63-1.61)	
> 5	77 (30)	385 (25)	1.27 (0.86-1.87)		71 (32)	326 (25)	1.31 (0.85-2.02)	
n	255	1532			221	1330		
TCM								
< 3	69 (27)	419 (27)	1.00*	0.462	60 (27)	354 (27)	1.00*	0.226
3 – 10	70 (27)	379 (25)	1.10 (0.75-1.62)		60 (27)	328 (25)	1.02 (0.66-1.57)	
10 – 30	60 (23)	421 (27)	0.80 (0.54-1.17)		50 (23)	376 (28)	0.69 (0.44-1.06)	
> 30	56 (23)	313 (20)	1.00 (0.65-1.54)		51 (23)	272 (21)	1.07 (0.66-1.72)	
n	255	1532			221	1330		

* Referent group.

[a] Adjusted for sex, age, and province of recruitment.

[b] Adjusted for sex, age, province of recruitment, percent weight change, smoking, coffee, beer, liquor, total fat and energy intake.

[c] Average DBPs were based on an arithmetic mean of 30 years of exposure information from date of interview.

Acronyms: DBPs: Disinfection Byproducts, THM: Trihalomethanes, BDCM: Bromodichloromethane, and TCM: Chloroform.

Table 16: Estimated risk of pancreatic cancer and exposure to DBPs with 30-year exposure time window, Environmental Health Directorate 1993 water quality data.

- ***Females Only***
- ***Complete Exposure Information***

DBPs (ug/L)	Minimally Adjusted [a]				Fully Adjusted [b]			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR [b] (95% CI)	Type III X^2 *P* value
THM								
< 10	58 (31)	471 (30)	1.00*	0.102	49 (35)	405 (30)	1.00*	0.307
10 – 20	49 (26)	476 (31)	0.85 (0.56-1.30)		31 (22)	398 (30)	0.75 (0.45-1.25)	
20 – 50	64 (34)	406 (26)	1.33 (0.91-1.96)		46 (33)	354 (27)	1.07 (0.68-1.69)	
> 50	19 (10)	207 (13)	0.74 (0.34-1.43)		14 (10)	170 (13)	0.60 (0.30-1.31)	
n	190	1560			140	1327		
BDCM								
< 1	62 (33)	457 (29)	1.00*	0.556	52 (37)	399 (30)	1.00*	0.503
1 – 3	51 (27)	368 (24)	1.02 (0.68-1.53)		39 (28)	311 (23)	0.96 (0.60-1.56)	
3 – 5	40 (21)	337 (22)	0.91 (0.57-1.45)		25 (18)	281 (21)	0.77 (0.43-1.36)	
> 5	37 (19)	398 (25)	0.73 (0.45-1.18)		24 (17)	336 (25)	0.65 (0.36-1.20)	
n	190	1560			140	1327		
TCM								
< 3	46 (24)	346 (31)	1.00*	0.347	39 (30)	295 (22)	1.00*	0.210
3 – 10	46 (24)	427 (24)	0.75 (0.48-1.18)		28 (25)	401 (30)	0.57 (0.34-1.05)	
10 – 30	61 (32)	363 (23)	1.10 (0.71-1.69)		48 (24)	379 (29)	0.88 (0.54-1.50)	
> 30	37 (20)	242 (22)	1.10 (0.66-1.83)		25 (21)	252 (19)	0.70 (0.29-1.01)	
n	190	1560			140	1327		

* Referent group.

[a] Adjusted for sex, age, and province of recruitment.

[b] Adjusted for sex, age, province of recruitment, BMI, education, percent weight change, smoking, coffee, age at first menstruation, number of pregnancies, and total fat and energy intake.

[c] Average DBPs were based on an arithmetic mean of 30 years of exposure information from date of interview.

Acronyms: DBPs: Disinfection Byproducts, THM: Trihalomethanes, BDCM: Bromodichloromethane, and TCM: Chloroform.

Tables 17 to 19 provide pancreatic cancer risk estimates for exposure to THM, BDCM, and TCM for those with at least 20 years of valid exposure information. In total, 515 cases and 3,644 controls met the exposure requirement to be included in this part of the analysis. After deletion of subjects with missing data for potential confounders, the number of cases and controls in the fully adjusted model was reduced to 435 and 3,201 respectively.

As in the previous section, exposure to THM and TCM did not show a significant increased risk of pancreatic cancer for all analyses. Consistent exposure-response relationships were not observed. Although not significant, an increased risk of pancreatic cancer was associated with higher exposure to BDCM among male subjects. The risk estimate was highest when comparing those with average exposure of more than 5 ug/L to the referent group (OR= 1.28, 95% CI, 0.85-1.92).

Table 17: Estimated risk of pancreatic cancer and exposure to DBPs with 30-year exposure time window, Environmental Health Directorate 1993 water quality data.

- ***Males and Females***
- ***At least 20 year of exposure information***

DBPs[c] (ug/L)	Minimally Adjusted [a]				Fully Adjusted [b]			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR [b] (95% CI)	Type III X^2 *P* value
THM								
< 10	158 (31)	1068 (29)	1.00*	0.329	138 (32)	925 (29)	1.00*	0.387
10 – 20	133 (26)	1040 (29)	0.84 (0.65-1.09)		108 (25)	915 (29)	0.81 (0.61-1.08)	
20 – 50	157 (30)	1049 (29)	1.06 (0.83-1.36)		132 (30)	944 (29)	1.01 (0.77-1.33)	
> 50	67 (13)	487 (13)	0.90 (0.63-1.30)		57 (13)	417 (13)	0.88 (0.59-1.31)	
n	515	3644			435	3201		
BDCM								
< 1	147 (29)	1061 (29)	1.00*	0.866	129 (30)	945 (30)	1.00*	0.814
1 – 3	125 (24)	951 (26)	0.91 (0.70-1.18)		104 (24)	844 (26)	0.89 (0.67-1.19)	
3 – 5	115 (22)	761 (21)	1.00 (0.75-1.34)		90 (20)	650 (20)	0.96 (0.67-1.33)	
> 5	128 (25)	871 (24)	1.02 (0.77-1.35)		112 (26)	762 (24)	1.02 (0.75-1.41)	
n	515	3644			435	3201		
TCM								
< 3	118 (23)	791 (22)	1.00*	0.287	105 (24)	680 (21)	1.00*	0.158
3 – 10	143 (28)	1028 (28)	0.93 (0.71-1.23)		114 (26)	889 (28)	0.86 (0.63-1.17)	
10 – 30	143 (28)	1141 (31)	0.90 (0.68-1.18)		121 (28)	1032 (32)	0.81 (0.60-1.10)	
> 30	111 (21)	684 (19)	1.20 (0.88-1.64)		95 (22)	600 (19)	1.16 (0.82-1.64)	
n	515	3644			435	3201		

* Referent group.

[a] Adjusted for sex, age, and province of recruitment.

[b] Adjusted for sex, age, province of recruitment, BMI, percent weight change, education, smoking, coffee, beer, liquor, total fat and energy intake.

[c] Average DBPs were based on an arithmetic mean of 30 years of available and imputed exposure information from date of interview.

Acronyms: DBPs: Disinfection Byproducts, THM: Trihalomethanes, BDCM: Bromodichloromethane, and TCM: Chloroform.

Table 18: **Estimated risk of pancreatic cancer and exposure to DBPs with 30-year exposure time window, Environmental Health Directorate 1993 water quality data.**

- ***Males***
- ***At least 20 year of exposure information***

DBPs[c] (ug/L)	Minimally Adjusted [a]				Fully Adjusted [b]			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR [b] (95% CI)	Type III X^2 *P* value
THM								
< 10	96 (32)	544 (30)	1.00*	0.730	83 (32)	462 (30)	1.00*	0.8667
10 – 20	74 (24)	460 (26)	0.83 (0.59-1.17)		64 (25)	405 (26)	0.80 (0.55-1.17)	
20 – 50	82 (29)	527 (30)	0.89 (0.64-1.23)		71 (28)	469 (30)	0.85 (0.59-1.21)	
> 50	46 (15)	255 (14)	0.97 (0.62-1.53)		40 (15)	219 (14)	0.94 (0.56-1.55)	
n	298	1786			258	1555		
BDCM								
< 1	83 (29)	552 (31)	1.00*	0.124	70 (30)	482 (31)	1.00*	0.143
1 – 3	62 (21)	452 (25)	0.79 (0.55-1.13)		55 (20)	405 (26)	0.78 (0.52-1.16)	
3 – 5	65 (26)	359 (20)	1.03 (0.70-1.52)		53 (25)	308 (20)	0.95 (0.61-1.46)	
> 5	88 (24)	423 (24)	1.28 (0.88-1.84)		80 (25)	360 (23)	1.28 (0.85-1.92)	
n	298	1786			258	1555		
TCM								
< 3	70 (23)	429 (24)	1.00*	0.215	61 (24)	364 (23)	1.00*	0.090
3 – 10	86 (29)	446 (25)	1.08 (0.75-1.55)		74 (28)	382 (25)	1.00 (0.67-1.51)	
10 – 30	74 (25)	561 (31)	0.79 (0.54-1.14)		62 (24)	503 (32)	0.69 (0.46-1.04)	
> 30	68 (23)	350 (20)	1.18 (0.79-1.77)		61 (24)	306 (20)	1.20 (0.77-1.88)	
n	298	1786			258	1555		

* Referent group.

[a] Adjusted for sex, age, and province of recruitment.

[b] Adjusted for sex, age, province of recruitment, percent weight change, smoking, coffee, beer, liquor, total fat and energy intake.

[c] Average DBPs were based on an arithmetic mean of 30 years of available and imputed exposure information from date of interview.

Acronyms: DBPs: Disinfection Byproducts, THM: Trihalomethanes, BDCM: Bromodichloromethane, and TCM: Chloroform.

Table 19: Estimated risk of pancreatic cancer and exposure to DBPs with 30-year exposure time window, Environmental Health Directorate 1993 water quality data.

- ***Females***
- ***At least 20 year of exposure information***

DBPs[c] (ug/L)	Minimally Adjusted [a]				Fully Adjusted [b]			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR [b] (95% CI)	Type III X^2 *P* value
THM								
< 10	62 (29)	524 (31)	1.00*	0.094	49 (32)	449 (28)	1.00*	0.264
10 – 20	59 (27)	580 (34)	0.86 (0.58-1.27)		34 (22)	484 (31)	0.77 (0.47-1.26)	
20 – 50	75 (34)	522 (23)	1.32 (0.91-1.90)		53 (35)	452 (29)	1.16 (0.75-1.80)	
> 50	21 (10)	232 (12)	0.78 (0.42-1.46)		16 (11)	190 (12)	0.69 (0.33-1.43)	
n	217	1858			152	1575		
BDCM								
< 1	64 (30)	509 (27)	1.00*	0.364	52 (36)	447 (28)	1.00*	0.237
1 – 3	63 (29)	499 (27)	1.02 (0.70-1.48)		46 (32)	418 (27)	0.97 (0.62-1.52)	
3 – 5	50 (23)	402 (22)	0.92 (0.60-1.42)		29 (19)	332 (21)	0.87 (0.50-1.49)	
> 5	40 (18)	448 (14)	0.69 (0.43-1.10)		25 (13)	378 (24)	0.64 (0.35-1.15)	
n	217	1858			152	1575		
TCM								
< 3	48 (22)	362 (20)	1.00*	0.267	39 (26)	309 (20)	1.00*	0.198
3 – 10	57 (26)	582 (31)	0.77 (0.50-1.17)		30 (20)	483 (31)	0.57 (0.33-0.97)	
10 – 30	69 (32)	580 (31)	1.05 (0.70-1.59)		54 (35)	501 (32)	0.89 (0.55-1.44)	
> 30	43 (20)	334 (18)	1.21 (0.75-1.96)		29 (19)	282 (18)	0.82 (0.45-1.49)	
n	217	1858			152	1575		

* Referent group.

[a] Adjusted for sex, age, and province of recruitment.

[b] Adjusted for sex, age, province of recruitment, BMI, education, percent weight change, smoking, coffee, age at first menstruation, number of pregnancies, and total fat and energy intake.

[c] Average DBPs were based on an arithmetic mean of 30 years of available and imputed exposure information from date of interview.

Acronyms: DBPs: Disinfection Byproducts, THM: Trihalomethanes, BDCM: Bromodichloromethane, and TCM: Chloroform.

Tables 20 to 22 provide pancreatic cancer risk estimates for exposure to THM, BDCM, and TCM. In this analysis, no minimum known years of exposure was required with missing exposure information imputed using OCMI. With this criterion, the total cases and controls included in this analysis increased to 576 and 4,105 respectively. After deletion of subjects with missing data for potential confounders, the number of cases and controls in the fully adjusted model was reduced to 477 and 3,206 respectively.

As in the previous two sections, exposure to THM or TCM did not show a significant increased risk of pancreatic cancer for all analyses. No consistent exposure-response patterns were observed. Among males, an increased risk of pancreatic cancer was associated with higher exposure to BDCM. However, the association was not statistically significant. When comparing those with average exposure of more than 5 ug/L to the referent group (<1 ug/L) , those in the higher exposed group had an odds ratio of 1.25 (95% CI, 0.84-1.79).

Table 20: Estimated risk of pancreatic cancer and exposure to DBPs with 30-year exposure time window, Environmental Health Directorate 1993 water quality data.

- ***Males and Females***
- ***No minimum years of exposure information required***

DBPs[c] (ug/L)	Minimally Adjusted [a]				Fully Adjusted [b]			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR [b] (95% CI)	Type III X^2 *P* value
THM								
< 10	159 (28)	1072 (26)	1.00*	0.269	138 (29)	926 (26)	1.00*	0.374
10 – 20	142 (24)	1123 (27)	0.84 (0.66-1.08)		116 (24)	990 (28)	0.83 (0.63-1.10)	
20 – 50	206 (36)	1408 (34)	1.05 (0.84-1.33)		165 (35)	1210 (34)	1.03 (0.80-1.33)	
> 50	69 (12)	502 (12)	0.90 (0.63-1.29)		58 (13)	429 (12)	0.88 (0.59-1.31)	
n	576	4105			477	3555		
BDCM								
< 1	147 (25)	1061 (26)	1.00*	0.852	129 (27)	945 (27)	1.00*	0.845
1 – 3	165 (29)	1250 (30)	0.93 (0.73-1.18)		132 (28)	1073 (30)	0.91 (0.71-1.20)	
3 – 5	132 (23)	904 (22)	1.00 (0.76-1.31)		102 (21)	760 (21)	0.96 (0.71-1.31)	
> 5	132 (23)	890 (22)	1.04 (0.79-1.37)		114 (24)	777 (22)	1.04 (0.76-1.41)	
n	576	4105			477	3555		
TCM								
< 3	118 (21)	791 (19)	1.00*	0.398	105 (22)	680 (20)	1.00*	0.297
3 – 10	146 (25)	1044 (25)	0.94 (0.72-1.24)		116 (24)	901 (25)	0.87 (0.64-1.18)	
10 – 30	198 (34)	1560 (38)	0.93 (0.72-1.20)		159 (33)	1353 (38)	0.87 (0.65-1.15)	
> 30	114 (20)	710 (18)	1.18 (0.87-1.60)		97 (21)	621 (17)	1.14 (0.82-1.61)	
n	576	4105			477	3555		

* Referent group.

[a] Adjusted for sex, age, and province of recruitment.

[b] Adjusted for sex, age, province of recruitment, BMI, percent weight change, education, smoking, coffee, beer, liquor, total fat and energy intake.

[c] Average DBPs were based on an arithmetic mean of 30 years of available and imputed exposure information from date of interview.

Acronyms: DBPs: Disinfection Byproducts, THM: Trihalomethanes, BDCM: Bromodichloromethane, and TCM: Chloroform.

Table 21: Estimated risk of pancreatic cancer and exposure to DBPs with 30-year exposure time window, Environmental Health Directorate 1993 water quality data.

- ***Males***
- ***No minimum years of exposure information required***

DBPs[c] (ug/L)	Minimally Adjusted [a]				Fully Adjusted [b]			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR [b] (95% CI)	Type III X^2 *P* value
THM								
< 10	97 (30)	548 (27)	1.00*	0.484	84 (32)	464 (26)	1.00*	0.530
10 – 20	76 (23)	504 (24)	0.79 (0.56-1.11)		65 (26)	445 (25)	0.77 (0.56-1.13)	
20 – 50	103 (32)	751 (36)	0.82 (0.60-1.12)		88 (29)	646 (36)	0.81 (0.53-1.14)	
> 50	48 (15)	263 (13)	0.84 (0.61-1.46)		42 (13)	226 (13)	0.91 (0.55-1.49)	
n	324	2066			279	1781		
BDCM								
< 1	83 (25)	552 (27)	1.00*	0.046	70 (25)	482 (27)	1.00*	0 118
1 – 3	80 (25)	661 (32)	0.75 (0.54-1.04)		69 (25)	573 (32)	0.78 (0.54-1.44)	
3 – 5	71 (22)	423 (20)	0.96 (0.66-1.39)		58 (21)	359 (20)	0.91 (0.60-2.05)	
> 5	90 (28)	430 (21)	1.25 (0.87-1.79)		82 (29)	367 (21)	1.25 (0.84-1.86)	
n	324	2066			279	1781		
TCM								
< 3	70 (22)	429 (21)	1.00*	0.068	61 (22)	364 (20)	1.00*	0.053
3 – 10	88 (26)	456 (22)	1.11 (0.77-1.59)		76 (27)	390 (22)	1.06 (0.71-1.58)	
10 – 30	96 (30)	819 (40)	0.74 (0.53-1.05)		79 (28)	711 (40)	0.69 (0.47-1.01)	
> 30	70 (22)	362 (17)	1.12 (0.76-1.68)		63 (23)	316 (18)	1.15 (0.74-1.78)	
n	324	2066			279	1781		

* Referent group.

[a] Adjusted for sex, age, and province of recruitment.

[b] Adjusted for sex, age, province of recruitment, percent weight change, smoking, coffee, beer, liquor, total fat and energy intake.

[c] Average DBPs were based on an arithmetic mean of 30 years of available and imputed exposure information from date of interview.

Acronyms: DBPs: Disinfection Byproducts, THM: Trihalomethanes, BDCM: Bromodichloromethane, and TCM: Chloroform.

Table 22: **Estimated risk of pancreatic cancer and exposure to DBPs with 30-year exposure time window, Environmental Health Directorate 1993 water quality data.**

- ***Females***
- ***No minimum years of exposure information required***

DBPs[c] (ug/L)	Minimally Adjusted [a]				Fully Adjusted [b]			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR [b] (95% CI)	Type III X^2 *P* value
THM								
< 10	62 (26)	524 (26)	1.00*	0.022	49 (30)	449 (27)	1.00*	0.394
10 – 20	66 (25)	619 (30)	0.91 (0.62-1.34)		39 (24)	514 (30)	0.83 (0.52-1.33)	
20 – 50	103 (41)	657 (32)	1.44 (1.02-2.03)		60 (36)	539 (32)	1.14 (0.74-1.74)	
> 50	21 (8)	239 (12)	0.81 (0.44-1.51)		16 (10)	195 (11)	0.71 (0.34-1.47)	
n	252	2039			164	1697		
BDCM								
< 1	64 (25)	509 (25)	1.00*	0.282	52 (27)	447 (26)	1.00*	0.644
1 – 3	85 (34)	589 (29)	1.16 (0.82-1.66)		53 (36)	478 (28)	1.00 (0.65-1.54)	
3 – 5	61 (24)	481 (24)	1.01 (0.67-1.52)		33 (24)	387 (23)	0.90 (0.53-1.51)	
> 5	42 (17)	460 (22)	0.76 (0.49-1.20)		26 (13)	385 (23)	0.71 (0.40-1.26)	
n	252	2039			164	1697		
TCM								
< 3	48 (19)	362 (18)	1.00*	0.099	39 (24)	309 (18)	1.00*	0.219
3 – 10	58 (23)	588 (29)	0.78 (0.51-1.19)		31 (19)	488 (29)	0.59 (0.34-0.99)	
10 – 30	102 (40)	741 (36)	1.20 (0.82-1.76)		64 (39)	607 (36)	0.89 (0.56-1.40)	
> 30	44 (18)	348 (17)	1.24 (0.77-2.01)		30 (18)	293 (17)	0.88 (0.49-1.58)	
n	252	2039			164	1697		

* Referent group.

[a] Adjusted for sex, age, and province of recruitment.

[b] Adjusted for sex, age, province of recruitment, BMI, education, percent weight change, smoking, coffee, age at first menstruation, number of pregnancies, and total fat and energy intake.

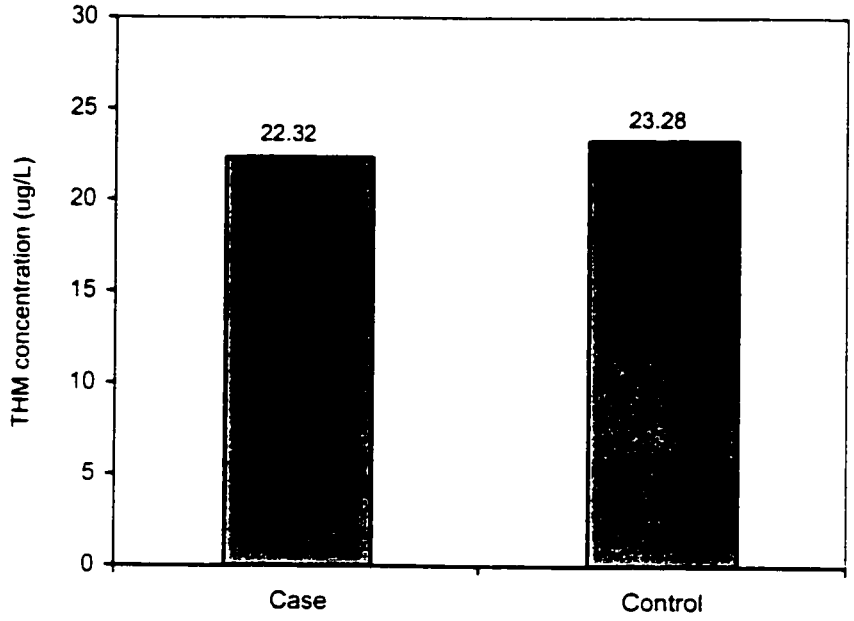
[c] Average DBPs were based on an arithmetic mean of 30 years of available and imputed exposure information from date of interview.

Acronyms: DBPs: Disinfection Byproducts, THM: Trihalomethanes, BDCM: Bromodichloromethane, and TCM: Chloroform.

Pancreatic Cancer Risk According to DBPs (PMW Water Quality Data)

Figure 16 compares the averages of known THM concentration for cases and controls based on the Provincial and Municipal Water (PMW) Monitoring data. The average THM concentration to which the controls were exposed were 23.28 ug/L while the cases were exposed to an average of 22.32 ug/L.

Figure 16: Average exposure to THM for cases and controls based on the Provincial and Municipal Water (PMW) Monitoring data.



In this part of the analysis, three approaches were used to assess pancreatic cancer risks associated with exposure to THM according to the PMW monitoring data. The first approach included subjects with complete exposure information, and therefore imputation was not necessary. The other two approaches required different degrees of imputation. Table 23 provides a summary of the percent of exposure information that was imputed.

For the model requiring at least 20 years of known exposure information, approximately 9 percent of the exposure data in the 30-year ETW was imputed. The frequency of imputation was similar between cases and controls.

For the third model (that did not require a minimum number of years of known exposure), the percent of imputation increased to approximately 20 percent. Like the previous model, the frequency of imputation was similar for cases and controls.

Table 23: **Comparison of percent of imputation for two exposure models (at least 20 years of exposure information and full imputation) using the Provincial Municipal 1990-1996 water monitoring data.**

Subject Status	Total Person Years *without* Imputation	Total Person Years *with* Imputation	Percent Imputation
At Least 20 yrs of Exposure Information			
Cases	13,031	13,740	9.48
Controls	91,474	96,420	9.49
Total	104,505	110,160	9.49
Full Imputation Model			
Cases	13,801	17,280	20.13
Controls	98,203	123,150	20.25
Total	112,004	140,430	20.24

In these analyses, risk estimates were obtained for males and females combined and separately. In addition, the effects of latency periods of 0-year, 5-year and 10-years on the risk estimates were also considered. Only THM could be evaluated.

In the model requiring complete exposure history, 328 cases and 2,335 controls met this inclusion criterion. Tables 24 to 26 provide crude and adjusted pancreatic cancer risk estimates for exposure to THM with respect to different latency periods. The risk estimates were very similar for males and females combined and separately. When 5-year and 10-year latency periods were considered, the risk estimates did not change appreciably. Of all the risk estimates obtained in the complete exposure model, only the comparison between those with average exposure between 20-50 ug/L and the referent group (<10 ug/L) in the combined analysis yielded the highest (but not significant) pancreatic cancer risk (OR=1.37, 95% CI 097-2.20).

Table 24: **Estimated risk of pancreatic cancer and exposure to THM with 30-year exposure time window, Provincial Municipal 1990-1996 water monitoring data.**

- ***Complete exposure information***
- ***No latency***

THM[e] (ug/L)	Minimally Adjusted [a]				Fully Adjusted			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR (95% CI)	Type III X^2 *P* value
				Male and Female [b]				
< 10	96 (29)	774 (33)	1.00*	0.006	82 (30)	673 (33)	1.00*	0.017
10 – 20	91 (28)	632 (27)	1.39 (0.98-1.97)		79 (28)	553 (27)	1.49 (1.02-2.20)	
20 – 50	104 (32)	581 (25)	1.44 (1.06-1.96)		87 (31)	521 (26)	1.37 (0.97-1.94)	
> 50	37 (11)	348 (15)	0.66 (0.40-1.08)		30 (11)	292 (14)	0.65 (0.37-1.12)	
n	328	2335			278	2039		
				Male [c]				
< 10	61 (32)	413 (35)	1.00*	0.170	51 (32)	352 (34)	1.00*	0.278
10 – 20	51 (27)	291 (25)	1.44 (0.90-2.28)		45 (28)	257 (25)	1.40 (0.83-2.37)	
20 – 50	50 (27)	295 (25)	1.15 (0.76-1.75)		43 (27)	260 (26)	1.10 (0.68-1.77)	
> 50	26 (14)	180 (15)	0.67 (0.36-1.23)		22 (13)	153 (15)	0.64 (0.32-1.29)	
n	188	1179			161	1022		
				Female [d]				
< 10	35 (26)	361 (31)	1.00*	0.009	28 (27)	308 (32)	1.00*	0.053
10 – 20	40 (30)	341 (30)	1.38 (0.80-2.37)		27 (26)	281 (29)	1.70 (0.89-3.28)	
20 – 50	54 (36)	286 (25)	1.95 (1.22-3.13)		40 (39)	242 (25)	1.79 (1.02-3.14)	
> 50	11 (8)	168 (14)	0.63 (0.27-1.48)		8 (8)	134 (14)	0.57 (0.20-1.63)	
n	140	1156			103	965		

* Referent group.

[a] Minimally adjusted for sex, age, and province of recruitment.

[b] Full model adjusted for sex, age, province of recruitment, BMI, percent weight change, education, smoking, coffee, beer, and total fat and energy intake.

[c] Full model adjusted for age, province of recruitment, percent weight change, smoking, coffee, beer, liquor, and total fat and energy intake.

[d] Full model adjusted for age, province of recruitment, BMI, percent weight change, education, smoking, age at first menstruation, number of pregnancies, coffee, and total fat intake.

[e] Average DBPs were based on an arithmetic mean of 30 years of available exposure information from date of interview.

Table 25: Estimated risk of pancreatic cancer and exposure to THM with 30-year exposure time window, Provincial Municipal 1990-1996 water monitoring data.

- ***Complete exposure information***
- ***5-year latency.***

THM[c] (ug/L)	Minimally Adjusted [a]				Fully Adjusted			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR (95% CI)	Type III X^2 *P* value
				Male and Female [b]				
< 10	100 (32)	769 (33)	1.00*	0.045	85 (31)	668 (33)	1.00*	0.139
10 – 20	85 (23)	642 (27)	1.13 (0.80-1.69)		74 (27)	562 (27)	1.22 (0.83-1.80)	
20 – 50	102 (32)	568 (24)	1.38 (1.02-1.89)		85 (31)	511 (25)	1.32 (0.93-1.87)	
> 50	41 (13)	356 (16)	0.73 (0.45-1.17)		34 (12)	298 (16)	0.73 (0.43-1.24)	
n	328	2335			278	2039		
				Male [c]				
< 10	63 (34)	413 (35)	1.00*	0.716	52 (33)	353 (35)	1.00*	0.760
10 – 20	49 (26)	295 (25)	1.20 (0.75-1.88)		44 (27)	259 (25)	1.21 (0.72-2.08)	
20 – 50	46 (24)	285 (24)	1.05 (0.68-1.60)		39 (24)	253 (25)	1.00 (0.61-1.62)	
> 50	30 (16)	186 (16)	0.80 (0.45-1.44)		26 (16)	157 (15)	0.81 (0.42-1.57)	
n	188	1179			161	1022		
				Female [d]				
< 10	37 (29)	356 (31)	1.00*	0.006	30 (29)	303 (31)	1.00*	0.056
10 – 20	36 (23)	347 (30)	1.12 (0.65-1.91)		23 (22)	285 (30)	1.25 (0.65-2.40)	
20 – 50	56 (38)	283 (24)	1.95 (1.25-3.09)		42 (41)	241 (25)	1.76 (1.02-3.06)	
> 50	11 (10)	170 (15)	0.69 (0.26-1.37)		8 (8)	136 (14)	0.52 (0.19-1.46)	
n	140	1156			103	965		

* Referent group.

[a] Minimally adjusted for sex, age, and province of recruitment.

[b] Full model adjusted for sex, age, province of recruitment, BMI, percent weight change, education, smoking, coffee, beer, and total fat and energy intake.

[c] Full model adjusted for age, province of recruitment, percent weight change, smoking, coffee, beer, liquor, and total fat and energy intake.

[d] Full model adjusted for age, province of recruitment, BMI, percent weight change, education, smoking, age at first menstruation, number of pregnancies, coffee, and total fat intake.

[e] Average DBPs were based on an arithmetic mean of 30 years of available exposure information from date of interview.

Table 26: Estimated risk of pancreatic cancer and exposure to THM with 30-year exposure time window, Provincial Municipal 1990-1996 water monitoring data.

- ***Complete exposure information***
- ***10-year latency.***

THM[c] (ug/L)	Minimally Adjusted [a]				Fully Adjusted			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR (95% CI)	Type III X^2 *P* value
Male and Female [b]								
< 10	101 (31)	764 (33)	1.00*	0.034	86 (31)	665 (33)	1.00*	0.044
10 – 20	87 (27)	647 (28)	1.17 (0.82-1.65)		75 (27)	567 (27)	1.22 (0.83-1.79)	
20 – 50	100 (30)	564 (24)	1.35 (0.99-1.84)		85 (31)	503 (25)	1.34 (0.95-1.90)	
> 50	40 (12)	360 (15)	0.67 (0.41-1.07)		32 (11)	304 (15)	0.83 (0.36-1.06)	
n	328	2335			278	2039		
Male [c]								
< 10	64 (34)	409 (34)	1.00*	0.809	53 (33)	351 (34)	1.00*	0.893
10 – 20	49 (26)	302 (26)	1.12 (0.71-1.77)		44 (27)	267 (26)	1.08 (0.64-1.80)	
20 – 50	45 (24)	282 (24)	1.00 (0.67-1.54)		38 (24)	247 (24)	0.97 (0.59-1.57)	
> 50	30 (16)	186 (16)	0.96 (0.45-1.43)		26 (16)	157 (16)	0.81 (0.42-1.55)	
n	188	1179			161	1022		
Female [d]								
< 10	37 (27)	355 (31)	1.00*	0.002	30 (29)	303 (31)	1.00*	0.006
10 – 20	38 (27)	345 (30)	1.23 (0.72-2.13)		23 (22)	285 (30)	1.29 (0.68-2.48)	
20 – 50	55 (39)	282 (24)	1.93 (1.21-3.07)		42 (41)	241 (25)	1.85 (1.07-3.22)	
> 50	10 (7)	174 (15)	0.44 (0.18-1.07)		8 (8)	136 (14)	0.30 (0.10-0.91)	
n	140	1156			103	965		

* Referent group.

[a] Minimally adjusted for sex, age, and province of recruitment.

[b] Full model adjusted for sex, age, province of recruitment, BMI, percent weight change, education, smoking, coffee, beer, and total fat and energy intake.

[c] Full model adjusted for age, province of recruitment, percent weight change, smoking, coffee, beer, liquor, and total fat and energy intake.

[d] Full model adjusted for age, province of recruitment, BMI, percent weight change, education, smoking, age at first menstruation, number of pregnancies, coffee, and total fat intake.

[e] Average DBPs were based on an arithmetic mean of 30 years of available exposure information from date of interview.

Tables 27 to 29 provide pancreatic cancer risk estimates for exposure to THM. In these analyses, subjects were required to have at least 20 years of exposure information. Overall, 458 cases and 3,214 controls were included in these analyses. Like the previous analyses that required complete exposure information, the different latency periods did not change the risk estimates appreciably. A increase (but not significant) in risk of pancreatic cancer with exposure to THMs was observed in the combined analysis. Those with average exposure between 20-50 ug/L exhibited an adjusted increased risk compared to the referent group (OR=1.32; 95% CI, 0.99-1.77).

Table 27: Estimated risk of pancreatic cancer and exposure to THM with 30-year exposure time window, Provincial Municipal 1990-1996 water monitoring data.

- ***At least 20 years of exposure information***
- ***No latency.***

THM[e] (ug/L)	Minimally Adjusted [a]				Fully Adjusted			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR (95% CI)	Type III X^2 *P* value
Male and Female [b]								
< 10	123 (27)	959 (30)	1.00*	0.054	106 (27)	836 (30)	1.00*	0.169
10 – 20	131 (29)	908 (28)	1.17 (0.87-1.56)		107 (28)	799 (28)	1.16 (0.84-1.60)	
20 – 50	151 (33)	920 (29)	1.34 (1.02-1.75)		130 (33)	820 (29)	1.32 (0.99-1.77)	
> 50	53 (11)	427 (13)	0.81 (0.53-1.23)		46 (12)	362 (13)	0.86 (0.68-1.46)	
n	458	3214			389	2817		
Male [c]								
< 10	73 (27)	501 (32)	1.00*	0.260	63 (27)	426 (31)	1.00*	0.575
10 – 20	74 (28)	384 (24)	1.30 (0.88-1.91)		63 (27)	339 (25)	1.14 (0.74-1.75)	
20 – 50	81 (31)	466 (29)	1.20 (0.86-1.76)		72 (31)	411 (30)	1.16 (0.78-1.71)	
> 50	36 (14)	230 (15)	0.78 (0.46-1.34)		32 (14)	197 (14)	0.77 (0.42-1.42)	
n	264	1581			230	1373		
Female [d]								
< 10	50 (26)	458 (28)	1.00*	0.105	38 (26)	392 (28)	1.00*	0.335
10 – 20	57 (29)	524 (32)	1.02 (0.66-1.60)		33 (29)	440 (32)	1.07 (0.62-1.85)	
20 – 50	70 (36)	454 (28)	1.52 (1.01-2.27)		52 (36)	385 (28)	1.50 (0.93-2.42)	
> 50	17 (9)	197 (12)	0.87 (0.43-1.75)		14 (9)	159 (12)	1.04 (0.45-2.37)	
n	194	1633			137	1376		

* Referent group.

[a] Minimally adjusted for sex, age, and province of recruitment.

[b] Full model adjusted for sex, age, province of recruitment, BMI, percent weight change, education, smoking, coffee, beer, and total fat and energy intake.

[c] Full model adjusted for age, province of recruitment, percent weight change, smoking, coffee, beer, liquor, and total fat and energy intake.

[d] Full model adjusted for age, province of recruitment, BMI, percent weight change, education, smoking, age at first menstruation, number of pregnancies, coffee, and total fat intake.

[e] Average DBPs were based on an arithmetic mean of 30 years of available and imputed exposure information from date of interview.

Table 28: Estimated risk of pancreatic cancer and exposure to THM with 30-year exposure time window, Provincial Municipal 1990-1996 water monitoring data.

- ***At least 20 years of exposure information***
- ***5-year latency***

THM[c] (ug/L)	Minimally Adjusted [a]				Fully Adjusted			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR (95% CI)	Type III X^2 *P* value
Male and Female [b]								
< 10	127 (28)	947 (29)	1.00*	0.153	109 (28)	828 (29)	1.00*	0.345
10 – 20	126 (28)	923 (29)	1.01 (0.76-1.35)		103 (26)	810 (29)	1.03 (0.74-1.42)	
20 – 50	148 (32)	912 (28)	1.27 (0.98-1.66)		127 (33)	815 (29)	1.25 (0.94-1.69)	
> 50	57 (12)	432 (13)	0.86 (0.57-1.30)		50 (13)	364 (13)	0.93 (0.60-1.46)	
n	458	3214			389	2817		
Male [c]								
< 10	74 (28)	498 (33)	1.00*	0.811	63 (28)	426 (31)	1.00*	0.953
10 – 20	73 (28)	390 (26)	1.13 (0.74-1.79)		63 (28)	341 (25)	1.06 (0.69-1.64)	
20 – 50	77 (29)	459 (26)	1.13 (0.79-1.62)		68 (29)	407 (29)	1.08 (0.73-1.61)	
> 50	40 (15)	234 (15)	0.92 (0.55-1.54)		36 (15)	199 (15)	0.93 (0.53-1.64)	
n	264	1581			230	1373		
Female [d]								
< 10	53 (27)	449 (27)	1.00*	0.047	41 (30)	383 (28)	1.00*	0.129
10 – 20	53 (27)	533 (33)	0.89 (0.57-1.38)		28 (21)	447 (32)	0.81 (0.46-1.42)	
20 – 50	71 (37)	453 (28)	1.48 (1.00-2.21)		54 (39)	387 (28)	1.46 (0.91-2.32)	
> 50	17 (9)	198 (12)	0.79 (0.39-1.58)		14 (10)	159 (12)	0.91 (0.40-2.04)	
n	194	1633			137	1376		

* Referent group.

[a] Minimally adjusted for sex, age, and province of recruitment.

[b] Full model adjusted for sex, age, province of recruitment, BMI, percent weight change, education, smoking, coffee, beer, and total fat and energy intake.

[c] Full model adjusted for age, province of recruitment, percent weight change, smoking, coffee, beer, liquor, and total fat and energy intake.

[d] Full model adjusted for age, province of recruitment, BMI, percent weight change, education, smoking, age at first menstruation, number of pregnancies, coffee, and total fat intake.

[e] Average DBPs were based on an arithmetic mean of 30 years of available and imputed exposure information from date of interview.

Table 29: Estimated risk of pancreatic cancer and exposure to THM with 30-year exposure time window, Provincial Municipal 1990-1996 water monitoring data.

- ***At least 20 years of exposure information***
- ***10-year latency***

THM[c] (ug/L)	Minimally Adjusted [a]				Fully Adjusted			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR (95% CI)	Type III X^2 *P* value
Male and Female [b]								
< 10	129 (29)	933 (29)	1.00*	0.137	110 (28)	816 (29)	1.00*	0.137
10 – 20	127 (28)	946 (29)	0.98 (0.74-1.30)		104 (27)	834 (29)	0.99 (0.72-1.37)	
20 – 50	145 (30)	893 (28)	1.24 (0.95-1.62)		127 (33)	792 (28)	1.28 (0.95-1.71)	
> 50	57 (13)	442 (14)	0.80 (0.54-1.21)		48 (12)	375 (14)	0.80 (0.51-1.25)	
n	458	3214			389	2817		
Male [c]								
< 10	76 (29)	485 (31)	1.00*	0.829	65 (28)	416 (32)	1.00*	0.811
10 – 20	71 (27)	409 (26)	1.00 (0.68-1.46)		61 (27)	361 (26)	0.89 (0.58-1.36)	
20 – 50	77 (29)	449 (28)	1.11 (0.77-1.58)		68 (30)	393 (27)	1.06 (0.71-1.59)	
> 50	40 (15)	238 (15)	0.87 (0.52-1.46)		36 (15)	203 (15)	1.87 (0.50-1.52)	
n	264	1581			230	1373		
Female [d]								
< 10	53 (27)	448 (27)	1.00*	0.100	40 (29)	382 (28)	1.00*	0051
10 – 20	56 (29)	537 (33)	0.96 (0.62-1.49)		30 (22)	451 (32)	0.90 (0.52-1.57)	
20 – 50	68 (35)	444 (27)	1.44 (0.96-2.15)		55 (40)	379 (28)	1.57 (0.98-2.51)	
> 50	17 (9)	204 (13)	0.72 (0.36-1.44)		12 (9)	164 (12)	0.65 (0.28-1.50)	
n	194	1633			137	1376		

* Referent group.

[a] Minimally adjusted for sex, age, and province of recruitment.

[b] Full model adjusted for sex, age, province of recruitment, BMI, percent weight change, education, smoking, coffee, beer, and total fat and energy intake.

[c] Full model adjusted for age, province of recruitment, percent weight change, smoking, coffee, beer, liquor, and total fat and energy intake.

[d] Full model adjusted for age, province of recruitment, BMI, percent weight change, education, smoking, age at first menstruation, number of pregnancies, coffee, and total fat intake.

[e] Average DBPs were based on an arithmetic mean of 30 years of available and imputed exposure information from date of interview.

The Full Imputation model for missing exposure contained 576 cases with 4,105 controls. Like the previous two models, latency effects do not appear to affect pancreatic cancer risk estimates. An increase in adjusted odds ratio in the 0-year latency of the combined analysis was 1.28 (95% CI, 0.97-1.65) comparing those with average exposure of 20-50 ug/L with the referent group (<10 ug/L) while the adjusted odds ratio in the 10-year latency was 1.22 (95% CI, 0.91-1.54) for the same comparison.

Association of Pancreatic Cancer with Potential Confounders (Fully Adjusted Model)

Table 33 shows the relationship between potential confounders adjusted for other potential confounders in the table and pancreatic cancer (DBPs are not included in the analysis). The potential confounders that appears to be significantly associated with pancreatic cancer were BMI, percent weight change from lifetime maximum weight, and tobacco smoke.

Table 30: **Estimated risk of pancreatic cancer and exposure to THM with 30-year exposure time window, Provincial Municipal 1990-1996 water monitoring data.**

- ***No minimum years of exposure information required***
- ***No latency***

THM[e] (ug/L)	Minimally Adjusted [a]				Fully Adjusted			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR (95% CI)	Type III X^2 *P* value
Male and Female [b]								
< 10	124 (21)	970 (24)	1.00*	0.091	107 (23)	845 (24)	1.00*	0.232
10 – 20	160 (28)	1122 (27)	1.17 (0.89-1.52)		131 (27)	985 (28)	1.17 (0.87-1.58)	
20 – 50	236 (41)	1564 (38)	1.28 (1.01-1.63)		191 (40)	1345 (38)	1.26 (0.97-1.65)	
> 50	56 (10)	449 (11)	0.86 (0.58-1.29)		48 (10)	380 (10)	0.90 (0.58-1.40)	
n	576	4105			477	3555		
Male [c]								
< 10	73 (23)	507 (24)	1.00*	0.518	63 (23)	432 (24)	1.00*	0.831
10 – 20	88 (27)	483 (23)	1.25 (0.88-1.80)		75 (27)	426 (24)	1.12 (0.75-1.68)	
20 – 50	124 (38)	837 (41)	1.12 (0.81-1.54)		106 (38)	719 (40)	1.08 (0.75-1.54)	
> 50	39 (12)	239 (12)	0.89 (0.54-1.48)		35 (12)	204 (12)	0.87 (0.50-1.51)	
n	324	2066			279	1781		
Female [d]								
< 10	51 (20)	463 (23)	1.00*	0.033	39 (24)	397 (23)	1.00*	0.563
10 – 20	72 (29)	639 (31)	1.08 (0.72-1.63)		42 (26)	535 (32)	1.13 (0.68-1.88)	
20 – 50	112 (44)	727 (36)	1.53 (1.06-2.21)		69 (41)	595 (35)	1.34 (0.86-2.09)	
> 50	17 (7)	210 (10)	0.82 (0.42-1.63)		14 (9)	170 (10)	0.94 (0.42-2.12)	
n	252	2039			164	1697		

* Referent group.

[a] Minimally adjusted for sex, age, and province of recruitment.

[b] Full model adjusted for sex, age, province of recruitment, BMI, percent weight change, education, smoking, coffee, beer, and total fat and energy intake.

[c] Full model adjusted for age, province of recruitment, percent weight change, smoking, coffee, beer, liquor, and total fat and energy intake.

[d] Full model adjusted for age, province of recruitment, BMI, percent weight change, education, smoking, age at first menstruation, number of pregnancies, coffee, and total fat intake.

[e] Average DBPs were based on an arithmetic mean of 30 years of available and imputed exposure information from date of interview.

Table 31: Estimated risk of pancreatic cancer and exposure to THM with 30-year exposure time window, Provincial Municipal 1990-1996 water monitoring data.

- ***No minimum years of exposure information required***
- ***5-year latency***

THM[c] (ug/L)	Minimally Adjusted [a]				Fully Adjusted			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR (95% CI)	Type III X^2 *P* value
Male and Female [b]								
< 10	129 (22)	964 (23)	1.00*	0.207	111 (23)	843 (24)	1.00*	0.332
10 – 20	152 (26)	1101 (27)	1.05 (0.80-1.38)		124 (26)	964 (27)	1.07 (0.79-1.44)	
20 – 50	237 (41)	1590 (39)	1.20 (0.95-1.53)		192 (40)	1367 (38)	1.22 (0.93-1.59)	
> 50	58 (11)	450 (11)	0.86 (0.58-1.28)		50 (11)	381 (11)	0.90 (0.58-1.38)	
n	576	4105			477	3555		
Male [c]								
< 10	75 (23)	506 (24)	1.00*	0.831	64 (24)	434 (24)	1.00*	0.929
10 – 20	86 (26)	473 (23)	1.15 (0.80-1.65)		74 (26)	414 (23)	1.09 (0.73-1.63)	
20 – 50	122 (38)	845 (41)	1.03 (0.75-1.42)		104 (37)	727 (41)	1.03 (0.72-1.47)	
> 50	41 (13)	242 (12)	0.93 (0.57-1.52)		37 (13)	206 (12)	0.90 (0.53-1.55)	
n	324	2066			279	1781		
Female [d]								
< 10	54 (21)	458 (22)	1.00*	0.019	42 (26)	391 (23)	1.00*	0.337
10 – 20	66 (26)	628 (31)	0.97 (0.64-1.45)		36 (22)	526 (31)	0.89 (0.53-1.49)	
20 – 50	115 (46)	745 (37)	1.49 (1.03-2.11)		72 (44)	611 (36)	1.28 (0.83-1.98)	
> 50	17 (7)	208 (10)	0.76 (0.39-1.50)		14 (9)	169 (10)	0.83 (0.38-1.83)	
n	252	2039			164	1697		

* Referent group.

[a] Minimally adjusted for sex, age, and province of recruitment.

[b] Full model adjusted for sex, age, province of recruitment, BMI, percent weight change, education, smoking, coffee, beer, and total fat and energy intake.

[c] Full model adjusted for age, province of recruitment, percent weight change, smoking, coffee, beer, liquor, and total fat and energy intake.

[d] Full model adjusted for age, province of recruitment, BMI, percent weight change, education, smoking, age at first menstruation, number of pregnancies, coffee, and total fat intake.

[e] Average DBPs were based on an arithmetic mean of 30 years of available and imputed exposure information from date of interview.

Table 32: Estimated risk of pancreatic cancer and exposure to THM with 30-year exposure time window, Provincial Municipal 1990-1996 water monitoring data.

- ***No minimum years of exposure information required***
- ***10-year latency***

THM[c] (ug/L)	Minimally Adjusted [a]				Fully Adjusted			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR (95% CI)	Type III X^2 *P* value
				Male and Female [b]				
< 10	135 (23)	959 (25)	1.00*	0.242	115 (24)	840 (23)	1.00*	0.200
10 – 20	147 (27)	1071 (27)	1.00 (0.76-1.31)		120 (25)	946 (27)	1.02 (0.75-1.38)	
20 – 50	237 (40)	1618 (36)	1.13 (0.89-1.43)		194 (41)	1380 (39)	1.18 (0.91-1.54)	
> 50	57 (10)	457 (12)	0.78 (0.53-1.15)		48 (10)	389 (11)	0.77 (0.50-1.20)	
n	576	4105			477	3555		
				Male [c]				
< 10	79 (24)	494 (26)	1.00*	0.906	67 (24)	425 (26)	1.00*	0.776
10 – 20	80 (27)	471 (24)	0.98 (0.69-1.41)		69 (25)	417 (24)	0.91 (0.61-1.36)	
20 – 50	125 (36)	856 (38)	0.98 (0.71-1.34)		107 (38)	730 (38)	1.00 (0.70-1.42)	
> 50	40 (13)	245 (12)	0.83 (0.51-1.36)		36 (13)	209 (12)	0.78 (0.46-1.33)	
n	324	2066			279	1781		
				Female [d]				
< 10	56 (22)	465 (23)	1.00*	0.076	43 (26)	398 (23)	1.00*	0.2650
10 – 20	67 (27)	600 (29)	1.03 (0.69-1.56)		37 (23)	508 (31)	0.95 (0.57-1.59)	
20 – 50	112 (44)	762 (37)	1.38 (0.96-1.96)		72 (44)	619 (36)	1.23 (0.80-1.90)	
> 50	17 (7)	212 (11)	0.69 (0.35-1.36)		12 (7)	172 (10)	0.60 (0.26-1.35)	
n	252	2039			164	1697		

* Referent group.

[a] Minimally adjusted for sex, age, and province of recruitment.

[b] Full model adjusted for sex, age, province of recruitment, BMI, percent weight change, education, smoking, coffee, beer, and total fat and energy intake.

[c] Full model adjusted for age, province of recruitment, percent weight change, smoking, coffee, beer, liquor, and total fat and energy intake.

[d] Full model adjusted for age, province of recruitment, BMI, percent weight change, education, smoking, age at first menstruation, number of pregnancies, coffee, and total fat intake.

[e] Average DBPs were based on an arithmetic mean of 30 years of available and imputed exposure information from date of interview.

Table 33: Estimated risk of pancreatic cancer by selected characteristics of study subjects (Fully adjusted model).

- **Males and Females**

Characteristics	No. of Cases (%)	No. of Controls (%)	OR[a] (95% CI)	Wald X^2 P Value	Type III X^2 *P* value
BMI (kg/m^2)					
≤ 23	126 (26)	1109 (29)	1.00*		
23 – 27	176 (36)	1516 (40)	0.83 (0.65 – 1.07)	0.158	0.019
27 – 30	88 (18)	673 (18)	0.87 (0.64 – 1.18)	0.374	
> 30	99 (20)	514 (13)	1.28 (0.94 – 1.74)	0.115	
% Weight Change[T]					
≤ 2.9	155 (32)	827 (22)	1.00*		<0.001
2.9 - < 5.7	85 (17)	844 (22)	0.56 (0.42 – 0.75)	<0.001	
5.7 - <10.2	119 (24)	1074 (28)	0.66 (0.50 – 0.85)	0.002	
> 10.2	130 (26)	1067 (28)	0.71 (0.55 – 0.93)	0.012	
Education (total yrs)					
≤ 9	110 (22)	726 (19)	1.00*		0.685
9 – 12	209 (43)	1433 (38)	1.12 (0.86 – 1.45)	0.399	
> 12	170 (35)	1653 (43)	1.01 (0.76 – 1.33)	0.956	
Total Fat Intake (g/wk)					
≤ 236	98 (20)	907 (23)	1.00*		0.896
237 – 323	108 (22)	942 (24)	1.04 (0.76 – 1.43)	0.802	
324 – 420	125 (26)	912 (24)	1.11 (0.78 – 1.59)	0.546	
> 420	158 (32)	1051 (29)	1.16 (0.77 – 1.72)	0.471	
Total Energy Intake (Cal/day)					
≤ 1,370	124 (25)	1146 (30)	1.00*		0.227
1,370 – 1,710	109 (22)	979 (26)	0.91 (0.66 – 1.24)	0.537	
1,710 – 2,050	117 (24)	759 (20)	1.24 (0.88 – 1.76)	0.223	
> 2,050	139 (28)	928 (24)	1.07 (0.72 – 1.59)	0.737	
Smoking (pack years)					
0	159 (32)	1493 (39)	1.00*		<0.001
1 - 15	99 (20)	1155 (30)	0.78 (0.59 – 1.03)	0.080	
15 – 35	150 (31)	799 (21)	1.38 (1.05 – 1.80)	0.019	
> 35	81 (17)	365 (10)	1.36 (0.98 – 1.90)	0.069	

Characteristics	No. of Cases (%)	No. of Controls (%)	OR[a] (95% CI)	Wald X^2 P Value	Type III X^2 *P* value
Tap Water (glasses per week)					
< 3.57	111 (23)	1046 (27)	1.00*		0.638
3.57 – 5.00	117 (24)	845 (22)	1.13 (0.83 – 1.49)	0.742	
5.00 – 7.86	182 (37)	1314 (35)	1.06 (0.81 – 1.40)	0.652	
> 7.86	79 (16)	607 (16)	0.92 (0.65 – 1.30)	0.622	
Coffee					
≤ 4 cups/wk	52 (11)	546 (14)	1.00*		0.580
5 – 7 cups/wk	124 (25)	1042 (27)	0.99 (0.69 – 1.41)	0.938	
2 – 3 cups/day	183 (37)	1416 (37)	0.97 (0.68 – 1.37)	0.852	
> 3 cups/day	130 (27)	806 (21)	1.16 (0.79 – 1.72)	0.447	
Beer					
0 – 3 times per month	359 (73)	2971 (78)	1.00*		0.365
1 – 6 times per week	48 (10)	340 (9)	1.14 (0.81 – 1.62)	0.454	
≥ 1 per day	82 (17)	501 (13)	1.23 (0.91 – 1.65)	0.179	
Wine					
0 – 3 times per month	399 (82)	3162 (83)	1.00*		0.404
1 – 6 times per week	44 (9)	313 (8)	1.19 (0.83 – 1.70)	0.209	
≥ 1 per day	46 (9)	337 (9)	0.94 (0.66 – 1.33)	0.766	
Liquor					
0 – 3 times per month	375 (76)	3162 (82)	1.00*		0.048
1 – 6 times per week	44 (7)	313 (9)	0.76 (0.51 – 1.12)	0.165	
≥ 1 per day	46 (17)	337 (9)	1.34 (1.00 – 1.80)	0.045	

* Referent group.

[a] Adjusted for sex, age, province of recruitment, and other variables in table.

[T] Percent weight change from maximum lifetime weight and weight reported 2 years prior to interview.

CHAPTER 6 - DISCUSSION

Summary of Results

The present study explores potential pancreatic cancer risks associated with exposure to chlorination disinfection byproducts (CDBPs). Overall, we have found no significant evidence that long-term exposure to THM, BDCM, and TCM is associated with an increased risk of pancreatic cancer.

We used two different data sources to estimate exposure: the Environmental Health Directorate (EHD) 1993 Water Sampling Data and Provincial Municipal Water (PMW) Monitoring Data. The EHD water quality data was available only as lifetime aggregated DBP estimates for each subject. It was used to estimate pancreatic cancer risks for exposure to THM, BDCM, and TCM. The PMW data was provided to us at a disaggregated level, allowing us to estimate exposures for each subject at each of their residences. Although limited only to THM levels, this data source provided the opportunity to assess the effects of latency on pancreatic cancer risk. For both water data sources, we used three approaches to handling subjects with missing exposure information:

1) Exclusion of subjects with any missing exposure information;
2) Exclusion of subjects with more than 10 years of missing exposure information, with OCMI imputation for missing exposure levels in the subjects in the analysis; and,
3) OCMI imputation for any missing exposure information.

For each these approaches, the risk of pancreatic cancer was assessed for males and females combined and separately.

Environmental Health Directorate Water Quality Data

Based on the combined analyses of the EHD water quality data, no significant increased (or decreased) risk of pancreatic cancer was observed for exposure to THM, BDCM, and TCM in analyses based on those with; (1) complete exposure information, (2) at least 20 years of exposure information, and (3) full imputation. In a separate analysis for males only, a modest increased risk was observed for exposure to BDCM, but not for THM or TCM. When compared to the referent group (< 1 ug/L), males with complete exposure information for the 30-year exposure time window and an average exposure of more than 5 ug/L of BDCM, had a 31 percent increased risk of pancreatic cancer after adjusting for other potential confounders (OR=1.31; 95% CI, 0.85-2.02). However, the increased risk did not achieve statistical significance.

Provincial Municipal Water Monitoring Data

The analyses based on the PWM exposure data found some evidence of an increase in pancreatic cancer risks associated with exposure to THM. For the combined analysis (no latency) requiring complete exposure information, males and females with average exposure of 10-20 ug/L of THM had a 49 percent increase in pancreatic cancer as compared to those with less than 10ug/L (OR=1.49, 95% CI 1.02-2.20) after adjusting for potential confounders. The increase pancreatic cancer risk remained elevated for analyses requiring at least 20 years of exposure information and full imputation. However, the associations were not statistically significant.

Females appeared to have slightly higher pancreatic cancer risk than males. When comparing females with average exposure of 20-50 ug/L and the referent group (<10ug/L) those with the higher exposed group had an adjusted odds ratio of 1.85 (95%

CI 1.07-3.22). The comparison was based on females with complete exposure and 10 year latency adjustment. In contrast, the highest risk estimate for males was based on a comparison of those with average exposure of 10-20 ug/L to the referent group (OR=1.40, 95% CI 0.83-2.37) with complete exposure information with no latency adjustment.

Comparison with Previous Studies: Potential Confounders

We confirmed the observation from most previous studies [56, 58, 59, 63] that smoking is a significant risk factor for pancreatic cancer (OR's between 1.39 and 2.00 when comparing those with more than 35 pack-years to those with 0 pack-years). This increased risk was evident among both males and females. In this study, we observed a much higher risk for women as compared to men. For women, we observed a two-fold increase in pancreatic cancer risk (OR=2.00; 95% CI, 1.23-3.28) when comparing those who had at least 35 pack-years of tobacco smoking to non-smokers (0 pack-years). The impact of tobacco smoke on pancreatic cancer risk is lower among men (OR=1.39; 95% CI, 0.97-2.00) for the same comparison. The differential impact of tobacco smoking on women and men has been previously documented [94]. In their case control study, Muscat and colleagues found higher risks among women than men for both duration and amount smoked. For women, a significant increase of 84 percent after adjusting age and province of recruitment while the men had an insignificant increased risk of 46 percent with same adjustments. When smoking was adjusted for other confounders (in Table 33) in the male and female combined analysis, the increased risk remained high when comparing those with average 15-35 pack-years to non-smokers (OR=1.38; 95% CI, 1.05-1.80).

The current study showed that BMI is associated with increased risk of pancreatic cancer among those with BMI of more than 30 kg/m^2. When comparing with the referent group (<23 kg/m^2), those with a BMI of greater than 30 kg/m^2 had a 36 percent increased in pancreatic cancer risk (OR=1.36; 95% CI 1.05-1.77) after adjusting for age, sex, and province of recruitment. Although the association was not statistically significant, those with BMI between 23 and 30 kg/m^2 appeared to have a protective effect when compared to the referent group. For example, when comparing to the referent group ([23 kg/m^2), those with BMI between 23 and 27 kg/m^2 had an odds ratio of 0.86 (95% CI, 0.68-1.07). Similarly, those with BMI between 27 and 30 kg/m^2 had an odds ratio of 0.96 (95% CI, 0.74-1.25) as compared to the referent group. A similar trend was also observed for analyses stratified by sex. Results from the current study are consistent with a previous study [67] and support Health Canada's guideline that good health is associated with moderate BMI while poorer health is associated with low or high BMI [95].

Increased percent weight change from lifetime maximum weight to weight reported 2 years prior to interview was associated with reduced risk for pancreatic cancer. This observation is consistent with an earlier report based on a sub-population of the NECSS [68]. In the combined analysis adjusted for sex, age, and province of recruitment, those with more than 10.2% change from maximum lifetime weight had an adjusted OR of 0.69 (95% CI, 0.54-0.85) when compared to those with weight change of less than 2.9%. A similar odds ratio was obtained for analyses based on females alone (OR=0.61; 95% CI, 0.43-0.86) for the same comparison. Among men, the reduced risk (OR=0.75; 95% CI, 0.55-1.02) was also observed, but the reduced risk was not as significant.

Comparison with Previous Studies: DBPs

Of the recent investigations, the study conducted by IJsselmuiden and colleagues [37] is most comparable to the current study. Like the current study, IJsselmuiden *et al* recruited cases identified from cancer registries with non-decedent controls. Exposure was assessed based on information collected from the 1975 census. Using a logistic regression analysis, IJsselmuiden and colleagues provided an estimated risk of pancreatic cancer of 2.18 (95% CI, 1.20-3.95) for those exposed to municipal chlorinated water compared to non-chlorinated water sources after adjusting for age and smoking. The magnitude of the risk estimate in the IJsselmuiden study is higher than those observed in the current study. In the current study, the largest adjusted risk estimate for exposure to THM was 1.49 (95% CI, 1.00-2.24) when comparing those with an average exposure between 10-20 ug/L to the referent group (< 10 ug/L of THM). The differences in risk estimates could likely be due to differences in the way the exposure was assessed. In the IJsselmuiden study, exposure information was collected through the 1975 census. As is the case with information collected from death certificates, cross-sectional information from the census does not adjust for the temporal variation in the water and place of residence. Furthermore, information regarding individual THM exposure information was not available and therefore exposure was assessed based on dichotomous categories of exposed and non-exposed. A random survey conducted in the late 1970s, showed that the average THM was 107 ug/L which is much higher than the average concentration of THM in the current study of 22.5 ug/L. Higher THM levels in the IJsselmuiden study could have translated into higher risk estimates as compared to the current study.

A recent Finnish study conducted by Kukkula and Löfroth [38] observed a decreased risk in pancreatic cancer with increasing years of exposure to CDBPs. However, their study is hard to interpret and is counter to the current literature.

Exposure Assessment: comparison with previous studies

Since the discovery of CDBPs in the mid 1970s, progress has been made in terms of assessing exposure to chlorination disinfection byproducts. Earlier analytical studies assessed exposure based on the address appearing on a person's death certificate [35, 36, 82-84]. However, this address will not reflect the full residence for many subjects [96]. More recent studies examining the relationship between CDBPs and pancreatic cancer have assessed exposure using residence information collected from indirect sources such as census data [37, 38]. To date, no known studies in pancreatic cancer have used residence specific information collected directly from study participants to re-construct individual exposure CDBP profiles.

Unlike previous studies, the current study assesses exposure using residence-specific information collected directly from study participants. The residence information collected from study participants was linked to water quality data in order to re-construct individual exposure profiles. Furthermore, the current study assessed pancreatic cancer risks for specific DBPs at different average known exposures.

Other recent studies that have examined the association between chlorination of drinking water and pancreatic cancer have provided mixed results. In an ecological and a historical cohort study conducted by Koivusalo and colleagues in Finland [31, 47], no increase in pancreatic cancer risk was associated with the mutagenicity of treated water. In those studies, water mutagenicity was highly correlated with the concentration of a

mutagenic compound termed MX [3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone] found in chlorine treated water. The risk estimate for those who were exposed as compared to those not exposed to MX was 1.19 (95% CI, 1.09-1.29) for the ecological study and 1.01 (95% CI, 0.83-1.22) for the cohort study.

Exposure Assessment: Validity and limitations

Despite the advantages of the current method in assessing exposure, there remain limitations that could lead to misclassification of exposure. The first limitation involved the extrapolation of relatively recent DBPs information to estimate historical exposure. Since CDBPs were only discovered in the mid 1970s [20, 21], information regarding CDBP levels prior to then can only be extrapolated retrospectively based on the water source and treatment processes used. Exposure estimates based on this technique could introduce systematic errors. This concern was somewhat lessened by a recent British study showing high correlation between annual readings for THM, BDCM, and TCM taken in different years [97]. In a five-year study, samples were taken from various water treatment plants over a five-year period and analyzed for various DBPs including THM, BDCM, and TCM. Overall, the correlation between years was high (r=0.88) [97]. This high correlation provides some support that historical estimation of DBPs exposure for the current study is valid. In our study, we used two sources of water quality data to assess exposure. We have shown (Table 4) that the two sources were highly correlated (r=0.903). Despite the high correlation, we cannot rule out misclassification of exposure as a source of systematic bias.

A second concern has to do with changing DBP characteristics as a function of residence time in the distribution system. Health Canada [98, 99] has shown that levels of

CDBPs can increase or decrease depending on season, temperature, and distance from the source. Subjects living close to the treatment plant may be subject to less variability as compared to those living further away from the source, although the same treated water was used. To correct this potential problem, intimate knowledge of water distribution systems (distance from source, residence time) and other environmental factors (pH, temperature) would need to be known and adjusted for THM readings at the water treatment plants. Currently such knowledge is not available for epidemiological studies.

Thirdly, behavioural activities may also alter the level of exposure. Since exposure can occur via ingestion, inhalation, and dermal contact, variability in these activities could result in variability in exposure. Individuals with swimming pools will have increased exposure through dermal contact with chlorinated swimming water and those with personal water filtration systems capable of removing THMs could reduce exposure through ingestion. The increased popularity of bottled water (non-chlorinated) could also increase misclassification of exposure.

Ideally, study subjects should be equipped with devices to monitor daily DBP exposure. However, the technology is currently unavailable and the large exposure time window required makes this approach infeasible.

Latency Effects

Although the biological mechanism of pancreo-carcinogenesis is not known, the initiation of the carcinogenic process is likely to occur with the initial exposure to the mutagenic agent such as chlorine by-products. Once exposed, the repeated interaction between the mutagenic agent and host cells could result in the alteration of the normal cell cycle.

The initial interaction with mutagenic chlorine by-products and the alteration of normal cycle is referred to as the *induction period* [100]. The time interval between disease onset and detection has been termed the *latency period* [100, 101]. The combined induction and latency period has been termed the *empirical induction period* [101] and *empirical latent period* [102]. The latency period and latency effects of CDBPs on cancer risk estimates have not been considered previously. The current study assessed cancer risks associated with exposure to CDBPs using empirical latent periods (latency period) of 5 and 10 years.

When the latency period was not considered, the exposure occurring between disease initiation and diagnosis contributes to the overall exposure estimate even though it does not contribute to disease development. As a result, the 'excess' exposure can 'dilute' the overall risk estimate making it smaller.

The PWM data contains residence specific information that provides the opportunity to assess the latency effects on cancer risks. In the current study, 0, 5, and 10-years were discounted from the date of year of diagnosis/interview. The association between the average of the remaining years (of the 30-year ETW) and pancreatic cancer was examined. The results did not show an increase in pancreatic cancer risks when latency effects were considered. Perhaps the absence of latency effect was due to the way in which exposure was assigned. This topic should be re-visited should more refined exposure information become available.

Imputation

Missing information is unavoidable in epidemiological studies. The approaches used in dealing with missing data are a topic of much debate. Among the different approaches in dealing with missing information, the most conservative approach is to

simply delete all subjects with any missing information and retain those with complete-subject information (case-wise deletion). This is one of the most commonly used approaches. However, this approach can result in a loss of large number of subjects (if missing rates are high) and biases the study toward those with complete information [103]. Even if the complete-subject analysis is valid, it is inefficient and provides estimates with a larger variance [103]. Greenland and Finkle [103] advocated using more complex methods (such as multiple imputation, maximum likelihood, and weighted estimation equations) when large proportions of data are missing [103].

Like other epidemiological studies, the current study had missing information among covariates and exposure information. Because the percentage of missing information for covariates was low (e.g., pack-years of cigarette smoke is missing in only two percent of subjects), it was decided that complete-subject approach would be used. However, for exposure information based on residence specific DBP information, missing exposure information was imputed using observed control mean imputation (OCMI), a method that assigns to each 'missing epoch the (arithmetic) mean across all measured control epochs in the study' [90]. The robustness of the approach was demonstrated by Weinberg using various simulations of gaps in indoor radon gas measurements. The results of the simulations showed that despite gaps in exposure information, OCMI method produced valid risk estimates without bias [90].

Potential biases due to imputation did not appear to be a factor in the current study. The risk estimates for pancreatic cancer did not change dramatically when comparing the risk estimates for models using complete exposure information with those using full imputation. When comparing the risk estimates for those with average 30-year

exposure of between 10-20 ug/L to the referent group, the adjusted risk estimate shown in Table 14 was 0.87 (95% CI, 0.63-1.20). With at least 20 years of exposure information (Table 17) for the same comparison, the odds ratio increased slightly to 0.95 (95% CI, 0.72-1.25). For the full model (Table 20), the odds ratio was 0.93 (95% CI, 0.71-1.22).

Other Potential Confounders

The study attempted to control for potential confounders that may have biased the risk estimates. However, it was not possible to control for all covariates that were potentially associated with both the exposure (CDBPs) and pancreatic cancer. Of particular concern are risk factors that have been shown to be highly correlated with pancreatic cancer such as previous history of chronic pancreatitis [56] and diabetes [58, 59]. Both of these factors were not included in the fully adjusted model since information regarding pancreatitis and diabetes was not collected. The NECSS was designed to collect individual information for 18 cancer sites. To ensure that the task of completing the questionnaire was not too onerous for participants, some details regarding site-specific risk factors such as history of pancreatitis and diabetes were sacrificed.

For a risk factor to be a confounder, it must have independent association with the outcome (pancreatic cancer) and the exposure (DBPs). While diabetes and history of pancreatitis have been associated with pancreatic cancer, it is unclear how these biological factors could be associated with exposure to DBPs. While it is possible that diabetics and those with chronic pancreatitis drink more water or take showers more often, and thereby are exposed to higher level of THMs, the relationship has not been demonstrated. Therefore, it is unlikely that these biological risk factors would have a dramatic effect on pancreatic cancer risks and exposure to DBPs.

The different approaches used by respective provinces in recruiting study participants could potentially introduce two sources of systematic errors: 1) confounding, and 2) selection bias. Our analyses showed that province is related to the level of THMs found in drinking water. CDBPs for the respective provinces were similar except for Manitoba. A confounding relationship would exist if pancreatic cancer was also associated with province of recruitment, and the association is valid (i.e. real) and not an artefact due to selection bias.

While we cannot rule out selection bias, it is unlikely that selection bias is a major issue for the following reasons. Firstly, pancreatic cancer is a rare cancer; as such, the NECSS attempted to recruit a census of pancreatic cancer cases. Thus, the basic design minimized potential selection bias by province. Secondly, we excluded subjects (both cases and controls) from provinces (Newfoundland and Prince Edward Island) where the number of cases recruited was low.

The NECCS does not release province-specific response rate due to issues related to confidentiality. However, we estimated provincial response rates based on the number of cases observed in our study compared with the expected incidence rate based on published statistics from the Canadian Cancer Society. We observed that Manitoba (with the highest average THM exposure level) had the highest response rate. However, the range of the estimated response rates was relatively narrow (30-55%) suggesting that selection effects would likely be small. Furthermore, in addition to the risk estimates presented in the results section, we also performed additional sub-analyses excluding Manitoba (we chose Manitoba since it had a much higher average lifetime THM exposure than the other provinces). The risk estimates with and without Manitoba

remained virtually identical. These additional analyses provide some support that selection bias, if existed, is unlikely to affect our results in a significant way.

Proxy Interviews

The Ontario arm of the NECCS case-control component permitted the use of case information even though some cases were unable to complete the study interview personally. In this situation, proxy interviews were conducted, usually with a close family member. This decision is particularly important in this study of pancreatic cancer for two reasons. First, pancreatic cancer is a disease with a poor prognosis and short survival period. The median survival time following the diagnosis of pancreatic cancer is only 3 months [59]. The five-year survival rate for pancreatic cancer is less than one percent [16]. As such, many potential subjects would have died before they were contacted to participate in the study. Proxies could provide the information that would otherwise be lost. Secondly, it could provide valid information for the key exposure of interest in this study, residence history. Since most proxies were spouses of the subjects (74 percent), and since the average age of subjects for whom proxies provided responses was 65 years of age (median 66), it is reasonable to assume that the proxy respondent would have a good knowledge of the subject's residence history for the most relevant portion of the subject's life.

Given the frequent use of proxies in pancreatic cancer studies, Lyon and colleagues investigated the impact of proxy responses on exposure estimation [104] looking at life-style risk factors for pancreatic cancer. Results of the study found that non-spousal proxies misclassified exposures more often than spousal proxies with the exception of tobacco use [104]. Given that, in the current study, the majority of the

proxies (74 percent) were spouses or close relatives (6 percent, daughter and son), it is likely that the information collected is fairly accurate.

Table 34 in Appendix 3 compares the odds ratio obtained from analyses with and without proxy subjects. When comparing those with average 30-year exposure (with at least 20 years of exposure information) between 10-20 ug/L of THM with the referent group (<10ug/L of THM), the odds ratio decreased slightly for analyses excluding proxy subjects (OR=0.83; 95% CI, 0.60-1.14) as compared to those included proxy subjects (OR=0.95; 95% CI, 0.72-1.25). However, when comparing those with average 30-years exposure of 20-50 ug/L to the referent group, the odds ratios remain unchanged (*Proxy included*: OR=1.16; 95%CI, 0.89-1.52, *Proxy excluded*: OR=1.16; 95% CI, 0.86-1.57). When comparing the highest exposed group (>50ug/L) to the referent group, analyses with proxy subjects had a lower risk estimate (OR=0.86; 95% CI, 0.60-1.24) as compared to analysis without proxy subjects (OR=0.99; 95% CI, 0.68-1.45). The overall net effect of using proxy subjects does not appear to be a major factor in assessing pancreatic cancer risk with exposure to DBPs.

Other Potential Sources of Bias

Like any study design, a case-control design is susceptible to potential biases that can systematically influence the results. Bias refers to 'any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth' [105]. In addition to misclassification of exposure and inadequate control of potential confounders, other biases can also occur. Some of these biases include the following: recall, response, and selection biases.

As a retrospective study, the current study would be susceptible to recall bias. Recall bias refers to the 'systematic error due to differences in accuracy or completeness

of recall to memory of past events or experiences' [105]. Recall bias in this study is minimized for the following reasons. At the time of the interview, the respondent did not know the purpose of the study. It is possible that cases often ruminate about possible things which could have caused their disease while controls do not. However, rumination will unlikely lead to differential recall of residential history (or cause people to remember a particular type of residential location more than any other) between cases and controls. Therefore, the residential history used to reconstruct exposure is unlikely to be differentially biased.

As Villeneuve and colleagues [69] pointed out in their discussion, it is possible that cases may try harder to recall behaviours and that a prospective cohort study would solve this problem. However, cancer of the pancreas is a rare disease thereby making the sample requirements for a cohort study very large in order to have sufficient number of cases for analysis. The expenses associated with such a study render the possibility of its execution unlikely.

With the number of analyses conducted in this study, it is possible that some of the significant associations occurred by chance and therefore, one could argue that risk estimates should potentially be adjusted for multiple comparisons. In this study, we did not adjust for multiple comparisons for 2 reasons. First, the comparisons were determined *a priori* and thereby eliminated reporting bias. Secondly, our analysis of the data did not provide sufficient positive associations to merit adjustments for multiple comparisons.

Strengths of Study

Although the current study used a similar study design (case-control) and analytical strategy (logistic regression) to those of published studies in this field, there are

differences in the approach used to estimate exposure. Unlike the current study, most previous studies assessed exposure based on a dichotomous exposure assessment, which classified subjects into two groups: one drinking chlorinated water and the other drinking non-chlorinated water [36, 37, 82-85]. Our study attempted to obtain a quantitative estimate of lifetime exposure. We also examined potential cancer risks associated with exposure to specific CDBPs (THM, BDCM, and TCM).

In addition, most previous studies assessed exposure based on the address appearing on the death certificates. This practice would have resulted in significant misclassification of exposure due to subject mobility. For example, many subjects in the NECSS database had resided at more than 10 different places of residence by the time of interview, each with different levels of CDBPs in their drinking water. Assigning exposure based on the last place of residence would introduce misclassification of exposure since it does not take into account all other places of residence that are likely to have different levels of CDBPs. The strengths of the current study involve using residence-specific information collected directly from study participants to assess exposure.

Secondly, the current study controlled for potential confounders such as smoking, diet, coffee, and alcoholic consumption. Furthermore, previous studies did not assess the effects of latency even though the literature supports a long latency period for solid tumour induction.

Implications of Study Results

In 1993, the Federal-Provincial-Territorial Subcommittee on Drinking Water (DWS) established an interim guideline for THM of 100 ug/L. This guideline was largely based on animal studies showing modest evidence of cancer. Since the promulgation of

this recommendation, more evidence has been produced suggesting a possible risk of cancer and adverse reproductive health effects in human. In response to this evidence, a CDBP task group was established to re-examine the evidence and to identify options for reducing the risks.

The Canadian drinking water guidelines are currently under review. In 2001, Public Works and Government Services of Canada, on behalf of the Environmental Health Directorate of Health Canada, issued two requests for proposals (RFPs), one for a toxicological and the other for an epidemiological review of the literature (since 1993) regarding the risks associated with exposure to THMs. Recently, a third RFP was issued requesting the services of a consulting firm to organize a "Workshop to Identify Critical Endpoints for Assessment of Health Risks related to THMs in Drinking Water" [106]. The goal of the workshop is to gather experts around the world to discuss the evidence and to reach a consensus on the risks associated with exposure to THMs. The information from the workshop will undoubtedly assist the Drinking Water Subcommittee in revising the Canadian drinking water guideline.

The results from this dissertation can be added to the current body of evidence regarding pancreatic caner risk associated with exposure to THMs. Unique to this study is the assessment of the pancreatic cancer risks based on quantitative measures of DBPs.

Further Research

Since the discovery of CDBPs back in the mid-1970s, tremendous achievements have been made in terms of understanding the relationships between CDBPs and potential adverse health effects. Findings of adverse health effects in animal and human studies have, in part, prompted changes in the way water is treated and experimentation with other methods of water treatment such as ozonation and potential applications of ultraviolet light.

The demand for clean drinking water will be a greater challenge in the future as we face growing global population in face of diminishing natural resources. To meet this challenge, future studies should be a collaborative effort of scientists from different disciplines. In addition to toxicologists and epidemiologists, this area of research requires the expertise of biochemists for biological research and water treatment engineers to assist in modeling of water behaviour as a function of treatment process and water distribution.

Exposure assessment to CDBPs will be an even greater issue in future research as water treatment processes become more customized to the physical characteristics of the water supplies. Introduction of different treatment processes such as ozonation and UV light can create different types of DBPs. With the introduction of personal water treatment filters, some of which have the capability to remove THMs, researchers must be aware of these practices and account for them accordingly. As new techniques of water treatment and filtration are introduced, more uncertainty is created in the exposure estimate.

More information regarding the risk of pancreatic cancer associated with exposure to CDBPs is needed. Specifically, pancreatic cancer risks associated with specific DBPs

(e.g. HAAs, HANs, MX etc.) are needed. Exposure assessment based on chlorinated and non-chlorination of drinking water is inadequate. The existence of a dose response relationship, either linear or threshold, remains to be clarified. Future studies should also explore the potential use of water billing records as another approach to assess exposure.

Conclusion

The results presented in this dissertation support the overall observation that long-term exposure to THM, BDCM, and TCM is not associated with increased risk of pancreatic cancer. However, uncertainties related to exposure measurement error may have precluded the finding of a significant association.

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Appendix A - National Enhanced Cancer Surveillance System Questionnaire

Health Canada Santé Canada

Environmental Health Survey

(Confidential when completed)

ID Number
First name/Middle name/Last name
Mailing Address: Street and Number/P.O. Box No.
Town/Province
Postal Code

This form asks a variety of questions about you and your environment, which may affect or be related to your health. The information you provide will help Canadians to understand more about preventing disease.

Please complete each question as best you can even if you are not sure of your answer.

You do not need to fill in the entire questionnaire all at once. You may wish to take a brief rest in the middle.

If you have any questions about the survey or would like help filling it out, please call

_____

at _____ .

Please return this questionnaire by

Guide to filling in this Questionnaire:

Please choose answers by:
completely filling in the circle; ○ → ●

writing in the boxes; ☐ → 37

or filling in the blank spaces provided. *April*

☐ **Si vous préférez répondre en français, veuillez cocher la case et renvoyer le questionnaire dans l'enveloppe adressée ci-jointe.**

GENERAL INFORMATION

1. Today's date _____ (*Month*) / ☐☐ (*Day*) / 19☐☐ (*Year*)

2. **Is anyone helping you** (the person whose name appears on the front of the questionnaire) to complete this questionnaire?
   - o No
   - o Yes → o Spouse
   - o Other -- Please specify: _____

3. When were you born?
   _____ (*Month*) / ☐☐ (*Day*) / 19☐☐ (*Year*)

4. Are you
   - o Female
   - o Male

5. To which **ethnic or cultural group(s)** did **your ancestors** belong?

   Mark or specify as many as applicable.

   - o French
   - o English
   - o German
   - o Scottish
   - o Italian
   - o Irish
   - o Ukrainian
   - o Chinese
   - o Dutch
   - o Jewish
   - o Polish
   - o Black
   - o Aboriginal
   - o Métis
   - o Inuit
   - o Other ethnic or cultural group(s) -- Please specify: _____

   Examples of other ethnic or cultural groups are: Portuguese, Greek, Indian, Pakistani, Vietnamese, Japanese, Lebanese, Haitian, etc.

6. What is your **marital status**?
   - o Single
   - o Married
   - o Common law
   - o Widowed
   - o Divorced/Separated
   - o Other

7. What is the **highest grade** (or year) of high school or elementary school that you have completed?
   Grade ☐☐ o Never attended school

8. How many **years of post-secondary** school have you completed?
   ☐☐ years o none

☐☐☐☐☐☐☐

9. Have you smoked **at least 100 cigarettes** in your entire life?
   - o No → Go to 10
   - o Yes

   About how old were you when you **first started** smoking cigarettes? ☐☐ years old

   About **how many years** in total did you smoke ? ☐☐ years

   Of the entire time you smoked, how many **cigarettes**, on the average, did you smoke **per day**? ☐☐ per day

   Do you smoke cigarettes now?

   - o No → How old were you when you **stopped** smoking? ☐☐ years old
   - o Yes → On the average, about how many **cigarettes a day** do you smoke now? ☐☐ per day

10. Have you ever smoked a **pipe or cigars** regularly?
    - o No → Go to 11
    - o Yes

    For how many years? ☐☐ years
    About how many pipes or cigars? ☐☐ per day or ☐☐ per week

11. Have you ever used **chewing tobacco** regularly?
    - o No → Go to 12
    - o Yes

    For how many years? ☐☐ years
    About how many plugs? ☐☐ per day or ☐☐ per week

12. How **tall** are you?
    ☐ feet ☐☐ inches or ☐☐☐ centimetres

13. How much did you **weigh** about 2 years ago?
    ☐☐☐ pounds or ☐☐☐ kilograms

14. What is the **most you have ever weighed**? (Women should not include pregnancy.)
    ☐☐☐ pounds or ☐☐☐ kilograms

RESIDENTIAL HISTORY

15. Please list each of the places in **Canada** you have lived for at least 1 year. Start with the most recent residence and follow back to your childhood. (If you cannot remember exact details, provide your best recollection, for example, nearest cross-street or intersection.)

	TIME PERIOD	ADDRESS			
	First Year *Last Year*	Street and Number or Lot, Concession and Township **(If you don't remember the exact address, give the nearest cross-street or intersection.)**	City, Town, or Municipality	County or District, if rural	Province
	Example: 19 8 9 to 19 9 3	*97 Greargate Rd.*	*Brandon*		*Manitoba*
1	19 to 19				
2	19 to 19				
3	19 to 19				
4	19 to 19				
5	19 to 19				
6	19 to 19				
7	19 to 19				
8	19 to 19				
9	19 to 19				
10	19 to 19				
11	19 to 19				
12	19 to 19				

ADDRESS Postal Code	Main source of drinking water Town/city water / Dug well / Drilled well / Bottled / Other / Don't know	Primary types of home heating (Mark those which apply.) Oil / Natural gas/propane / Electric / Wood / Coal / Other / Don't know	Were you aware of dusts or odours from industry while living at this residence? Never / At least once a month / At least once a week / At least once a day	How many regular smokers usually lived in this home with you? None / 1 / 2 / 3 or more / Don't know
R7A 8A7	● ○ ○ ○ ○ ○	○ ○ ● ○ ○ ○ ○	○ ○ ● ○	○ ○ ○ ● ○
	○ ○ ○ ○ ○ ○	○ ○ ○ ○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
	○ ○ ○ ○ ○ ○	○ ○ ○ ○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
	○ ○ ○ ○ ○ ○	○ ○ ○ ○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
	○ ○ ○ ○ ○ ○	○ ○ ○ ○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
	○ ○ ○ ○ ○ ○	○ ○ ○ ○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
	○ ○ ○ ○ ○ ○	○ ○ ○ ○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
	○ ○ ○ ○ ○ ○	○ ○ ○ ○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
	○ ○ ○ ○ ○ ○	○ ○ ○ ○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
	○ ○ ○ ○ ○ ○	○ ○ ○ ○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
	○ ○ ○ ○ ○ ○	○ ○ ○ ○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
	○ ○ ○ ○ ○ ○	○ ○ ○ ○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
	○ ○ ○ ○ ○ ○	○ ○ ○ ○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○

EMPLOYMENT HISTORY

16. Please tell us about **each job you had for at least 12 months in Canada or elsewhere.** Include seasonal work, part-time, etc., if you worked the equivalent of 12 months or more. Begin with your most recent job and continue back to your first job. Please estimate the time period if you cannot remember exact years. (Even if you have retired, we still require the information.)
If you have never been employed, check here ☐ and continue to Question 17.

	TIME PEROID *First Year* *Last Year*	Type of Industry, Business, or Service and Company Name	Main Job Duties
	Example: 19 8.9 to 19 9.3	*Oil industry, Bluestar Oil Company*	*Process powerhouse and sulphur plant operations.*
1	19 ☐☐ to 19 ☐☐		
2	19 ☐☐ to 19 ☐☐		
3	19 ☐☐ to 19 ☐☐		
4	19 ☐☐ to 19 ☐☐		
5	19 ☐☐ to 19 ☐☐		
6	19 ☐☐ to 19 ☐☐		
7	19 ☐☐ to 19 ☐☐		
8	19 ☐☐ to 19 ☐☐		
9	19 ☐☐ to 19 ☐☐		
10	19 ☐☐ to 19 ☐☐		

Job Location(s) *City/town and province*	Job Title	Status Full time / Part time / Seasonal / Other	At this work-place, were you aware of **dusts or odours** from industry? Never / At least once a month / At least once a week / At least once a day	About how many people **smoked regularly** in your **immediate work area?** None / 1 or 2 / 3 to 5 / 6 or more / Don't know
Rocky Mountain House, Alberta	*Gas plant operator*	● ○ ○ ○	○ ○ ○ ●	○ ○ ○ ● ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○
		○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ○

17. Have you ever worked with any of the following **for more than one year?**

	Never	Don't know	At work	At home	How many years in total?
Asbestos	○	○	○	○	
Arsenic salts	○	○	○	○	
Chromium salts	○	○	○	○	
Cadmium salts	○	○	○	○	
Coal tar, soot, pitch, creosote, asphalt	○	○	○	○	
Mineral, cutting or lubricating oil	○	○	○	○	
Benzidine	○	○	○	○	
Benzene	○	○	○	○	
Isopropyl oil	○	○	○	○	
Dyestuffs	○	○	○	○	
Vinyl chloride	○	○	○	○	
Pesticides	○	○	○	○	
Herbicides	○	○	○	○	
Mustard gas	○	○	○	○	
Radiation sources	○	○	○	○	
Welding	○	○	○	○	
Wood dust	○	○	○	○	

You are more than halfway through the questionnaire. This is a good place to take a short break, if you wish.

DIET INFORMATION

18. During the past 20 years have you ever taken any of the following vitamin or mineral supplements?

Vitamin and Mineral type	How often?			For how many years in total?					
	No	Yes, but not regularly	Yes, fairly regularly	Less than 1 year	1 to 2 years	3 to 5 years	6 to 9 years	10 to 19 years	20 + years
Multiple vitamins	○	○	○	○	○	○	○	○	○
Vitamin A	○	○	○	○	○	○	○	○	○
Beta-carotene	○	○	○	○	○	○	○	○	○
B-complex vitamins	○	○	○	○	○	○	○	○	○
Vitamin C	○	○	○	○	○	○	○	○	○
Vitamin E	○	○	○	○	○	○	○	○	○
Calcium	○	○	○	○	○	○	○	○	○
Iron	○	○	○	○	○	○	○	○	○
Zinc	○	○	○	○	○	○	○	○	○
Selenium	○	○	○	○	○	○	○	○	○

19. This section asks about your eating habits **about two years ago.** We ask you to mark the column th. best describes how often you ate or drank each of the following foods and beverages at that time.

	Never or less than 1 per month	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day
BEVERAGES MADE WITH WATER									
Coffee (1 cup)	o	o	o	o	o	o	o	o	o
Tea (1 cup)	o	o	o	o	o	o	o	o	o
Orange or grapefruit juice from frozen concentrate (4 oz/115 ml glass)	o	o	o	o	o	o	o	o	o
Other juices or drinks from frozen concentrate (4 oz/115 ml glass)	o	o	o	o	o	o	o	o	o
Drinks from powdered drink crystals (4 oz/115 ml glass)	o	o	o	o	o	o	o	o	o
Tap water (8 oz/230 ml glass)	o	o	o	o	o	o	o	o	o
Bottled water (8 oz/230 ml glass)	o	o	o	o	o	o	o	o	o
OTHER BEVERAGES									
Whole milk (8 oz/230 ml glass)	o	o	o	o	o	o	o	o	o
2% milk (8 oz/230 ml glass)	o	o	o	o	o	o	o	o	o
1% milk (8 oz/230 ml glass)	o	o	o	o	o	o	o	o	o
Skim milk (8 oz/230 ml glass)	o	o	o	o	o	o	o	o	o
Orange or grapefruit juice, fresh, bottled or canned (4 oz/115 ml glass)	o	o	o	o	o	o	o	o	o
Other juices or drinks, fresh, bottled or canned (4 oz/115 ml glass)	o	o	o	o	o	o	o	o	o
Tomato or vegetable juices (4 oz/115 ml glass)	o	o	o	o	o	o	o	o	o
Soft drinks (1 glass/bottle/can)	o	o	o	o	o	o	o	o	o
Beer (1 bottle/can)	o	o	o	o	o	o	o	o	o
Wine (1 glass)	o	o	o	o	o	o	o	o	o
Liquor (1 drink or shot)	o	o	o	o	o	o	o	o	o

(continued)

19. (continued) Please mark the column that best describes how often, on average, you ate these foods **about two years ago.**

	Never or less than 1 per month	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6 + per day
FRUIT									
Apples or pears (1)	O	O	O	O	O	O	O	O	O
Oranges (1)	O	O	O	O	O	O	O	O	O
Bananas (1)	O	O	O	O	O	O	O	O	O
Cantaloupe (¼ melon)	O	O	O	O	O	O	O	O	O
Other fruit, fresh or canned (1 piece or ½ cup)	O	O	O	O	O	O	O	O	O
VEGETABLES									
Tomatoes (1 or ½ cup)	O	O	O	O	O	O	O	O	O
Carrots (1 whole or ½ cup)	O	O	O	O	O	O	O	O	O
Broccoli (½ cup)	O	O	O	O	O	O	O	O	O
Cabbage, cauliflower, brussels sprouts (½ cup)	O	O	O	O	O	O	O	O	O
Spinach or other greens (1 serving)	O	O	O	O	O	O	O	O	O
Yellow (winter) squash (½ cup)	O	O	O	O	O	O	O	O	O
Any other vegetable including green beans, corn and peas (½ cup)	O	O	O	O	O	O	O	O	O
Soups with vegetables (1 cup)	O	O	O	O	O	O	O	O	O
Potatoes: baked, boiled (1) or mashed (1 cup)	O	O	O	O	O	O	O	O	O
French fries or fried potatoes (½ cup)	O	O	O	O	O	O	O	O	O
Sweet potatoes (1 or ½ cup)	O	O	O	O	O	O	O	O	O
Tofu or soybeans (3-4 oz/115 ml)	O	O	O	O	O	O	O	O	O
Baked beans or lentils (½ cup)	O	O	O	O	O	O	O	O	O
BREADS AND CEREALS									
Bran or granola cereals, shredded wheat (1 cup)	O	O	O	O	O	O	O	O	O
Other cold cereals (1 cup)	O	O	O	O	O	O	O	O	O
Cooked cereals (1 cup)	O	O	O	O	O	O	O	O	O
White bread (1 slice) or rolls (1)	O	O	O	O	O	O	O	O	O
Dark or whole grain bread (1 slice) or rolls (1)	O	O	O	O	O	O	O	O	O
Rice (1 cup)	O	O	O	O	O	O	O	O	O
Macaroni, spaghetti or noodles (1 cup)	O	O	O	O	O	O	O	O	O

(continued)

19. (continued) Please mark the column that best describes how often, on average, you ate these foods **about two years ago.**

	Never or less than 1 per month	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6 + per day
MEAT, POULTRY, FISH, EGGS & CHEESE									
Chicken or turkey (4 oz/115 ml)	o	o	o	o	o	o	o	o	o
Beef, pork or lamb as a main dish (steak, roast, ham) (4 oz/115 ml)	o	o	o	o	o	o	o	o	o
Beef, pork or lamb as a mixed dish (stew or casserole, pasta dish) (4 oz/115 ml)	o	o	o	o	o	o	o	o	o
Hamburger (1)	o	o	o	o	o	o	o	o	o
Hot dogs (1)	o	o	o	o	o	o	o	o	o
Luncheon meats (salami, bologna) (1 piece or slice)	o	o	o	o	o	o	o	o	o
Smoked meat or corned beef (1 piece or slice)	o	o	o	o	o	o	o	o	o
Bacon (1 slice)	o	o	o	o	o	o	o	o	o
Sausage (1)	o	o	o	o	o	o	o	o	o
Liver (4 oz/115 ml)	o	o	o	o	o	o	o	o	o
Fish, fresh, frozen or canned (4 oz/115 ml)	o	o	o	o	o	o	o	o	o
Fish, smoked, salted or dried (4 oz/115 ml)	o	o	o	o	o	o	o	o	o
Eggs (1)	o	o	o	o	o	o	o	o	o
Cheese other than cottage cheese (1 slice or 1 oz)	o	o	o	o	o	o	o	o	o
SWEETS									
Cake (1 slice)	o	o	o	o	o	o	o	o	o
Cookies (1)	o	o	o	o	o	o	o	o	o
Doughnuts, pastry (1)	o	o	o	o	o	o	o	o	o
Pies (1 slice)	o	o	o	o	o	o	o	o	o
Ice cream (½ cup)	o	o	o	o	o	o	o	o	o
Chocolate (1 small bar or 1 oz)	o	o	o	o	o	o	o	o	o
MISCELLANEOUS									
Potato chips (small bag or 45g)	o	o	o	o	o	o	o	o	o
Peanut butter (1 tbsp)	o	o	o	o	o	o	o	o	o
Nuts (1 oz/30g)	o	o	o	o	o	o	o	o	o
Margarine on bread or vegetables (1 pat or tsp)	o	o	o	o	o	o	o	o	o
Butter on bread or vegetables (1 pat or tsp)	o	o	o	o	o	o	o	o	o
Mayonnaise or salad dressing on bread or in salads (1 tbsp)	o	o	o	o	o	o	o	o	o

20. About two years ago:

	Seldom or Never	Sometimes	Often or Always
How often did you **add salt** to your food?	o	o	o
How often did you **add pepper** to your food?	o	o	o
How often did you have **onions or garlic** in your food?	o	o	o
How often did you **eat the skin on chicken**?	o	o	o
How often did you **eat the fat on meat**?	o	o	o

21. What kinds of **fat** did **you usually use** in cooking about 2 years ago?
Mark only 1 or 2.

- o Block or stick margarine
- o Soft tub margarine
- o Low-calorie margarine
- o Shortening
- o Butter
- o Oil
- o Lard, baconfat, fatback
- o Non-stick spray or no fat
- o Don't know or don't cook

22. What kinds of **fat** did **you usually put** on bread, potatoes and vegetables about 2 years ago?
Mark only 1 or 2.

- o Block or stick margarine
- o Soft tub margarine
- o Low-calorie margarine
- o Butter
- o Cream cheese
- o Didn't add fat

23. Summary Questions

About 2 years ago:

	Never or less than 1 per month	Less than 1 per week	1 to 2 per week	3 to 4 per week	5 to 6 per week	1 per day	1½ per day	2 per day	3 per day	4 + per day
How often did you use **fat or oil in cooking**?	o	o	o	o	o	o	o	o	o	o
Not counting salad or potatoes, **how many servings of vegetables** did you eat?	o	o	o	o	o	o	o	o	o	o
Not counting juices, how many **servings of fruit** did you eat?	o	o	o	o	o	o	o	o	o	o
How often did you eat **fried food** from a **restaurant or take-out**? (for example, french fries, fried chicken, fried fish)	o	o	o	o	o	o	o	o	o	o

24. We have a few questions about your **usual eating habits 20 years ago**. What you have just told us about the different places you have lived and worked might help in remembering back to your eating habits at that time.

For each of the following foods and beverages, please indicate **whether you usually ate or drank more or less 20 years ago** than you did about 2 years ago. Please mark the appropriate column for each food or beverage.

Compared to 2 years ago, 20 years ago I used to consume:	Much less	Some-what less	About the same amount	Some-what more	Much more
Beef, pork or lamb	o	o	o	o	o
Chicken or fish	o	o	o	o	o
Milk	o	o	o	o	o
Vegetables	o	o	o	o	o
Fruit	o	o	o	o	o
Bread	o	o	o	o	o
Margarine	o	o	o	o	o
Butter	o	o	o	o	o
Fried foods	o	o	o	o	o
Sweets	o	o	o	o	o
Tea	o	o	o	o	o
Coffee	o	o	o	o	o
Soft Drinks	o	o	o	o	o
Alcohol	o	o	o	o	o

25. About **how many times** have you gone on a **diet to lose weight** during your adult life?

- o Never
- o 1 to 2 times
- o 3 to 5 times
- o 6 to 8 times
- o 9 to 11 times
- o 12 or more times

PHYSICAL ACTIVITY

26. About 2 years ago, how often did you do the following activities, on average?

	Which seasons?					How often?					Time per session			
	Never	Spring	Summer	Fall	Winter	Less than 1 per month	1-3 per month	1-2 per week	3-6 per week	Every day	Less than 15 minutes	15-30 minutes	31-60 minutes	60+ minutes
Walking for exercise	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Jogging or running	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Gardening or yard work	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Home exercises or exercise class	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Golf	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Tennis or squash	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Bowling or curling	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Swimming or water exercises	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Skiing or skating	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Bicycling	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Social dancing	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Other strenuous exercise	o	o	o	o	o	o	o	o	o	o	o	o	o	o

OTHER GENERAL INFORMATION

27. What was the **approximate total income for all household members** from all sources, **before income taxes**, in an average year during the last 5 years?

- o less than $10,000
- o $10,000 - $19,999
- o $20,000 - $29,999
- o $30,000 - $49,999
- o $50,000 - $99,999
- o greater than $100,000
- o prefer not to answer

28. How many members are there in your household in total?

[ ] persons

WOMEN:
Please continue to the next page.

MEN:
You have now completed the questionnaire.

Please take a moment to fill in any questions you may have missed.

THANK YOU VERY MUCH
for taking the time to fill out this questionnaire. Your participation is sincerely appreciated.

Please return this completed questionnaire in the self-addressed envelope.

QUESTIONS FOR FEMALES ONLY

MENSTRUATION

29. How old were you when you had your first menstrual period?

    ☐ years old
    o Don't remember
    o Haven't menstruated → Go to 33

30. Between the ages of 10 and 30, did your menstrual periods tend to occur regularly or irregularly (menstrual cycles varied by more than 10 days in length)? Please exclude any time when you were pregnant or using birth control pills.

    o Regularly o Irregularly

31. **How old** were you when you had your **last menstrual period**?

    ☐ years old
    o Still menstruate → Go to 33

32. How did your **menstrual periods stop?**
    o Naturally--that is, as part of the change of life
    o As a result of a hysterectomy (removal of womb)
    o Following radiation
    o Other -- Please specify:

    _____

33. Have you had an operation to remove **BOTH your ovaries?**
    o No
    o Yes → At what age? If they were removed on two separate occasions, record when your second ovary was removed.
    At age ☐ years

34. Do you have **mammograms** (x-rays of the breast) performed on a **routine** basis (every two years)?
    o No
    o Yes → First mammogram at age ☐ years

PREGNANCIES

35. Have you ever been pregnant?
    o No → Go to bottom of page.
    o Yes

36. **How many times have you been pregnant?** Include live births, stillbirths, miscarriages, abortions and ectopic (tubal) pregnancies.
    ☐ times

37. How old were you at the end of your first **pregnancy**?

    ☐ years old

38. How many **of your pregnancies** were live births?
    ☐ live births o none

39. How old were you at the end of your first pregnancy which lasted 5 months or more?
    ☐ years old

40. For how many **months** in total did you **breastfeed**? (Add the number of months that you breastfed after each birth to give the total number of months.)
    ☐ months o never breastfed

Please take a moment to fill in any questions you may have missed.

THANK YOU VERY MUCH for taking the time to fill out this questionnaire. Your participation is sincerely appreciated.

Please return this completed questionnaire in the self-addressed envelope.

Appendix B – Proxy Subjects

Table 34: **Estimated risk of pancreatic cancer and exposure to DBPs with 30-year exposure time window, Environmental Health Directorate 1993 water quality data.**

- ***Proxies included vs non-Proxy only***
- ***At least 20 year of exposure information***

DBPs[c] (ug/L)	Proxies Included				Proxies Excluded			
	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value	No. of Cases (%)	No. of Controls (%)	OR [a] (95% CI)	Type III X^2 *P* value
THM								
< 10	139 (33)	933 (32)	1.00*	0.331	112 (34)	933 (32)	1.00*	0.206
10 – 20	112 (27)	896 (31)	0.95 (0.72-1.25)		72 (22)	896 (31)	0.83 (0.60-1.14)	
20 – 50	121 (29)	721 (25)	1.16 (0.89-1.52)		98 (30)	721 (25)	1.16 (0.86-1.57)	
> 50	47 (11)	355 (12)	0.86 (0.60-1.24)		46 (14)	355 (12)	0.99 (0.68-1.45)	
n	419	2905			328	2903		

* Referent group.

[a] Adjusted for sex, age, province of recruitment, BMI, percent weight change, education, smoking, coffee, beer, liquor, total fat and energy intake.

[c] Average THM were based on an arithmetic mean of 30 years of available and imputed exposure information from date of interview.