Human Health Risks of Persistent Organic Pollutant Exposures in the Canadian Arctic

by

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Dedication

I am fortunate to have the two strongest pillars and, at the same time, the two softest cushions, by my side. I always know where to fall. I am grateful for their support these past four years, which helped me to accomplish my long time wish to do research in an environmental field. And I thank them for putting up with me for all these years.

This one is dedicated to you, Mom and Dad.

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Abstract

The persistent organic pollutants (POPs) refer to many different chemicals that, upon release into the environment, remain intact for several decades. These contaminants travel long distances through repeated cycles of deposition and evaporation, and eventually deposit in the Arctic regions. The purpose of this work was to examine the potential human health implications of POP exposures among the Canadian Inuit, using modelling and epidemiological approaches. Blood guideline values were developed for the organochlorine pesticides, chlordane and toxaphene, and the polychlorinated biphenyls (PCBs) using the concept of biomonitoring equivalents (BEs), which are based on toxicity endpoints and toxicokinetic modelling to convert an oral reference dose to an equivalent blood concentration. The biomonitoring data from the Adult Inuit Health Survey (2007-2008) and the Canadian Health Measures Survey (CHMS, Cycle 1 2007-2009) were compared with the derived guideline values to assess population-level risks of exposures for the Inuit and the general Canadian population, respectively. Epidemiological analyses were also conducted to explore if POPs were associated with diabetes and high cholesterol, using data from the Inuit Health Survey. A set of BE values were derived for chlordane isomers and metabolite, three abundant toxaphene isomers, and the PCBs. The derived values are in a similar range of the BEs of other POPs in the literature. Among the Inuit, a large percentage exceeded the trans-nonachlor guideline value, particularly among the elderly. Fewer exceedances were observed for cis-nonachlor and oxychlordane, none for toxaphene, and minimally for the PCBs. In comparison, no exceedances for any of the POPs were observed in the general Canadian population. Highest vs. lowest quartile exposures to PCBs and p,p'-DDE were associated with increased risk of diabetes and an increase in fasting glucose among the Inuit. In addition, PCBs were associated with increased risk of high cholesterol, and higher levels of serum triglycerides, total cholesterol, and low-density lipoprotein cholesterol (LDL-C), but not high-density lipoprotein cholesterol (HDL-C). The results of this work suggest that exposures to POPs remain a potential health concern among the Canadian Inuit. Future research efforts should be devoted to collecting updated contaminant concentrations for the Inuit, measuring contaminants in prepared food samples, conducting cohort studies on contaminant exposures and health outcomes, and assessing the effects of chemical mixtures using statistical approaches and toxicokinetic modelling.

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Commonly Used Abbreviations

AFSSA = Agence Francaise de Sécurité Sanitaire des Aliments

Ah = aryl hydrocarbon

AMAP = Arctic Monitoring and Assessment Program

ATSDR = Agency for Toxic Substances and Disease Registry

AUC = area under the curve

BE = biomonitoring equivalent

BMI = body mass index

BW = body weight

BWF = body weight fat

CHMS = Canadian Health Measures Survey

CI = confidence interval

DDE = dichlorodiphenyldichloroethylene

DDT = dichlorodiphenyltrichloroethane

DL-PCB = dioxin-like polychlorinated biphenyl

EPA = Environmental Protection Agency

GM = geometric mean

HCB = hexachlorobenzene

HDL-C = high-density lipoprotein cholesterol

HQ = hazard quotient

IHS = Inuit Health Survey

ISR = Inuvialuit Settlement Region

IV = intravenous

JECFA = Joint FAO/WHO Expert Committee on Food Additives

JMPR = Joint FAO/WHO Meeting on Pesticide Residues

LC50 = 50% lethal concentration

LDL-C = low-density lipoprotein cholesterol

LOAEL = lowest-observed adverse effect level

LOD = limit of detection

MATT = Monitoring, Analysis, and Toxicity of Toxaphene in Marine Foodstuffs

MRL = minimum risk level

NCP = Northern Contaminants Program

NDL-PCB = non-dioxin like polychlorinated biphenyl

NOAEL = no-observed adverse effect level

OR = odds ratio

PBDE = polybrominated diphenyl ethers

PBPK/PBTK = physiologically-based pharmacokinetic/toxicokinetic

PCB = polychlorinated biphenyl

POD = point of departure

POP = persistent organic pollutant

RfD = reference dose

RR = relative risk

TCDD = tetrachlorodibenzodioxin

TDI = tolerable daily intake

TEF = toxic equivalency factor

TEQ = toxic equivalent

UF = uncertainty factor

1.0 Introduction

The Arctic region is comprised of the circumpolar land masses of Canada, the United States, Denmark (Greenland), Iceland, Norway, Sweden, Finland, and Russia. About four million people live in the Arctic, of whom a large percentage are indigenous, such as the Sami (Finland, Sweden, Norway and Russia), the Chukchi, Evenk, and Nenets (Russia), the Kalaallit Inuit (Greenland), the Inupiat (Alaska, United States), and the Inuit (Canada).[1] The Canadian Arctic encompasses 40 percent of the total Canadian land mass and is home to more than 70 percent of the 60 000 Inuit in Canada.[2] The Inuit Nunangat (homeland) in Canada, includes the Inuvialuit Settlement Region (ISR) in the Northwest Territories, Nunavut, Nunavik in Northern Quebec, and Nunatsiavut on the northern coast of Newfoundland, Labrador (Figure 1). Most Inuit reside in Nunavut (62%) and Nunavik (25%), followed by the ISR (8%), and Nunatsiavut (5%).[3]

The unique cultural traditions of the Inuit, based on close connection with the land and its wildlife, developed over hundreds to thousands of years[1] and have fostered the survival and growth of the population in the harsh conditions of the north. Modern developments, unfortunately, have presented the Inuit with formidable challenges, such as climate change and contaminants, that threaten the delicate balance of life in the Arctic. The very foundation of the Inuit homeland is disappearing, as rising temperatures melt ice and permafrost at unprecedented rates. The presence of contaminants in Arctic wildlife is adversely affecting the food supply of the Inuit, which provide essential nutrients, social cohesion, and continuation of traditions. The Inuit of Canada, and the indigenous populations of other circumpolar countries, are amidst a rapidly changing world. The Arctic Council, which is an intergovernmental forum established in 1996, encourages cooperation and coordination among the Arctic states to respond to the environmental and social effects imposed by climate change and contaminants.

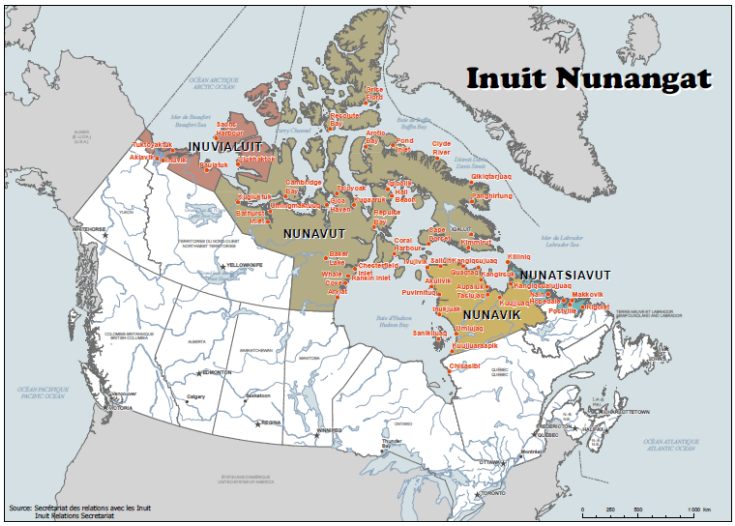

Figure 1: The Inuit Nunangat
Source: Reprinted from Government of Canada *(*www.aadnc-aandc.gc.ca/eng/1290453474688/1290453673970*)*

1.1 Persistent Organic Pollutants and the Arctic

The group of contaminants, known as persistent organic pollutants (POPs), remain in the environment for decades and biomagnify in food chains. They include the polychlorinated biphenyls (PCBs); organochlorine pesticides, such as chlordane, toxaphene, hexachlorobenzene (HCB), and dichlorodiphenyltrichloroethane (DDT); the polybrominated diphenyl ethers (PBDEs); perfluorinated compounds such as perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS); and unintentional by-products of combustion such as dioxins and furans. The Inuit are especially vulnerable to POP exposure through the consumption of high trophic level marine mammals, which accumulate high concentrations of lipophilic contaminants in blubber.[4] In the Arctic, POPs arrive from local or, more commonly, from distant sources.[5] Local sources include mining, oil and gas production sites, landfills, and abandoned distant early warning line radar stations.[5,6] Long-range transport from southern latitudes occurs through the atmosphere, water currents, and sea-ice drift through repeated deposition and evaporation, in a process known as the "grasshopper effect".[5] The Arctic thus acts as a sink for contaminants that were released from point sources hundreds to thousands of kilometers distant.[7]

1.1.1 A Surprise Finding: POPs in the Arctic

The Arctic is often viewed as a pristine environment, far separated from the pollution and contamination resulting from industrial activities. It came as a surprise when high levels of contaminants were detected in the breast milk and blood of Inuit and other indigenous peoples of Canada's North in the 1980s.[7] The initial identification of contaminants in the Arctic occurred through a survey in Quebec to monitor chlorinated organic compounds in breast milk.[7] Samples from Puvignirtuk, Nunavik were collected as a blank control however, contrary to expectations, these samples were found to contain many different organochlorine chemicals at high concentrations. Subsequently, several research studies have been conducted to monitor contaminants in the Arctic environment, biota, and human beings. The Arctic Monitoring and Assessment Program (AMAP), which was established in 1991 as a working group of the Arctic Council, collects long-term scientifically validated data on the transport, transformation, and distribution of contaminants in the Arctic atmosphere.[8] The Northern Contaminants Program (NCP) was also established in 1991 by the Government of Canada to provide information about contaminants in traditional foods.[9]

1.1.2 Arctic Air and Biota

The AMAP has provided long-term trends of POPs in the Arctic atmosphere, collected from four air monitoring stations located in Alert (Ellesmere Island, Canada), Stórhöfði (Iceland), Zeppelin (Svalbard, Norway), and Pallas (Finland). The following information comes from the most recent AMAP 2015 report, which provides POP trends in Arctic air and biota from 1993 - 2012.[10] At Alert, Ellesmere Island, declines in air concentrations have been observed for several POPs, including chlordanes, heptachlor epoxide, HCB, and PCBs. The concentration of DDT has remained constant at Alert, whereas Zeppelin, Svalbard is the only station at which all

isomers of DDT have been decreasing. No trend was observed in concentrations of PBDE-47 and PBDE-99 at Alert, whereas at the other European stations, concentrations decreased and were lower than the Canadian site. The higher PBDE concentrations in Canada are likely due to a nearby military base and the higher usage of these compounds in North America compared with Europe.[10] Toxaphene is monitored routinely only at Stórhöfði, Iceland, and this station has found a continuous decline in the concentrations of Parlars 26 and 50 since 2004 (13% annual decline, 2000-2012). In Arctic biota, decreases have been observed for trans-nonachlor, (0.6% annually since 2000), trans-chlordane (6.8%), DDT (2.4%), DDE (3.6%), PCBs (2.5% for PCB-153), and toxaphene (5.9% Parlar 26 and 0.8% Parlar 50). Decreases have also been observed for PBDE-47 and PBDE-99, although there was an increase in one time-series of PBDE-99 in ringed seal from Canada since 2000. Hexachlorobenzene underwent no average change in biota from all time-series since 2000, and increased in three time-series from Greenland, which reflects its continual release into the environment as a by-product of chlorinated chemicals and incomplete combustion processes.[10] The highest concentrations of chlordanes, DDT, PCBs, PBDEs, and toxaphene have been detected in pilot whales of the Faroe Islands. Polar bears of Greenland also have high concentrations of chlordanes, PCBs, and PFOS, whereas beluga whales in Canada have high concentration of DDT.

1.1.3 Human Populations of the Arctic

In the Canadian North, major human biomonitoring studies have taken place in Nunavik (Nunavik Inuit Health Survey, 2004 and Nunavik Child Development Study) and in the ISR, Nunavut, and Nunatsiavut (Inuit Health Survey, 2007-2008). In the Nunavik Inuit Health Survey, blood samples were collected from 925 Inuit adults across 14 coastal villages and provided data on blood contaminant levels, which were originally collected in a 1992 survey by Santé

Québec.[11] An updated survey in Nunavik, the Qanuilirpitaa 2017, is currently underway and will provide more recent data on exposures.[12] The Nunavik Child Development Study was a prospective biomonitoring study of mother-child pairs to examine the effects of pre- and postnatal exposure to organochlorines, lead, and mercury.[13] In the International Polar Year Inuit Health Survey for Adults 2007-2008, clinical parameters and blood concentrations of contaminants were collected from 2 595 Inuit participants across 33 coastal and three inland communities in the ISR, Nunavut, and Nunatsiavut.[14] The survey was cross-sectional in design and included adults 18 years of age or older, with the exclusion of pregnant women.

The concentrations of POPs have generally been found to be highest among Inuit from Nunavik, followed by Nunavut, and lowest among Inuit from Nunatsiavut, due to differences in patterns of traditional food consumption.[13] In time-series data, available from Nunavik and Baffin (Nunavut), the concentrations of many POPs have decreased.[13] Among pregnant Inuit women in Nunavik, blood concentrations of POPs are available over a 20-year time period from 1992 to 2013. Persistent organic pollutants have declined by an average of 80% and trans-nonachlor, specifically, by 64% over these two decades.[13] Between 2004 and 2012, toxaphene, PBDE-47, PFOS, and pentachlorophenol (PCP) decreased approximately by a factor of 2, whereas PBDE-153 slightly increased (geometric mean: 2.0 μg/kg plasma lipid in 2004 to 2.9 μg/kg plasma lipid in 2012). Laird et al. (2013) compared contaminant levels among Inuit from the Inuit Health Survey with levels among general Canadians from the Canadian Health Measures Survey (CHMS).[15] Toxaphene (sum of Parlars No. 26 and 50), total PCBs (sum of 14 congeners), cadmium, and lead were 17, 4, 3.7, and 2-fold higher in Inuit, respectively, compared with general Canadians. In particular, among elderly Inuit 61 years of age and older, chlordane (sum of cis-nonachlor, trans-nonachlor, and oxychlordane) was 32-fold and total DDT

(sum of p,p'-DDE and p,p'-DDT) 3.3-fold higher than general Canadians of the same age range.

Biomonitoring surveys have also taken place in other Arctic countries, such as the MISA mother and child contaminant cohort in Norway; the Tromso study in Norway to characterize POP exposures; the Chukotka cross-sectional study of POP exposures in Russia; and the INUENDO cohort from Greenland, Poland, and Ukraine to examine the effects of organochlorines on fertility. Among all Arctic regions, the Greenland population is the most highly exposed to POPs, and has the highest concentrations of trans-nonachlor, p,p'-DDE, PCB-153, HCB, and PFOS.[13] The concentrations of PBDEs, however, are lower in Greenland and highest in mothers from Alaska (PBDE-47 and PBDE-99).[13] In the Russian North, contaminant levels were measured in blood of indigenous populations and overall concentrations were similar to those of coastal Greenland or northern Canada.[16] When compared on the international scale, Canadian Inuit have the second highest concentration of p,p'-DDE (Nunavik) and lower concentrations of PCB-153 (ISR and Nunatsiavut) and PFOA/PFOS (Nunavik).[13]

1.2 The Global Response to Persistent Organic Pollutants

The global community has recognized the importance of regulating POPs to protect the environment and human health. Although POPs continue to be detected around the world, due to their persistence, long-range atmospheric transport, and bioaccumulative potential, the global action that started in the late 1980s played a critical role in preventing further escalation of POP concentrations. The effectiveness of these efforts is evident by the declining POP concentrations observed in Arctic air, biota, and human populations.

1.2.1 The Aarhus Protocol

The first international cooperative action aimed at eliminating these substances was the Aarhus Protocol on Persistent Organic Pollutants, which was adopted in June 1998 in Aarhus,

Denmark and entered into force in 2003, with currently 29 parties.[17] The Aarhus Protocol was an addition to the Convention on Long-Range Transboundary Air Pollution (CLRTAP), which was originally a regional agreement between North America, Europe, and the former Soviet Union to address acidification and eutrophication.[7] The scope of CLRTAP expanded to the international regulation of POPs in response to evidence produced by Indigenous and Northern Affairs Canada (INAC) and the Swedish Environmental Protection Agency (SEPA) of the presence of organic chemicals in the Arctic and Sweden/Baltic region, respectively.[7] The detection of POPs in remote areas made it clear that this was not an issue restricted to one country or geographical area, and that a worldwide coordinated response was needed to address the long-range, transboundary, transport of these chemicals. The Aarhus Protocol prohibits the production and use of some chemicals (e.g. chlordane and toxaphene), details proper handling of wastes, and requires reduction in the emissions of dioxins, furans, polycyclic aromatic hydrocarbons (PAHs), and HCB.[17] The original protocol covered 16 substances: aldrin, dieldrin, endrin, chlordane, chlordecone, hexabromobiphenyl, mirex, toxaphene; DDT, heptachlor, HCB, PCBs, hexachlorocyclohexane (α-HCH, β-HCH, and γ-HCH), HCB, PAHs, and dioxins/furans (polychlorinated dibenzo p-dioxins, PCDD and polychlorinated dibenzofurans, PCDF).[10,17] In 2009, this list was expanded to cover an additional seven chemicals: pentachlorobenzene, hexabromodiphenyl ether and heptabromodiphenyl ether, PFOS and perfluorooctane sulfonyl fluoride, tetrabromodiphenyl ether and pentabromodiphenyl ether, short-chained chlorinated paraffins (SCCPs), polychlorinated naphthalenes (PCNs), and hexachlorobutadiene (HCBD).[10,17]

1.2.2 The Stockholm Convention

The Stockholm Convention, under the United Nations Environment Programme (UNEP), was adopted in 2001 in Stockholm, Sweden and entered into force in 2004 as the first global

treaty "to protect human health and the environment from persistent organic pollutants".[18] There are 182 parties to the Convention, including Canada which signed and ratified in 2001.[18] Initially, 12 POPs known as the "dirty dozen", were recognized for their potential to exert adverse effects on humans and ecosystems: aldrin, dieldrin, endrin, chlordane, heptachlor, DDT, HCB, mirex, toxaphene, PCBs, PCDDs, and PCDFs.[10] Since 2004, the following 14 additional POPs have been added: chlordecone, α-HCH, β-HCH, lindane (γ-HCH), pentachlorobenzene, hexabromobiphenyl, hexabromodiphenyl ether and heptabromodiphenyl ether, PFOS and perfluorooctane sulfonyl fluoride, tetrabromodiphenyl ether and pentabromodiphenyl ether, technical endosulfan and its related isomers, hexabromocyclododecane (HBCDD), PCNs, HCBD, and PCP.[10] Another four POPs (i.e. SCCPs, decabromodiphenyl ether, dicofol, and pentadecafluorooctanoic acid and its salts) have been proposed for listing.[10] The Stockholm Convention requires that its parties eliminate the production, use, and trade of certain POPs; minimize emissions of those POPs that cannot be eliminated; and avoid production and use of new POPs.[7] The listed substances are categorized into either Annex A for elimination, Annex B for restriction, or Annex C for reduction in unintentional production.[10] For example, PCBs are listed under Annex A, which requires measures to eliminate their production and use, whereas p,p'-DDT is listed under Annex B, which restricts production but allows for continued use to control disease vectors. The dioxins (i.e. PCDD) and furans (i.e. PCDF) are listed under Annex C because they are unintentional by-products of combustion and chemical manufacture.

1.2.3 The Basel and Rotterdam Conventions

The Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal was in response to public concerns about toxic wastes that were imported from abroad into Africa and other developing countries.[19] It was adopted in 1989,

entered into force in 1992, and has 186 parties. The Basel Convention aims to reduce the generation of hazardous wastes, promote proper waste management, restrict transboundary movement of wastes, and to provide a regulatory system for ensuring that any transboundary movements that are permissible occur with consent. The Rotterdam Convention entered into force in 2004, as a legally binding treaty to govern the international trade of hazardous chemicals.[20] It includes 50 different pesticides and industrial chemicals that have been banned or severely restricted for environmental or human health considerations by at least two parties.

1.3 Risk Assessment

1.3.1 The Risk Assessment-Risk Management Paradigm

While it has been known for several decades now that POPs travel across the globe, the implications of these exposures to human health are still largely unclear. A determination of the health effects of POPs is a complex endeavor because exposures tend to occur as mixtures, rather than as single entities, and humans are simultaneously susceptible to many other risk factors of disease, such as genetic predisposition, poor diet, smoking, and lack of physical activity. Therefore, it is difficult to decipher the effects of a single chemical, or even a known mixture of chemicals, apart from all other influences on health in human populations.

Environmental health risk assessment is a systematic and scientific approach to understanding the potential adverse effects of exposures to hazardous chemicals, and has been adopted by regulatory agencies to make evidence-based decisions.[21] The risk assessment – risk management paradigm is the basis of environmental health risk assessment and was established in 1983 by the United States National Research Council, in a publication known as the *Red Book*.[22] As shown in Figure 2, the four components of the risk assessment paradigm are: hazard identification, dose-response assessment, exposure assessment, and risk characterization.[21] In

hazard identification, an attempt is made to determine if there is a cause-effect relationship between a hazard and an outcome, using *in vitro* or *in vivo* tests, bioassays, or structure-activity analyses. Dose-response assessment examines if the risk of outcome increases as exposure to the hazard increases, which provides further support of a cause-effect relationship. Exposure assessment determines if a population is exposed to the hazard and at what level. Lastly in the risk assessment paradigm, risk characterization synthesizes the information from the first three components to make conclusions about the hazard, and these conclusions are considered in making decisions about how to manage risks.

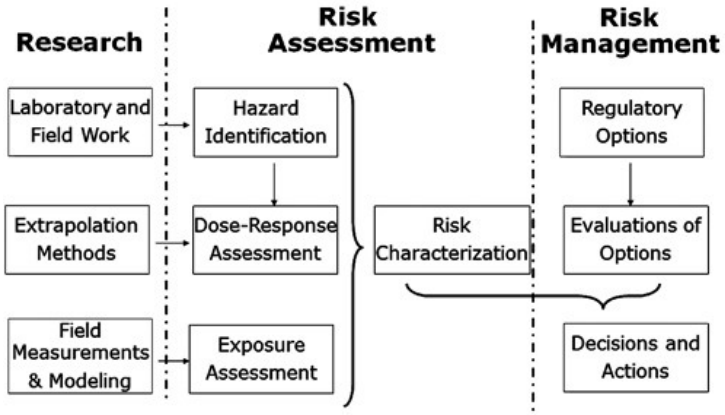

Figure 2: The risk assessment – risk management paradigm
Source: Reprinted from Sexton K. Evolution of public participation in the assessment and management of environmental health risks: a brief history of developments in the United States. Journal of Public Health Research 2013:2; p.108. Available from: www.jphres.org/index.php/jphres/article/view/jphr.2013.e18.

1.3.2 Risk Assessment in the Arctic

In the Arctic regions, data on human exposure to POPs has been extensively documented through biomonitoring surveys and, in some cases, time-series data are available, from which temporal trends can be examined, as described in Section 1.1.3. The detected POPs, such as PCBs and the organochlorine pesticides, have been recognized by the Stockholm Convention as known hazards, that have exerted toxic effects in animal models, wildlife, and human populations. The PCBs, for example, were implicated in the mass food poisonings incidents in Japan (Yusho) and Taiwan (Yu-Cheng), which affected hundreds of people and caused adverse

effects on the liver, vomiting and diarrhea, respiratory symptoms, pigmentation of nails and skin, and chloracne.[23] A description of epidemiological studies that have examined association of POPs with health outcomes in Arctic indigenous populations is provided in Chapter 6.

Studies in the Arctic have also compared human contaminant concentrations with reference values, which are threshold levels known to cause adverse outcomes. Most of these analyses have concentrated on the heavy metals, lead and methyl mercury (MeHg), for which blood reference values are available. Among participants of the Inuit Health Survey, 10.1% (highest in ISR, 12%) exceeded the Canadian lead intervention level of 100 μg/L whole blood and 23.2% (highest in Nunavut, 27.9%) exceeded the Canadian MeHg guideline of 20 μg/L whole blood.[13] For women of child-bearing age and pregnant women, the Canadian provisional MeHg guideline is 8 μg/L; in the Inuit Health Survey, 30.6% women of child-bearing age exceeded this value (highest in Nunavut, 36%) and in Nunavik 53.2% equalled or exceeded this value.[13] Laird et al. (2013) also assessed the Inuit Health Survey biomonitoring data against trigger/intervention guideline values available from Health Canada, the Centers for Disease Control, and the Occupational Safety and Health Administration.[15] The cadmium trigger guideline of 1 μg/L, corresponding to increased risk of low bone density, was exceeded by 69.5% of the sample population. Also, 27.9% women of child-bearing age exceeded the Health Canada Aroclor 1260 guideline of 5 μg/L. For other POPs, such as chlordane and toxaphene, no blood guideline values were available to assess the biomonitoring data. Hazard quotients (HQs) can be calculated by dividing the contaminant concentration in the population by the contaminant reference value to indicate the margin of exposure in the population.[13] The HQ concept can only be applied to non-cancer effects, which have a threshold and, therefore a corresponding, reference value.

1.3.3 Toxicokinetic Modelling

Toxicokinetic models mathematically describe the movement of a chemical in an organism, which is simulated as either a single compartment or as a series of compartments connected by a blood supply. Depending on the purpose of the model, it may contain only one compartment (e.g. adipose) into which a chemical is absorbed and eliminated, or it may contain several compartments (e.g. adipose, liver, kidney, brain, muscle) to fully represent the absorption, distribution, metabolism, and excretion properties of a chemical. The latter is known as a physiologically-based toxicokinetic model (PBTK) and is described by a series of differential equations that are solved by mass-balance. Although PBTK models will more accurately represent the behaviour of a chemical in the body, they require the input of several parameters, such as absorption and elimination rate constants (i.e. feces, urine), metabolic rate constant (i.e. liver), volume and blood flow to each compartment, and chemical partition-coefficients between blood and each compartment.[24] In addition, the model will be flow-limited if the transport of the chemical between blood and compartments occurs passively, or diffusion-limited if there is active transport or protein binding.[25]

Biomonitoring surveys will often collect only a cross-sectional (i.e. single-time) sample of contaminant concentrations in only one matrix (e.g. blood). Toxicokinetic modelling has been incorporated into risk assessment by extrapolating exposures to critical time periods, such as pre- and postnatally, predicting exposures over a lifetime, and determining exposures in specific compartments that are relevant to toxicity (e.g. concentrations in brain or liver). Toxicokinetic modelling can also be used to predict internal contaminant concentrations from dietary intakes (forward dosimetry), or vice versa (reverse dosimetry).[13] Greater insights into exposures can thereby be gleaned by using this modelling approach.

In Arctic populations, PBTK models have been employed to predict POP exposures from dietary intakes, to understand lactational transfer to infants, to reconstruct exposures during windows of susceptibility, and to estimate lifetime exposure.[26–29] Sonne et al. (2014) used a PBTK model to estimate concentrations of POPs (p,p'-DDE, HCB, PCB-153, PCB-99, and oxychlordane) in the liver, blood, muscle, and adipose tissue of Greenland Inuit after long-term exposure to traditional foods.[26] The model accurately predicted blood concentrations by a factor of 2 to 3 of actual measurements. Based on model predictions, blood POP concentrations increased after the consumption of meals and remained high even several years after switching to diets low in contaminant levels. The authors suggested that PBTK modelling was a useful approach for conducting human health exposure and effect estimates in Greenland Inuit.[26] Several models have been developed to understand body burdens of PCB-153, which is the most abundant of the PCB congeners. A five-compartment model, consisting of liver, fat, mammary tissue, rest of body, and blood, was used to simulate the lactational transfer of PCB-153 from mother to infant.[27] The model was applied to estimate the dietary intake of PCB-153 in Inuit mothers from Nunavik, who have the highest breast milk PCB-153 concentrations in the world, based on observed milk concentrations and reverse dosimetry. A daily PCB-153 intake rate of 0.294 μg/hg/kg b.w. produced breast milk concentrations similar to actual measurements. Verner et al. (2010) developed a PBTK model consisting of maternal and infant compartments, linked by placental and lactational transfer, to simulate PCB-153 concentrations during specific pre- and postnatal periods and to relate these concentrations to outcomes of infant behaviour.[28] PCB-153 concentrations were simulated at delivery, and month by month for the first year, among Inuit infants enrolled in a Nunavik longitudinal study. The predicted prenatal PCB-153 concentration in infants was associated with inattention, whereas postnatal concentrations were

associated with activity level, and the strongest associations were observed for PCB-153 concentration during the fourth month of life. This analysis demonstrated that the effects of PCBs may occur during critical periods of susceptibility, and this could not have been detected by examining exposures only at a single time point.[28] Abass et al. (2013) estimated human lifetime health risks of PCB-153 in Arctic indigenous populations by using a one-compartment model to simulate body burden over entire lifespan, and inputting the body burden into calculations of HQ and cancer risk.[29] For the 50th population percentile, HQ was greater than 1 during 1956-1984 and cancer risk ranged from 3.6×10^{-5} to 1.4×10^{-10} between 1930-2049.

1.3.4 Biomonitoring Equivalents

Agencies that are responsible for protecting the public against environmental hazards, such as The United States Environmental Protection Agency (EPA) and Health Canada, establish maximum recommended daily intake values for contaminants. The EPA, for example, develops reference doses (RfD) for contaminants, which is defined as the daily oral dose in human populations (including sensitive subpopulations) that is likely without risk of adverse non-cancer effects in a lifetime.[30] Similarly, the Agency for Toxic Substances and Disease Registry (ATSDR) publishes minimum risk levels (MRLs) for daily oral dose likely to be without adverse non-cancer effects, for acute (1-14 days), intermediate (15-364 days), and chronic (1 year or longer) exposures.[30] Tolerable daily intake (TDI) is another term used to denote maximum oral exposures without adverse non-cancer effects over a lifetime. These values are derived by dividing a selected no-observed adverse effect level (NOAEL), lowest-observed adverse effect level (LOAEL), or a benchmark dose (BMD) with uncertainty factors that account for considerations such as interspecies extrapolation, intraspecies variation, use of a LOAEL rather than NOAEL, and deficiencies in the experimental data.[30]

Biomonitoring equivalents (BEs) are internal concentrations of a chemical in a biological medium, such as blood, urine, or breast milk, that correspond to an external exposure guideline.[31] Biomonitoring data for a contaminant can be compared directly with a BE, given that both are in the same biological medium. Such comparisons will provide a more accurate tally of the number of people within or exceeding a guideline, than comparing with the external exposure value.[25] The BE concept can be used to screen environmental contaminants as low, medium, or high priority for further monitoring.[32] The AMAP has recognized that BEs may be a valuable tool to interpret Arctic biomonitoring data at the population level.[13]

The Biomonitoring Equivalents Expert Panel published guidelines for deriving BEs (Figure 3).[31] Toxicokinetic modelling is used to convert an external exposure guideline, such as an RfD, MRL, or TDI, to an equivalent internal dose.[31] Theoretically, it is possible to arrive at the BE by following Path 1 or Path 2 +3, as shown in Figure 3. In Path 1, the human exposure guidance value is converted directly to a BE by using human toxicokinetic parameters. No further uncertainty factors are applied in this case because the exposure guidance value has already taken these into consideration. In Path 2 + 3, the starting point is the point of departure (i.e. NOAEL, LOAEL, or BMD) from experimental animal data. A toxicokinetic model is developed for the animal model to convert the point of departure to an internal concentration, which is also in the animal (Path 2). This internal concentration is converted to a human BE by taking into consideration: (a) interspecies toxicokinetic variability (i.e. extrapolating from animal to humans) and, (b) intraspecies toxicokinetic and toxicodynamic variability (i.e. variability within human population). Interspecies variability can be accounted for by an uncertainty factor or allometric scaling, whereas intraspecies variability is described by uncertainty factors.[31]

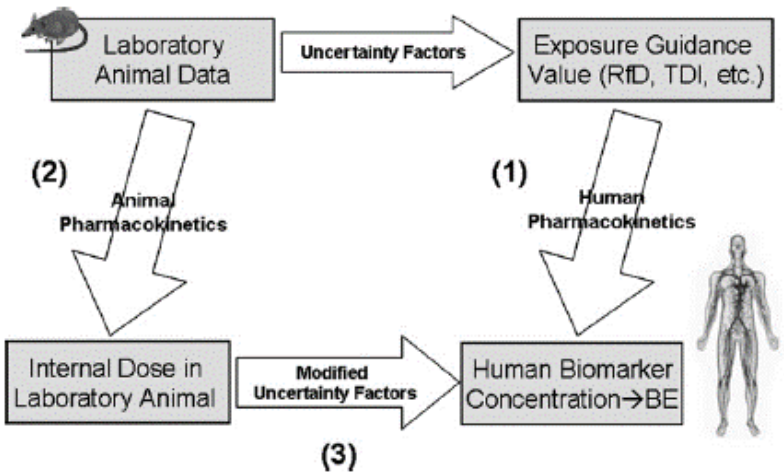

Figure 3: Derivation of BE values
Source: Reprinted from Regulatory Toxicology and Pharmacology, 51, Hays SM et al., Guidelines for the derivation of biomonitoring equivalents: report from the Biomonitoring Equivalents Expert Workshop, p.S5, Copyright (2008), with permission from Elsevier.

Biomonitoring equivalents have been developed for more than 100 compounds, including PBDE-99[33], HCB[34], and DDE/DDT[35]. The BE for PBDE-99 was based on the benchmark lower dose confidence limit (BMDL) of 0.29 mg/kg/d for neurobehavioural effects in adult female mice administered a single dose.[33] The BMDL was divided by an uncertainty factor of 30 (UF = 3 for single dose to chronic exposure and UF = 10 for interspecies extrapolation), to arrive at a point of departure in humans. This point of departure was converted to an equivalent lipid-adjusted blood concentration of 52 mg/kg lipid, using a one-compartment adipose tissue model and human toxicokinetic data. A final BE of 0.52 mg/kg lipid was calculated by dividing the 52 mg/kg value with an uncertainty factor of 100 to account for intraspecies variability (UF = 10) and database deficiencies (UF = 10). The BE derivation for the non-cancer effects of HCB started with the NOAELs and LOAELs for hepatic toxicity in rodent models.[34] Toxicokinetic data in rodents were applied to convert the NOAELs and LOAELs to concentrations in the lipid fraction of the liver, which is the relevant dose metric for toxicity.[34] This dose metric was then converted to a human value by dividing with uncertainty factors to account for use of LOAEL

rather than NOAEL, interspecies extrapolation, and intraspecies variation. Similarly, BEs for the non-cancer effects of DDT and its metabolites were derived by starting with the NOAELs for effects on rat pup growth and liver, and converting the NOAELs to lipid concentrations by using toxicokinetic data in rats.[35] The lipid concentrations were then converted to human BEs by dividing with uncertainty factors for interspecies extrapolation and intraspecies variation.[35] While there are guidelines for how to derive BEs[31], the actual process is flexible and depends on several factors, such as the relevant dose metric, the availability of toxicokinetic data, properties of the chemical under consideration (i.e. short-lived or persistent), and limitations in the experimental toxicity data. Generally, the BE derivations are not based on complicated PBTK models, as they are primarily used as a screening tool for risk assessment.[32] Therefore, it may be reasonable to make simplified assumptions about the absorption, distribution, metabolism, and excretion properties of a compound.

1.4 Thesis Objectives

The objective of this thesis project was to examine the risks of POP exposures in the Canadian Artic using modelling and epidemiological approaches. Although risk assessments have been conducted in the Nunavik region, fewer analyses are available for the ISR, Nunavut, and Nunatsiavut. The present work focussed on these three regions and on chlordane, toxaphene, and PCBs, which were identified as priority contaminants for the development of BEs by the NCP. Chlordane is an organochlorine pesticide that was historically used as a broad-spectrum insecticide on agricultural crops and as a termiticide in house foundations. Toxaphene is also an organochlorine pesticide that was commonly applied to cotton crops in the United States. The coolant and lubricant properties of PCBs were used in several products, such as electrical equipment. All three contaminants are listed under Annex A of the Stockholm Convention.

1.4.1 Metabolic Pathways of the POPs of Interest

Figures 4-6 show the metabolic pathways of chlordane (Figure 4), a specific compound isolated from toxaphene (Figure 5), and the PCBs (Figure 6). Chlordane is primarily oxidized in the liver by cytochrome P450 enzymes to oxychlordane, which may undergo further, but slow, degradation by epoxide hydrolase. Chlordane may also undergo dehydrochlorination, which converts chlordane to heptachlor, or dehalogenation followed by either hydrolysis and conjugation or replacement of the chlorine with a hydroxyl group.[36] Most products of chlordane are eliminated in bile and feces and smaller amounts through urine.[36] The principal metabolic pathways for toxaphene are dechlorination, dehydrodechlorination, and oxidation.[37] Toxaphene is a complex mixture of chlorinated bornanes and camphenes with hundreds of congeners found in the environment.[38] Figure 5 depicts the metabolism of one particular isolated component, heptachlorobornane. Most absorbed toxaphene is metabolized and eliminated primarily in feces and smaller amounts in urine.[37] The PCBs are metabolized by cytochrome P450 enzymes to metabolites, which undergo conjugation with glutathione and glucuronic acid. Arene oxides of PCBs are transformed to hydroxylated aromatic compounds or methylsulfonyl metabolites. Phenolic metabolites predominate, although other metabolites such as trans-dihydrodiols, polyhydroxylated congeners, and methyl ether derivatives may also be formed.[23] PCBs are eliminated mostly in feces as parent form and as metabolites in urine and bile.[23]

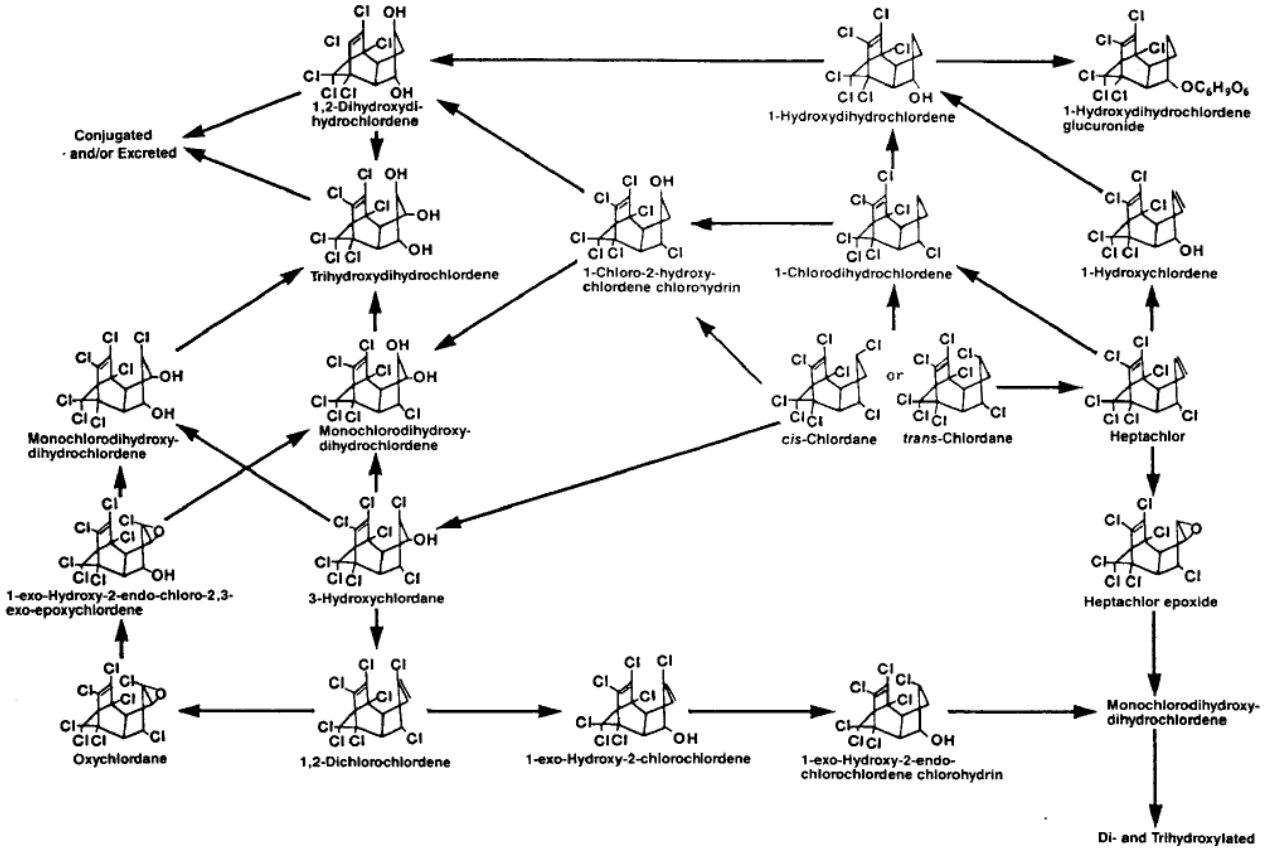

Figure 4: Metabolism of chlordane (cis- and trans-chlordane)

Source: Reprinted by permission from Springer Customer Service Centre GmbH: Springer Nature, Reviews of Environmental Contamination and Toxicology, Metabolism of chlordane in mammals, Nomeir AA & Hajjar NP, Copyright (1987).

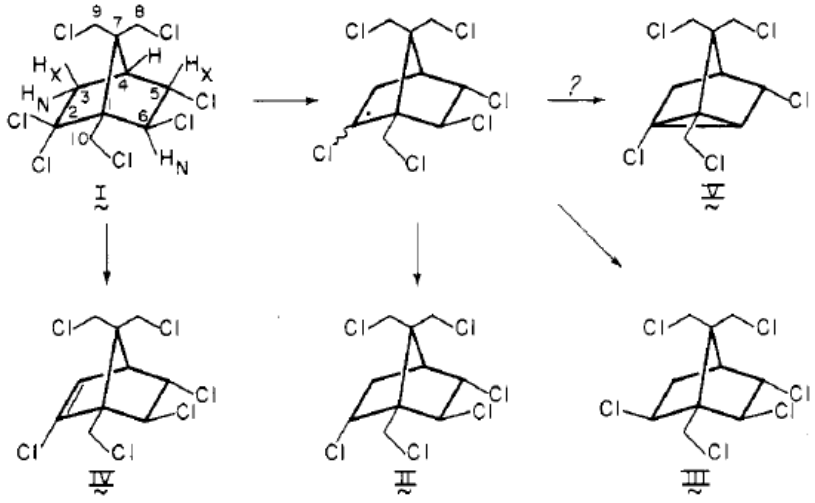

Figure 5: Metabolism of an isolated toxaphene toxicant (heptachlorobornane)

Source: Reprinted with permission from Saleh MA & Casida JE, Reductive dechlorination of the toxaphene component 2,2,5-endo,6-exo,8,9,10-heptachlorobornane in various chemical, photochemical, and metabolic systems, Journal of Agricultural and Food Chemistry, 26, p.584. Copyright (1978) American Chemical Society.

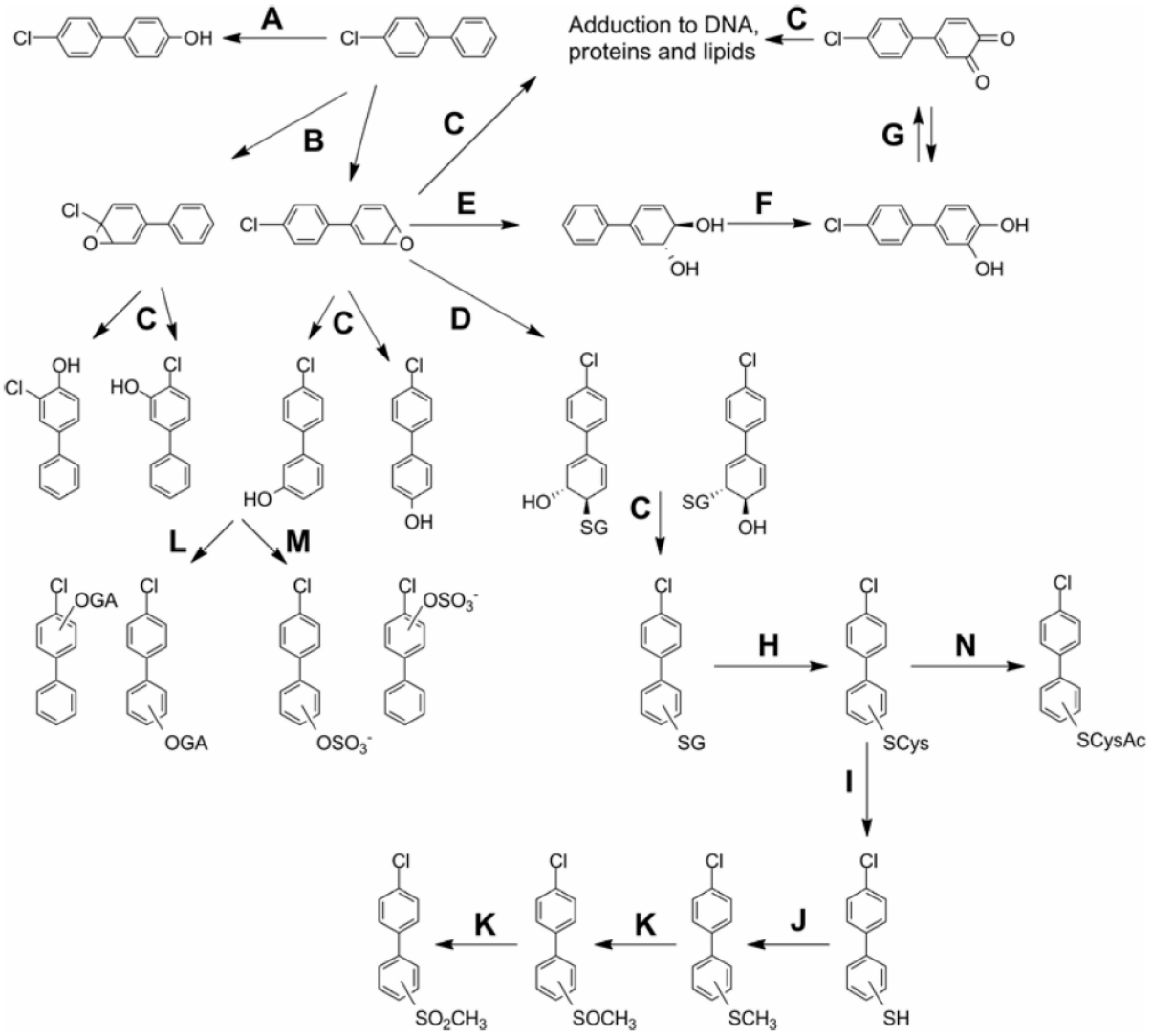

Figure 6: Metabolism of PCBs

Source: Reprinted from Grimm FA et al. Metabolism and metabolites of polychlorinated biphenyls (PCBs). Critical Reviews in Toxicology 2015:100; p.37.

1.4.2 Research Questions

The following research questions guided the thesis work:

1. What are the BE values for chlordane, toxaphene, and PCBs?
2. What percentage of the Canadian Inuit population exceeds the BE values for chlordane, toxaphene, and PCBs? How does this compare with the general Canadian population?
3. How does the interpretation of #2 change when different threshold values are used to calculate BEs (i.e. NOAEL vs. LOAEL)?
4. Are POPs associated with adverse health outcomes in the Canadian Inuit? What are the risks of POPs compared with other well-established disease risk factors, such as lack of exercise, poor diet, and smoking?
5. Are the research results applicable to Northern communities and, if so, what measures can be implemented to reduce the risks of POP exposures?

1.4.3 Thesis Layout

In Chapter 2, the process for deriving BEs for chlordane and toxaphene are described. These compounds were assumed to distribute entirely into adipose tissue and, therefore, one-compartment models were used to simulate the absorption and elimination of individual chlordane isomers, chlordane metabolite, and abundant toxaphene isomers. The technical form of chlordane was used to derive BEs for the individual isomers. To examine if the BE values may require modification based on differential toxicities, Chapter 2 additionally provides the results of a HEPG2 cell culture experiment that quantified the 50% lethal concentration (LC50) for technical chlordane, cis-chlordane, trans-chlordane, cis-nonachlor, trans-nonachlor, and oxychlordane. HEPG2 is a human liver cancer cell line and it was chosen to test the hepatic toxicity of chlordane, which is the most sensitive endpoint. In Chapter 3, data needs and

approaches for deriving BEs for the PCBs are provided. Chapter 4 describes the derivation of BEs for non-dioxin like PCBs and dioxin-like PCBs, using human toxicokinetic data. In Chapter 5, the derived BE values for chlordane, toxaphene, and PCBs are applied to the Inuit and general Canadian populations by determining the percentage that equal or exceed the values. For contaminants with significant exceedances, HQs were also calculated to quantify the margin of exposure. Chapter 6 is an examination of studies that evaluated contaminants and health outcomes, in pediatric and adult indigenous populations of the circumpolar regions. Chapters 7 and 8 describe the results of epidemiological analyses of the association of PCBs and p,p'-DDE on diabetes and high cholesterol among the Canadian Inuit.

Chapter 2: Biomonitoring Equivalents for Chlordane & Toxaphene

Abstract

Biomonitoring equivalents (BEs) are conversions of an external reference dose to an internal dose, against which biomonitoring data can be directly compared. In this work, BEs were developed for chlordane and toxaphene using one-compartment pharmacokinetic models. Since the technical form of chlordane was used in deriving BEs for the individual isomers, a secondary objective of this study was to examine the toxicities of the components of technical chlordane in a HEPG2 cell culture experiment. Oral reference doses were identified from various national and international regulatory agencies and sources. Pharmacokinetic parameters for chlordane and toxaphene were obtained from experimental data in rodent models. A set of BEs have been derived for the main chlordane isomers, cis-chlordane, trans-chlordane, cis-nonachlor, and trans-nonachlor, and the chlordane metabolite, oxychlordane. BEs were also derived for the main toxaphene isomers found in biota, Parlars No. 26, 50, and 62. Based on the LC50 from the *in vitro* study, trans-nonachlor was the most toxic, and the trans-isomers were more toxic than the cis-isomers (LC50: trans-nonachlor 0.010 mM; technical chlordane 0.051 mM; trans-chlordane 0.052 mM; oxychlordane 0.063 mM; cis-chlordane 0.077 mM; cis-nonachlor 0.088 mM). The derived BE values can be used as screening guidelines to assess the risk of biomonitoring data in human populations. The results of a HEPG2 cell culture experiment suggest that trans-nonachlor is more toxic than technical chlordane and, therefore, the BE for this compound may need to be further lowered.

Introduction

Chlordane is an organochlorine pesticide that was historically used on agricultural crops, and in house foundations to control termites, in the 1940s up to the 1980s. Toxaphene is also an organochlorine pesticide that was commonly applied to crops, such as cotton, and to control pests in livestock and poultry in the 1960s and 70s. Since the end of 1995, all sales and uses of chlordane were suspended in Canada and were listed under the *Pest Control Products Act*.[1] The United States continued to produce chlordane for export until 1999.[1] Most uses for toxaphene were banned in Canada in 1982 and the United States banned it in 1990.[2] Globally, both chlordane and toxaphene were listed in the 12 initial persistent organic pollutants (POPs) of the Stockholm Convention, under Annex A, which requires the elimination of chemical production and use.[3] Dearth and Hites 1991 estimated that more than 70 000 tons of technical chlordane was produced since 1946.[4] At least 1.3 million tonnes of toxaphene have been used around the world.[5]

Chlordane was manufactured as a technical form, which comprised more than 120 structurally related compounds. The predominant isomers in technical chlordane are cis-chlordane (19%), trans-chlordane (24%), cis-nonachlor (2.7%), trans-nonachlor (9.7%), and heptachlor (10%).[6] In biota, the relative percentages of isomers changes, with trans-nonachlor at highest level in marine mammal blubber (54.9%), followed by cis-nonachlor (8.3%), cis-chlordane (1.7%), and trans-chlordane (1.4%). In addition, biota metabolize cis- and trans-chlordane to oxychlordane, which makes up 27% of the chlordane found in marine mammals.[6] In human breast milk samples from southern and northern Canadians, trans-nonachlor and oxychlordane comprised more than 90% of the total chlordane residues.[7] Toxaphene was also manufactured as a technical form that consisted of a complex mixture of chlorinated camphenes,

bornanes, bornenes, bornadienes, and dihydrocamphenes, with more than 32 000 congeners, 100 to 200 of which have been detected in the environment.[6] The most abundant congeners of toxaphene in fish, marine mammals, and humans are Parlars No. 26, 50, and 62.[8] Although restrictions in the production and use of chlordane and toxaphene have been in place for more than two decades, biomonitoring surveys continue to detect their presence in the environment and humans.[8–11] Chlordane may remain in soils for 20 years[12] and travel long-distances to higher latitudes through repeated deposition and evaporation.[13] Similarly, toxaphene is highly resistant to degradation in the environment and travels to upper latitudes, far removed from point sources.[13,14]

Humans may be exposed to chlordane and toxaphene through oral, inhalational, or dermal routes, although environmental exposures occur primarily through ingestion of contaminated foods.[12,14] Chlordane initially accumulates in the kidney and liver, and it is then redistributed to adipose tissue, where it can be stored for several years due to its high lipophilicity; half-lives of 21-88 days have been reported in the literature.[12] Trans-nonachlor and oxychlordane are more stable than cis- and trans-chlordane, and are found in higher amounts in adipose tissue.[12] The liver metabolizes cis- and trans-chlordane into oxychlordane through CYP P450 mediated pathways.[12] Toxaphene is initially found in higher amounts in the liver, and is then redistributed to adipose tissue and muscle.[14] Most of the absorbed toxaphene is metabolized by dechlorination, dehydrodechlorination, and oxidation, and the products of metabolism are rapidly eliminated.[14] Chlordane and toxaphene are excreted through feces, and in smaller amounts through urine. Lactation is another route of excretion for both chemicals.[12,14]

Among the general Canadian population 20-79 years of age, the geometric means for trans-nonachlor and oxychlordane were 5.98 μg/kg lipid and 4.21 μg/kg lipid, respectively.[9] For

cis-nonachlor and Parlars No. 26 and 50, more than 40% of observations were below the limits of detection.[9] Concentrations of chlordane and toxaphene among Northern populations are much higher.[7,10] The health implications of these levels of exposure are currently unclear. Evidence of adverse health effects in humans comes from high dose exposures in occupational settings and acute poisonings.[12,14] Exposure to large quantities of chlordane has resulted in convulsions, headaches, irritation, confusion, vision problems, digestive symptoms, and even death. The liver is the most sensitive organ for chlordane toxicity in animals and, chronic toxicity in humans appears to occur only in the liver. Toxaphene in large quantities has been found to have adverse effects on the heart, liver, respiratory and nervous systems, and has also resulted in death. The International Agency for Research on Cancer (IARC) classifies chlordane and toxaphene as possibly carcinogenic to humans (Group 2B).[15,16]

Laird et al. (2013) assessed concentrations of POPs and heavy metals among the Canadian Inuit against guideline values.[10] The concentrations of chlordane and toxaphene were higher than the general Canadian population, however no blood guidelines were available for these chemicals to evaluate potential risks of the observed concentrations.[10] External oral reference doses are available for chlordane and toxaphene, however these are not directly comparable with biomonitoring data because chemicals will undergo processes of absorption, distribution, metabolism, and excretion and these processes will transform the external dose into a chemical-specific internal dose, which is the true parameter of interest in characterizing risk. The development of biomonitoring equivalents (BEs) uses the methods of pharmacokinetic modelling to convert an external reference dose (e.g. tolerable daily intake, benchmark dose, minimal risk level) to an internal dose, against which biomonitoring data can be directly compared.[17,18] These comparisons will provide a more accurate tally of the number of people

within or exceeding a guideline value than comparing with the oral value. Biomonitoring equivalents have been developed for several contaminants, such as PBDE-99, hexachlorobenzene, and dichlorodiphenyltrichloroethane (DDT).[19–21]

The main objective of this study was to develop blood guideline values for chlordane and toxaphene, for use in the risk assessment of human biomonitoring data. Biomonitoring equivalents were developed for the isomers and metabolites of chlordane, and for the most abundant toxaphene congeners found in biota, Parlars No. 26, 50 and 62. The technical form of chlordane was used in deriving BEs for the individual isomers. Therefore, a secondary objective of this study was to examine the relative toxicities of the components of technical chlordane (i.e. cis-chlordane, trans-chlordane, cis-nonachlor, and trans-nonachlor) and the main chlordane metabolite (i.e. oxychlordane).

Methods

Data Sources:

Comprehensive database and grey literature searches were conducted to identify oral reference doses for chlordane and toxaphene. For chlordane, oral reference doses were chosen from the Agency for Toxic Substances and Disease Registry (ATSDR), the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), and the Environmental Protection Agency (EPA). These doses applied to technical chlordane, which is a mixture of cis-chlordane, trans-chlordane, cis-nonachlor, and trans-nonachlor. A separate search for toxicological studies and relevant toxicological endpoints for oxychlordane was conducted and used to derive a provisional BE for this metabolite. A NOAEL of 0.1 mg/kg/d was chosen based on the study by Bondy et al. (2003) in female rats.[22] In that study, no effects were observed in clinical chemistry, pathology, body weight, organ weight, morbidity, or food and water consumption at a dose of 1.0 mg/kg/d.

However, at a dose of 10 mg/kg/d, 100% of rats experienced morbidity, defined as weight loss, unkempt appearance, and hunched posture. Therefore, the next lower dose of 0.1 mg/kg/d was chosen to calculate a BE value. For toxaphene, the oral dose derived by the Investigation into the Monitoring, Analysis, and Toxicity of Toxaphene in Marine Foodstuffs (MATT), for weathered toxaphene, was used.

Pharmacokinetic parameters for the isomers of chlordane and toxaphene were obtained from published studies, which were identified by searching through Medline, Scopus, Toxline, and Toxnet. In addition, relevant references from the ATSDR Toxicological Profiles were retrieved and reviewed. For chlordane and toxaphene, elimination rate constants were derived from concentration vs. time profiles of cis-chlordane, trans-chlordane, cis-nonachlor, trans-nonachlor, oxychlordane, Parlars No. 26, 50, and 62 in adipose tissue of rodent models.

Derivation of BE:

Framework (Figure 1): For chlordane and toxaphene, the no-observed adverse effect level (NOAEL) from toxicological studies in rodents were converted to equivalent steady state BE concentrations using pharmacokinetic parameters, also in rodents. This strategy was followed for chlordane and toxaphene because there is limited pharmacokinetic data available in humans. The rodent BE values were then allometrically scaled to human values as described below. For PCBs (Chapter 3), measurements of half-lives in humans were available and, therefore, the oral reference doses in humans were converted directly to BEs using human pharmacokinetic data.

Pharmacokinetic Modelling: A one compartment model consisting of a fat compartment and first-order kinetics were used to simulate the behaviour of both chemicals (Figure 2). Although there is some evidence to indicate multi-compartmental distribution[23], a one-compartment model was chosen for sake of simplicity and the high log octanol-water (k_{ow})

values (i.e. 5.54 for chlordane and 3.3-6.6 for toxaphene)[12,14,24]. The BEs in rodent models were calculated as steady-state concentration (C_{ss}), using the following formula

$$BE_{POD\text{-}animal} = C_{ss(rodent)} = F*Dose/k_eV_d \quad \text{(Eq.1)}$$

Where F is bioavailability, Dose is the NOAEL oral reference dose (mg/d), k_e is elimination rate constant (d^{-1}), and V_D (kg) is volume of distribution of fat compartment. The C_{ss} value is equal to units of mg/kg lipid, assuming that adipose and lipid levels are equivalent[25]. The volume of the fat compartment was assumed to be 25% of body weight for rodents, with rats assumed weight of 250 g and mice 25 g.[26] Chlordane isomers and metabolite (i.e. cis-chlordane, trans-chlordane, cis-nonachlor, trans-nonachlor, and oxychlordane), and toxaphene isomers (i.e. Parlars No. 26, 50, and 62), were modeled individually.

For chlordane and toxaphene, the C_{ss} values were obtained in rodents and were allometrically scaled to human values using human-animal body weight (BW) ratio raised to the power ¾ as recommended by the Environmental Protection Agency (EPA) for scaling of oral reference doses[27], using the following equation:

$$BE_{human} = [C_{ss(rodent)}BWF_{rodent}(BW_{human}/BW_{rodent})^{3/4}]/BWF_{human} \quad \text{(Eq.2)}$$

The above equation is equivalent to conversion based on ratio of animal-human body weight fat (BWF) raised to the power ¼, in the case where *percent* BWF is equal in animal and humans.

$$BE_{human} = C_{ss(rodent)} * [BWF_{rodent}/BWF_{human}]^{1/4} \quad \text{(Eq.3)}$$

An additional uncertainty factor of 3 was applied to account for human pharmacodynamic variability.[18]

Differential Toxicity of Technical Chlordane, Chlordane Isomers and Metabolite:

In the BE derivation for chlordane, an oral reference dose for technical chlordane was utilized (Table 1). This oral reference dose was applied to the individual isomers of chlordane, which assumes that the toxicities of the isomers are equivalent to the toxicity of technical

chlordane. To test this assumption, the relative toxicities of technical chlordane, the isomers of chlordane (i.e. cis-chlordane, trans-chlordane, cis-nonachlor, and trans-nonachlor) and the main metabolite of chlordane (i.e. oxychlordane) were examined in an HEPG2 cell culture experiment, which was conducted at the University of Ottawa.

HepG2 cells were cultured on T75 cm^2 flasks (BD Inc, Mississauga, ON, Canada) in MEM media (Sigma-Aldrich, Oakville, ON, Canada), supplemented with 10% (v/v) heat-inactivated fetal bovine serum, 100 U/ml penicillin, and 100 μg/ml streptomycin (Life Technologies Inc., Burlington, ON, Canada) in an incubator with an atmosphere of 5% CO_2 at 37°C. Cells were passaged every 3-7 days and seeded on to 96-well plates at a density of 5 x 10^5 cells/mL. Technical chlordane, cis-chlordane, trans-chlordane, cis-nonachlor, trans-nonachlor, and oxychlordane (Sigma-Aldrich, Oakville, ON, Canada) were made into solution with DMSO. The seeded cells were exposed for 24 hours to the following concentrations in 2.5% DMSO, with 3 replicates per concentration: 0.01, 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.4, 0.5, and 1.0 mM. Controls (i.e. seeded cells with MEM + 2.5% DMSO) and blanks (MEM + 2.5% DMSO) were also run. After 24 hours of exposure, cells were washed with PBS and 100 μL of MTT solution (5 mg/mL in PBS) was added to each well. The plates were then wrapped in aluminum foil and kept in an incubator for two hours. Thereafter, the MTT solution was removed and 150 μL DMSO was added to each well. Absorbance measurements were read on a microplate reader at 570 nm. Dose-response analysis was conducted in Sigma-Plot 14.0. The data for 1.0 mM trans-nonachlor were excluded from analysis due to probable interference of absorbance readings by a precipitate of trans-nonachlor, which formed prior to the addition of MTT solution.

Results

Oral Reference Doses:

Table 1 shows the human oral reference doses for chlordane and toxaphene, along with the supporting documentation of how these oral reference doses were derived by the respective agencies. For chlordane, no reference doses were available for individual isomers but, rather, all pertained to the technical chlordane form. For toxaphene, the oral reference dose was relevant to the weathered form, which was obtained by administering technical toxaphene to farmed cod fish and extracting toxaphene residues from liver.[28] While this reference dose applies to those toxaphene isomers that accumulate in biota (e.g. Parlars No. 26, 50, and 62), values for individual isomers were not available. Summative toxicity was not assumed for chlordane or toxaphene and, thus, the full technical reference dose for chlordane and the weathered reference dose for toxaphene were used to model the individual isomers.

Elimination Rate Constant:

In Table 2, the elimination rate constants (k_e) for chlordane and toxaphene are provided. The chlordane and toxaphene parameters pertain to elimination specifically from adipose tissue in rats or mice.

1. *Chlordane:* The k_es for chlordane were available from studies of rats and mice.

Dearth et al. (1991) administered a diet containing 10 ppm technical chlordane for 28 days to male Holtzman rats and followed the depuration of chlordane compounds for 32 days.[29] Measurements in adipose tissue were conducted in 21 rats and elimination rate constants of cis-chlordane, trans-chlordane, cis-nonachlor, trans-nonachlor, and oxychlordane were provided. Ohno et al. (1986) orally administered trans-chlordane (50 μg/kg – 10 mg/kg) as a single dose to male Wister rats.[30] Concentration verses time profiles in adipose tissue were provided for the low (50 μg/kg) and high (10 mg/kg) doses. These profiles were used to derive elimination rate

constants for trans-chlordane. Ewing et al. (1985) administered cis-chlordane (1.0 mg/kg) to male Sprague-Dawley rats and provided a concentration versus time profile in adipose tissue based on four time points (12 hrs, 1 day, 7 days, 14 days).[31] The Ewing and Ohno studies were used to validate the k_es from Dearth et al. (1991) for cis-chlordane and trans-chlordane respectively.

Ewing et al. (1985) also provided k_e for cis-chlordane in male C57BL/6JX mice.[31] Hirasawa et al. (1989) administered 0.48 mg technical chlordane to ddy-strain male mice orally by gavage every other day for 29 days.[32] Formulas for whole body absorption and elimination profiles were provided for cis-chlordane, trans-chlordane, cis-nonachlor, and trans-nonachlor. Only the parameter for cis-nonachlor was used in modelling for mice because the parameters for other chlordane isomers were 10 times greater than those found in the study by Dearth et al. (1991) in rat adipose tissue and by Ewing et al. (1985) in mouse adipose tissue.

2. Toxaphene: The k_es for toxaphene were obtained from two studies conducted in rats.

Skopp et al. (2002) administered a single intravenous (IV) injection of a mixture of Parlars No. 26, 32, 50, and 62 to 32 female Wistar rats.[33] Concentration verses time profiles in adipose tissue for individual Parlars were provided, and these were used to obtain elimination rate parameters for Parlars No. 26, 50, and 62. In the second study, Drenth et al. (2000) administered a single oral dose of a mixture of Parlars No. 26, 32, 50, and 62 within a food pellet to 18 female Wistar rats.[34] Elimination rates were obtained from concentration verses time profiles of Parlars No. 26, 50, and 62 in adipose tissue.

Oral Bioavailability:

The oral bioavailability (F) of all chlordane isomers was taken as 80% based on the study of trans-chlordane by Ohno et al. (1986).[30] The absorbed fraction was estimated as the area under the curve ($AUC^{0-\infty}$) of oral dose divided by IV dose and was 82.9% for the 100 μg/kg group and

80.1% for the 1 mg/kg group. As a sensitivity analyses, a lower limit of 50% was also inputted.[35] When validating the Dearth et al. (1991) elimination rate constant parameter for cis-chlordane and trans-chlordane with the studies by Ewing et al. (1985) and Ohno et al. (1986) respectively, maximum overlap of curves occurred when bioavailability was 30% for cis-chlordane, 70% for trans-chlordane low dose group, and 40% for trans-chlordane high dose group. Therefore, while the 30% and 40% values are likely underestimates of the true bioavailabilities, these were also inputted as sensitivity analyses for cis-chlordane and trans-chlordane respectively. For toxaphene, limited data were available for oral bioavailability. Drenth et al. (2000) reported values of 97.8% to 133% in rats.[34] A more conservative estimate, akin to chlordane, of 50 or 80% was used for this analysis.

BE Values:

In Tables 3 and 4, the derived BE values for chlordane and toxaphene are provided. The range of BE values is due to input of different values for elimination rate constant and bioavailability, as described above. In addition, for cis-chlordane, trans-chlordane, cis-nonachlor, and trans-nonachlor, the ranges incorporate input of the three NOAELs that were used to derive the oral reference doses as shown in Table 1. The BE for oxychlordane is not directly comparable with the BEs of other chlordane isomers because it is based on a separate NOAEL, as described in the "Data Sources" section.

Toxicity of Technical Chlordane, Isomers, and Metabolite:

Figure 3 shows the dose-response curves for all chlordane compounds, and the LC50 values, which were calculated from these curves. Based on the LC50 from the best fit logarithm curve, trans-nonachlor was the most toxic, and trans-isomers were more toxic than the cis-isomers. The 95% confidence bands for the LC50 values demonstrated considerable overlap

between technical chlordane, trans-chlordane, oxychlordane, cis-chlordane, and cis-nonachlor, shown in Figure 4.

Discussion

A set of BE values have been developed for the isomers and metabolite of chlordane and the most abundant congeners of toxaphene. These values can be used for the purposes of risk assessment to evaluate potential population-level human health risks of observed exposure levels. The derived BE values are useful for assessing risk of chlordane and toxaphene exposures in adult populations where the primary route is through ingestion. The percentage of a population that exceeds the BE values will provide an indication of whether the compound poses risks to the population and if further assessment of exposure is warranted. Importantly, exceedances of a BE value will not provide any information about risks to a person, and cannot be used to make decisions at the individual level. In cases where other routes of exposure are dominant (e.g. dermal or inhalational, as may occur in occupational situations), lactational exposure in infants, or assessing the risk of exposures in children, the BE values may not be directly applicable.

The derived BE values compare well with BEs of other POPs (Figure 5). For hexachlorobenzene, an oral reference dose of 0.0005 mg/kg/d (same as chlordane) was used to derive a BE value of 0.25 mg/kg lipid based on hepatic effects.[21] The BE range for toxaphene (0.87-12.22 mg/kg lipid) includes the BE derived for hexabromocyclododecane (HBCD) of 10 mg/kg lipid and sum of DDT and DDE of 5 mg/kg lipid.[36] The toxaphene BEs are higher than chlordane, which is due to the larger oral reference dose for weathered toxaphene compared with technical chlordane, as shown in Table 1. Evidence suggests that toxaphene in humans is metabolized and the products of metabolism are rapidly eliminated, whereas chlordane may be stored in adipose tissue for several years.[14] The presence of toxaphene in blood reflects more

recent exposures (< week).[14] The larger BE values for toxaphene compared with chlordane, therefore, appropriately suggests that toxaphene may have a higher exposure threshold.

There is no information on the relative toxicity of technical chlordane, chlordane isomers (cis-chlordane, trans-chlordane, cis-nonachlor, trans-nonachlor), and oxychlordane in one cell line or animal model. The results of the HEPG2 cell culture experiment provide evidence, for the first time, that trans-nonachlor is five times more toxic than technical chlordane. The oral reference dose for technical chlordane, upon which the BE for trans-nonachlor was based, may therefore underestimate the toxicity of trans-nonachlor. Bondy et al. (2000) examined the toxicities of cis-nonachlor, trans-nonachlor, and technical chlordane in rats given doses of 0.25 to 25 mg/kg body weight for 28 days by gavage.[37] The liver was the target organ for toxicity, which included increased liver weight and histopathological changes. The ranking of toxicity, from highest to lowest, was trans-nonachlor > technical chlordane > cis-nonachlor. This result is supported by the findings of the HEPG2 *in vitro* study (LC50: trans-nonachlor 0.010 mM, technical chlordane 0.051 mM, and cis-nonachlor 0.088 mM). Dehn et al. (2005) exposed HepG2 cells with technical grade chlordane at a concentration of 5 mM for 24 hours and found cell viability was 55.5 ± 14.3%.[38] It appears that the 5 mM estimate may be too high and may have resulted from the formation of a precipitate that interfered with absorbance readings of the MTT assay. In the present HEPG2 experiment, an LC50 two orders of magnitude lower was observed for technical chlordane.

In this work, a systematic search of oral reference doses and pharmacokinetic parameters from published and grey literature was conducted to arrive at a set of BE values for chlordane and toxaphene. The simplicity of the one-compartment strategy means that it can be easily tailored to different populations by varying the body weight and body fat percentage variables

only. However, the downside of this approach is that the actual complexities of the absorption, distribution, metabolism, and excretion processes are omitted from consideration. Thus, factors such as metabolism by the liver, genetic differences in metabolism, and distribution to other compartments have not been accounted for. A three-compartment model, consisting of blood, fat, and liver compartments was attempted for trans-nonachlor, however, there was insufficient data available specifically for trans-nonachlor to parameterize the model. The pharmacokinetic data available for chlordane and toxaphene were limited and, aside from a few cases of poisoning incidents, no human data were available. None of the models were validated with external datasets of pharmacokinetic data, which were unavailable to the author's knowledge. In addition, the oral reference doses were based on either technical chlordane or weathered toxaphene and these values were inputted for the individual isomers and congeners, respectively. In the current method of BE development, it is not possible to ascribe toxicity to the individual isomers of chlordane or congeners of toxaphene.

To take into account the details of the absorption, distribution, metabolism, and excretion pathways, multi-compartment models should be evaluated for trans-nonachlor and oxychlordane, which are the most stable of chlordane components in biota, and Parlars No. 26 and 50, which are the most abundant toxaphene congeners (33% and 55% of total toxaphene burden, respectively).[14] These models should be parameterized with data that are specific to the compound to derive accurate BE estimates. Given the scarcity of pharmacokinetic data available for trans-nonachlor and toxaphene congeners in the literature, these models will require *in vivo* pharmacokinetic studies to obtain parameters such as metabolic rate in liver and elimination rate from kidney. Secondly, optimization of the cell culture experiment with MTT assay should be attempted to arrive at a quantitative estimate of the LC50 trans-nonachlor/technical chlordane

ratio. To prevent the formation of a precipitate in the MTT assay, potential solutions are use of liposomes, glycerol formal, or cyclodextrins (Health Canada, personal communication).

In conclusion, this study has arrived at a preliminary set of blood guidance values for the isomers of chlordane, a metabolite of chlordane, and the abundant congeners of toxaphene in the form of BEs. These values can be used as a screening guideline to assess the risk of biomonitoring data in human populations. A HEPG2 cell culture experiment suggests that trans-nonachlor is more toxic than technical chlordane and, therefore, the BE for this compound may need to be further lowered.

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Table 1: Human oral reference doses

	Chlordane			Toxaphene
	ATSDR 1994[12]	**JMPR 1994**[39]	**EPA 2009**[40]	**MATT 2012**[28]
Chemical Form	Technical	Technical	Technical	Weathered*
Animal Model	Rat	Rat	Mouse	Rat
Endpoint	Hepatocellular hypertrophy	Hepatic toxicity**	Hepatic necrosis	Altered hepatic foci expressing placental glutathione-S-transferase***
NOAEL (mg/kg/d)	0.055	0.05	0.15	1.8
Uncertainty Factor	100	100	300	100
Human Oral Reference Dose (mg/kg/d)	MRL: 0.0006	pTDI: 0.0005	RfD: 0.0005	pTDI: 0.018

* Technical toxaphene administered to farmed cod fish and toxaphene residues from liver extracted.

** Unpublished study submitted to FAO/WHO – specific toxicity endpoint unclear.

*** Indication of tumour promotion.

Abbreviations: ATSDR = Agency for Toxic Substances and Disease Registry; EPA = Environmental Protection Agency; JMPR = Joint FAO/WHO Meeting on Pesticide Residues; MATT = Investigation into the Monitoring, Analysis, and Toxicity of Toxaphene in Marine Foodstuffs; MRL = minimum risk level; NOAEL = no-observed adverse effect level; pTDI = provisional tolerable daily intake; RfD = reference dose; TDI = tolerable daily intake

Table 2: Pharmacokinetic parameters

	k_e (d^{-1}) - rat	k_e (d^{-1}) - mouse
Chlordane		
cis-chlordane	0.168[29,31*]	0.096[31]
trans-chlordane	0.087; 0.099[29,30**]	0.096[29***]
cis-nonachlor	0.072[29]	0.084[32]
trans-nonachlor	0.048[29]	0.048[29***]
oxychlordane	0.029[29]	N/A
Toxaphene		
Parlar No. 26	0.024[34]; 0.336[33]	N/A
Parlar No. 50	0.048[34]; 0.144[33]	
Parlar No. 62	0.096[33]; 0.144[34]	

[*] Fitted parameter value based on data from Dearth 1991 and Ewing 1985.

[**] Fitted parameter values based on data from Dearth 1991 and Ohno 1986.

[***] Value for rat imputed for mouse.

Table 3: Derivation of BE values for chlordane

	Cis-Chlordane	Trans-Chlordane	Cis-Nonachlor	Trans-Nonachlor	Oxychlordane
POD (mg/kg/d)	R: 0.055; M: 0.15	R: 0.055; M: 0.15	R: 0.055; M: 0.15	R: 0.055; M: 0.15	R: 0.1*
$BE_{POD\text{-}animal}$ (mg/kg lipid)	R: 0.36-1.05 M: 0.94-5.00	R: 0.81-2.02 M: 3.13-5.00	R: 1.39-2.44 M: 3.57-5.71	R: 2.08-3.67 M: 6.25-10.00	R: 6.94-11.11
Allometric Scaling Factor**	R:4; M:7	R:4; M: 7	R:4; M: 7	R: 4; M: 7	R:4
$UF_{H\text{-}PD}$	3	3	3	3	3
BE_{human} (mg/kg lipid)***	0.03-0.23	0.07-0.23	0.11-0.26	0.17-0.46	0.57-0.91

* NOAEL from Bondy et al. (2003)

** Rounded to nearest whole number (Eq. 3)

*** Range based on rat and mouse data and exact allometric scaling factor (i.e. not rounded to nearest whole number).

Abbreviations: BE = biomonitoring equivalent; M = mouse; POD = point of departure; R = rat; $UF_{H\text{-}PD}$ = uncertainty factor for human pharmacodynamic variability

Table 4: Derivation of BE values for toxaphene

	Parlar No. 26	**Parlar No. 50**	**Parlar No. 62**
BE_{POD} (mg/kg/d)	R: 1.8	R: 1.8	R: 1.8
$BE_{POD\text{-}animal}$ (mg/kg lipid)	R: 10.71-150.00	R: 25.00-75.00	R: 25.00-60.00
Allometric Scaling Factor*	4	4	4
$UF_{H\text{-}PD}$	3	3	3
BE_{human} (mg/kg lipid)**	0.87-12.22	2.04-6.11	2.04-4.89

* Rounded to nearest whole number (Eq. 3)

** Range based on exact allometric scaling factor (i.e. not rounded to nearest whole number).

Abbreviations: BE = biomonitoring equivalent; POD = point of departure; R = rat; $UF_{H\text{-}PD}$ = uncertainty factor for human pharmacodynamic variability

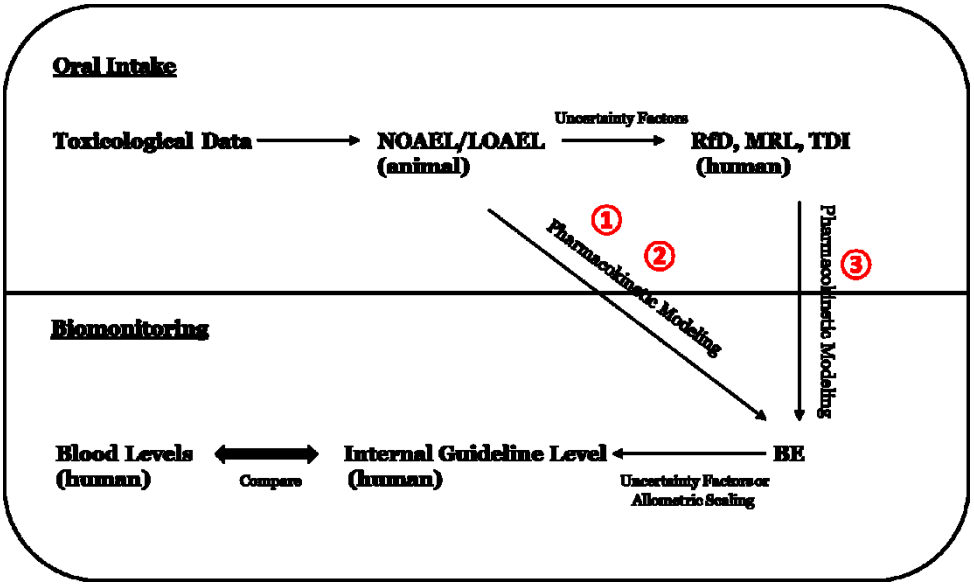

Figure 1: Framework for BE derivation

Note: ①and ②correspond to chlordane and toxaphene and ③to PCBs

BE = biomonitoring equivalent; LOAEL = lowest observed adverse effect level; MRL = minimum risk level; NOAEL = No observed adverse effect level; RfD = reference dose; TDI = tolerable daily intake

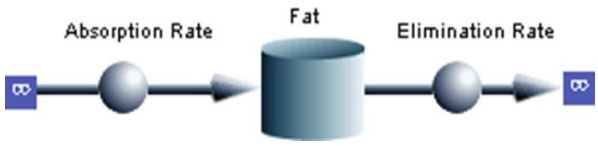

Figure 2: One-compartment model to simulate chlordane and toxaphene

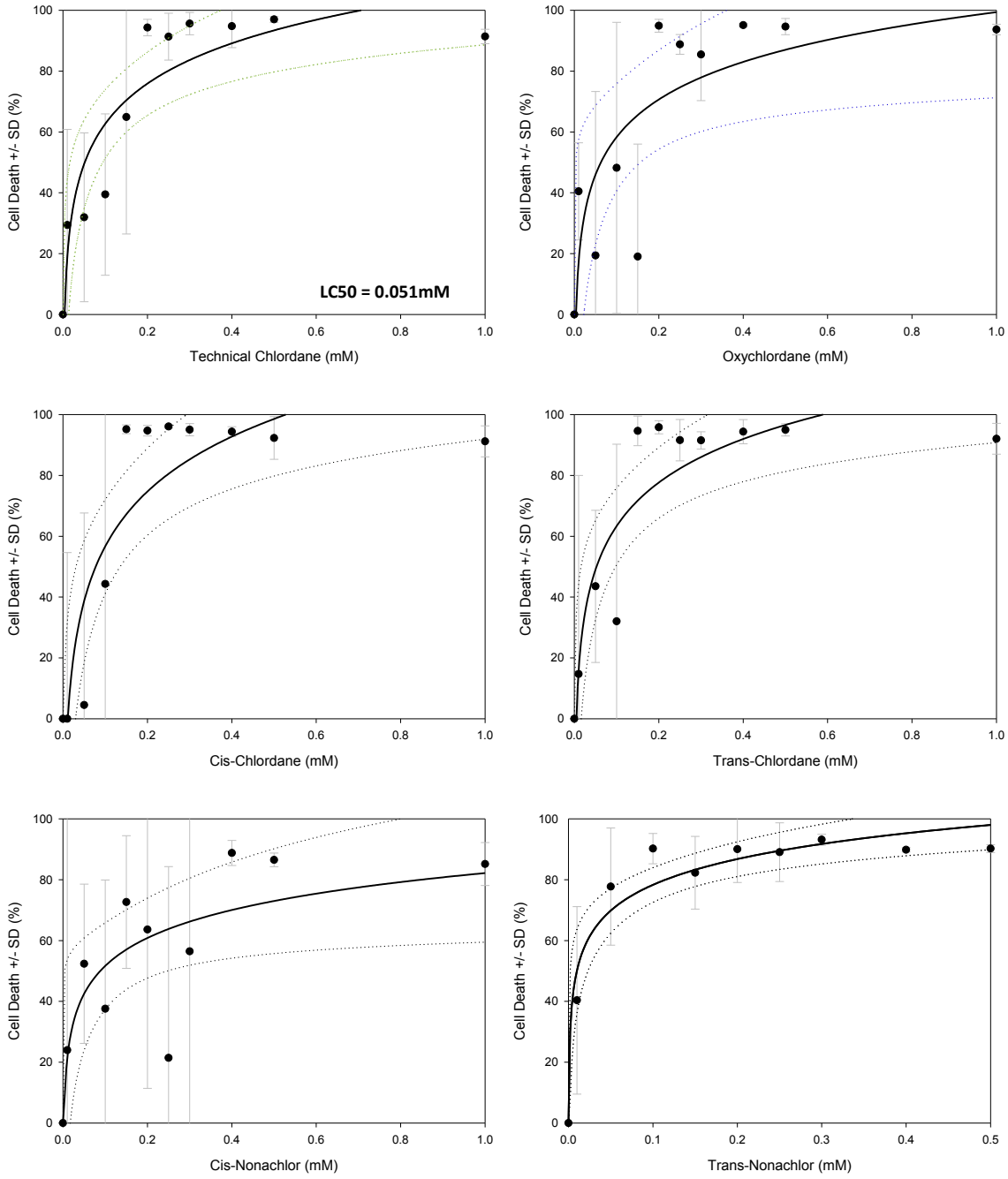

Figure 3: Dose-response curves for technical chlordane, oxychlordane, and chlordane isomers (Dotted curves represent 95% confidence bands)

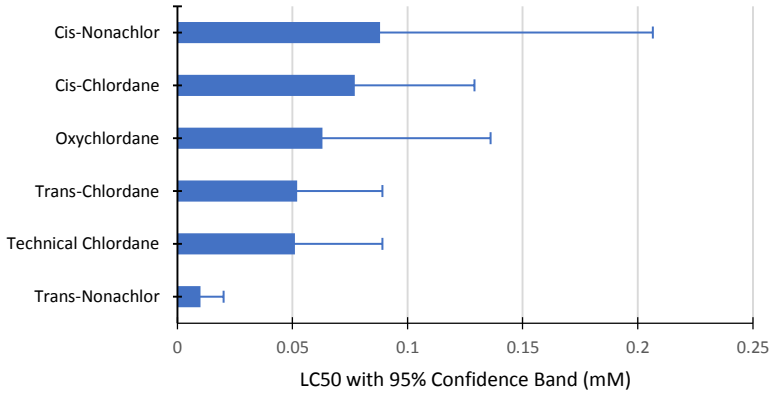

Figure 4: LC50 values and 95% confidence bands for technical chlordane, oxychlordane, and chlordane isomers

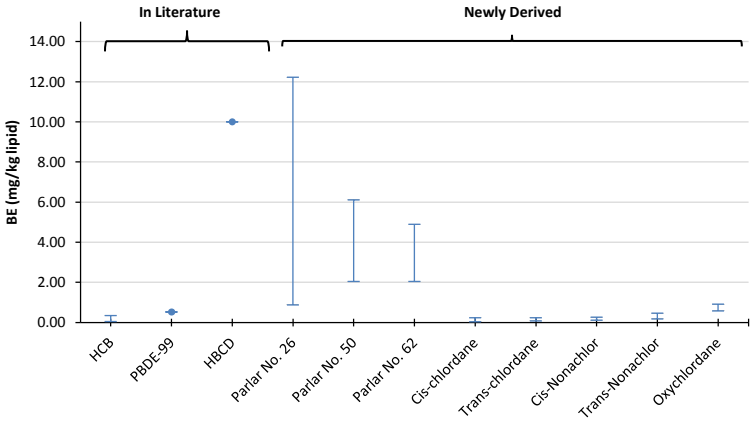

Figure 5: Comparison of chlordane and toxaphene BE values

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Chapter 3: Developing Biomonitoring Equivalents for Polychlorinated Biphenyls – Approach and Data Requirements

Preface: This chapter was published:

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K. Singh reviewed the literature and drafted the manuscript. A. Nong and M. Feeley critically reviewed the manuscript and provided feedback. H.M. Chan gave the concept and also critically reviewed the final manuscript.

Abstract:

A number of exposure guideline values for environmental contaminants are established by various agencies for risk assessment purposes. Biomonitoring equivalents are conversions of external guideline values to internal doses, against which biomonitoring data can be directly compared. Several biomonitoring equivalents have been developed for the interpretation of blood concentrations of environmental contaminants, but none has yet been developed for polychlorinated biphenyls (PCBs). In this paper, we describe information needed to develop biomonitoring equivalents for PCBs and discuss anticipated challenges. We provide a broad overview of PCB absorption, distribution, metabolism and excretion, PCB guideline values, and PCB pharmacokinetic modelling efforts in animals and humans. We also provide strategies to address anticipated challenges in deriving biomonitoring equivalents for this complex contaminant. Biomonitoring equivalents will be useful for the interpretation of the PCB biomonitoring data that are currently available for populations around the globe through national surveys and research of specific populations.

Introduction

Guideline values for environmental contaminants describe exposure thresholds likely to have minimal risk of adverse effects in humans. The Environmental Protection Agency, for example, uses the concept of reference dose (RfD) or reference concentration (RfC), which are estimates of daily oral or inhalational exposures, respectively, in humans that are likely to have no adverse non-cancer effects over a lifetime. These estimates take into consideration effects of chemicals on sensitive human subpopulations [1,2]. The Agency for Toxic Substances and Disease Registry (ATSDR) defines minimum risk level (MRL) of acute (1− 14 days), intermediate (15− 364 days), or chronic duration (1 year or longer) to describe oral and inhalational exposures without risk for adverse non-cancer effects [3]. Tolerable daily intakes (TDI) are used by Health Canada to describe oral exposures without adverse non-cancer effects over a lifetime [4]. Guideline values are often derived by applying uncertainty factors to estimates of no observed adverse effect level (NOAEL), lowest observed adverse effect level (LOAEL) or benchmark dose (BMD) from toxicological studies in animals. Uncertainty factors may account for uncertainties in extrapolating from animal data to humans, extrapolating from a LOAEL to a NOAEL, length of exposure (e.g. from acute to chronic), and variation among human populations [5].

The magnitude of internal exposure has often been inferred based on estimates of external intake. While this method provides a rough estimate of exposure it may not be representative of the dose that ultimately arrives in the bloodstream or at target organs where toxicity occurs [6]. Chemicals are known to undergo processes of absorption, distribution, metabolism, and excretion—these pharmacokinetic processes will transform the external dose into a chemical-specific internal dose, which is the true parameter of interest in characterizing risk. A biomonitoring equivalent is the conversion of an external guideline value, such as a RfD, MRL, or TDI, to an internal dose against

which biomonitoring data can be directly compared [7,8]. Biomonitoring equivalents have been developed for several environmental contaminants, such as polybrominated diphenyl ether (PBDE) -99 [9], dichlorodiphenyldichloroethylene (p,p'-DDE) and dichlorodiphenyltrichloroethane (DDT) [10], toluene [11], hexachlorobenzene [12], and 2,4-dichlorophenoxyacetic acid [13].

To our knowledge, biomonitoring equivalents have not yet been developed for polychlorinated biphenyls (PCBs), a ubiquitous class of environmental contaminant. Levels of PCBs have been measured in human populations around the world. In a risk assessment context, biomonitoring equivalents for PCBs could more accurately guide the interpretation of the available human biomonitoring data. Polychlorinated biphenyls contain up to 209 congeners and each congener has different chemical properties, such as biological half-life. Therefore, the development of biomonitoring equivalents for PCBs is a challenge. In this paper we provide a broad overview of the information needed to develop biomonitoring equivalents for PCBs. We begin by describing background information and worldwide PCB biomonitoring data, followed by a summary of ADME (absorption, distribution, metabolism, excretion) processes, external guideline values, and pharmacokinetic modelling studies of PCBs in animals and humans. Lastly, we present some strategies to address anticipated research challenges in the development of biomonitoring equivalents for this complex contaminant.

Background on polychlorinated biphenyls

Although the production, use, and trade of PCBs was prohibited under the Stockholm Convention since 2004 [14] and international production stopped since 1993 [15], these chemicals persist in air, water, soil, biota, and human tissues. PCBs are synthetic materials that were produced for coolant and lubricant properties in electrical equipment, such as capacitors and transformers, and

in plasticizers, oils, inks, paints, adhesives, and waxes [15]. Breivik et al. (2002) estimated that total global production of PCBs amounted to about 1.3 million tons, of which greater than 70 percent were tri-, tetra-, and pentachlorinated homologues [16]. About half of this production came from the United States and nearly all consumption occurred in the Northern hemisphere [16].

Individual PCB congeners vary in the degree and position of chlorine atoms, resulting in 209 possible congeners. The industrial manufacture of PCBs was mostly in the form of complex commercial PCB mixtures defined by degree of chlorination patterns, such as Aroclors in the United States, Kanechlors in Japan, and Clophens in Germany. The number and positioning of chlorine atoms on the biphenyl ring will determine potential for atmospheric volatilization, environmental degradation, bioaccumulation, and metabolism. Generally, the higher chlorinated PCB congeners are more resistant to environmental breakdown and bioaccumulate in biota [5]. In addition, the positioning of the chlorine atoms will determine toxic effects. Dioxin-like congeners, for example, have a coplanar structure with no or maximum of one chlorine atom in the ortho positions. These congeners act through the aryl hydrocarbon receptor and cause toxicity similar to 2,3,7,8-tetrachlorodibenzodioxin (TCDD) [17].

Exposure to PCBs has been shown to have many adverse effects in wildlife and humans and, therefore, their persistence in the environment is of high concern. Most effects in humans have been observed in the settings of occupational exposures or poisoning incidents and include increase in liver enzymes, gastrointestinal symptoms, increased thyroid gland volume and risk for goiter, upper respiratory tract symptoms, joint pain, skin irritation and chloracne, hematological and immunological effects, neurological effects, reproductive effects, and cancer [5]. The International Agency for Research on Cancer has classified PCBs as Group 2A, probably carcinogenic to humans [18].

Worldwide biomonitoring data

PCB biomonitoring data for children, adolescents, and adults are available from several countries through national surveys, such as the National Health and Nutrition Examination Survey (NHANES) in the United States, the Canadian Health Measures Survey (CHMS), and the German Environmental Survey (GerES). Table 1 presents data from United States, Canada, Australia, Germany, Spain, and Belgium. In addition, monitoring of PCBs in remote populations, such as the Inuit, has been conducted [20,21]. Table 2 shows the sum of PCB congeners detected in breast milk samples around the world. Biomonitoring equivalents could be used to interpret this worldwide PCB biomonitoring data.

Absorption, distribution, metabolism, and excretion (ADME)

The ATSDR contains comprehensive data on the ADME of PCB congeners in animals and humans. The information described in this section comes mostly from that report [5,22]. The primary route of human exposure to PCBs is through oral ingestion from contaminated foods, drinking water, and breast milk. Other minor routes of exposure are inhalational and dermal absorption [22]. PCBs are lipophilic chemicals and, therefore, absorption from the gastrointestinal tract to blood lipids occurs passively. Once PCBs are absorbed they distribute preferentially to adipose tissue and liver where they may remain for years. Commonly detected congeners in human tissues are PCB-138, 153, and 180 [22].

PCBs can be metabolized by cytochrome P450 isozymes to polar metabolites which can then undergo phase 2 metabolism by conjugation with glutathione and glucuronic acid. Arene oxides of PCBs are formed by CYP 1A1, CYP 1A2, CYP 2B1, CYP 2B2, and CYP 3A and are transformed to hydroxylated aromatic compounds or methylsulfonyl metabolites. The rate of metabolism decreases with higher chlorinated congeners. Phenolic metabolites predominate, although other metabolites

such as trans-dihydrodiols, polyhydroxylated congeners, and methyl ether derivatives may also be formed. Hydroxylated metabolites accumulate in lung, liver, and kidneys. Due to metabolism of parent compounds and selective retention of certain congeners in body tissues (e.g. PCB-153), the original mixture of PCBs ingested will not be the same as the congeners subsequently detected in serum, adipose, and breast milk.

PCBs are primarily eliminated in feces as parent form and as metabolites in urine and bile. Elimination half-lives vary greatly depending on congener; for example, half-life for PCB-28 is estimated at 1.4 years whereas the half-life for PCB-163 is more than 20 years. Other congeners have been found to have infinite half-lives, indicating repeated exposures or absence of decline over the experimental duration.

Guideline values

Guideline values for PCBs were collected from sources of the World Health Organization, European and North American jurisdictions (e.g. French Food Safety Agency, Health Canada, Environmental Protection Agency), and occupational organizations (e.g. National Institute for Occupational Safety and Health) (Tables 3 and Table 4) [5,22,24-30]. The reference values pertain to total PCBs, total non-dioxin like PCBs, dioxin-like PCBs, or PCB mixtures (e.g. Aroclor 1254) and ingestion through food, water or breast milk. The maximum reference value for ingestion is 5 µg/kg/day based on toxic effects of Phenochlor-DP6 in rats (CSHPF 1991). More recent sources have lowered ingestion references values, ranging from a low of 0.01 µg/kg/day for seven PCB indicators in food (AFSSA 2007) to a high of 0.13 µg/kg/day for total non-dioxin like PCBs (Health Canada 2010). For dioxins, a reference value of 2.33 pg TEQ/kg/day has been specified by the Joint FAO/WHO Expert Committee on Food Additives (JECFA 2001). A theoretical TDI for dioxin-like

PCBs is 1.63 pg TEQ/kg/day, given that these PCBs constitute 70% of dioxin mixtures [29]. The European Food Safety Authority 2005 indicated benchmark dose lower confidence limits in breast milk of 0.63–0.71 μg/g lipid for total PCBs based on cognitive outcomes in children exposed prenatally and 65 pg TEQ/g lipid for dioxin-like PCBs, polychlorinated dibenzo-p-dioxins (PCDD) and polychlorinated dibenzofurans (PCDF) based on neurological and immune effects with perinatal exposures. Three occupational reference standards for inhalational and dermal exposures were identified for Aroclor 1242 and Aroclor 1254 of either 0.5 mg/m^3 or 1 mg/m^3.

Pharmacokinetic modelling

The conversion of an external PCB reference value to a corresponding internal dose requires the use of a pharmacokinetic model that describes the absorption, distribution, metabolism and excretion of a chemical in the body. The model description can vary from simple relationship between dose exposure and internal metrics to highly complex structures with saturable processes. The level of detail in the model structure will depend on the quality and quantity of data available.

Modelling in animals

Several pharmacokinetic modelling studies of PCBs have been conducted in wildlife species, such as marine mammals, birds, and polar bears [31-39]. Pharmacokinetic modelling of PCBs has also been carried out in experimental animals, such as rats, mice and fish [40-49] and in swine and sheep [49]. PCB-153 has been most commonly modeled, although some work has also been done with other congeners and with PCB mixtures, such as Aroclor 1242, 1254, and 1260. One study focused on dioxin-like PCBs and their transfer from feed and soils to eggs of laying hens [50].

Models of various complexities have been developed with the simplest using a single

compartment model that represented the whole organism [48]. In the single compartment model, bioaccumulation and elimination of Aroclor 1254 was studied in striped bass and parameters for absorption rate constant and elimination rate constant were estimated. Several studies employed a two-compartment model to represent, for example, blubber and rest of body in pilot whales [30], gut and rest of body in ringed seal [33], central and fat in laying hens [50], and yolk + albumen and embryo in herring gulls [36]. The most complex scheme was a physiologically-based pharmacokinetic (PBPK) model that incorporated multiple compartments to represent lungs, blood, perfused adipose, deep adipose, bone, brain, muscle, kidney, liver, and intestine in East Greenland polar bears [38]. A risk quotient analysis was conducted by estimating critical body residues of many contaminants, including PCBs, based on reproductive endpoints and then comparing observed contaminant levels measured in polar bears with the critical body residues to determine the proportion at risk for reproductive toxicity [38]. Other studies introduced greater complexity by modelling pregnancy, birth, and lactational processes in females [35] and incorporating time-dependent variations in pharmacokinetic parameters [38,43,46,52].

The pharmacokinetic models were used to estimate lifetime exposure and bioaccumulation [31,32,33,36,37,52], influence of blubber temperature gradients on PCB concentrations [33], mother-offspring transfer of PCBs [35,36,41], protein binding [39], interactions between congeners [41,43], and the effect of chlorine position on PCB kinetic behaviour [43].

Modelling in humans

Pharmacokinetic modelling of PCBs has been conducted in pregnant women [52], lactating women [54,55,56], infants and children [57,58,59], women with breast cancer [60,61], Inuit [56,58,59,62,63,64] workers in a contaminated building [64], and general populations [66-69]

(Table 5). As with animal modelling studies, the human pharmacokinetic models varied in complexity from simple one-compartment models [55,63,66,68,69], two-compartment models representing maternal and fetal lipids or liver and fat [53,64], to a 22 compartment model in lactating women [53]. The most commonly modeled congener was PCB-153, although other congeners, such as PCB-28, PCB-99, PCB-138, PCB-180, and PCB-199 were also examined. In breast cancer studies, pharmacokinetic models were used to estimate lifetime exposure or exposure during susceptible time windows, which may more accurately represent exposures at the time of cancer diagnosis [60,61]. Similarly, pharmacokinetic modelling was used to simulate exposures during specific time periods (i.e. prenatal, lactational, postnatal) and their association with mental and psychomotor development or behaviour in infants and children [57,58].

The modelling studies conducted for Inuit estimated PCB-153 intake through breast milk using reverse dosimetry [55], simulation of PCB-153 prenatal and postnatal exposures [57], infant exposure to PCB-138, 153, and 180 through placental transfer and breast feeding [58], fate of PCB-99 and PCB-153 in blood and other tissues using a generic PBPK model [61], estimation of PCB-153 cancer risk based on prenatal, postnatal, and lifetime exposures [62], and estimation of daily intake doses of PCB-77, PCB-126, PCB-153, and PCB-169 with comparison to a reference value [63].

Addressing challenges for the development of biomonitoring equivalents

The development of biomonitoring equivalents using pharmacokinetic modelling is complex for PCBs because of the presence of multiple congeners with different pharmacokinetic and toxicological properties. In addition, there are multiple pathways of exposure (e.g. ingestion, inhalation, dermal absorption, placental and lactational transfer), species differences in kinetics, and adverse endpoints which must be taken into consideration when modelling PCB pharmacokinetics.

The following is a list of procedural steps that needed to be followed to develop useful biomonitoring equivalents based on existing information:

Deciding which congeners to model: A list of PCB congeners that are abundant in biota and/or have high potential for toxicity, are shown in Box 1. These congeners fall under five homologue groups (i.e. tri-, tetra-, penta-, hexa-, and hepta-). Prioritization should be given to developing biomonitoring equivalents for these congeners as they are most relevant for risk assessments.

Choosing a guidance value: As described in Tables 3 and Table 4, different organizations have formulated various guideline values based mostly on mixtures of PCB congeners rather than individual congeners. Therefore, it will be necessary to make assumptions about the constitution of these mixtures so that biomonitoring equivalents for individual congeners can be derived.

Parameterization of pharmacokinetic models: A full PBPK model requires input of several parameters. Where possible, these parameters should be based on human data to minimize species differences. However, in the absence of such data, animal data or theoretical structural equations, both of which introduce greater degrees of uncertainty in the models, can be used. The ATSDR contains data on the absorption, distribution, metabolism, and excretion of PCB congeners as described previously [5,22]. In addition, Parham et al. (1997) and Parham et al. (1998) devised structural regression formula to calculate blood-adipose partition coefficients and metabolic rates for any of the 209 congeners based on structural characteristics [76,77]. An important component of the modelling process will be to evaluate and transparently declare the confidence in the inputted parameters.

Minimizing complex scenarios: Depending on the research question, initial modelling attempts should focus on the most common routes of exposure. In general populations, ingestion of

contaminated foods will be the primary exposure pathway. For lactating women, elimination of PCBs through breast milk should additionally be considered.

Conclusion

Biomonitoring equivalents for PCBs will be useful from a risk assessment standpoint because they can be used to interpret the biomonitoring data collected from populations around the globe. The percentage within and exceeding guidance values can be calculated for full survey samples, as well as for sensitive sub-populations, such as children, pregnant women, women of childbearing age and the elderly. These comparisons will help to contextualize the results of biomonitoring surveys and provide evidence on which to base public health interventions for the percentage of the population exceeding guidelines. In this paper we have reviewed key information and challenges for deriving biomonitoring equivalents for PCBs. Modelers, environmental epidemiologists, and risk assessors can make use of this information to evaluate worldwide PCB biomonitoring data and develop international guidelines.

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Table 1: Worldwide biomonitoring data

Country	Population	Sample Size	Congener(s)	Level	Source
United States*	NHANES: 12+ years (2003–2004)	1896	PCB-153	GM (95% CI) (ng/g lipid): 19.8 (18.8, 20.9)	[21]
Canada*	CHMS: 20–79 years (2007–2009)	1666	PCB-118 PCB-138 PCB-146 PCB-153 PCB-156 PCB-163 PCB-170 PCB-180 PCB-187 PCB-194 PCB-201 PCB-203	GM (95% CI) (ng/g lipid): 4.43 (3.78, 5.20) 10.13 (8.92, 11.51) 2.02 (1.76, 2.32) 18.31 (15.83, 21.16) 2.64 (2.40, 2.92) 3.22 (2.85, 3.65) 4.60 (4.09, 5.17) 15.21 (13.52, 17.11) 3.72 (3.21, 4.31) 2.91 (2.59, 3.29) 2.60 (2.33, 2.89) 2.25 (2.04, 2.47)	[22]
Canada	Adult IHS: 18+ years (2007–2008)	2162	∑PCB	GM (95% CI) (ng/g lipid): 409 (389, 430)	[20]
Australia*	Pooled samples: 61+ years (2011–2012)	4 pools of 100 samples	PCB-138 PCB-153 PCB-180	AM (95% CI) (ng/g lipid): 13.4 (11.0, 15.7) 18.9 (16.9, 20.9) 18.5 (15.3, 21.6)	[69]
Germany*	GerES: 18–69 years (1998)	2823 2818 2822	PCB-138 PCB-153 PCB-180	GM (95% CI) (µg/L w.b.): 0.42 (0.41, 0.43) 0.68 (0.66, 0.70) 0.44 (0.42, 0.45)	[70]
Spain (Catalonia)*	CHIS: 18–74 years (2001–2002)	919	PCB-118 PCB-138 PCB-153 PCB-180	GM (range) (ng/g lipid): 17.4 (0.7, 465.0) 63.5 (0.7, 1829.7) 91.2 (0.7, 1912.1) 75.1 (2.6, 2047.2)	[71]
Belgium (Flanders)*	FLEHS: newborns (2002–2003)	1051 1054 1065 1050 1071	PCB-118 PCB-138 PCB-153 PCB-170 PCB-180	GM (95% CI) (ng/g lipid): 10.5 (10.1, 11) 15.3 (14.6, 16.2) 25.9 (24.5, 27.5) 7.7 (7.5, 8.0) 20.4 (19.5, 21.3)	[72]
	FLEHS: adolescents (2002–2006)	1645	∑PCB	GM (95% CI) (ng/g lipid): 68.0 (66.0 ,70.0)	[73]
	FLEHS: 50–65 years (2002–2006)	1530	∑PCB	GM (95% CI) (ng/g lipid): 333.0 (325.0, 341.0)	

Abbreviations: AM = arithmetic mean; CHIS = Catalan Health Interview Survey; CHMS = Canadian Health Measures Survey; CI = confidence interval; FLEHS = Flemish Environment and Health Survey; GerES = German Environmental Survey; GM = geometric mean; IHS = Inuit Health Survey; NHANES = National Health and Nutrition Examination Survey; PCB = polychlorinated biphenyl; w.b. = whole blood

* Data for PCB-138, PCB-153, and PCB-180 stratified by age groups presented in Aylward et al. (2014) [69].

Table 2: Worldwide biomonitoring data—breast milk (∑PCB)

Country	Population	Sample Size	Level (ng/g lipid)	Source
Canada	National Canadian Study (1992)	497	Mean: 238	[5]
Canada (Northern)	Women from Keewatin (1996–1997)	12	Mean: 247	[5]
United States—Akwesasne	Mohawk women residing near three hazardous waste sites (1991–1992)	40	Mean: 254	[5]
United States (rural New York)	Caucasian women (1991–1992)	45	Mean: 318	[5]
United States (New York)	Women residing in counties adjacent to Lake Ontario (1991–1993)	213	Mean: 271	[5]
Sweden	National Sweden Study (1992)	380	Mean: 380	[5]
Finland (urban)	Women giving birth in a maternity clinic in Helsinki (1992–1994)	20	Mean: 296	[5]
Finland (rural)	Women giving birth in a maternity clinic in Kuopio (1992–1993)	64	Mean: 198	[5]
Germany	Women 27–31 years, primiparous	14	Median: 450	[5,74]
Croatia	Women nursing hospitalized children (1994–1995)	45	Median: 212	[5]
Russia (industrialized)	Women from Murmansk (1993)	15	Mean: 429.4	[5]
Russia (industrialized)	Women from Monchegorsk (1993)	15	Mean: 490.5	[5]

Abbreviations: PCB = polychlorinated biphenyl; SD = standard deviation

Table 3: Non-occupational PCB reference values

Source	Route of Exposure	Reference Value
AFSSA 2013	All	Critical Concentration Threshold (vulnerable populations - pregnant women, women of child-bearing age, lactating women, and children under 3 years of age): 0.7 µg total PCB/g plasma lipids (rest of population): 1.8 µg total PCB/g plasma lipids
Health Canada 2010	Ingestion	TDI (total NDL-PCBs): 0.13 µg/kg/d
AFSSA 2007	Ingestion	TDI: 0.01 µg/kg/d (PCB indicators in food)
WHO 2003	Ingestion	TDI: 0.02 µg/kg/d (Aroclor 1254)
JECFA 2001	Ingestion	TDI (dioxins): 2.33 pg TEQ/kg/d Theoretical TDI for DL-PCBs (based on 70% of dioxin mixture): 1.63 pg TEQ/kg/d
EPA 2000	Ingestion	RfD Aroclor 1254: 0.02 µg/kg/d Aroclor 1016: 0.07 µg/kg/d Aroclor: 1248: not verifiable
ATSDR 2000	Ingestion	MRL (intermediate duration): 0.03 µg/kg/d MRL (chronic duration): 0.02 µg/kg/d (Aroclor 1254)
CSHPF 1991	Ingestion	TDI: 5 µg/kg/d (Phenochlor-DP6)
EFSA 2005	Ingestion (breast milk)	BMD: 0.94–1.05 µg total PCB/g lipid BMDL: 0.63–0.71 µg/g lipid
EFSA 2005	Ingestion (breast milk)	BMDL (PCDD/PCDF/PCB TEQ): 65 pg TEQ/g lipid

Abbreviations: AFSSA = French Food Safety Agency; ATSDR = Agency for Toxic Substances and Disease Registry; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; CSHPF = French High Council for Public Hygiene; DL-PCBs = dioxin-like polychlorinated biphenyls; EFSA = European Food Safety Authority; EPA = Environmental Protection Agency; JECFA = Joint FAO/WHO Expert Committee on Food Additives; MRL = minimal risk level; NDL-PCBs = non dioxin-like polychlorinated biphenyls; PCB = polychlorinated biphenyl; PCDD = polychlorinated dibenzo-p-dioxins; PCDF = polychlorinated dibenzofurans; RfD = reference dose (oral); TDI = tolerable daily intake; TEQ = toxic equivalent; WHO = World Health Organization

Table 4: Occupational PCB reference values

Source	Route of Exposure	Reference Standard
NIOSH 2000	Inhalation	REL (10-hour) Chlorodiphenyl (42% or 54% Cl): 1 µg/m^3
ACGIH 1998	Inhalation, dermal	TLV (8 hour) Aroclor 1242: 1 mg/m^3 Aroclor 1254: 0.5 mg/m^3
OSHA 1998	Inhalation, dermal	PEL (8-hours) Aroclor 1242: 1 mg/m^3 Aroclor 1254: 0.5 mg/m^3

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; Cl = chlorine; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure level; REL = recommended exposure limit; TLV = threshold limit value

Table 5: Pharmacokinetic modelling of PCBs in humans

Population	Model Purpose	Congener	Methods	Compartment	Selected Results	Reference
Pregnancy						
Pregnant women	Influence of pharmacokinetics on the association between prenatal PCB-153 exposure and reduced birthweight	PCB-153	Monte Carlo simulations run on model and simulated data used in linear regression analyses to estimate association between PCB-153 and birthweight	N = 2 Maternal lipids Fetal lipids	Model validated with observed data in 10 pregnant women Association was confounded by effects of gestational weight gain	[52]
Lactation						
Italian women	To estimate exposure scenarios	PCB-138 PCB-153 PCB-180	PBPK Model: Food was only source of exposure considered	N = 22	Model adequately predicted observed results for PCB-153 and PCB-180, but not for PCB-138	[53]
Mother-infant birth cohort from Slovakia	To use longitudinal measurements in development of exposure metrics	PCB-153	System type model	N = 1 Fat	PCB body burden was associated with duration of breast feeding in most children	[54]
Women (25-year old)	Population-scale lactational model	PCB-153	PBPK Model: Derived from a model in pregnant and lactating mice Reverse dosimetry to estimate PCB intake in Canadian Inuit	N = 5 Liver Fat Mammary tissue Blood Rest of body Flow-limited	Model predicted human biomonitoring data of milk content from all over the world Estimated intake in Canadian Inuit 0.294 µg/hr/kg—this intake generated milk levels similar to those reported	[55]

Infants and Children						
Spanish children	To investigate if lactational exposure is associated with effects on mental and psychomotor development; To compare with prenatal exposure	PCB-153	PBPK Model: To simulate prenatal and postnatal PCB-153 exposure Association between simulated PCB-153 concentrations and mental/psychomotor scores estimated with linear regression model	Same as Verner 2009 [58]	No association found between postnatal exposure and mental or psychomotor scores Prenatal exposure was associated with worse mental and psychomotor score	[56]
Inuit infants from Arctic Quebec	To simulate PCB levels during specific pre- and postnatal periods and assess association with infant behaviour	PCB-153	PBPK Model: To simulate prenatal and postnatal PCB-153 exposure Association between simulated PCB-153 concentrations and behavioural measures estimated with linear regression model	Same as Verner 2009 [58]	Pre- and postnatal exposures associated with inattention and increased activity at 11 months of age—inattention related to prenatal exposure and activity with postnatal exposure Strongest association during 4th month of life	[57]
Mothers and infants—validation with data from Nunavik population	Development of a generic PBPK for POPs to estimate infant exposure through placental transfer and breast feeding	PCB-138 PCB-153 PCB-180	PBPK Model: Absorption assumed to be 100% and direct input to liver	Mother: N = 9 Liver Brain Fat Richly-perfused Poorly-perfused Mammary tissue Uterus Placenta Fetus	Model predicted observed concentrations in mothers and infants from a Northern Quebec Inuit population	[58]

				Infant: N = 5 Liver Fat Richly-perfused Poorly-perfused Brain		
Women with Breast Cancer						
French women	To estimate lifetime pharmacokinetic profile of PCB-153 and compare with levels measured at the time of breast cancer diagnosis	PCB-153	PBPK Model: Exposure via oral intake, assuming complete bioavailability from GI tract and direct input to liver Area under lipid-adjusted blood concentration vs. time curve for each decade (proxy for total internal exposure) compared with measured concentrations	Same as Verner 2008 [60]	Single point PCB levels measured at time of diagnosis do not fully represent early-life exposures	[59]
Women in general	To estimate lifetime POP blood/tissue exposure during any time window of susceptibility for breast cancer (from 0–55 years of age)	PCB-153 PCB-180	PBPK Model: Exposure via oral intake, assuming complete bioavailability from GI tract and direct input to liver To simulate exposures throughout life, compartment size, blood flow, and biochemical properties change as a function of age, body weight, body height, and pregnancy periods	N = 9 Fetus Placenta Uterine tissue Brain Fat Richly-perfused Slowly-perfused Liver Mammary tissue—all perfused by blood circulation	Lactation periods and weight profile had greatest impact on lifetime pharmacokinetic profile	[60]

Inuit						
Greenlandic Inuit	To estimate fate of POPs in liver, blood, muscle, fat tissue	PCB-99 PCB-153	PBPK Model: General model for POPs	Based on model by Cahill (2003)	PCB-99 estimated mean: Blood—0.03 ng/g Fat—5.3 ng/g Liver—0.3 ng/g Muscle—0.2 ng/g PCB-153 estimated mean: Blood—1.4 ng/g Fat—313 ng/g Liver—18 ng/g Muscle—13 ng/g	[61]
Inuit	To estimate human lifetime health risks using pharmacokinetic modelling	PCB-153	Pharmacokinetic Model: PCB-153 concentration in total body lipid modelled as a function of age and calendar time Three life stages—prenatal exposure, postnatal exposure, lifetime exposure Non-cancer (HQ) and cancer risks estimated	N = 1 Fat	HQ > 1 between 1955–1987 for 90^{th} population percentile and during 1956–1984 for 50^{th} population percentile Cancer risk ranged from 4.6×10^{-5} to 1.8×10^{-6} for 90^{th} percentile and 3.6×10^{-5} to 1.4×10^{-10} for 50^{th} percentile with upper bound slope factor	[62]
Inuit (Arctic Quebec)	To estimate daily intake dose based on milk fat content and compare with reference intake	PCB-153 Non-ortho PCBs (PCB-77, 126, 169)	Modelling and comparison with reference intake	Based on model by Carrier (1991)[c] N = 2 Liver Fat	Estimated daily intake: PCB-153: 0.04 µg/kg/d PCDD/PCDF/NOC PCB: 7×10^{-6} µg/kg/d Calculated PCB-153 exceeds acceptable daily intake	[63]
Workers						

Contaminated building	To develop pharmacokinetic model for degradation in adult humans based on data from workers in a contaminated building	PCB-28 PCB-52	Model—first order elimination kinetics: $y_t = y_o (1 - e^{-kt})$	N/A	Estimated half-lives: PCB-28: 2.18 (95% CI: 1.91–2.54) y PCB-52: 3.95 (95% CI: 3.55–4.45) y	[64]
General Populations						
General	To estimate chemical half-lives	PCB-199	Whole body primary biotransformation half-life (HL_B) estimated from whole body total elimination half-life (HL_T) using a one-compartment model	N = 1	Half-life of 83 000 days calculated Low rates of predicted passive chemical elimination (HL_B approximates HL_T)	[65]
General	To develop a generic model that estimates bioaccumulative potential of a chemical (hBCF)	PCB-77 PCB-80 PCB-136 PCB-153 PCB-155	PBPK Model: Assumed 100% intestinal absorption	N = 4 Absorption compartment Portal vein Systemic compartment Liver	Model was validated for several chemicals by comparing model simulations with literature human data and PBPK model results	[66]
General	To estimate intrinsic human elimination half-lives of PCBs (i.e. correcting for body weight and ongoing exposure) using population data	PCB-28 PCB-52 PCB-105 PCB-118 PCB-138 PCB-153 PCB-170 PCB-180 PCB-187	PBPK Model: Described changes in body concentrations as function of age and calendar time (incorporated age-dependent growth of body and lipid mass, age- and body-weight dependent dietary intake) Derived from Ritter 2009[75]	N = 1	Intrinsic half-lives derived e.g. PCB-153: 14.4 y PCB-170: 15.5 y PCB-180: 11.5 y Distinction is needed between apparent and intrinsic half-lives	[67]
General	To model POPs burden and	PCB-101	Simple model with an age-	N = 1	Model reconstructed lifetime	[68]

	clearance throughout a lifetime, taking into account changes in age, body composition, and environmental concentrations		dependent function allowing for growth in body fat and subsequent compound dilution with age	Fat	exposure in UK population born between 1920 and 1980	

Abbreviations: CI = confidence interval; GI = gastrointestinal; hBCF = human bioconcentration factor; HQ = hazard quotient; NOC = non-ortho coplanar; PBPK = physiologically-based pharmacokinetic; PCB = polychlorinated biphenyl; PCDD = polychlorinated dibenzodioxin; PCDF = polychlorinated dibenzofuran; POP = persistent organic pollutant; UK = United Kingdom

Box 1: Abundant and/or toxic PCB congeners

PCB-28 (2,4,4I trichlorobiphenyl)	PCB-105 (2,3,3I,4,4I pentachlorobiphenyl)	PCB-156 (2,3,3I,4,4I,5 hexachlorobiphenyl)
PCB-52 (2,2I,5,5I tetrachlorobiphenyl)	PCB-118 (2,3I,4,4I,5 pentachlorobiphenyl)	PCB-163 (2,3,3I,4I,5,6 hexachlorobiphenyl)
PCB-74 (2,4,4I,5 tetrachlorobiphenyl)	PCB-125 (2I,3,4,5,6I pentachlorobiphenyl)	PCB-168 (2,3I,4,4I,5I,6 hexachlorobiphenyl)
PCB-77 (3,3I,4,4I tetrachlorobiphenyl)	PCB-126 (3,3I,4,4I,5 pentachlorobiphenyl)	PCB-169 (3,3I,4,4I,5,5I hexachlorobiphenyl)
PCB-100 (2,2I,4,4I,6 pentachlorobiphenyl)	PCB-128 (2,2I,3,3I,4,4I hexachlorobiphenyl)	PCB-170 (2,2I,3,3I,4,4I,5 heptachlorobiphenyl)
PCB-101 (2,2I,4,5,5I pentachlorobiphenyl)	PCB-138 (2,2I,3,4,4I,5I hexachlorobiphenyl)	PCB-180 (2,2I,3,4,4I,5,5I heptachlorobophenyl)
PCB-104 (2,2I,4,6,6I pentachlorobiphenyl)	PCB-153 (2,2I,4,4I,5,5I hexachlorobiphenyl)	PCB-190 (2,3,3I,4,4I,5,6 heptachlorobiphenyl)

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Chapter 4: Biomonitoring Equivalents for Polychlorinated Biphenyls

Abstract

Polychlorinated biphenyls (PCBs) are ubiquitous persistent organic pollutants that are included in many biomonitoring programs. In this study, Biomonitoring Equivalents (BEs) were developed for individual non-dioxin like and dioxin-like PCB congeners using one-compartment pharmacokinetic models. Oral reference doses for sum of non-dioxin like PCBs and sum of dioxin-like PCBs were identified from Health Canada and from the Joint FAO/WHO Expert Committee on Food Additives (JECFA) respectively. Elimination rate constants were obtained from human studies conducted in general populations and occupationally exposed workers. The BEs for non-dioxin like and dioxin-like PCBs ranged from 0.36-7.21 mg/kg lipid and 0.00003-7.14 mg/kg lipid respectively, based on weight of 70 kg and body fat of 25%. The derived BE values compare well with BEs of other persistent organic pollutants, such as hexachlorobenzene, PBDE-99, and 2,3,7,8-TCDD. The BEs derived for PCBs can be used as a risk assessment tool to evaluate observed exposure levels in human populations.

Keywords: biomonitoring equivalent; polychlorinated biphenyls; risk assessment

Introduction

The measurement of contaminants in human biological matrices, known as biomonitoring, has been carried out in national surveys by different countries for many years. In Canada, the Canadian Health Measures Survey (CHMS) is a biennial survey that started in 2007 and provides data on contaminants and heavy metals in plasma and urine.[1] In the United States, the National Health and Nutrition Examination Survey (NHANES) conducts measurement of many environmental chemicals in blood, serum and urine of the American population.[2] Other countries, such as Korea (KNHANES)[3] and Germany (GerES)[4], have also conducted similar national biomonitoring surveys. In addition, studies of environmental contaminants in smaller cohorts of specific communities at higher risk of exposures, such as the Inuit[5], the First Nations[6], and residents around the Great Lakes[7] in Canada have been conducted.

Human biomonitoring data are valuable for tracking temporal variability of exposures. However, the health implications associated with the exposure levels are difficult to interpret because reference or guidance values are often not available for many contaminants. Risk assessments of chemical exposures usually establish oral reference doses (e.g. tolerable daily intake, benchmark dose, and minimal risk level) for the purposes of public health protection. These values are not directly comparable to biomonitoring data, which represent the internal dose and eventual steady-state concentrations that are determined by processes of absorption, distribution, metabolism and excretion.[8,9] Thus, an internal metric that corresponds to the external reference dose is needed to make more accurate assessments about the potential health risks of contaminant exposures.

This internal metric is known as a biomonitoring equivalent (BE). The development of BEs uses the methods of pharmacokinetic modelling to convert an external reference dose to an

internal dose, against which biomonitoring data can be directly compared.[8,9] Hays et al. (2008) provided guidelines for developing BEs.[9] The process generally starts with a point of departure (POD), such as a no-observed adverse effect level (NOAEL) from an animal toxicity study, upon which a reference dose in humans is based. The POD is converted to an internal concentration using pharmacokinetic modelling and, if this value was derived in an animal model, it is subsequently scaled to a human internal concentration by the application of uncertainty factors.[9] BEs have already been developed for several environmental contaminants, including pentabromodiphenyl ether-99 (PBDE-99)[10], toluene[11], hexachlorobenzene (HCB)[12], 2,4-dichlorophenoxyacetic acid[13], and dichlorodiphenyl-dichloroethylene/dichlorodiphenyltrichloroethane (DDE/DDT)[14]. Currently, no BEs have been developed for the polychlorinated biphenyls (PCBs).

PCBs are a ubiquitous group of chemicals that include both non-dioxin like and dioxin-like congeners (NDL-PCBs and DL-PCBs). They were used historically in electrical equipment (e.g. capacitors and transformers) for coolant and lubricant properties, and in plasticizers, oils, inks, paints, adhesives, and waxes.[15] Although PCBs are no longer manufactured or used, they persist in biota and have been detected in human populations worldwide. The French Agency for Food, Environmental and Occupational Health and Safety (ANSES) derived levels of concerns for total PCBs of 0.7 mg/kg lipid for susceptible subgroups (i.e. pregnant women, women of child-bearing age, lactating women, and children under 3 years of age) and 1.8 mg/kg lipid for adult men, women past child-bearing age, and boys over 3 years of age.[16] The lower level of concern is based on mental and motor development of children exposed to PCBs in utero and the upper level of concern is based on epidemiological studies showing adverse neurological and thyroid hormone effects.[16] The German Federal Environment Agency established human

biomonitoring (HBM) values for non-carcinogenic effects of total PCBs ($\sum PCB_{138, 153,180}$ x 2), based on neurological impairment, thyroid metabolism, and altered response to vaccines.[17] Adverse effects are not expected at the HBM value of 3.5 μg/L serum wet-weight, but are of concern in susceptible subgroups at the HBM II value of 7 μg/L.[17]

While the ANSES levels of concern and the HBM values provide guidance to assess total PCB levels, there is currently no guidance available for individual PCB congeners, including the DL-PCBs, which exert toxicity through the aryl hydrocarbon (Ah) receptor. The objective of this work, therefore, was to develop a risk assessment tool for PCBs by developing BE values for the indicator NDL-PCBs and the DL-PCB congeners, based on human tolerable daily intakes (TDI) established by Health Canada and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The indicator NDL-PCBs, which include PCB-28, PCB-52, PCB-101, PCB-138, PCB-153, and PCB-180, are highly persistent and are commonly found in food items of animal origin and in human adipose tissue.[18]

Methods

Data Sources:

Comprehensive database and grey literature searches were conducted to identify oral reference doses for PCBs. Oral reference doses were available for NDL-PCBs from Health Canada and for DL-PCBs from the JECFA in the form of TDIs, which represent an amount an individual can ingest daily over a lifetime without any risk to health. Pharmacokinetic parameters for PCB congeners were obtained from published studies, which were identified by searching Medline, Scopus, Toxline, and Toxnet. Elimination rate constants were derived from half-lives of lipid-adjusted concentrations or adipose tissue levels in humans.

Derivation of Biomonitoring Equivalents:

A one compartment model consisting of a fat compartment and first-order kinetics were used to simulate the behaviour of all congeners (Figure 1). A one-compartment model was chosen for sake of simplicity and the high log octanol-water (k_{ow}) values of higher chlorinated PCBs (i.e. 6.72-8.35 for PCB-153).[15] The BEs were calculated as steady-state concentration (C_{ss}), using the following formula:

$$C_{ss} = F*Dose/k_eV_d \quad \text{(Eq.1)}$$

Where F is bioavailability, k_e is elimination rate constant (d^{-1}), and V_d (kg) is volume of distribution of fat compartment. Body fat weight of 17.5 kg was inputted for V_d (70 kg x 0.25). Dose was the TDI established by Health Canada for ∑NDL-PCBs, based on Aroclor 1248; the TDI was multiplied by 70 kg to obtain dose in units of mg/d. For DL-PCBs, the TDI was in units of toxicity equivalent (TEQ) and, therefore, the dose was additionally divided by the congener's toxic equivalency factor (TEF)[19] to obtain units of mg/d.

$$Css = [F*(Dose/TEF)/k_eV_d] \quad \text{(Eq.2)}$$

The C_{ss} value was derived in units of mg/kg lipid, assuming that adipose and lipid levels are equivalent.[20] A generic set of BE values was calculated based on a body weight of 70 kg and body fat of 25%.

The NDL indicator PCBs for which half-life data were available (PCB-28, PCB-52, PCB-138, PCB-153, PCB-180) and DL-PCBs (PCB-77, PCB-81, PCB-105, PCB-114, PCB-118, PCB-123, PCB-126, PCB-156, PCB-157, PCB-167, PCB-169, and PCB-189) were modeled individually. The Aroclor 1248 TDI was used for each indicator NDL-PCB (i.e. the TDI was not apportioned among the congeners) as additive toxicity could not be assumed. Similarly, the TDI based on 2,3,7,8-TCDD was used for each DL-PCB congener, although the congener's potency

was taken into consideration by dividing the TDI by the congener's TEF, as shown in Eq.2.

Results

Oral Reference Doses and Pharmacokinetic Parameters:

Table 1 describes the PCB human oral reference doses chosen for the BE derivation. In Table 2, the elimination rate constants (k_e) and half-lives ($T_{1/2}$) for the indicator NDL-PCBs and DL-PCBs are provided. Human data were available from studies of poisoning incidents (e.g. Yusho and Yucheng), occupational exposures, volunteers, and general populations.[21–37] However, most studies reported apparent half-lives, which may over-estimate intrinsic half-lives because apparent half-lives include the influence of ongoing exposures. For this modelling exercise, half-lives reported from lipid-adjusted or adipose tissue measurements from three general population studies[21,31,32] and one occupational study[28] were used. Ritter et al. (2011) estimated intrinsic elimination half-lives based on lipid-adjusted biomonitoring data from 229 individuals residing in the United Kingdom.[32] Aylward et al. (2014) estimated apparent elimination half-lives from PCB measurements in adipose tissue of 43 subjects in the United States.[21] Ogura et al. (2004) also measured elimination half-lives based on PCB adipose tissue concentrations in 10 Japanese subjects.[31] Luotamo et al. (1991) analyzed adipose tissue levels of PCBs in occupational workers (12 males) after release and partial burning of a commercial PCB mixture in a pulp mill.[28] Concentrations in adipose tissue were provided for one day (14.85 μg/kg) and one month (14.33 μg/kg) after the accident and this data was used to derive the apparent elimination rate constant for PCB-156.

No estimate of PCB bioavailability based on comparison with an intravenous (IV) administered dose was identified. Although the available evidence suggests that PCBs are well absorbed after oral administration, there is likely heterogeneity based on number of chlorines and

interindividual differences. Estimates of percent absorbed (i.e. difference between PCB input and PCB output with feces, divided by the input dose) were obtained in seven adult volunteers aged 24-81 years.[38] For several congeners, percent absorbed was > 90%. However, absorption varied according to PCB congener, subject age, and body burden. Similarly, in rhesus monkeys, >90% of a single dose of Aroclor 1248 was absorbed from the gastrointestinal tract.[39] For this study, each congener was inputted with a bioavailability value of 50 or 90% to account for potential heterogeneity in PCB bioavailability.

BE Values:

Table 3 provides the derived BE values for the NDL indicator PCBs and DL-PCBs. The range of BE values is due to input of different values for bioavailability or elimination rate constant, as shown in Table 2.

Discussion

A set of BE values have been developed for several PCB congeners. These values can be used for the purposes of risk assessment to evaluate potential population-level human health risks of observed exposure levels. The values should be adjusted based on the body weight and fat of the population to which they are applied. Larger deviations in fat and body weights of a population will result in larger differences in population-specific BE values. The derived BE values are useful for assessing risk of PCBs in adult populations where the primary route of exposure is through ingestion. In cases where other routes of exposure are dominant (e.g. dermal or inhalational for lower chlorinated PCB congeners), lactational exposure in infants, or assessing the risk of PCB exposures in children, the BE values may not be applicable.

According to Hays et al. (2008), the POD that is the basis of an exposure guidance value is recommended to be the starting point of a BE derivation.[9] In our BE derivation process, we

chose to utilize the considerable amount of PCB human pharmacokinetic data available and derive the BE values directly from the human reference value rather than the animal POD. We conducted a search for animal pharmacokinetic data upon which the PODs were established (i.e. NDL-PCBs: Aroclor 1248 in rhesus monkey and DL-PCBs: TCDD in rats). A single study of Aroclor 1248 administration was identified in rhesus monkeys, however half-life was not reported and could not be derived from the data provided.[39] A rough calculation based on the POD for DL-PCBs (i.e. 12.5 ng/kg TCDD) and a half-life of 19 days for TCDD in rats[40] led to a BE of 0.00009 mg/kg lipid, which is close to the upper BE limit found for PCB-126.

No validation was conducted to compare the PCB pharmacokinetic model outputs with external data because human PCB congener-specific pharmacokinetic profiles were not available. However, a comparison with the BE values of other chemicals indicated the relative placement of the derived PCB BE values. For NDL-PCBs, the BE range (0.36-7.21 mg/kg lipid) corresponds to the BE for HCB of 0.25 mg/kg lipid[41], PBDE-99 BE of 0.52 mg/kg lipid.[10], and the lower BE range for the sum of DDT and its metabolites (5-40 mg/kg) (Figure 2). The minimum limit of the DL-PCB BE range is 10 000 times lower than that of non-dioxin like PCBs. Most of the half-life data in humans for DL-PCBs came from a single study of only 10 subjects[31] with a wide range of reported values depending on PCB congener. Dioxin-like compounds are expected to have lower toxicity threshold compared with other contaminants. Aylward et al. (2008) calculated a BE of 0.000031 mg/kg for 2,3,7,8-TCDD based on reproductive effects on male rats exposed in utero.[42] This value is similar to the minimum BE range of the most potent DL congener, PCB-126.

In this work, a systematic search of oral reference doses and pharmacokinetic parameters from published and grey literature was conducted to arrive at a set of BE values for PCBs. The

simplicity of the one-compartment strategy means that it can be easily tailored to different populations by varying the body weight and body fat percentage variables only. However, the downside of this approach is that the actual complexities of the absorption, distribution, metabolism, and excretion processes of these contaminants are omitted from consideration.[43] Thus, factors such as metabolism by the liver, genetic differences in metabolism, and distribution to other compartments have not been accounted for. Second, none of the models were validated with external datasets of pharmacokinetic data of PCB congeners in humans, which were unavailable to the authors' knowledge. Second, the oral reference dose for NDL-PCBs was based on the sum and this value was inputted for the individual congeners. In the current method of BE development, it is not possible to ascribe toxicity specifically to the individual NDL congeners. Additionally, BE values could not be derived for all abundant and/or toxic PCB congeners.[43] Third, the half-lives for PCBs were obtained from occupational cohorts or general populations from the United Kingdom, United States, and Japan; these half-lives were assumed to apply to the general Canadian population. No additional uncertainty factor for human variability was applied to arrive at the final BE values because the TDIs for both NDL and DL-PCBs have already accounted for intraspecies variability.

In summary, the BEs derived for PCBs can be used as a risk assessment tool to evaluate observed exposure levels in human populations. Exceedances of BEs can be used to identify potential population-level human health risks.

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Table 1: PCB oral human reference doses

	PCBs	
	HC 2010[44]	**JECFA 2001/ AFSSA 2007**[18,45]
Chemical Form	∑NDL-PCBs	∑DL-PCBs
Animal Model	Rhesus monkey	Rat
Endpoint	Locomotor activity	Developmental effects in male offspring
NOAEL	0.013 mg/kg/d*	12.5 ng/kg bolus**
UF	100 10 - Interspecies Variability 10 – Intraspecies Variability	3.2 Intraspecies Variability***
Human Oral Reference Dose	TDI: 0.00013 mg/kg/d	TDI: 1.63 pg TEQ/kg/d

* Based on administration of Aroclor 1248.

** Administration of 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). The NOAEL was used to derive a TDI of 2.33 pg TEQ/kg/d for dioxins. The JECFA concluded that this TDI is applicable to polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and coplanar PCBs. Coplanar PCBs were assumed by AFSSA to constitute 70% of the dioxin mixture, resulting in a TDI of 1.63 pg TEQ/kg/d (i.e. 0.70 x 2.33).

*** According to the derivation document[45], a safety factor for interspecies variation was not needed because body burdens were used to scale doses from laboratory animals to equivalent human doses.

Abbreviations: AFSSA = Agence Francaise de Sécurité Sanitaire des Aliments; DL-PCBs = dioxin-like polychlorinated biphenyl; HC = Health Canada; JECFA = Joint FAO/WHO Expert Committee on Food Additives; NDL-PCB = non-dioxin like polychlorinated biphenyl; NOAEL = no-observed adverse effect level; PCBs = polychlorinated biphenyls; TDI = tolerable daily intake; TEQ = toxic equivalency; UF = uncertainty factor

Table 2: Elimination rate constants for PCBs in humans

	k_e (d^{-1})	$T_{1/2}$ (yr)
NDL-PCBs:		
PCB-28	0.0003	5.5[32]
PCB-52	0.0007	2.6[32]
PCB-138	0.0001; 0.0002	10.8; 15.9[20,31]
PCB-153	0.00010; 0.00013	14.4; 19.9[21,32]
PCB-180	0.0001; 0.0002	11.5; 29.2[21,32]
DL-PCBs:		
PCB-77	0.0173; 0.0190; 0.0380	0.05 (18.3 d); 0.1 (36.5 d); 0.11 (40.2 d)[31]
PCB-81	0.0016; 0.0027; 0.0047	0.4 (146 d); 0.7 (255.5 d); 1.2[31]
PCB-105	0.0002; 0.0004; 0.0007	2.7; 5.2; 9.3[21,31,32]
PCB-114	0.00005; 0.00008; 0.00012	16; 25; 40[31]
PCB-118	0.00019; 0.00020; 0.00045	4.2; 9.3; 10.1[21,31,32]
PCB-123	0.0001; 0.0002; 0.0003	5.8; 12; 25[31]
PCB-126	0.0004; 0.0007; 0.0012	1.6; 2.7; 4.5[31]
PCB-156	0.00005; 0.00008; 0.00050	3.8; 23; 38[28,31]
PCB-157	0.00004; 0.00007; 0.00012	16; 27; 44[31]
PCB-167	0.0001; 0.0002; 0.0004	5.2; 10; 19[31]
PCB-169	0.00010; 0.00015; 0.00022	8.8; 13; 19[31]
PCB-189	0.00003; 0.00005; 0.00008	24; 41; 69[31]

Abbreviations: DL-PCB = dioxin-like polychlorinated biphenyl; NDL-PCB = non-dioxin like polychlorinated biphenyl; PCB = polychlorinated biphenyl

Table 3: Derived BE values for PCBs

	BE (mg/kg lipid)
NDL-PCBs	
PCB-28	0.75-1.36
PCB-52	0.36-0.64
PCB-138	1.48-3.92
PCB-153	1.97-4.91
PCB-180	1.57-7.21
DL-PCBs	
PCB-77	0.0009-0.0034
PCB-81	0.0023-0.0124
PCB-105	0.15-0.96
PCB-114	0.92-4.13
PCB-118	0.24-1.04
PCB-123	0.33-2.58
PCB-126	0.00003-0.0001
PCB-156	0.22-3.92
PCB-157	0.92-4.52
PCB-167	0.30-1.96
PCB-169	0.0005-0.0020
PCB-189	1.37-7.14

Abbreviations: BE = biomonitoring equivalent; DL-PCB = dioxin-like polychlorinated biphenyl; NDL-PCB = non-dioxin like polychlorinated biphenyl; NOAEL = no observed adverse effect level; PCB = polychlorinated biphenyl; TDI = tolerable daily intake; UF = uncertainty factor

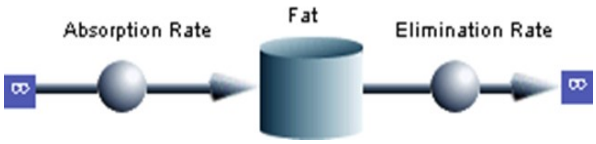

Figure 1: One-compartment model to simulate PCBs

(Berkeley Madonna 8.3.18)

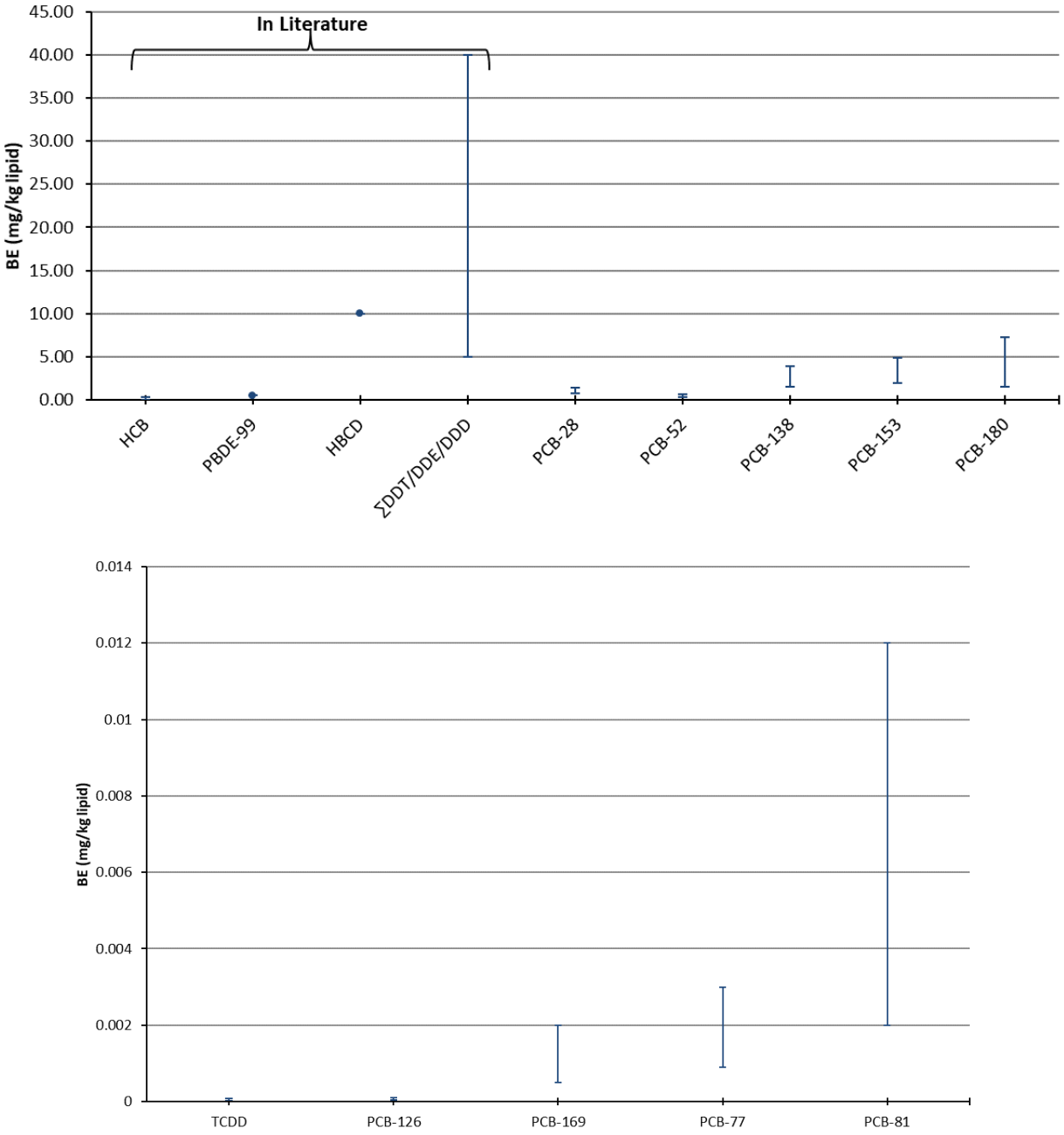

Figure 2: Comparison of PCB BE values

(top panel – NDL-PCBs and bottom panel – DL-PCBs)

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Chapter 5: Application of Biomonitoring Equivalents to Inuit and General Canadian Populations

Abstract: The organochlorine pesticides, chlordane and toxaphene, and the polychlorinated biphenyls (PCBs), are found in the Arctic environment. The concentrations of these contaminants among the Inuit are higher than southern populations, however the impacts to health are currently unclear. Comparison of contaminant levels with health-based guideline values can provide insights into population-level risks. The objective of this study was to apply the derived biomonitoring equivalents (BEs) for chlordane, toxaphene, and PCBs to the contaminant concentrations of the general Canadian and Inuit populations. The BEs were tailored to general Canadians and Inuit by inputting population-specific average body and fat weights into one-compartment pharmacokinetic equations. The percentage that equaled or exceeded the midpoints of the BE ranges were calculated for general Canadians and Inuit, using biomonitoring data from the Canadian Health Measures Survey (CHMS) Cycle 1 (2007-2009) and Inuit Health Survey (IHS, 2008-2009), respectively. The analyses were stratified by males, females, women of child-bearing age (18-44), young adults (18-25), middle-aged (40-55), and elderly (≥60). Among the general Canadian population, no exceedances of chlordane or toxaphene BEs were observed. The general Canadian and Inuit populations both had minimal exceedances of the PCB BE values. However, among the Inuit population, 28% equaled or exceeded the BE for trans-nonachlor, and the highest exceedances were in the elderly subgroup (76%). The hazard quotients (99^{th} percentile/BE) for trans-nonachlor were > 1 for the whole Inuit sample and for the subgroups of, males, females, the middle-aged, and the elderly. The results suggest that trans-nonachlor exposures among the Inuit in 2007-2008 were high with respect to health-based guidance values based on liver endpoints, and that ongoing biomonitoring of this contaminant in the Arctic is warranted.

Introduction

The presence of persistent organic pollutants (POPs) in Northern environments, and their implications on the health of the peoples who reside in the North, have been studied since the 1990s through various multidisciplinary projects, such as the Arctic Monitoring Assessment Programme (AMAP).[1] In the Arctic, POPs arrive from local or, more commonly, from distant sources.[2] Local sources include mining, oil and gas production sites, landfills, and abandoned Distant Early Warning Line radar stations.[2,3] Long-range transport from southern latitudes occurs through the atmosphere, water currents, and sea-ice drift, through a global distillation process, known as the "grasshopper" effect, whereby pollutants undergo repeated evaporation into the atmosphere and deposition onto land or water until they reach the cold environment of the North.[2]

Studies have shown that indigenous populations in the Arctic have higher body burden of contaminants than other populations. Donaldson et al. (2010) reported higher concentrations of heavy metals and POPs in Inuit mothers from Inuvik compared with Dene/Metis and non-aboriginal women.[4] High levels were also measured in Inuit mothers from Nunavik and the Baffin region of Nunavut, although levels decreased from 1992 to 2007.[4] In the Russian North, contaminant levels were measured in blood, cord blood, and breast milk of indigenous women, and blood of adult indigenous populations and controls residing in urban locations.[5] Mothers from the Chukotsky District had the highest contaminant concentrations in blood and breast milk. Overall, blood contaminant levels in indigenous populations of Arctic Russia were similar to those of coastal Greenland and Northern Canada.[5] *(Paragraph adapted from Singh K et al. IJCH 2014; 73: 25808. Available from: www.tandfonline.com/doi/abs/10.3402/ijch.v73.25808.)*

The organochlorine pesticides, chlordane and toxaphene, and the polychlorinated

biphenyls (PCBs), are two ubiquitous groups of POPs that are found in the blubber of marine mammals, such as seals and whales, which are important foods in the traditional diets of the Canadian Inuit.[6] These POPs have also been found in blood samples of the Canadian Inuit, at concentrations much higher than the general Canadian population.[7] In the International Polar Year Inuit Health Survey (IHS) for Adults 2007-2008, questionnaire and clinical data, including blood levels of POPs, were collected from participants across three jurisdictions in the Canadian Inuit Nunangat.[8] The average chlordane concentration among Inuit 61 years of age and older, defined as the sum of cis-nonachlor, trans-nonachlor, and oxychlordane, was 32 times higher than the general Canadian population of the same age range, as measured in the Canadian Health Measures Survey (CHMS), Cycle 1.[7] The concentration of toxaphene, calculated from sum of Parlar No. 26 and 50, among Inuit was 17 times higher than the general Canadian population.[7] Total PCB, which was calculated from the sum of 14 congeners, was four times higher for Inuit compared with general Canadians.[7] The Health Canada intervention guideline of 100 μg/L for Aroclor 1260 was exceeded by about 1% of the Inuit sample, and about 22% exceeded the trigger guideline of 20 μg/L. For women of child-bearing age (18-45), the Health Canada trigger guideline for Aroclor 1260 was 5 μg/L and this was exceeded by nearly 28% of Inuit women of this age range.[7]

While it has been known that the concentrations of POPs among Inuit are higher than southern counterparts, the impacts of the observed concentration to health are currently unclear. Comparison of contaminant concentrations with health-based guideline values can provide insight into whether the observed concentrations pose risks to the population. St. Amand et al. (2014), for example, assessed contaminant exposures among the general Canadian population of the CHMS, Cycle 1 by comparing exposure levels with available biomonitoring equivalents

(BEs), including those for hexachlorobenzene (HCB), PBDE-99, and dichlorodiphenyl-dichloroethylene (DDE).[9] For most contaminants, hazard quotients (HQs) were less than 1, which suggested that contaminant exposures among Canadians do not pose risks.[9] However, there were exceedances for the heavy metals arsenic and cadmium.[9]

The objective of this study was to apply the derived BEs for chlordane, toxaphene, and PCBs (Chapters 2 and 4) to the contaminant concentrations of the general Canadian and Inuit populations, as observed in the CHMS, Cycle 1 (2007-2009) and IHS (2008-2009), respectively. This evaluation will be used to determine if exposures to these contaminants have potential population-level health risks.

Method*s*

The Canadian Health Measures Survey and Total Diet Study:

The CHMS Cycle 1 2007-2009 database was accessed at Carleton, Ottawa, Outaouais Research Data Center (COOL-RDC). The CHMS is a nationally representative, cross-sectional, direct health measures survey conducted every two years, starting in 2007. In Cycle 1, about 5600 respondents between 6-79 years of age were sampled. They represented 96.3% of the Canadian population of this age range residing in the 10 provinces and three territories. A complex, multi-stage sampling strategy was used across 15 collection sites in five standard regional boundaries: Atlantic region (Newfoundland and Labrador, Prince Edward Island, Nova Scotia, and New Brunswick), Quebec region, Ontario region, Prairies region (Alberta, Manitoba, and Saskatchewan and including Yellowknife), and British Columbia region (including Whitehorse). Excluded from the survey were full-time members of the Canadian Forces, institutionalized individuals, and persons living on reserves and other Aboriginal settlements, and in certain remote regions and areas with a low population density.[10] Chlordane (cis-

chlordane, trans-chlordane, cis-nonachlor, trans-nonachlor, and oxychlordane), toxaphene (Parlars No. 26 and 50), and PCBs (PCB-28, PCB-52, PCB-66, PCB-74, PCB-99, PCB-101, PCB-105, PCB-118, PCB-128, PCB-138, PCB-146, PCB-153, PCB-156, PCB-163, PCB-167, PCB-170, PCB-178, PCB-180, PCB-183, PCB-187, PCB-194, PCB-201, PCB-203, and PCB-206) were measured in plasma in 1696 eligible respondents 20-79 years of age. To allow for direct comparison with the derived BEs, which were based in adipose tissue, the plasma concentrations were converted to lipid-adjusted measurements by dividing them by total lipids. Total lipids were calculated according to the following formula[11]:

$$\text{total lipids (mg/dL)} = 2.27*\text{total cholesterol} + \text{triglycerides} + 62.3 \quad \text{(Eq.1)}$$

Levels below the limit of detection (LOD) were recoded as LOD/2. Observations with missing values for contaminant or total lipid were excluded from analyses. To produce estimates that were representative of the entire Canadian population, the analyses incorporated the survey sample weights generated by Statistics Canada. Estimates based on small cell numbers (i.e. <10) have not been reported, according to Statistics Canada guidelines.

The human oral reference doses for chlordane and PCBs, upon which the BEs were derived, and the no-observed adverse effect level (NOAEL) for oxychlordane (with an applied uncertainty factor of 100 to account for intra- and interspecies variation), were also compared with dietary intakes in the Canadian population as measured by the Canadian Total Diet Study (TDS).[12] The TDS has been conducted in different major Canadian cities over six time periods since 1969. Concentrations of contaminants in the food items were measured and combined with estimates of Canadian food intake to calculate dietary intakes of contaminants among different age groups and by gender (from 0-1 month to 65+ years).[12] In this study, the highest average

dietary contaminant intake among subgroups 20+ years of age was compared with the corresponding human oral reference dose (ratio<1 indicated no exceedance).

The Inuit Health Survey:

The Adult IHS (2007-2008) was a cross-sectional survey of Canadian Inuit across 33 coastal communities and three inland communities in the Inuvialuit Settlement Region (ISR), Nunavut Territory, and Nunatsiavut and was conducted as part of the International Polar Year program.[8] A total of 2595 Inuit who were 18 years of age or older participated in the survey (68% participation rate) and 2172 provided blood samples. Pregnant women were excluded. Heavy metals and persistent organic pollutants were measured in plasma, including chlordane (cis-nonachlor, trans-nonachlor, and oxychlordane), toxaphene (Parlars No. 26 and 50), and PCBs (PCB-28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 163, 170, 180, 183, and 187). All work was approved by the research ethics boards of the University of Northern British Columbia, McGill University and the University of Ottawa.

The plasma contaminant concentrations were converted to lipid-adjusted measurements by dividing them by total lipids, according to Eq.1. Values below the LOD were recoded as half the detection limit value. Observations with missing values for contaminant or total serum lipid were excluded.

Tailoring BE Values for General Canadian and Inuit Populations:

Chapters 2 and 4 present generic BE values for chlordane, toxaphene, and PCBs, which were based on 70 kg human body weight and 25% body fat. BE values for chlordane and toxaphene were tailored to the Canadian population by inputting the population-specific average body weight and body fat weight, obtained from the CHMS Cycle 1 and the IHS respectively, into the allometric scaling factor provided in Chapter 2 Eq.2 (parameters: body weight inputted

into BW_{human}, and body fat weight inputted into BWF_{human}). In the CHMS, skinfold thickness measurements were made, however body fat was not assessed with bioelectrical impedance. The estimation of body fat from skin fold thickness has been made using various formulas.[13] For this study, we chose to estimate body fat for each participant based on body mass index (BMI), age, and sex according to the following formula, where male is assigned a value of 1 and female 0[14]:

$$\text{Body Fat (\%)} = 1.20*\text{BMI} + 0.23*\text{Age} - 10.8*\text{Sex} - 5.4 \quad \text{(Eq.2)}$$

In the IHS, body fat was measured with bioelectrical impedance and, therefore, these measurements were used to calculate the population's average body fat percentage.

PCB BE values were tailored to the general Canadian and Inuit populations by inputting the population-specific average body weight and body fat weight, obtained from the CHMS Cycle 1 and the IHS respectively, into Chapter 4 Eq.1 for NDL-PCBs or Chapter 4 Eq. 2 for DL-PCBs (parameters: body weight inputted into Dose to obtain in units of mg/d, and body fat weight inputted into V_d).

The BE values were tailored to the whole CHMS and IHS populations, as well as to the subgroups of males, females, women of child-bearing age (18-44), young adults (18-25), middle-aged (40-55), and elderly (≥60) within the CHMS and IHS.

Analyses:

The percentages of the CHMS and IHS populations that equaled or exceeded the midpoints of the population-specific BE ranges for chlordane, toxaphene, and PCBs were calculated. The analyses were stratified by males, females, women of child-bearing age (18-44), young adults (18-25), middle-aged (40-55), and elderly (≥60). If a large percentage equaled or exceeded a BE value, then the analysis was repeated using a BE based on the lowest-observed adverse effect level (LOAEL). A BE based on the LOAEL was calculated using the same

methods of a one-compartment pharmacokinetic model, as described in Chapter 2. Hazard quotients (HQs) were calculated for those contaminants with high exceedances, by dividing the 95th percentile concentration by the BE value.

The CHMS, Cycle 1 analyses were conducted in Stata, version 14.0 and the IHS analyses in R, version 3.4.1.

Results

Tailoring of BE values:

The population-specific BE values for chlordane, toxaphene, and PCBs are presented in Table 1, along with the generic BE values (based on 70 kg and 25% body fat) for reference. The mean body weights and body fats for the general Canadian and Inuit populations are shown in Appendix 1, Table A1.1-1.

The chlordane BE values, tailored for the Inuit population subgroups of males, females, women of child-bearing age, young adults, middle-aged, and elderly, are presented in Appendix 1, Table A1.1-2.

Percentage of population that equaled or exceeded BE values:

No exceedances of chlordane or toxaphene BEs were observed among the general Canadian population (Table 2). However, among the Inuit population, 28% equaled or exceeded the BE for trans-nonachlor. In addition, 3.5% and 9.1% of the Inuit population equaled or exceeded the BE for cis-nonachlor and oxychlordane, respectively.

The general Canadian and Inuit populations both had minimal exceedances of the PCB BE values (Table 3). Among the Inuit population, 1% equaled or exceeded the BE for PCB-153.

The ratios of dietary intakes of contaminants from the Canadian TDS, with the corresponding human oral reference doses, are provided in Table 4. Dietary intakes of total

chlordane, trans-nonachlor, oxychlordane, and total PCBs were much below the oral dose for technical chlordane, the NOAEL for oxychlordane with an applied uncertainty factor of 100, and the oral dose for ∑NDL-PCBs.

Chlordane and the Inuit Population

Given the higher percentage of the Inuit population that exceeded the BEs for chlordane, further analyses were conducted. Table 5 shows the percentage of Inuit population subgroups that equaled or exceeded the BE for cis-nonachlor, trans-nonachlor, and oxychlordane. The highest percentages in all subgroups were for trans-nonachlor, especially among the elderly (nearly 76%). A large percentage of the elderly also equaled or exceeded the BE for cis-nonachlor (≈ 23%) and oxychlordane (≈ 41%).

When the percentages were re-calculated using BEs based on the LOAEL rather than NOAEL (see Appendix 1, Table A1.1-3 for chlordane BE values based on LOAEL), the exceedances for cis-nonachlor and oxychlordane were minimal (Table 6). The exceedances for trans-nonachlor also decreased considerably, although among the elderly the percentage remained high (35.5%).

Figures 1 and 2 are plots of the HQs for cis-nonachlor, trans-nonachlor, and oxychlordane for the Inuit population, using BEs based on NOAEL and LOAEL, respectively. The HQs for trans-nonachlor were much greater than cis-nonachlor and oxychlordane, and were greater than 1 for the whole population, males, females, the middle-aged, and the elderly (Figure 1). When using the BEs based on the LOAEL, the HQs for trans-nonachlor declined considerably, although remained slightly above 1 for the whole population, males, and females, and above 2 for the elderly (Figure 2).

Discussion

Biomonitoring equivalent values for chlordane, toxaphene, and PCBs have been tailored to the Canadian population covered by the CHMS and Inuit sample of the IHS, based on the average body and fat weights of the populations. Larger deviations from the generic values (i.e. 17.5 kg for body fat and 70 kg for body weight) will result in larger differences in the population-specific BE values. The BEs for general Canadians were slightly lower than the generic BE values because the average fat weight was about 26 kg and body weight 77 kg. In the absence of bioelectrical impedance measurements, the average fat weight of general Canadians was estimated from a prediction equation based on age, BMI and sex, which may overestimate body fat among obese individuals.[14] The BEs for the Inuit, which were tailored based on bioelectrical impedance measurements of body fat (average 23 kg), were also slightly lower than the generic BE values.

Among the general Canadian population, no exceedances of chlordane, toxaphene, or PCB congeners were observed. These results suggest that the human health risks of chlordane, toxaphene, and PCBs, with respect to the toxicity endpoints of the oral reference doses used to derive the BEs, are minimal for the Canadian population covered under the CHMS. The small ratios (<1) between the dietary intakes of chlordane, oxychlordane, and total PCBs from the TDS, with the corresponding oral reference doses, provide additional support that these contaminants pose limited risk to general Canadians. However, emerging evidence of association between PCBs and chronic diseases[15–18], require further research to fully characterize the risks of contaminant exposures across the spectrum of potential health outcomes.

The highest percentage of exceedances were observed for trans-nonachlor among the Inuit population (28%). A large percentage of the Inuit subgroups of males (29.5%), females

(25.6%), middle-aged (31.4%), and elderly (75.9%) also equaled or exceeded the trans-nonachlor BE. Trans-nonachlor consists of nine chlorine atoms bonded to two 5-carbon rings, with the chlorine atoms in a trans-conformation across the C5 and C6 double bond (molecular formula: $C_{10}H_5Cl_9$). Tashiro & Matsumura compared the metabolism of trans-nonachlor in rats and humans using liver microsomal preparations.[19] In the liver preparations of rats, trans-nonachlor was efficiently metabolized to trans-chlordane, however the liver preparations from humans did not carry out this dechlorination step, which may explain why trans-nonachlor accumulates in humans.[19] Studies in animal models[20–22], wildlife[23,24], and humans[25–30] have observed that trans-nonachlor is more bioaccumulative and persistent than other components of chlordane.

In human populations of the Arctic regions, trans-nonachlor has been detected in umbilical cord blood, human milk, and blood plasma.[30] Among mothers of the Kola Penninsula, Russia, milk samples contained trans-nonachlor at two times higher concentration than cis-nonachlor.[25] In maternal blood plasma samples from the Northwest Territories and Nunavut, trans-nonachlor was detected more often, and at slightly higher level, than oxychlordane.[27] Umbilical cord blood of the same region contained low levels of trans-nonachlor and oxychlordane, however these contaminants were detected more frequently among Inuit participants compared with Dene/Metis.[27] The concentration of trans-nonachlor in maternal blood of Inuit populations in Greenland, Canada, and Alaska were higher than oxychlordane, and samples from Greenland contained the highest concentration (trans-nonachlor: 91 μg/kg lipid vs. 56 μg/kg lipid in Nunavik, Canada).[28]

The primary source of trans-nonachlor exposure among the Inuit is the consumption of marine mammals, such as ringed seal and narwhal, which accumulate high concentrations of organochlorines as top trophic level organisms.[6,23,24,31,32] Kuhnlein 1995 studied traditional food

consumption among men of the eastern and western Arctic and found that exposure to organochlorines was higher with food systems that included sea mammals.[31] Among females of the Baffin Inuit, the foods that contributed the most to organochlorine intake were meat and blubber of ringed seal, blubber of walrus and mattak and blubber of narwhal.[33] Van Oostdam et al. (2004) also noted that blood organochlorine concentrations of circumpolar mothers were determined by the amounts and types of traditional foods consumed, with the highest contribution by marine mammals.[28] Appendix 1, Figure A1.1-1 shows the sum of chlordanes (all chlordane related compounds, including heptachlor) measured in Arctic marine mammals from the Canadian Arctic Contaminant Assessment Report (CACAR III, raw data courtesy of Dr. Derek Muir). The highest concentrations of chlordanes were in polar bear, followed by narwhal, beluga, ringed seal, and walrus. In the IHS, contaminant concentrations were not measured in food items, although a 24-hour food recall and food frequency questionnaire were conducted. Participants who equaled or exceeded the BE of trans-nonachlor consumed more marine mammals and total traditional foods compared with those who were below the BE for trans-nonachlor (Appendix 1, Figure A1.1-2). Although the majority of organochlorine exposure in the Arctic occurs through traditional foods, they are also central to providing nutrients, such as zinc, iron, copper, magnesium, protein, essential fatty acids, and vitamins, and maintaining the cultural identities of Arctic communities.[31] Therefore, given the many known benefits of traditional food systems, they are still recommended over market foods, which tend to be energy-dense and of lower nutritional value.

The exceedances for trans-nonachlor provide insight into the potential population-level risks of exposures among the Canadian Inuit population, however this data cannot be used to interpret risk to an individual or to make decisions about an individual's care. The results suggest

that trans-nonachlor exposures among the Inuit in 2007-2008 were high with respect to health-based guidance values based on liver endpoints, and that ongoing biomonitoring of this contaminant in the population is warranted. Time-series of chlordane measurements in the Arctic environment, from prior to 2000, have found overall decreasing trends.[6] Annual decreases of 3.6% for trans-nonachlor and 9.7% for trans-chlordane were present in biota.[6] The trans-nonachlor blood concentrations in mothers from Nunavik have decreased by 64% from 1992-2013.[30] The decreasing levels of chlordane in the Arctic indicate that international efforts to control POP production and use are effective.[30] The decreases are expected to continue, but at a gradual rate because chlordanes degrade very slowly in the environment.[34]

The exceedances for BEs based on the LOAEL were close to zero for cis-nonachlor and oxychlordane, and about 7% for trans-nonachlor among the whole Inuit sample. Of most concern, however, is the high percentage among the elderly who equaled or exceeded the LOAEL BE for trans-nonachlor (nearly 36%) and the corresponding elevated hazard quotient (> 2). Contaminant levels are higher in the elderly due to bioaccumulation over time and higher consumption of traditional foods compared with younger individuals.[31]

Kuhnlein et al. (1995) calculated daily contaminant intake among Arctic women based on dietary estimates and found that more than 50% of the food recalls exceeded the Health Canada oral guidelines for chlordane (TDI: 0.05 μg/kg, for sum of chlordane isomers and metabolites) and toxaphene (TDI: 0.2 μg/kg for sum of toxaphene residues).[33] The present analysis also found high exceedances for chlordane, particularly trans-nonachlor, even though the lower guideline value range was derived from the Environmental Protection Agency RfD of 0.5 μg/kg (technical chlordane), which is a magnitude larger than the Health Canada TDI. For toxaphene, however, no exceedances were observed based on a TDI for weathered toxaphene (18 μg/kg), which is

more representative of the pattern of toxaphene congeners found in biota than the technical form. Health Canada's whole blood guidelines for Aroclor 1260 are an intervention value of 100 μg/L, a trigger value of 20 μg/L for the general population, and a trigger value of 5 μg/L for women of child-bearing age.[35] Laird et al. (2013) compared the IHS concentrations with these values and found that 1.4% exceeded the 100 μg/L threshold, 21.9% exceeded 20 μg/L, and 27.9% of women of child-bearing age exceeded the 5 μg/L threshold.[7] Van Oostdam et al. (2004) compared Inuit maternal blood PCB concentrations with the Health Canada guidelines and found more than 60% of mothers in Nunavik and more than 40% in Kitikmeot exceeded 5 μg/L, although none exceeded 100 μg/L.[28] These results differ from the findings of the present analysis, in which only about 1% of Inuit equaled or exceeded the BE for PCB-153. The Health Canada blood guidelines were established in 1978 and are based on Aroclor 1260, a commercial mixture of PCB-congeners, rather than individual congeners.[35] Also, the guidelines are for whole blood measurements rather than plasma or lipid-adjusted concentrations, as was measured in the IHS. This is the first analysis, to the author's knowledge, that provides an assessment of risk for PCB concentrations among the Inuit based on individual congeners and lipid-adjusted concentrations.

The IHS data is now a decade old and, therefore, updated biomonitoring data of contaminants for the Canadian Inuit population is needed to determine the present status of exceedances with respect to health-based guidance values. Given the evidence of decline of chlordane in the Arctic environment, it would be useful to evaluate if exceedances of the trans-nonachlor BE have experienced a corresponding decrease. In addition, an inventory of contaminant concentrations found in commonly consumed traditional foods, such as ringed seal and narwhal, and the effects of food preparation on contaminant levels, is needed for the

Canadian Arctic. This inventory will provide accurate estimations of which items are contributing most to intake of contaminants and assist with recommendations about how to reduce exposures, particularly for those contaminants that have been identified as posing potential population-level risks, such as trans-nonachlor.

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Table 1: BE values tailored to the general Canadian and Inuit populations

	Generic BE (mg/kg lipid)	General Canadian Population-Specific BE (mg/kg lipid)	Inuit Population-Specific BE (mg/kg lipid)
Chlordane			
Cis-Chlordane	0.03-0.23	0.02-0.17	0.02-0.18
Trans-Chlordane	0.07-0.23	0.05-0.17	0.05-0.18
Cis-Nonachlor	0.11-0.26	0.08-0.19	0.09-0.20
Trans-Nonachlor	0.17-0.46	0.12-0.34	0.13-0.35
Oxychlordane	0.57-0.91	0.42-0.67	0.44-0.70
Toxaphene			
Parlar No. 26	0.87-12.22	0.64-9.01	0.67-9.42
Parlar No. 50	2.04-6.11	1.50-4.50	1.57-4.71
Parlar No. 62	2.04-4.89	1.50-3.60	1.57-3.77
NDL-PCBs			
PCB-28	0.75-1.36	0.57-1.02	0.58-1.05
PCB-52	0.36-0.64	0.27-0.48	0.28-0.50
PCB-138	1.48-3.92	1.12-2.96	1.15-3.04
PCB-153	1.97-4.91	1.49-3.71	1.53-3.81
PCB-180	1.57-7.21	1.19-5.45	1.22-5.59
DL-PCBs			
PCB-77	0.0009-0.0034	0.0006-0.0026	0.0007-0.0026
PCB-81	0.0023-0.0124	0.002-0.009	0.002-0.010
PCB-105	0.15-0.96	0.12-0.72	0.12-0.74
PCB-114	0.92-4.13	0.69-3.12	0.71-3.20
PCB-118	0.24-1.04	0.18-0.79	0.19-0.81
PCB-123	0.33-2.58	0.25-1.95	0.26-2.00
PCB-126	0.00003-0.0001	0.00002-0.00011	0.00002-0.00011
PCB-156	0.22-3.92	0.16-2.97	0.17-3.04
PCB-157	0.92-4.52	0.69-3.42	0.71-3.51
PCB-167	0.30-1.96	0.22-1.48	0.23-1.52
PCB-169	0.0005-0.0020	0.0004-0.0015	0.0004-0.0015
PCB-189	1.37-7.14	1.04-5.40	1.06-5.54

Abbreviations: BE = biomonitoring equivalent; DL-PCB = dioxin-like polychlorinated biphenyl; NDL-PCB = non-dioxin like polychlorinated biphenyl; NOAEL = no observed adverse effect level; PCB = polychlorinated biphenyl; TDI = tolerable daily intake; UF = uncertainty factor

Table 2: Exceedances of chlordane and toxaphene concentrations in the CHMS and IHS

	CHMS, Cycle 1 (2007-2009)		IHS (2007-2008)	
	99th Percentile (mg/kg lipid)	**% Equal to or Exceeding BE***	**99th Percentile (mg/kg lipid)**	**% Equal to or Exceeding BE***
Chlordane				
Cis-Chlordane	0.0014	0.0	N/A	N/A
Trans-Chlordane	0.00074	0.0	N/A	N/A
Cis-Nonachlor	0.0067	0.0	0.22	3.5
Trans-Nonachlor	0.040	0.0	1.46	28.0
Oxychlordane	0.021	0.0	1.68	9.1
Toxaphene**				
Parlar No. 26	0.0026	0.0	0.27	0.0
Parlar No. 50	0.0042	0.0	0.33	0.0

* Midpoint value of BE ranges presented in Table 1. Percentages exclude missing values.

** Parlar No. 62 was not measured in the CHMS or IHS.

Abbreviations: BE = biomonitoring equivalent; CHMS = Canadian Health Measures Survey; IHS = Inuit Health Survey

Table 3: Exceedances of PCB concentrations in the CHMS and IHS

	CHMS, Cycle 1 (2007-2009)		IHS (2007-2008)	
	99th Percentile (mg/kg lipid)	**% Equal to or Exceeding BE***	**99th Percentile (mg/kg lipid)**	**% Equal to or Exceeding BE***
NDL-PCBs				
PCB-28	0.008	0.0	0.008	0.0
PCB-52	0.043**	0.0	0.044	0.0
PCB-138	0.079	0.0	0.737	0.0
PCB-153	0.150	0.0	2.677	1.0
PCB-180	0.170	0.0	1.514	0.1
DL-PCBs				
PCB-105	0.008	0.0	0.052	0.0
PCB-118	0.042	0.0	0.257	0.1
PCB-156	0.023	0.0	0.126	0.0
PCB-167	0.006	0.0	N/A	N/A

* Midpoint value of BE ranges presented in Table 1. Percentages exclude missing values.

** All observations were below LOD.

Abbreviations: BE = biomonitoring equivalent; CHMS = Canadian Health Measures Survey; IHS = Inuit Health Survey

Table 4: Comparison of human oral dose values with dietary intakes from the Canadian TDS

Canadian TDS[12]	Contaminant	A. Highest Average Dietary Intake in 20+ Years of Age (mg/kg bw/d)	B. Human Oral Dose (mg/kg bw/d)[36–38]	Ratio (A/B)
1998 Whitehorse	Total chlordane	9.0×10^{-8}	5.0×10^{-4}	1.8×10^{-4}
	Trans-nonachlor	1.1×10^{-7}	5.0×10^{-4}	2.2×10^{-4}
	Oxychlordane	0.0	$1.0 \times 10^{-3*}$	0.0
1993-1996 Montreal	Total chlordane	1.3×10^{-7}	5.0×10^{-4}	2.6×10^{-4}
	Trans-nonachlor	2.0×10^{-8}	5.0×10^{-4}	4.0×10^{-5}
	Oxychlordane	2.0×10^{-8}	$1.0 \times 10^{-3*}$	2.0×10^{-5}
2002 Vancouver	Total PCBs	2.67×10^{-6}	1.3×10^{-4}	2.1×10^{-2}
2000 Ottawa	Total PCBs	2.99×10^{-6}	1.3×10^{-4}	2.3×10^{-2}
1996 Toronto	Total PCBs	7.17×10^{-6}	1.3×10^{-4}	5.5×10^{-2}
1994 Winnipeg	Total PCBs	5.24×10^{-6}	1.3×10^{-4}	4.0×10^{-2}
1994 Halifax	Total PCBs	8.76×10^{-6}	1.3×10^{-4}	6.7×10^{-2}
1993 Montreal	Total PCBs	6.73×10^{-6}	1.3×10^{-4}	5.2×10^{-2}

* Compared with NOAEL of 0.1 mg/kg/d in rats – applied uncertainty factor of 10 for intraspecies variation and 10 for interspecies variation (UF=100) = 0.001 mg/kg/d

Abbreviations: bw = body weight; PCB = polychlorinated biphenyl; TDS = Total Diet Study

Table 5: Exceedances of chlordane concentration among Inuit population subgroups

(% equal to or exceeding BE based on NOAEL)*

	Cis-Nonachlor	Trans-Nonachlor	Oxychlordane
Males	2.0	29.5	7.8
Females	3.9	25.6	8.8
Females Child-Bearing Age (18-44)	0.0	5.8	0.1
Young Adults (18-25)	0.0	2.2	0.0
Middle-Aged (40-55)	1.4	31.4	6.2
Elderly (≥60)	23.2	75.9	41.3

* Midpoint value of BE ranges presented in Appendix 1, Table A1.1-2. Percentages exclude missing values.

Table 6: Exceedances of chlordane concentration among Inuit population subgroups

(% equal to or exceeding BE based on LOAEL)*

	Cis-Nonachlor	Trans-Nonachlor	Oxychlordane
Whole Population	0.0	7.1	0.0
Males	0.0	6.0	0.0
Females	0.1	6.6	0.1
Females Child-Bearing Age (18-44)	0.0	0.0	0.0
Young Adults (18-25)	0.0	0.0	0.0
Middle-Aged (40-55)	0.0	3.7	0.0
Elderly (≥60)	0.3	35.5	0.0

* BE values based on LOAEL presented in Appendix 1, Table A1.1-3. Percentages exclude missing values.

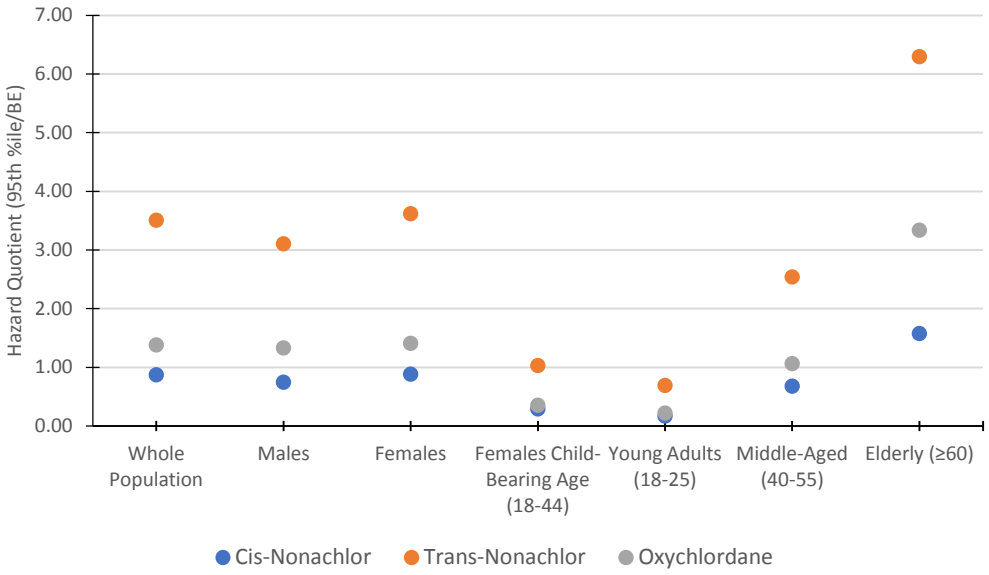

Figure 1: Hazard quotients for the Inuit population (BE based on NOAEL)

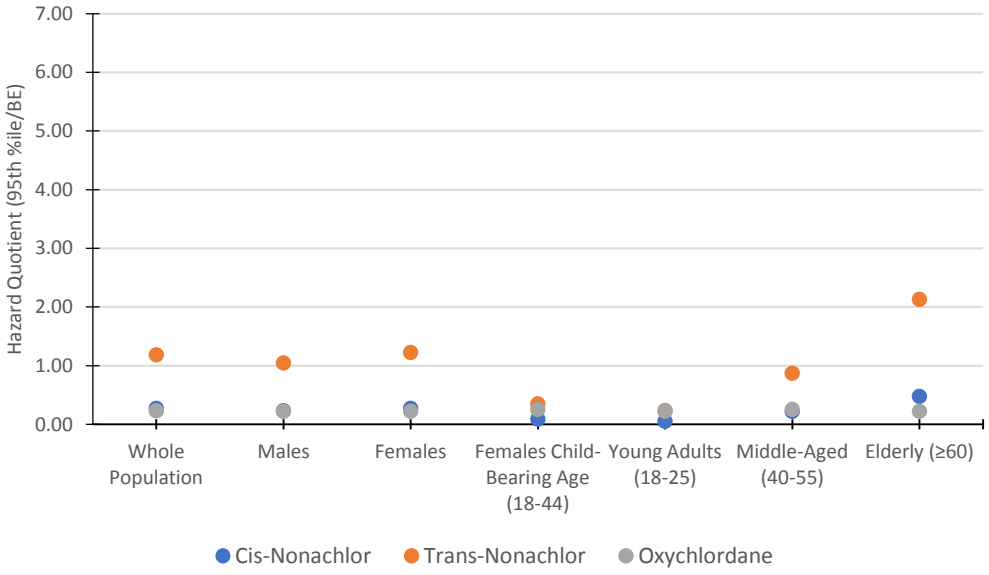

Figure 2: Hazard quotients for the Inuit population (BE based on LOAEL)

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Chapter 6: A Review of Contaminants and Health Outcomes in Arctic Indigenous Populations

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Abstract:

Since the 1990s, research has been carried out to monitor environmental contaminants and their effects on human health in the Arctic. Although evidence shows that Arctic indigenous peoples are exposed to higher levels of contaminants and do worse on several dimensions of health compared with other populations, the contribution of such exposures on adverse outcomes are unclear. The purpose of this review is to provide a synopsis of the published epidemiological literature that has examined association between environmental contaminants and health outcomes in Arctic indigenous populations. A literature search was conducted in OVID Medline (1946-January 2014) using search terms that combined concepts of contaminant and indigenous populations in the Arctic. No language or date restrictions were applied. The reference lists of review articles were hand-searched. Of 559 citations, 60 studies were relevant. The studies fell under the following categories: pediatric (n=18), reproductive health (n=18), obstetrics and gynecology (n=9), cardiology (n=7), bone health (n=2), oncology (n=2), endocrinology (n=2), and other (n=2). All studies, except one from Arctic Finland, were either from Nunavik or Greenland. Most studies assessed polychlorinated biphenyls (n=43) and organochlorine

pesticides (n=29). Fewer studies examined heavy metals, perfluorinated compounds, or polybrominated diphenyl ethers. Details of study results for each health category are provided. It is difficult to make conclusive statements about the effects of environmental contaminants on health due to mixed results, small number of studies, and studies being restricted to a small number of regions. Meta-analytical synthesis of the evidence should be considered for priority contaminants and health outcomes. The following research gaps should be addressed in future studies: association of contaminants and health in other Arctic regions (i.e. Inuvialuit Settlement Region, Nunavut, Nunatsiavut, Alaska, European North and Russian North); assessment of contaminants on chronic diseases; inclusion of clinical endpoints in assessments; and assessment of the emerging contaminants of perfluorinated compounds and polybrominated diphenyl ethers.
Key Words: Epidemiology; Review; Environment; Human Health; Polychlorinated biphenyls; Pesticides

Introduction

Indigenous populations residing in the Arctic regions (e.g. the Kalaallit in Greenland, the Inuit and Inuvialuit in Canada, the Inupiat and Yupik in Alaska, and the Yuit in Siberia) are encountering a myriad of environmental and health-related challenges, previously unknown to these communities. Despite residing in locations distant from industrial activity, Arctic populations are especially vulnerable to environmental contaminant exposure. Contaminants undergo long range transport from warmer to colder regions, thus making the Arctic a sink for contaminant deposition. Also, lipophilic chemicals, such as persistent organic pollutants, collect in fatty tissues of animals and bioaccumulate at the higher ends of the food chain. The consumption of marine mammals by Arctic populations thus leads to direct contaminant exposure. The presence of contaminants in the North has garnered the attention of researchers.

Since the 1990s, multidisciplinary international projects have been implemented to monitor contaminants and potential impacts on human health in the Arctic (1). The most important initiative, the Arctic Monitoring Assessment Programme (AMAP), includes all Arctic countries and had led to a series of reports detailing pollution and climate change issues (2–4).

Studies have shown that indigenous populations in the Arctic have higher body burden of contaminants than other populations. Donaldson et al. (2010) reported higher concentrations of heavy metals and persistent organic pollutants in Inuit mothers from Inuvik compared with Dene/Metis and non-aboriginal women (5). High levels were also measured in Inuit mothers from Nunavik and the Baffin region of Nunavut, although levels decreased from 1992 to 2007 (5). From the Adult Inuit Health Survey, Laird et al. (2013) reported several-fold higher contaminant levels in Canadian Inuit compared with the general Canadian population (6). In the Russian North, contaminant levels were measured in blood, cord blood, and breast milk of indigenous women, and blood of adult indigenous populations and controls residing in urban locations (3). Mothers from the Chukotsky District had the highest contaminant concentrations in blood and breast milk. Overall, blood contaminant levels in indigenous populations of Arctic Russia were similar to those of coastal Greenland and Northern Canada (3).

Many of the health issues faced by Arctic populations are related to the shift from traditional to modern lifestyles, which result in more sedentary behaviours and consumption of higher-fat content, nutrient poor market foods. The shift in lifestyle has resulted in a corresponding shift from infectious diseases to chronic, non-communicable diseases such as diabetes, cardiovascular disease, and cancer (3,7–9). The prevalence of diabetes among the Inuit, for instance, has historically been below the national average, but has now increased to an equivalent level (10). Chronic disease risk factors, such as obesity and smoking, are prevalent

among Northern communities. In 2009-2010, 58.3% of Inuit adults 18 years of age or older were overweight or obese, compared with 51.9% among the non-aboriginal population (10). Furthermore, 59.6% Inuit adults reported being physically inactive during leisure time (49.7% among non-aboriginal populations), 78.4% ate less than the recommended number of servings of fruit and vegetables per day, and 44.4% smoked tobacco (16% among non-aboriginal populations) (10).

While it is clear that Arctic populations are exposed to higher levels of environmental contaminants and fare worse on certain dimensions of health than other populations, the resulting impact of these exposures on health are still ambiguous. Contaminants do not exist in isolation – they are but one additional risk factor among a plethora of other factors, such as diet, smoking, genetic predisposition, and socioeconomic status, that contribute to disease. Isolating the effects of contaminants from these other contributors can be difficult in epidemiological studies of small populations (5). Nonetheless, the ongoing inquiry into the adverse health effects of contaminants is vital so that research methods undergo refinement to detect small, but relevant, associations and scientifically based messages of exposure and strategies for mitigation are conveyed to the populations at risk.

Because the Arctic indigenous peoples have distinct cultural practices, diet and socioeconomic factors that make them vulnerable to contaminant exposure and adverse health outcomes, the purpose of this review is to provide a synopsis of the published epidemiological research, available to date, that has examined association between environmental contaminants and health outcomes in these populations. The primary aim is to identify health topics that have received greater research attention and areas where more research is needed. Donaldson et al. (2010) provided an overview of the health effects of contaminants, though not restricted to

Arctic populations (5). This review updates this previous work. In addition, this review provides a systematic assessment of the literature in Arctic populations and graphical representations to detect research gaps.

Methods

A comprehensive search of the published literature was conducted in OVID Medline (1946-January 2014) using search terms that combined the concepts of contaminant and indigenous Arctic populations. To describe Arctic indigenous populations we included the following search terms: Inuit, Dene, Kalaallit, Yupik, Buryat, Chukchi, Evenk, Khanty, Koriak, Koryak, Nenet, Sami, Yukaghir, Mansi, Nganasan, and similar terms with variations of spelling. No language or date restrictions were applied. The titles and abstracts of all citations yielded by the searches were reviewed. Primary studies that examined the effect of at least one environmental contaminant on any type of health outcome in humans were retained and included in the review. The reference lists of selected review articles were also hand-searched for relevant primary studies. Studies reporting body burden, intake of contaminants, or health outcomes only were not included in this review.

The studies were organized into broad health categories. In addition, studies were tabulated according to location and environmental contaminant. Basic data characteristics, such as study design, sample size, contaminant exposure level, and overall results were extracted for individual studies and presented in tabular format.

Major cohort studies on the health effects of PCBs and mercury have been conducted in the Faroe Islands (11–13). Based on cultural and geographical differences, they are not included in this review, which focuses on indigenous populations of the circumpolar Arctic countries. In addition, several studies on the health effects of contaminants in Norway and Russia (14–18)

have been conducted, but they have not been included in this review because they were not limited to the indigenous populations of those regions.

Results

The Medline search yielded a total of 559 citations. Of these, and the references hand-searched from review articles, 60 primary studies were deemed to be relevant for this review (i.e. these studies included an evaluation of at least one association between an environmental contaminant and a health outcome in an indigenous population in the Arctic). Other excluded studies primarily measured levels of environmental contaminants in humans but did not link such measurements with health outcomes. The studies fell under the following broad categories: pediatric, reproductive health, obstetrics and gynecology, cardiology, bone health, oncology, endocrinology, and other. Studies that examined health outcomes of environmental contaminants in children under the age of 18 years of age were classified under the pediatric category and omitted from the other categories. Similarly, studies that examined health outcomes in pregnant women were classified under the obstetrics and gynecology category and omitted from other categories (e.g. assessment of thyroid function in pregnant women was classified under obstetrics and gynecology rather than endocrinology).

Figure 1 depicts the number of studies falling under each health category. Most studies examined associations between contaminants and health outcomes in pediatrics (N=18) and on reproductive health outcomes (N=18). Subsequent categories were obstetrics and gynecology (N=9) and cardiology (N=7). Only two studies were found in each of bone heath, oncology, and endocrinology. In addition, two studies that examined markers of oxidative stress were classified in the other category.

All studies were from either Nunavik or Greenland, except for one study from Arctic

Finland (Figure 2). The majority of pediatric studies examined Inuit from Nunavik whereas all reproductive health studies examined Inuit from Greenland.

As shown in Figure 3, most studies examined the adverse health impacts of PCBs (N=43) and organochlorine pesticides (N=29). Smaller number of studies examined heavy metals (Hg, N=20; Pb; N=9; Cd, N=2), perfluorinated compounds (N=4), polybrominated diphenyl ethers (PBDEs) (N=1), and other contaminants including octachlorostyrene, dioxin-like compounds, and unspecified persistent organic pollutants (N=5). Aside from cardiology, PCBs were examined by the largest number of studies in all health categories. Organochlorine pesticides or heavy metals fared second.

Pediatric

Pediatric studies have examined associations between PCBs or organochlorine pesticides with infections and immune status (19–22), neurological functions (23–26), indicators of behaviour (27–29), and thyroid function (30) (Table 1). Studies have also looked at heavy metals (i.e. Hg or Pb) and their effects on blood pressure and heart rate variability (31), neurological functions (23–26,32–34), and behaviour (27,29,35,36). Most studies were prospective cohorts of mother-child pairs that followed children from birth to infants or childhood. Sample sizes ranged from 10 to 400. Contaminant levels were measured in maternal blood, cord blood, breast milk and/or child blood and mercury hair levels were also measured in some studies. Most analyses adjusted for several demographic (e.g. age, gender), lifestyle (e.g. smoking), and other contaminant exposures.

Infections and Immune System:

For infection-related outcomes, studies presented mixed results. One study found no association between PCBs and organochlorine pesticides with otitis media (19). However,

Dallaire et al. (2006) found that cord PCB-153 was associated with higher incidence of acute otitis media (Adjusted RR = 1.37, 95% CI: 1.20-1.55 for most exposed compared with least exposed) and lower respiratory tract infections (LRTI) (Adjusted RR = 1.44, 95% CI: 1.20-1.72) (20). In addition, maternal PCB-153 was positively associated with LRTI in the first 6 months of life (Adjusted RR = 1.68, 95% CI: 1.00-2.81, for 3rd exposure quartile compared with least exposed) and gastrointestinal (GI) infections at 12 months (Adjusted RR = 1.59, 95% CI: 1.01-2.49, for 3rd exposure quartile compared with least exposed) (21). In the same study, maternal dichlorodiphenyldichloroethylene (p,p'-DDE) was found to be associated positively with upper respiratory tract infections (URTI), otitis media, and all infections during the first 6 months of life and URTI and GI infection at 12 months (21). Dewailly et al. (2000) found that organochlorine pesticides were associated with increased risk of acute otitis media but not with bronchopulmonary diseases (22).

Behaviour:

Boucher et al. (2012) observed a higher incidence of ADHD in children 11 years of age exposed to mercury prenatally and among those with higher levels of blood lead (27). No association was seen between ADHD and PCB-153 (27). However, other studies found that PCB-153 was associated positively with inattention and non-elicited activity in infants 11 months of age (28) and with unhappiness and anxiety in children 5 years of age (29). Child blood lead levels has been observed to be associated with greater impulsivity (29), irritability (29), and activity (36). Plusquellec et al. (2010) also found a positive association with inattention (29), but this was not detected in other studies (27,36). Prenatal exposure to lead was associated with greater frenetic activity and off-task duration in infants (35).

Neurological:

No association was detected between PCB-153 and visual brain development, but cord mercury and lead levels were associated with certain visual evoked potentials (i.e. N75 amplitude, N75 latency, and N150 latency) (23). Saint-Amour et al. (2006) found that child plasma PCB-153 and cord and child blood mercury levels were associated with alterations in visual brain processing, as assessed by visual evoked potentials (33). Child plasma levels of PCB-153 has also been significantly associated with slower reaction times (24) and an increase in transversal sway oscillations (26). Lead levels in cord and child blood have been associated with fewer correct responses on go and no-go trials (24) and adverse neuromotor functions (26). Mercury has also been found to adversely affect information processing (slower reaction times, incorrect responses) (25), increase tremors (26), and hand-eye coordination error score (34).

Cardiovascular and Endocrine:

Only one study assessed the effect of mercury on cardiovascular outcomes in children who were followed from birth to 11 years of age (31). No association was found between mercury levels and blood pressure. However, child mercury level was associated with certain measures of heart rate variability. A small study in newborns (n=10) evaluated the effect of PCB, pentachlorophenol (PCP), and octachlorostyrene exposure on thyroid function (30). PCP, ∑PCBs, and ∑PCB hydroxylated metabolites were found to be inversely associated with thyroid hormones.

Reproductive Health

Studies of reproductive health have primarily examined the effects of PCBs and organochlorine pesticides on estrogen, androgen, or aryl hydrocarbon receptor activities (37–42), fertility and markers of male reproductive function (43,44), sperm deoxyribonucleic acid (DNA) damage and apoptotic markers (45,46), epididymal and accessory sex gland functions (47),

reproductive hormone levels (48), and sperm Y:X ratio (49) (Table 2). Sample sizes range from 37 to 598. Several studies analyzed a cohort of Greenlandic Inuit men from the INUENDO project, which also recruited cohorts of men from Warsaw, Kharkiv, and Swedish fishermen for comparisons. The results presented in Table 2 are for the Inuit cohort only.

The effects of PCB-153 on reproductive outcomes have been mixed in the published literature. Some studies have found statistically significant inverse associations with sperm volume, progressive sperm, and neutral α-glucosidase activity in seminal plasma (an epididymal marker) (43,47) and statistically significant positive associations with luteinizing hormone (43,48). However, no associations have been found with time to conceive, apoptotic markers, sperm chromatin integrity, other reproductive hormones, sperm Y:X ratio, or fertility (43–49). Studies also present mixed results for p,p'-DDE. Significant positive associations were present for inhibin B and free testosterone, and inverse associations for sperm volume and progressive sperm (43,48). No associations were found for sperm chromatin integrity, apoptotic markers, epididymal and accessory sex gland function, sperm DNA fragmentation, other reproductive hormones, sperm Y:X ratio, or fertility (43–49).

Unspecified persistent organic pollutants, as evaluated by effects on estrogen, androgen, or aryl hydrocarbon receptors, were inversely associated with DNA fragmentation index, DNA damage, and the anti-apoptotic marker, Bcl-xL (50,51). No associations were found for DNA stainability, semen quality, or the apoptotic marker, Fas (50–52).

Additional studies examined the effects of mercury on semen quality and reproductive hormones (53) and perfluorinated compounds on sperm Y:X ratio (54). Mercury was positively associated with inhibin B but not with other semen characteristics or reproductive hormones (53). Perfluorooctanesulfonate (PFOS) was associated with lower sperm Y:X ratio, though no

association was present for perfluorooctanoic acid (PFOA) (54).

Obstetrics and Gynecology

Table 3 provides details of studies that examined environmental contaminants and effects on obstetrical or gynecological outcomes. A total of nine studies, with sample sizes ranging from 22 to 572, were found (55–63). Several inverse associations were observed between contaminants and birth outcomes. PCBs, organochlorine pesticides, and mercury were associated with shorter duration of pregnancy and fetal growth (55,60,63). In addition, PCB-153 and p,p'-DDE were associated with lower birth weight and shorter gestational age, but not with risk of preterm birth, in women with live singleton deliveries (56).

Thyroid hormone levels in relation to maternal, cord, or infant levels of PCBs and organochlorine pesticides were evaluated in one study (57). Maternal PCB hydroxylated metabolites, PCB-153, and pentachlorophenol and cord PCB-153 were associated with thyroid hormones. However, no associations were found with infant contaminant levels.

Menstrual cycle characteristics of women presenting for antenatal care at hospitals were examined in one study (58). PCB-153 and p,p'-DDE were associated with fewer long menstrual cycles. No association was found between PCB-153 or p,p'-DDE with average cycle length, irregular cycles, or short cycles.

Two small studies (n=35 and n=22) measured placental CYP1A1 activity (61,62). One study reported no association with PCBs (61), whereas the other study found increased CYP1A1 activity with higher exposures to PCB-153/PCB-118 and organochlorine pesticides, depending on smoking status (62).

An AMAP report of persistent toxic substances in indigenous populations of the Russian North is available (3). This report was not formally included in this review as it was not in the

published literature domain, but results from the report are summarized here. Premature births were associated with blood lead levels > 3.0 µg/L, cadmium > 1.0 µg/L, and Aroclor 1260 > 5.0 µg/L. Reduced birthweight was associated with cadmium and Aroclor at the same thresholds. In addition, women with stillbirths or births with serious structural malformations had PCB, DDT, and mercury levels 1.7-2.0 times higher compared with women with no adverse birth outcomes. An examination of dose-response relationship found that sum of PCBs in maternal serum > 2.0 µg/L was associated with birthweight and gestational age and > 4.0 µg/L with fatal pregnancy outcomes. In addition, the ArcRisk project, which examined environmental contaminants in Eastern Arctic regions, conducted meta-analyses of the association between PCBs and sex ratio and birthweight (4). No association was found between PCBs and sex ratio, but maternal PCB concentration was associated with low birthweight.

Cardiology

Surrogate outcomes of cardiovascular disease, most commonly blood pressure, have been assessed in several studies (64–69) (Table 4). Other outcomes include resting heart rate and pulse pressure, plasma lipids, and cardiac autonomic activity (65,68,70). The studies were large, with sample sizes ranging from 230 to 1861.

Two studies, including the largest one with 1861 participants, found that mercury was associated with lower diastolic blood pressure (65,66). However, two other studies (n=732 and n=280), found no association with diastolic blood pressure (67,68). Results were similarly inconclusive for systolic blood pressure (i.e. positive association in two studies but no association in others) (65–68). A study of reindeer herders in northernmost Arctic Finland found that hypertensive subjects had higher blood cadmium levels compared with normotensives and that blood cadmium was positively associated with systolic blood pressure when adjusted for

age, body mass index, smoking and alcohol consumption.(69) The risk of hypertension (i.e. blood pressure of ≥140/90 mm Hg or taking anti-hypertensive medication) was higher in younger individuals (18-39 years of age) exposed to dioxin-like PCBs (OR = 1.34, 95% CI: 1.03-1.74) or DDT (OR = 1.42, 95% CI: 1.08-1.85) (64). Interestingly, the risk was lower in older individuals (≥ 40 years) exposed to non-dioxin like PCBs or Mirex (64).

PFOS was inversely associated with triacylglycerol and ratio of total cholesterol/high density lipoprotein cholesterol (HDL-C) and positively with HDL-C after controlling for n-3 polyunsaturated fatty acids (70). No association was found between PFOS and low density lipoprotein cholesterol (LDL-C) or non HDL-C.

Endocrinology

In one study of 692 middle-aged men and women in Greenland, PCBs and organochlorine pesticides were not associated with impaired glucose tolerance or diabetes (71) (Table 4). Nor were they associated with the surrogate outcomes of fasting glucose, 2-hour glucose, or fasting insulin. Significant inverse associations were found between PCBs and organochlorine pesticides with 2-hour insulin and between PCBs and the homeostasis model assessment of β-cell function.

Dallaire et al. (2009) reported on thyroid hormone levels in relation to PCBs, organochlorine pesticides, PBDEs, PFOS, and dioxin-like compounds in 623 men and women 18 years of age or older in Nunavik (72). Significant inverse associations were observed for PCBs, hexachlorobenzene, β-hexachlorocyclohexane, and PFOS with total triiodothyronine, thyroxine-binding globulin, free thyroxine, and/or thyroid-stimulating hormone. p,p'-DDE and PBDEs, however, were not associated with any measure of thyroid function after adjusting for confounders.

Bone Health

Two studies assessed bone strength and bone ultrasound in relation to dioxin-like PCBs or PCBs and organochlorine pesticides respectively, in peri- and post-menopausal women (73,74) (Table 4). No association was present between bone strength and dioxin-like PCBs (73) or between PCB-153 and bone ultrasound quantitative parameters (74). PCB-156 congener was associated inversely with broadband ultrasound attenuation (indication of bone density and architecture), speed of sound (indication of bone density and elasticity), and stiffness index (indication of rigidity of bone structure).

Oncology

Breast cancer and exposure to PCBs, organochlorine pesticides, perfluorinated compounds, and heavy metals was examined in a case-control study in Greenland (n=31 cases and n=115 controls matched for age and district) (75) (Table 4). Perfluorinated compounds and the sum of persistent organic pollutants were associated positively with breast cancer (OR = 1.03, 95% CI: 1.00-1.05 and OR = 1.02, 95% CI: 1.01-1.04 respectively). PCB, as a continuous measure, was not associated with breast cancer, but within the highest quartile exposure was significantly higher for cases than controls. No association was found between organochlorine pesticides and heavy metals.

DNA hypomethylation, an epigenetic mechanism causing chromosomal instability and alteration of gene expression, was examined in a small study (n=70) consisting mostly of males 19-67 years of age in Greenland (76). PCBs, p,p'-DDE, DDT, other organochlorine pesticides, and the sum of persistent organic pollutants were all significantly associated with DNA hypomethylation based on the *Alu* assay but not based on the *LINE-1* assay. The authors suggest that the different mechanisms and transcription patterns in response to cellular stressors accounts

for the significant associations observed in one assay and non-significant associations in the other assay.

Other

The capacities of PCBs and mercury to induce oxidative stress was evaluated in two studies of men and women from Nunavik (n=99 each) (77,78) (Table 4). One study examined redox status of coenzyme Q10 and vitamin E (tocopherol) (78) and the other examined oxidation of LDL-C, homocysteine, glutathione peroxidase, glutathione reductase and glutathione (77). Based on tocopherol and coenzyme Q10 redox status, neither PCBs nor mercury increased oxidation, although the elevated ratio of ubiquinone-10 to coenzyme $Q10_{total}$ indicated that the population was experiencing oxidative stress (78). Similarly, in the second study, mercury did not increase oxidation (77). However, PCBs were associated with higher levels of oxidized LDL-C, suggesting that PCBs participate in oxidative stress (77).

Discussion

A broad range of epidemiological studies exist that assess the possible human health effects of environmental contaminants. However, there are only 60 published studies conducted in Arctic indigenous populations. Several of these studies found association of contaminants with children's immune status, behaviour, neurological function, heart rate variability and thyroid function. In addition, in adults several associations between contaminants and adverse outcomes have been observed, including those on reproductive outcomes, fetal growth and duration of pregnancy, blood pressure and hypertension, thyroid hormones, quantitative measures on bone ultrasound, breast cancer, DNA hypomethylation, and oxidative stress. Most of these studies attempted to adjust for several relevant confounders.

Unfortunately, we are yet far from being able to make any conclusive statements about

the health effects of most environmental contaminants. First, the evidence is largely interspersed with studies showing significant associations and studies showing no associations (i.e. statistical significance not reached). The latter may be due to studies with small sample sizes that are underpowered to detect significant differences. Also, of the studies with larger sample sizes (200+), participation rates ranged from 14% to 95%, with average of 65%, which suggests that there may be issues with the representativeness of study samples. Second, for many contaminant-outcome pairs, we have only one or two studies contributing data. Conclusions based on observational epidemiological evidence should be based on an accumulation of good quality data that points towards a common direction. Good quality data will come from well-designed observational studies that have representative samples, pre-defined outcomes and subgroup analyses, power calculations, and measurement of confounders. Admittedly, epidemiological studies are difficult to conduct in Arctic regions that have small populations and limited accessibility (79). One way to overcome the problems of small sample sizes in individual studies and few studies in Arctic populations, is to conduct a meta-analytical synthesis of the literature base on priority contaminants and health outcomes. A necessary component in synthesizing the literature will be to assess the quality of the individual studies. In particular, one issue that came to light during this review is the large number of statistical analyses (i.e. based on different contaminant congeners and subgroups) that were carried out by some studies. Such analyses may result in spuriously significant associations by chance alone. Therefore, it will be important to determine if such subgroup analyses were pre-specified and if they make biological sense.

There are several gaps in the literature, which require future research attention. Published epidemiological studies linking environmental contaminants to health outcomes have been primarily conducted in only two regions -- Nunavik and Greenland. Additionally, data on

obstetrical outcomes are available in indigenous populations of Russian and European North in AMAP reports. It would be informative if data can be accumulated and published from other Arctic populations in Canada (e.g. Inuvialuit Settlement Region, Nunavut, Nunasiavut), Alaska, Russian North and European North. Secondly, while the data in pediatrics and reproductive health are quite extensive, studies available for other areas are notably sparse. For instance, few studies are available on chronic diseases such as cardiovascular disease and diabetes, which make up a large burden of the health problems faced by Arctic populations. In addition, only surrogate outcome of cardiovascular disease have been measured. Future studies, therefore, should focus on clinical endpoints as well, such as incidence of heart disease or myocardial infarction. In these respects, analyses of the Adult Inuit Health Survey, which was a cross-sectional survey of about 2600 Inuit adults from Inuvialuit Settlement Region, Nunavut Territory, and Nunatsiavut, and which collected information on heart disease and diabetes will be useful (80). Lastly, as shown in Figure 3, only a few studies (4 in total) have evaluated PBDEs or perfluorinated compounds. Both have been classified as emerging contaminants in the Arctic (5) and, therefore, more studies on these contaminants and effects on human health are needed.

An important next step is to translate the findings of these and future research studies into meaningful communication messages to policy makers and the populations directly affected by contaminant exposures. Such messages must be evidence-based but also sensitive to the traditions and needs of Arctic regions. Traditional foods are integral to the Arctic peoples' cultures, through which social cohesion is maintained (5). In addition, traditional foods are a source of nutrients, such as essential fatty acids, which are not adequately obtained from market foods (5). Therefore, messages must incorporate a holistic approach to properly balance the risks of environmental contaminants in traditional foods with their benefits. Such communication is

likely to be successful through multi-stakeholder engagement that includes dialogue from the perspectives of science, policy, and communities.

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Table 1: Pediatric studies

Study	Contaminant	Outcome	Population	Results*
Infections				
Jensen (2013) (19)	PCBs and OCPs	Otitis Media	Mother-child pairs (n=400) and children 4-10 years of age at follow-up (n=223) *(participation rate: 56%)*	No association
Dallaire (2006) (20)	PCBs	Acute Respiratory Infection	Children 0-5 years of age (n=343) *(participation rate: 70%)*	**Cord PCB-153** • Acute otitis media: RR = 1.37, 95% CI: 1.20-1.55 • LRTI: RR = 1.44, 95% CI: 1.20-1.72 • URTI or hospitalization: No association
Dallaire (2004) (21)	PCBs and p,p'-DDE	Acute Infections	Infants during the first 12 months of life (n=199)	**Maternal PCB-153** • LRTI (first 6 months): RR =1.68, 95% CI: 1.00-2.81 (3rd exposure quartile) • GI infection (12 months): RR =1.59, 95% CI: 1.01-2.49 (3rd exposure quartile) **Maternal p,p'-DDE** • URTI (first 6 months): RR = 1.56, 95% CI: 1.05-2.33 (2nd exposure quartile) • URTI (12 months): RR = 1.34, 95% CI: 1.00-1.78 (2nd exposure quartile) • Otitis media (first 6 months): RR = 1.83, 95% CI: 1.09-3.07 (3rd exposure quartile) • All infections (first 6 months): RR = 1.33, 95% CI: 1.03-1.73 (3rd exposure quartile) • GI infection (12 months): RR = 1.59, 95% CI: 1.03-2.47 (2nd exposure quartile) **Child PCB or p,p'-DDE:** No association
Dewailly (2000) (22)	PCBs and OCPs	Infections and Immune Status	Newborns followed up to 12 months of age (n=171)	**Breast milk Mirex** • Acute otitis media (4-7 months): RR = 1.88, 95% CI: 1.14-3.08 (2nd exposure tertile) **Breast milk Dieldrin** • Acute Otitis Media (4-7 months): RR = 1.75, 95% CI: 1.05-2.91 (3rd exposure tertile) **Breast milk HCB** • Acute otitis media (first 12 months): RR = 1.49, 95% CI: 1.10-2.03) (3rd exposure tertile) **Breast milk p,p'-DDE**

				• Acute otitis media (first 12 months): RR = 1.52, 95% CI: 1.05-2.22) (3rd exposure tertile) **Breast milk PCBs:** No association **Bronchopulmonary diseases:** No association **Immunological parameters:** No association
Behavioural				
Boucher (2012) (27)	PCBs, Hg, and Pb	ADHD	Children followed from birth to 11 years of age (n=279) *(participation rate: 95%)*	**Cord Hg** • Attention problems: Positive association (β=0.13, 95% CI: 0.00-0.25) • Disruptive Behaviour Disorders score: OR=2.87, 95% CI: 1.04-7.94 (ADHD-inattentive type, 3rd exposure tertile) OR=2.92, 95% CI: 1.07-8.04 (ADHD-hyperactive impulsive type, 3rd exposure tertile) **Child blood Pb** • Externalizing problems: Positive association (β=0.14, 95% CI: 0.01-0.26) • Disruptive Behaviour Disorders score: OR=5.52, 95% CI: 1.38-22.12 (ADHD-hyperactive impulsive type, 3rd exposure tertile) **PCB-153:** No association
Verner (2010) (28)	PCBs	Attention and Activity	Infants followed from birth to 11 months of age (n=168)	**Cord PCB-153** • Inattention: Positive association (Spearman's correlation=0.205) **Infant blood PCB-153** • Non-elicited activity: Positive association (Spearman's correlation=0.182 at 11 months of age)
Plusquellec (2010) (29)	PCBs, Hg, and Pb	Behavioural Indicators	Children followed from birth to 5 years of age (n=110)	**Cord PCB-153** • Happiness: Inverse association (β=-0.22) • Anxiety: Positive association (β=0.26) • Global activity latency: Inverse association (β=-0.25) • Positive affect rate: Inverse association (β=-0.24) **Child blood Pb** • Impulsivity: Positive association (β=0.20) • Irritability: Positive association (β=0.20) • Inattention: Positive association (β=0.21) **Hg:** No association
Plusquellec (2007) (35)	Pb	Behavioural Function	Infants 11 months of age (n=169)	**Cord Pb** • Frenetic activity: Associated with greater activity (β=-0.16)

				• Off-task duration: Positive association (β=0.17) • Off-task latency: Inverse association (β=-0.20) No association with other measures.
Fraser (2006) (36)	Pb	Motor Function and Behaviour	Children 5 years of age (n=110)	**Child blood Pb** • Impulsivity: Positive association (Pearson correlation=0.25) • Activity: Positive association (Pearson correlation=0.25) No association with attention level.
Neurological				
Ethier (2012) (23)	PCBs, Hg, and Pb	Visual Brain Development	Children followed from birth to 10-13 years of age (n=172)	**Cord Hg** • N75 amplitude at 95% contract level: Positive association (β=0.206) • N75 latency at 12% contrast level: Positive association (β=0.285) **Cord Pb** • N150 latency: Positive association (β=0.238, 0.209, 0.251 at 95%, 12%, and 4% contrast levels respectively) **PCB-153:** No association
Boucher (2012) (24)	PCBs	Response Inhibition Error Monitoring	Children followed from birth to a mean age of 11 years (n=196)	**Child plasma PCB-153** • Reaction times: Positive association (i.e. slower times) (β=0.18 for go trials) • Amplitudes of P_e and P_c response-related potentials: Inverse association (β=-0.16 and -0.20 respectively) **Cord Pb:** • Correct responses: Inverse association (i.e. fewer correct responses) (β=-0.21 and -0.17 for correct go and no-go responses respectively) **Child blood Pb** • Correct responses on no-go trials (false alarms): Inverse association (more false alarms) (β=-0.16) • P3 amplitudes: Inverse association (β=-0.16 and -0.23 for go and no-go trials respectively **Hg:** No association
Boucher (2010) (25)	PCBs and Hg	Information Processing	Children followed from birth to 11 years of age (n=118)	**Cord PCB:** No association with sample as a whole • P3b amplitude in subgroup of children breast-fed for > 3 months: Inverse association (β=-0.32) **Cord Hg** • Reaction times: Positive association (i.e. slower time)

				(β=0.15) • False alarms: Inverse association (i.e. fewer false alarms) (β=-0.21) • N1 latency: Positive association (β=0.29) • N1 amplitude: Inverse association (β=-032)
Boucher (2009) (32)	Pb	Working Memory	Children 5 years of age (n=104) or 11 years of age (n=201) *(participation rate: 26% for ERP at 5 years and 55% for ERP at 11 years)*	**Cord Pb (5 years)** • P3b amplitude: Inverse association (β=-0.38) **Child blood Pb (5 years)** • P3b latency: Positive association (β=0.37) **Pb (11 years):** No association
Saint-Amour (2006) (33)	PCBs and Hg	Visual Brain Processing	Children followed from birth to 5-6 years of age (n=102)	**Child plasma PCB-153** • P100 latency at 95% contrast: Positive association (β=2.50) • N150 latency at 12% contrast: Positive association (β=5.58) • N75-P100 amplitude at 95% contrast: Inverse association (β=-3.74) **Cord Hg** • P100 latency at 30% contrast: Positive association (β=3.34) **Child blood Hg** • N75 early latency at 95% and 30% contrasts: Inverse association (β=-3.90 and -3.18 respectively) • P100 latency at 95% and 30% contrasts: Inverse association (β=-3.26 and -3.94 respectively)
Després (2005) (26)	PCBs, Hg, and Pb	Neuromotor Functions	Children followed from birth to pre-school (n=110)	**Child plasma PCB-153** • Sway oscillations: Positive association (β=0.22 for transversal sway) **Child blood Hg** • Tremor: Positive association (β=0.20) **Child blood Pb** • Reaction time: Positive association (i.e. slower time) (β=0.24) • Sway oscillations: Positive association (β=0.24, 0.22, 0.26 for velocity, sagittal, and transversal sway) • Movement irregularity: Positive association (β=0.22) • Coherence between hands: Inverse association (β=-0.29) • Synkinesis: Positive association (β=0.23) • Tremor: Positive association (β=0.24)
Weihe (2002)	Hg	Neurobehavioural	Children followed from birth	**Maternal hair Hg**

(34)		Performance	to 7-12 years of age (n=21) and children 7-12 years of age (n=22)	• Hand-eye coordination (error score): Positive association (r=0.44) Peak latencies on brainstem auditory evoked potentials prolonged at higher exposure levels when data combined with other cohorts (Faroes and Madeira).
Cardiovascular and Endocrine				
Valera (2012) (31)	Hg	Blood Pressure and Heart Rate Variability	Children followed from birth to 11 years of age (n=226) *(participation rate: 46%)*	**Child blood Hg** • HRV – low frequency: Inverse association (β=-0.24) • HRV – SDNN: Inverse association (β=-0.28) • HRV – SDANN: Inverse association (β=-0.32) • HRV – CVRR: Inverse association (β=-0.06) **Blood Pressure:** No association
Sandau (2002) (30)	PCBs, PCP, and octachlorostyrene	Thyroid Function	Newborns (n=10)	**Cord PCP** • T_3, TBG, and fT_4: Inverse association (r=-0.55, -0.44, -0.51 respectively) **Cord ∑PCBs and ∑PCB hydroxylated metabolites** • TSH: Inverse association (r=-0.46 and -0.45 respectively) **Sum of all cord chlorinated phenolic compounds** • T_3 and fT_4: Inverse association (r=-0.48 and -0.47 respectively)
Abbreviations: ADHD = attention deficit hyperactivity disorder; CI = confidence interval; CVRR = coefficient of variation of R-R intervals; DDE = dichlorodiphenyldichloroethylene; ERP = event-related potential; fT_4 = free thyroxine; GI = gastrointestinal; HCB = hexachlorobenzene; Hg = mercury; HRV = heart rate variability; LRTI = lower respiratory tract infection; OCPs = organochlorine pesticides; OR = odds ratio; Pb = lead; PCBs = polychlorinated biphenyls; PCP = pentachlorophenol; RR = relative risk; SDANN = standard deviation of R-R intervals measured over 5 min periods; SDNN = standard deviation of R-R intervals; T_3 = triiodothyronine; TBG = thyroxine-binding globulin; TSH = thyroid-stimulating hormone; URTI = upper respiratory tract infection				

* Adjusted estimates are presented where available. Presented estimates are statistically significant at $p \leq 0.05$ level.

Table 2: Studies of reproductive health

Study	Contaminant	Outcome	Population	Results*
Mocevic (2013) (53)	Hg	Semen Quality and Reproductive Hormones	Male partners of pregnant women (n=194)	Inhibin B: Positive association (β=0.074, 95% CI: 0.021-0.126) No association with other semen characteristics or reproductive hormones.
Kvist (2012) (54)	PFOA and PFOS	Sperm Y:X Ratio	Male partners of pregnant women (n=201) *(participation rate: 78.5%)*	**PFOS** • Inverse association (i.e. lower Y:X ratio) (β=-0.002, 95% CI: -0.004-0.000) **PFOA:** No association
Krüger (2012) (37)	PCBs and OCPs	ER, AR, and AhR Function	Men and women (n=247) *(participation rate: 41% of all Greenlandic AMAP population and 74% for XAR and XAR_{comp} outcomes)*	**∑PCBs** • ER transactivity (males): Inverse association (β=-0.36 and -0.24 for XER and XER_{comp} respectively) • ER transactivity (females): Inverse association (β=-0.41 for XER_{comp}) • AhR transactivity (males): No association • AhR transactivity (females): Inverse association (β=-0.61) **∑OCPs** • ER transactivity (males): Inverse association (β=-0.34 for XER) • ER transactivity (females): Inverse association (β=-0.36 for XER_{comp}) • AhR transactivity (males): Inverse association (β=-0.29) • AhR transactivity (females): Inverse association (β=-0.55) **AR transactivity:** No association
Krüger (2008) (38)	PCBs and OCPs	ER and AR Transactivity	Men and women (n=240) *(participation rate: 82% for XAR/XER outcome)*	**∑PCBs** • ER transactivity (males and females): No association upon adjustment • AR transactivity (males): Inverse association (β=-0.42) • AR transactivity (females): No association **∑OCPs** • ER transactivity (males): No association • ER transactivity (females): Inverse association when adjusted for age (β=-0.24) • AR transactivity (males): Inverse association (β=-0.36) • AR transactivity (females): No association
Bonde (2008) (43)	PCBs and	Fertility and Markers	Pregnant women and their	**PCB-153**

	p,p'-DDE	of Male Reproductive Function	spouses (n=598) *(participation rate: 90%)*	• LH: Positive association (β=0.07, 95% CI: 0.02-0.12) • Sperm volume: Inverse association (β=-0.11, 95% CI: -0.2 to -0.04) • Progressive sperm: Inverse association (β=-4, 95% CI: -6 to -1) • Sperm counts: low counts in subgroup of men with short androgen receptor CAG repeat length • Neutral α-glucosidase activity in seminal plasma: Inverse association (β=-0.1, 95% CI: -0.2 to -0.0) • No association with other measures (e.g. time to conceive, apoptotic markers, sperm chromatin integrity) **p,p'-DDE** • Inhibin B: Positive association (β=6.4, 95% CI: 1.7-13.8) • Free testosterone: Positive association (β=0.02, 95% CI: 0.0-0.04) • Sperm volume: Inverse association (β=-0.04, 95% CI: -0.16 to -0.01) • Progressive sperm: Inverse association (β=-0.01, 95% CI: unclear to -0.6) • No association with other measures (e.g. sperm chromatin integrity, apoptotic markers, epididymal and accessory sex gland function)
Krüger (2008) (50)	POPs (evaluated as effects on ER, AR, and AhR)	Sperm Chromatin Integrity	Male spouses of pregnant women (n=53)	• DNA fragmentation index: Inverse association with ER and AhR activities • DNA stainability: No association
Long (2007) (39)	PCBs and OCPs	AhR Transactivity	Men and women 18-77 years of age (n=357) *(participation rate: 48% for AhR_{comp} outcome)*	∑**PCBs:** • No association (males or females) with AhR-TEQ • Inverse association with AhR_{comp} in males and females combined (β=-0.18) ∑**OCPs** • Inverse association with AhR-TEQ (β=-0.31) in males; No association in females • Inverse association with AhR-TEQ (β=-0.21) in males and females combined • Inverse association with AhR_{comp} in males and females combined

				(β=-0.18)
Krüger (2007) (40)	PCBs and p,p'-DDE	Serum Xenoandrogenic Activity	Male spouses of pregnant women (n=37)	**PCB-153:** No association **p,p'-DDE:** No association
Toft (2007) (52)	POPs (evaluated as effects on ER, AR, and AhR)	Semen Quality	Male spouses of pregnant women (n=54)	No association specifically in Inuit. When data combined across all 4 populations (Warsaw, Greenland, Kharkiv, Sweden), ER activity associated with increase in sperm concentration and motility.
Long (2007) (51)	POPs (evaluated as effects on ER, AR, and AhR)	Sperm DNA Damage and Sperm Apoptotic Markers	Male spouses of pregnant women (n=54)	DNA damage: Inverse association with ER and AhR Bcl-xL marker: Inverse association with AR (Spearman's correlation=-0.46) No association with the sperm apoptotic marker, Fas.
Long (2006) (41)	PCBs and p,p'-DDE	AhR Activity	Males (n=75)	**PCB-153:** No association **p,p'-DDE:** No association
Stronati (2006) (45)	PCBs and p,p'-DDE	Sperm DNA Fragmentation and Sperm Apoptotic Markers	Male spouses of pregnant women (n=200) *(participation rate: 79%)*	**PCB-153:** No association **p,p'-DDE:** No association
Elzanaty (2006) (47)	PCBs and p,p'-DDE	Epididymal Function and Accessory Sex Gland Function	Male spouses of pregnant women (n=163)	**PCB-153** • Epididymal marker (neutral-α glucosidase): Inverse association (β=-0.2, 95% CI: -0.3 to -0.04) • No association with PSA, zinc, or fructose **p,p'-DDE:** No association
Giwercman (2006) (48)	PCBs and p,p'-DDE	Reproductive Hormone Levels	Male spouses of pregnant women (n=258) *(participation rate: 79%)*	**PCB-153** • LH: Positive association for highest exposure group compared with lowest exposure group (MD=1.4 IU/L, 95% CI: 1.1-1.7 IU/L) • No association with other reproductive hormones **p,p'-DDE** • Free testosterone: Positive association (β=0.011, 95% CI: 0.004-0.024) • Inhibin B: Positive association for highest exposure group compared with lowest exposure group (MD=35 ng/L, 95% CI: 1.5-69 ng/L) • No association with other reproductive hormones
Bonefeld-Jorgensen (2006) (42)	PCBs and p,p'-DDE	Serum Xenoestrogenic Activity	Male spouses of pregnant women (n=72)	**PCB-153:** No association **p,p'-DDE:** Inverse association (Spearman's correlation=-0.29 for XER)

Tiido (2006) (49)	PCBs and p,p'-DDE	Sperm Y:X Ratio	Male spouses of pregnant women (n=157)	**PCB-153:** No association **p,p'-DDE:** No association
Toft (2005) (44)	PCBs and p,p'-DDE	Fertility	Pregnant women (n=598) and their spouses (n=201) *(participation rate: 87%)*	**PCB-153:** No association **p,p'-DDE:** No association
Spanò (2005) (46)	PCBs and p,p'-DDE	Sperm Chromatin Integrity	Male spouses of pregnant women (n=193)	**PCB-153:** No association **p,p'-DDE:** No association

Abbreviations: AhR = aryl hydrocarbon receptor; AMAP = Arctic Monitoring Assessment Programme; AR = androgen receptor; CI = confidence interval; DDE = dichlorodiphenyldichloroethylene; DNA = deoxyribonucleic acid; ER = estrogen receptor; Hg = mercury; IU = international unit; LH = luteinizing hormone; MD = mean difference; OCPs = organochlorine pesticides; PCBs = polychlorinated biphenyls; PFOA = perfluorooctanoic acid; PFOS = perfluorooctanesulfonate; POPs = persistent organic pollutants; PSA = prostate specific antigen

* Adjusted estimates are presented where available. Presented estimates are statistically significant at $p \leq 0.05$ level.

Table 3: Studies of obstetrics and gynecology

Study	Contaminant	Outcome	Population	Results*
Dallaire (2013) (55)	PCBs, HCB, and Hg	Fetal Growth and Pregnancy Duration	Pregnant women (n=248) *(participation rate: 59%)*	**Cord PCB-153, HCB, and Hg** • Duration of pregnancy: Inverse association (β=-0.17 to -0.20) • Fetal growth (mediated through shorter gestation period): Inverse association for length (β=-0.16 to -0.18 for PCB-153 and HCB respectively)
Wojtyniak (2010) (56)	PCBs and p,p'-DDE	Birth Weight, Gestational Age and Preterm Birth	Women with singleton live births (n=572) *(participation rate: 86%)*	**PCB-153** • Birth weight: Inverse association (β=-59.2, 95% CI: -100.6 to -17.8) • Gestational age: Inverse association (β=-0.2, 95% CI: -0.4-0.0) **p,p'-DDE** • Birth weight: Inverse association (β=-39.4, 95% CI: -79.0-0.2) • Gestational age: Inverse association (β=-0.2, 95% CI: -0.4-0.0) No association with preterm birth.
Dallaire (2009) (57)	PCBs, HCB, and PCP	Thyroid Hormone Levels	Pregnant women (n=107) and infants up to 7 months of age (n=130)	**Thyroid hormone levels in women at delivery:** **Maternal PCB hydroxylated metabolites** • T_3: Positive association (β=0.57) • No association with other thyroid hormones **Maternal PCB-153, HCB, and PCP:** No association **Thyroid hormone levels in umbilical cord:** **Maternal and cord PCB-153** • TBG: Inverse association (β=-0.25 for maternal PCB-153 and -0.26 for cord PCB-153) • No association with other thyroid hormones **Maternal PCP** • fT_4: Inverse association (β=-0.59) • No association with other thyroid hormones **Maternal or cord HCB and PCB hydroxylated metabolites/cord PCP:** No association **Infant PCB-153 or HCB:** No association
Toft (2008) (58)	PCBs and p,p'-DDE	Menstrual Cycle	Pregnant women presenting for antenatal care at local	**PCB-153** • Long menstrual cycles: Inverse association (OR=0.7, 95% CI:

			hospitals (n=454) *(participation rate: 90%)*	0.5-0.96) • No association with average cycle length, irregular cycles, or short cycles **p,p'-DDE** • Long menstrual cycles: Inverse association (OR=0.7, 95% CI: 0.5-0.99) • No association with average cycle length, irregular cycles, or short cycles
Lucas (2004) (59)	PCBs and Hg	Birth Weight and Gestational Age	Pregnant women (n=491) *(participation rate: 30% for gestational age outcome)*	**Cord PCB-153** • Birth weight: Positive association in unadjusted analysis **Hg:** No association
Muckle (2004) (60) (Abstract only)	PCBs, OCPs, and Hg	Developmental Effects	Not provided	**OCs** • Physical growth at birth: Inverse association (estimate not provided) • Duration of pregnancy: Inverse association (estimate not provided) **Hg:** No information provided
Pereg (2002) (61)	PCBs	Placental CYP1A1 Activity	Pregnant women admitted to hospital upon delivery (n=35)	No association
Lagueux (1999) (62)	PCBs and OCPs	Placental CYP1A1 Activity & DNA Adducts	Women giving birth in regional hospitals (n=22)	**PCB-153, p,p'-DDE, HCB** • CYP1A1 activity: Positive association in moderate smokers (R^2 = 0.21, 0.51, 0.38 respectively) **PCB-118** • CYP1A1 activity: Positive association in heavy smokers (R^2 = 0.30) • Associated with bulky DNA adduct formation in non-smokers and moderate smokers across all cohorts, including non-Inuit **p,p'-DDE** • Associated with less bulky DNA adducts across all cohorts, including non-Inuit
Foldspang (1990) (63)	Hg	Gestational Length and Birth Weight	Mothers with singleton deliveries (n=376) *(participation rate: 45.9% newborns represented from one district)*	Birth weight: Inverse association (β=-7.1 for maternal blood mercury and -4.2 for offspring blood mercury) No association with gestational length.
Abbreviations: CI = confidence interval; DDE = dichlorodiphenyldichloroethylene; DNA = deoxyribonucleic acid; fT_4 = free thyroxine; HCB = hexachlorobenzene; Hg = mercury; OCs = organochlorines; OCPs = organochlorine pesticides; OR = odds ratio; PCBs = polychlorinated biphenyls; PCP = pentachlorophenol; T_3 = triiodothyronine; TBG = thyroxine-binding globulin				

* Adjusted estimates are presented where available. Presented estimates are statistically significant at $p \leq 0.05$ level.

Table 4: Studies of cardiology, endocrinology, bone health, oncology, and oxidative stress in adults

Study	Contaminant	Outcome	Population	Results*
Cardiology				
Valera (2013) (64)	PCBs and OCPs	Hypertension (≥140/90 mm Hg or taking anti-hypertensive medication)	Men and women ≥ 18 years of age (n=1614) *(participation rate: 52% from larger population)*	**∑ DL-PCBs** • Hypertension: Positive association in youngest age category (18-39 years) (OR = 1.34, 95% CI: 1.03-1.74) **∑ non DL-PCBs** • Hypertension: Inverse association in oldest age category (≥ 40 years) (OR = 0.81, 95% CI: 0.66-0.99) **DDT** • Hypertension: Positive association in youngest age category (18-39 years) (OR = 1.42, 95% CI: 1.08-1.85) **Aldrin, α-Chlordane, γ-Chlordane** • Hypertension: Inverse associations in youngest age category (18-39 years) (OR = 0.39, 95% CI: 0.20-0.78; OR = 0.38, 95% CI: 0.19-0.75; OR = 0.10, 95% CI: 0.03-0.38 respectively) **Mirex** • Hypertension: Inverse association in oldest age category (≥ 40 years) (OR = 0.80, 95% CI: 0.69-0.93) No association across all age categories.
Valera (2013) (65)	Hg	Blood Pressure, Resting Heart Rate and Pulse Pressure	Men and women ≥ 18 years of age (n=313) *(participation rate: 41%)*	Resting heart rate: Positive association Diastolic blood pressure: Inverse association No association with systolic blood pressure or pulse pressure.
Nielsen (2012) (66)	Hg	Blood Pressure	Men and women 30-69 years of age (n=1861) *(participation rate: 67.5%)*	Diastolic blood pressure: Inverse association in men (β=-0.04) Hypertension: Inverse association in men (OR = 0.99, 95% CI: 0.98-0.99) No association in women.
Valera (2009) (67)	Hg	Blood Pressure	Men and women ≥18 years of age (n=732) *(participation rate: 55%)*	Systolic blood pressure: Positive association (β=2.14, 95% CI: 0.94-3.33) Diastolic blood pressure: No association

Château-Degat (2010) (70)	PFOS	Plasma Lipids	Men and women 18-74 years of age (n=723) *(participation rate: 68%)*	Triacylglycerol: Inverse association in women (β=-0.0014) HDL-C: Positive association (β=0.0042 and 0.0016 for women and men respectively) Ratio TC/HDL-C: Inverse association (β=-0.0035) No association with LDL-C or non-HDL-C.
Valera (2008) (68)	Hg	Blood Pressure and Cardiac Autonomic Activity	Men and women ≥ 40 years of age (n=280) *(participation rate: 59%)*	SDANN: Inverse association (β=-0.086, 95% CI: -0.16 to -0.01) Systolic blood pressure: Positive association (β=4.77, 95% CI: 1.12-8.42) Pulse pressure: Positive association (β=3.40, 95% CI: 1.11-5.69) No association with diastolic blood pressure or other measures of cardiac autonomic activity.
Luoma (1995) (69)	Cd	Blood Pressure and Arterial Hypertensive Disease	Reindeer herders 20-82 years of age in Arctic Finland (n=230) *(participation rate: 14%)*	Systolic blood pressure: Positive association Diastolic blood pressure: No association
Endocrinology				
Jørgensen (2008) (71)	PCBs and OCPs	Glucose Intolerance	Men and women (mean age 49 years) (n=692) *(participation rate: 67%)*	**PCBs and OCPs** 2-hour insulin: Inverse association **DL-PCBs and non DL-PCBs** HOMA-B: Inverse association No association with mean fasting glucose, mean 2-hour glucose, or mean fasting insulin. No association with IGT or diabetes.
Dallaire (2009) (72)	PCBs, OCPs, PBDEs, PFOS, and Dioxin-like compounds	Thyroid Function	Men and women ≥ 18 years of age (n=623) *(participation rate: 50%)*	**PCBs** T_3: Inverse association (β=-0.020) (inverse association also for PCB metabolites) TBG: Inverse association (β=-0.037) (inverse association also for PCB metabolites) **HCB** T_3: Inverse association (β=-0.030) fT_4: Inverse association (β=-0.017) TBG: Inverse association (β=-0.054) **β-HCH** T_3: Inverse association (β=-0.028) TBG: Inverse association (β=-0.051) **PFOS** T_3: Inverse association (β=-0.017) fT_4: Positive association (β=0.014)

				TBG: Inverse association (β=-0.034) TSH: Inverse association (β=-0.102) No associations with p,p'-DDE or PBDEs after full adjustment for confounders.
Bone Health				
Paunescu (2013) (73)	DL-PCBs (evaluated as effects on AhR)	Bone Strength	Women 35-72 years of age (n=194)	No association
Côté (2006) (74)	PCBs and OCPs	Bone Ultrasound	Peri- and postmenopausal women 49-64 years of age (n=153)	**PCB-156** • Broadband ultrasound attenuation (indication of bone density and architecture): Inverse association (β=-8.12) • Speed of sound (indication of bone density and elasticity): Inverse association (β=-22.68) • Stiffness index (indication of rigidity of bone structure): Inverse association (β=-11.95) **PCB-153:** No association
Oncology				
Bonefeld-Jorgensen (2011) (75)	PCBs, OCPs, PFCs, and Heavy Metals	Breast Cancer	Cases (n=31) and controls (n=115)	**PCBs** • Highest quartile of exposure significantly higher for cases than controls. Otherwise no association. **PFCs** • Positive association with breast cancer (OR=1.03, 95% CI: 1.001-1.07 for PFOS and 1.03, 95% CI: 1.00-1.05 for ∑perfluorsulfonated acids) **∑POPs** • Positive association (OR=1.02, 95% CI: 1.01-1.04) **OCPs:** No association **Heavy metals:** No association
Rusiecki (2008) (76)	PCBs and OCPs	DNA Methylation (*Alu* and *LINE-1* assays)	Mostly males 19-67 years of age (n=70)	**∑PCBs** • Inverse association on *Alu* assay (β=-0.56) (i.e. DNA hypomethylation) **p,p'-DDE, DDT, other pesticides** • Inverse associations on *Alu* assay (β=-0.26 to -0.75) **∑POPs** • Inverse association on *Alu* assay (β=-0.48) No association on *LINE-1* assays.

Other				
Bélanger (2008) (78)	PCBs and Hg	Oxidative Stress (redox status of CoQ10 and Vitamin E)	Men and women (majority women) (n=99)	**∑PCBs** • Total tocopherols: Positive association (β=2.68) • α-tocopherol: Positive association (β=4.12) • Ratio α-tocopheryl quinone/α-tocopherol: Inverse association (β=-0.41) • Overall, no evidence of oxidative stress **Hg** • α-tocopheryl quinone: Inverse association (β=-0.30) • Overall, no evidence of oxidative stress No association with ubiquinol-10 or ubiquinone-10 and PCBs or Hg.
Bélanger (2006) (77)	PCBs and Hg	Oxidative Stress (plasma oxidized LDL-C, homocysteine, glutathione peroxidase, glutathione reductase, and glutathione)	Men and women (majority women) (n=99)	**PCBs** • Oxidized LDL-C: Positive association (β=0.11) **Hg:** No association

Abbreviations: AhR = aryl hydrocarbon receptor; Cd = cadmium; CI = confidence interval; DDE =dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; DL-PCBs = dioxin-like polychlorinated biphenyls; DNA = deoxyribonucleic acid; fT_4 = free thyroxine; HCB = hexachlorobenzene; HCH = hexachlorocyclohexane; HDL-C = high density lipoprotein cholesterol; Hg = mercury; HOMA-B = homeostasis model assessment of beta cell function; IGT = impaired glucose tolerance; LDL-C = low density lipoprotein cholesterol; OCPs = organochlorine pesticides; OR = odds ratio; PBDEs = polybrominated diphenyl ethers; PCBs = polychlorinated biphenyls; PFCs = perfluorinated compounds; PFOS = perfluorooctanesulfonate; POPs = persistent organic pollutants; SDANN = standard deviation of the average RR intervals calculated over 5 minute periods; T_3 = triiodothyronine; TBG = thyroxine-binding globulin; TC = total cholesterol; TSH = thyroid-stimulating hormone

* Adjusted estimates are presented where available. Presented estimates are statistically significant at $p \leq 0.05$ level.

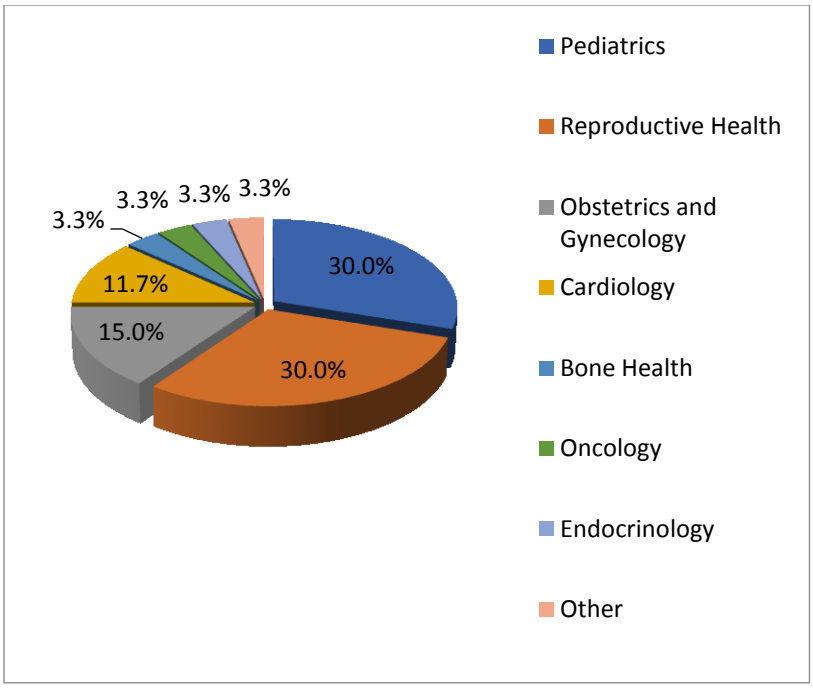

Figure 1: Breakdown of studies by health category

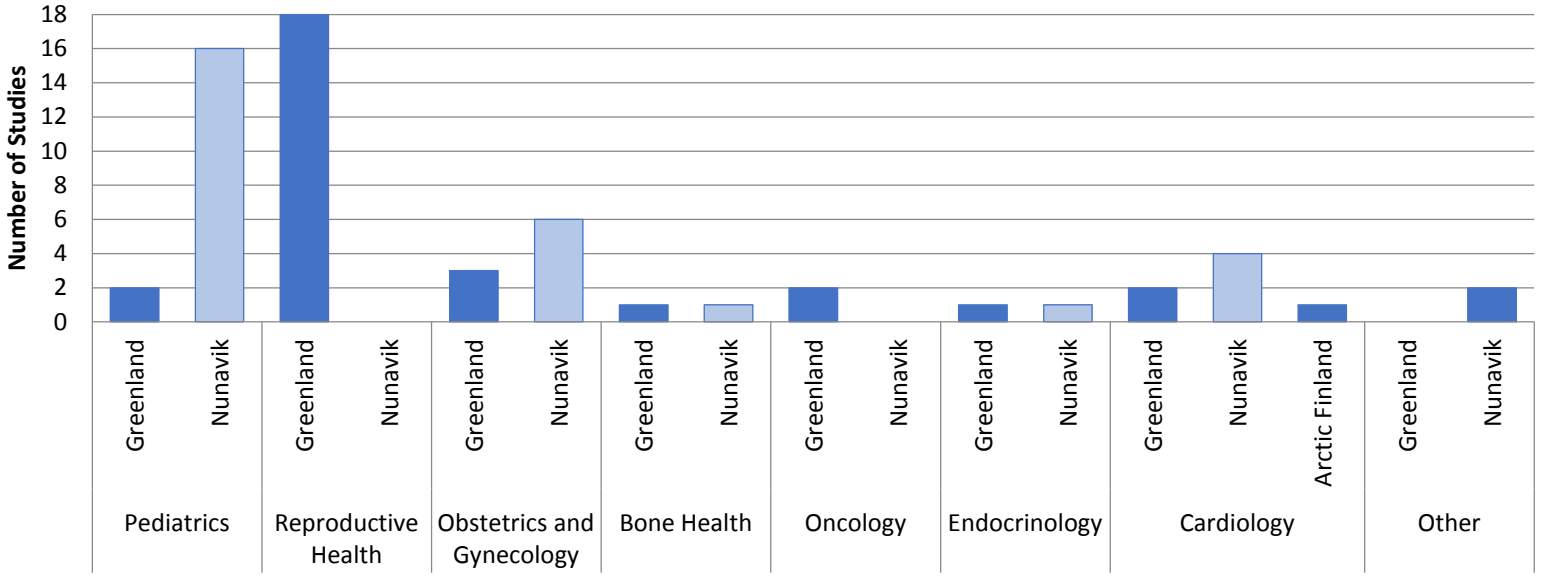

Figure 2: Breakdown of studies by health category and location

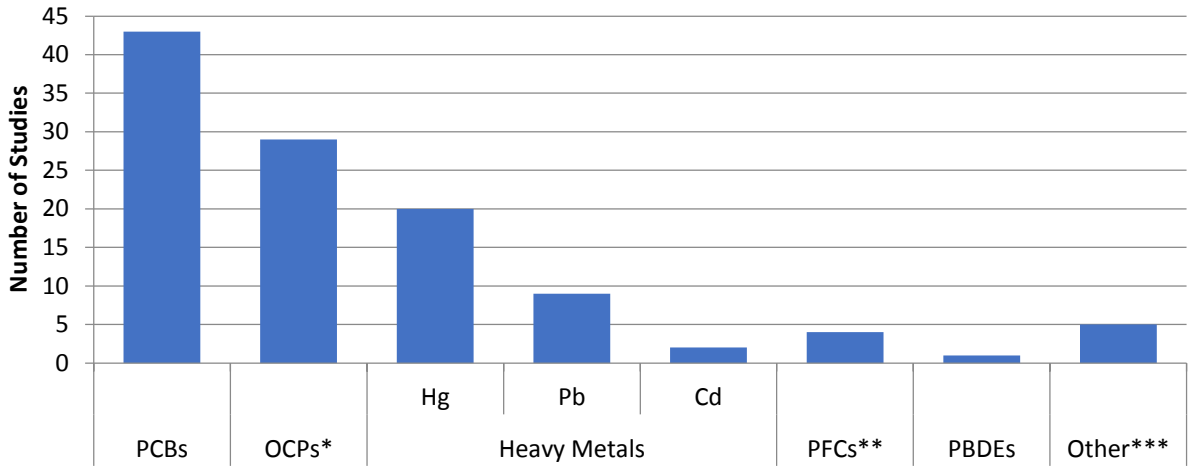

Figure 3: Breakdown of studies by contaminant

* OCPs - e.g. p,p'-DDE, DDT, HCB, PCP

** PFCs - e.g. PFOA, PFOS

*** Other - octachlorostyrene, dioxin-like compounds, POPs (specific compounds unspecified)

Abbreviations: Cd = cadmium; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; HCB = hexachlorobenzene; Hg = mercury; OCPs = organochlorine pesticides; Pb = lead; PBDEs = polybrominated diphenyl ethers; PCBs = polychlorinated biphenyls; PCP = pentachlorophenol; PFCs = perfluorinated compounds; PFOA = perfluorooctanoic acid; PFOS = perfluorooctanesulfonate; POPs = persistent organic pollutant

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Chapter 7: Association of PCBs and DDE with Diabetes among Inuit of Canada

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K. Singh conducted the analysis, interpreted the results, and drafted the manuscript. H.M. Chan critically reviewed the manuscript and provided feedback.

Abstract

Type 2 diabetes is a chronic metabolic disease that is of increasing concern in Inuit communities. Behavioural factors such as physical inactivity and poor diet are well-known risk factors. Exposure to persistent organic pollutants (POPs) has emerged as an additional factor in the pathogenesis of diabetes. In this study, association between polychlorinated biphenyls (PCBs) and p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE) with diabetes in Canadian Inuit was examined. Data from the Adult Inuit Health Survey (2007-2008) of Inuit participants from the Canadian Arctic were analyzed. Self-reported diabetes (excluding gestational diabetes) and clinical measurement of fasting glucose were examined as outcomes. Association with individual PCB congeners, sum of dioxin-like PCBs (∑DL-PCB), non-dioxin-like PCBs (∑NDL-PCB), total PCBs (∑PCB), and p,p'-DDE were investigated using multiple regression models adjusted for confounding factors. Using different methods to incorporate serum lipids, highest vs. lowest quartile exposures to PCB-105, PCB-118, PCB-153, PCB-156, PCB-170, PCB-180, PCB-183, ∑PCB, and p,p'-DDE were associated with increased risk of diabetes. For these PCBs, odds ratios (ORs) ranged from 1.9-3.5 (lower 95% CI: 0.8-1.4, upper 95% CI: 4.4-9.0) and for p,p'-DDE the OR was 2.5 (lower 95% CI: 1.1-1.2, upper 95% CI: 5.9-6.0). The highest vs. lowest quartile exposure to most PCBs and p,p'-DDE were associated with an increase of fasting glucose by 3-7%. PCBs and p,p'-DDE were associated with increased risk of diabetes and higher fasting glucose level in a cross-sectional survey of Canadian Inuit. Cause-effect relationships of

PCBs and p,p'-DDE with diabetes and diabetes-related outcomes need to be further investigated in a cohort study.

Keywords: Inuit, Diabetes, Persistent Organic Pollutants, Canada

Introduction

Diabetes is a chronic metabolic disease with incidence rates increasing around the world (WHO, 2016). In Canada, the prevalence of diabetes was 6.8% (2.4 million Canadians) in 2009 and is expected to rise to 3.7 million people by 2019 (PHAC, 2011). Nine out of ten have type 2 diabetes, which is characterized by increased hepatic glucose output, reduced insulin secretion, and insulin resistance (CDA, 2016). Although type 2 diabetes is generally diagnosed in adults over the age of 40 years, this condition is increasingly being detected in adolescents and children (PHAC, 2011). Since people with diabetes are more likely to be hospitalized and to require specialist care, the healthcare costs of diabetes are also significant. By 2020, diabetes-associated costs to the Canadian healthcare system are estimated to reach 16.9 billion dollars per year (CDA, 2011).

The Canadian Inuit population comprises nearly 60 000 people and about 75% reside in the northern Canadian regions of Nunatsiavut, Nunavik, Nunavut, and the Inuvialuit Settlement Region (Statistics Canada, 2011). Although diabetes prevalence in Canadian Inuit is similar to the general Canadian population, it is on the rise with increase from 2% in 2001 to 5% in 2012 (Tait, 2006; Wallace, 2014). This rise of prevalence in Inuit communities is of concern because diabetes is an independent risk factor for cardiovascular disease and leads to several health complications. Many risk factors for diabetes, such as physical inactivity, high caloric intake, shift in dietary pattern, and obesity are prevalent in the Inuit (Jørgensen, 2010). In addition, upstream factors that impact the social determinants of health such as housing conditions, food

insecurity, employment opportunities, and access to healthcare also have an impact on diabetes prevalence (PHAC, 2011). The Aboriginal Peoples Survey 2012 reported that 30% of Inuit 18 years of age or older were overweight and 26% were obese based on body mass index (BMI) (Wallace, 2014). In addition, 41% of Inuit 15 years of age or older experienced food insecurity in the past 12 months compared with 8% of the general Canadian population (Wallace, 2014).

Global pollution and long-range transport have caused accumulation of persistent organic pollutants (POPs) in the Arctic environment (Donaldson et al., 2010). Marine mammals have high concentrations of POPs, particularly in fat, due to biomagnification of contaminants to the top trophic levels of the food chain (Donaldson et al., 2010). Many studies have shown that Inuit have high exposure and body burden of POPs because of their traditional diets that include marine mammals (Donaldson et al., 2010). The association between POPs and diabetes has been investigated in human populations around the globe (Sharp, 2009; Taylor et al., 2013). In a review of epidemiological studies, the strongest positive association with type 2 diabetes was found with organochlorine pesticides and polychlorinated biphenyls (PCBs) (Taylor et al., 2013). In the Arctic, a cross-sectional study of 692 adult Greenlandic Inuit found that POPs were not associated with diabetes or impaired glucose tolerance but there was an inverse association with stimulated insulin concentration and homeostasis model assessment of beta cell function (HOMA-B) (Jørgensen et al., 2008). This study suggested that POPs may affect insulin secretion rather than insulin resistance. In a smaller study of 101 participants from a Canadian First Nations community, self-reported diabetes was positively associated with p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE) and PCBs (Philibert et al., 2009).

The purpose of this study was to investigate if there is association between blood PCBs or p,p'-DDE concentrations and diabetes in a sample population of Canadian Inuit. Self-reported

diabetes (excluding gestational diabetes) and measured fasting glucose were examined in this study. This is the first study, to our knowledge, that has evaluated the relationship between POP exposures and diabetes in this population.

Methods

2.1 Participants and Data Collection:

The Adult Inuit Health Survey (2007-2008) was a cross-sectional survey of Canadian Inuit across 33 coastal communities and three inland communities in the Inuvialuit Settlement Region, Nunavut Territory, and Nunatsiavut and was conducted as part of the International Polar Year program (Saudny et al., 2012). The survey included questionnaires about health status, chronic diseases, and behaviours such as exercise, smoking and alcohol intake. For self-reported conditions, respondents were asked the question "Did a doctor or a nurse ever tell you that you suffered from diabetes (other than during pregnancy)". Also included in the survey were tests of clinical parameters such as fasting glucose and blood levels of PCBs and organochlorine pesticides. A total of 2595 Inuit who were 18 years of age or older participated in the survey (68% participation rate) and 2172 provided blood samples. The following PCB congeners were measured in blood plasma: PCB-28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 163, 170, 180, 183, and 187. PCB-163 was excluded from analyses because about 56% of observations were not reported. Pregnant women were excluded. All work was approved by the research ethics boards of the University of Northern British Columbia, McGill University and the University of Ottawa.

2.2 Exposures:

The association with diabetes was explored with individual PCB congeners (PCB-99, 105, 118, 138, 153, 156, 170, 180, 183, 187); PCB groupings - sum of dioxin-like PCBs (∑DL-PCB), sum of non-dioxin like PCBs (∑NDL-PCB) and total PCBs (∑PCB); and the

organochlorine pesticide metabolite, p,p'-DDE. Details of analytic methods and quality control procedures have been described previously (Laird et al., 2013). Samples were analyzed by the Laboratoire de Toxicologie at the Institut National de Santé Publique du Québec. In this study, we grouped the PCB congeners into sum of dioxin-like PCBs (∑DL-PCB), sum of non-dioxin like PCBs (∑NDL-PCB) and total PCBs (∑PCB).

∑DL-PCB = PCB-105 + PCB-118 + PCB-156

∑NDL-PCB = PCB-28 + PCB-52 + PCB-99 + PCB-101 + PCB-128 + PCB-138 + PCB-153 + PCB-170 + PCB-180 + PCB-183 + PCB-187

∑PCB = ∑DL-PCB + ∑NDL-PCB

All contaminants were divided into quartile level on both lipid and wet-weight basis and the first quartile was set as the reference category (Table 1 provides concentration ranges of each quartile for each examined contaminant). The lipid-based quartile concentrations were calculated by dividing wet-weight concentration by total serum lipid. Total serum lipid was derived from total cholesterol and triglycerides using the equation (Bernert et al., 2007):

$$\text{Total Lipids (mg/dL)} = 2.27 * \text{Total Cholesterol} + \text{Triglycerides} + 62.3 \quad \text{(Eq. 1)}$$

Values below the limit of detection were recoded as half the detection limit value (Appendix 1, Table A1.2-1). Observations with missing values for contaminant or total serum lipid were excluded from analyses.

2.3 Outcomes:

Self-reported diabetes (excluding gestational diabetes) and measured fasting glucose were examined in this study. Type 1 and 2 diabetes were not differentiated, however, it could be assumed that the majority of the self-reported cases would be type 2 based on the epidemiology of diabetes (PHAC, 2011 p.8). The natural logarithm transformation of fasting glucose was

included in models. If respondents indicated that they did not have diabetes but reported that they were taking a medication for diabetes, they were reclassified as positive. Seven respondents were reclassified as positive based on medication use.

2.4 Statistical Analyses:

Multiple logistic regression models were developed to examine association between PCBs, p,p'-DDE, and diabetes self-reported dichotomously. Multiple linear regression models were also developed for fasting glucose. For linear regression models, the assumptions of linearity, normality, and homoscedasticity of residuals were verified qualitatively with plots. Models were run using wet-weight quartile categories, quartiles based on wet-weight divided by total serum lipids, and wet-weight quartile categories with total serum lipids as a covariate. The latter two are termed lipid standardized and lipid adjusted according to the nomenclature of Schisterman et al. (2005). All model results are available in Appendix 1, Tables A1.2-2 and A1.2-3. Here, results based on lipid standardized and lipid adjusted modelling are presented.

Covariates considered for inclusion in models were age; sex; marital status; education; income; total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), alcohol intake, cigarette smoking, exercise as measured with total metabolic equivalent (MET) score based on walking, moderate activity, and vigourous activity; BMI; blood levels of heavy metals (selenium, lead, mercury, and cadmium); total monounsaturated fatty acids (MUFA), total polyunsaturated fatty acids (PUFA), total saturated fats, omega-3 fatty acids, omega-6 fatty acids, and omega-3/omega-6 ratio in red blood cells; family history (diabetes in parent or sibling), and medication use. Covariates were examined in univariate analyses with each outcome and were considered for inclusion in full models based on statistical significance, missing data, and available degrees of freedom. Collinearity among

covariates was tested with the variance inflation factor (VIF).

Parameters in models were considered statistically significant if $p < 0.05$. All analyses were conducted in R version 3.3.1. Forest plots were created with Comprehensive Meta-Analysis version 3.

Results

Of 2595 respondents, 147 (5.7%) indicated that they have diabetes and this was approximately equally distributed among males and females (5.5% and 5.8% respectively) (Table 2). Percentage with diabetes increased with age (2.9% in 31-50 year category and 22.1% in 71-90 year category). In addition, a higher number of respondents in Nunatsiavut indicated they have diabetes compared to the other two regions (8.7% vs. 5.5% Nunavut and 3.9% Inuvialuit Settlement Region). Among respondents with diabetes, the majority (56.5%) had elementary or secondary school education, and a larger percentage had no education (21.1% vs. 6.4%). Those with diabetes had higher percentage of diabetes in the family, either parent (19.7% vs. 10.4 %) or sibling (20.4% vs. 4.5%). Alcohol consumption and current smoking was lower among diabetics (31.3% vs. 58.4% and 43.5 vs. 71.4% respectively).

Table 3 shows PCB and p,p'-DDE lipid concentrations for all respondents and for respondents with and without self-reported diabetes. All contaminant concentrations were higher in respondents with diabetes.

In Figure 1, the odd ratios (ORs) for self-reported diabetes for quartile 4 vs. quartile 1 contaminant categories are shown. These estimates were adjusted for age, sex, BMI, HDL-C, omega-3/omega-6 ratio, and education. Statistically significant positive ORs were found for PCB-105, PCB-118, PCB-153, PCB-156, PCB-170, PCB-180, PCB-183, ∑PCB, and p,p'-DDE with lipid standardization (OR range: 2.2-3.5, lower 95% limit: 1.04-1.42, upper 95% limit: 4.67-

8.95). With lipid adjustment, statistically significant positive ORs were found for PCB-118, PCB-156, PCB-170, PCB-183, and p,p'-DDE (OR range: 2.41-3.03, lower 95% limit: 1.02-1.25, upper 95% limit: 5.95-8.40). The point estimates for wet-weight analyses were in positive direction for quartile 4 vs. quartile 1, but not statistically significant (Appendix 1, Table A1.2-2).

Table 4 shows the fasting glucose β coefficients for PCB congeners and p,p'-DDE that were statistically significant based on lipid standardization or lipid adjustment. These models were adjusted for age, sex, BMI, HDL-C, triglycerides, alcohol intake, smoking, omega-3/omega-6 ratio, selenium, and education. The β coefficients for wet-weight analyses were positive and statistically significant for PCB-99, PCB-105, PCB-118, PCB-138, PCB-153, PCB-183, PCB-187, ∑DL-PCB, and p,p'-DDE (Appendix 1, Table A1.2-3). In Figure 2, the β coefficients from lipid adjusted models are translated into percentage increase in fasting glucose from quartile 1 to quartile 4 category of contaminant. The point estimates for increase in fasting glucose associated with elevated blood PCB or p,p'-DDE concentrations ranged from 3-7%.

We also classified diabetes by fasting plasma glucose ≥ 7 mmol/L and/or undergoing diabetes management (i.e. exercise, diet, medication) and found 104 cases (Appendix 1, Table A1.2-4). This is likely an under-estimate due to the effects of therapeutic treatment on fasting glucose. When using this definition to classify diabetes, none of the associations with PCBs or DDE were statistically significant, which may be due to the smaller number of cases.

Discussion

The 6% prevalence of diabetes in this sample population was similar to the 5% prevalence reported by the Aboriginal Peoples Survey 2012 (Wallace, 2014). The prevalence of diabetes among the Inuit is similar to the general Canadian population and much lower than First Nations communities living on reserve (15%), which have the highest prevalence of diabetes in Canada, and First Nations communities off-reserve (9%) (PHAC, 2011).

In this study, several PCB congeners and p,p'-DDE were found to be positively associated with self-reported diabetes in Canadian Inuit when comparing highest and lowest quartile categories of exposure. Also, PCBs and p,p'-DDE were both associated with higher fasting glucose level. Using PCB-183 as an example, a change in lipid-based blood concentration from Q1: [0.0005, 0.0019] μg/g lipid to Q4: (0.0163, 0.291] μg/g lipid was associated with an increase in fasting glucose of 4% (95% CI: 1%, 6%). A change in wet-weight blood concentration from Q1: [0.005, 0.01] μg/L to Q4: (0.11, 2.2] μg/L and adjustment for total serum lipids was associated with an increase in fasting glucose of 5% (95% CI: 2%, 7%). The corresponding increase in risk of diabetes was 3.3 (95% CI: 1.4, 8.4) and 2.9 (95% CI: 1.3, 6.9) respectively. For p,p'-DDE, a change in lipid-based blood concentration from Q1: [0.0014, 0.13] μg/g lipid to Q4: (0.764, 8.19] μg/g lipid was associated with 6% (95% CI: 3%, 8%) increase in fasting glucose and 2.5 (95% CI: 1.2, 5.9) increase in risk of diabetes. Similarly, a change in p,p'-DDE wet-weight blood concentration from Q1: [0.01, 0.75] μg/L to Q4: (4.9, 60] μg/L was associated with 4% (95% CI: 2%, 7%) and 2.5 (95% CI: 1.1, 6.0) increase in risk of diabetes. PCB-99, -138, ∑DL-PCB, and ∑NDL-PCB were associated with increase in fasting glucose, however risk estimates for self-reported diabetes were not statistically significant.

The results are in agreement with several studies that have shown positive associations between PCBs and p,p'-DDE with diabetes in different populations. In a First Nations community in Canada (n=101), lipid-adjusted p,p'-DDE >75th percentile verses ≤ 75th percentile, the OR for diabetes was borderline significant at 3.6 (95% CI: 0.97, 13.1) and sum of total PCB OR was significant at 5.5 (95% CI: 1.3-24.1) (Philibert et al., 2009). A study of a Mohawk Native American community (n=352) found that total PCBs were associated with diabetes (OR=3.2, 95% CI: 1.4, 7.5) based on fasting glucose >6.9 mmol/L or taking antidiabetic

medication (Codru et al., 2007). A positive association was also found for DDE (OR=6.2, 95% CI: 1.8-21.9 for highest tertile) (Codru et al., 2007). In a sample of Akwesasne Native Americans (n=601), the most significant association with diabetes was observed with lower chlorinated, more volatile, NDL-PCB congeners (Aminov et al., 2016). This study also observed that the effect estimates for total PCBs and DDE on diabetes became statistically non-significant after adjusting for total pesticides or total PCBs respectively (Aminov et al., 2016). We similarly found that adjustment for DDE or total PCBs led to a loss of statistical significance, however correlation was present between DDE and PCBs. The Inuit are exposed to multiple contaminants which are highly correlated and, therefore, deciphering the individual effects of the components of co-exposures remains a challenge. A review of 72 epidemiological studies evaluated contaminant and diabetes association in a broad range of populations, including Canadian and United States aboriginal communities, the National Health and Nutrition Examination Survey (NHANES), and South Korea (Taylor et al., 2013). The strongest positive associations with type 2 diabetes were with trans-nonachlor, DDE, PCBs, dioxins, and dioxin-like compounds.

Our results, however, differ from those reported by Jorgensen et al. (2008) in Greenlandic Inuit. In that study no significant association was detected between POPs and self-reported diabetes or measured fasting glucose. The Greenland study had a smaller sample size (n=692) than the Inuit Health Survey (n=2172) and, therefore, it may not have sufficient power to detect the small differences in these outcomes. Also, a different set of confounders were adjusted for which may have led to the different results. Models in that study were adjusted for age, sex, ethnicity, waist circumference, physical activity, alcohol consumption, smoking, and education. Additionally, the POPs were grouped into broad categories of DL-PCB, NDL-PCB, and organochlorine pesticides which included p,p'-DDE along with several other pesticides. In the

present study we examined individual PCB congeners and p,p'-DDE separately. The PCB and p,p'-DDE blood concentrations in the Greenland Inuit were somewhat higher compared with the Canadian Inuit and were relatively higher compared with the general populations of Denmark and Canada respectively (Morck et al., 2014; Health Canada, 2010). It has been hypothesized that an inverted U-shaped relationship exists between persistent organic pollutants and diabetes and that differences in study results may be due to differences in the distribution of exposures among populations (Lee et al., 2014). If an inverted U-shaped relationship is the true causal explanation, then a population that is all highly exposed may result in a null association if the data fall at the flatter part of the curve (Lee et al., 2014). In our data, the point estimates for self-reported diabetes for several PCBs followed an upright U-shaped pattern (i.e. odds ratios for Q3 vs. Q1 were lower than Q2 vs. Q1 and Q4 vs. Q1). This apparent trend, however, must be interpreted with caution because many of the point estimates were not statistically significant.

A considerable amount of evidence supports biological plausibility for the observed epidemiological effects of POPs on diabetes and diabetes-related outcomes. Experimental evidence suggests that organochlorine pesticides, dioxins, and NDL-PCB can induce insulin resistance (Carpenter, 2008; Sharp, 2009). POPs are lipophilic chemicals that bioaccumulate in fat and have been shown to exert obesogenic effects (Baillie-Hamilton, 2002). In animal studies, organochlorine pesticides increased proportion of body fat and disrupted hormones that are involved in controlling weight (e.g. insulin) with resulting changes in appetite and metabolism of fats, carbohydrates, and protein (Baillie-Hamilton, 2002). PCBs have been shown to cause morphological changes in pancreatic β-cell function (Carpenter, 2008). POPs that bind to the aryl-hydrocarbon (Ah) receptor, such as the DL-PCB, up or down-regulate genes involved in glucose tolerance (Carpenter, 2008). Ruiz et al. (2016) mapped out potential pathways by which

PCB-153, p,p'-DDE, and 2,3,7,8-tetrachlorodibenzodioxin (TCDD) lead to diabetes/insulin resistance, obesity, or metabolic syndrome.

A Northern contaminants mixture (NCM) of 22 organic and inorganic contaminants which is detected in the blood of populations in the Canadian Arctic was tested in JCR rats administered vehicle, 1.6 mg/kg NCM, or 16 mg/kg NCM for 4 weeks with or without 10% (v/v) alcohol (Mailloux et al., 2015). The NCM was observed to alter islet morphology and to cause direct islet injury, leading to decrease in circulating insulin and glucagon. In mouse insulin-secreting (MIN6) β cells, NCM inhibited insulin release and induced cell death (Mailloux et al., 2015). The NCM mixture was also studied for its effects on non-alcoholic fatty liver disease (NAFLD), which is associated with type 2 diabetes, in obese JCR rats (Mailloux et al., 2014). The mixture was observed to worsen existing hepatic steatosis by decreasing hepatic cholesterol export, increasing cholesterol uptake from the circulation, promoting lipid accumulation, and altering adenosine triphosphate homeostasis. Results of this animal dosing study suggest that exposure to POPs can increase the risk of diabetes either by alteration of insulin secretion and/or disruption of lipid metabolism.

The primary limitation of this study is the cross-sectional design of the survey, which precludes any inferences about temporal relationships between POP exposures and health outcomes. Also, it is unclear as to when respondents were diagnosed with diabetes. After a diagnosis, respondents may modify behaviours that alter clinical parameters and this may mask association with POPs. Multiple statistical analyses were carried out for different PCB congeners and quartile categories. Thus, while the potential for detecting significant findings by chance alone exists, we think that the consistent findings in the positive direction between quartiles 1 and 4 for fasting glucose and self-reported diabetes support existence of association. We chose to

use different methods to represent the body burden of organochlorines in our analyses (wet-weight, lipid standardized and lipid adjusted) as there is currently no consensus on one optimal method (Schisterman et al., 2005). The method that produces the least bias depends on the relationship of serum lipids to the exposure-outcome pathway. Lipid standardization was found to produce the highest bias in a simulation exercise (Schisterman et al., 2005). The different methods of analysis produced more consistent results for fasting glucose, but for self-reported diabetes the results were more variable.

Diabetes is a complex, multifactorial disease that is a relevant health concern to Inuit communities. This is the first analysis, to our knowledge, that has shown association between PCBs and p,p'-DDE with diabetes in Canadian Inuit. The findings were in a cross-sectional study and merit further investigation to understand if cause-effect relationships exist. To better understand the effects of PCBs, p,p'-DDE, and other POPs on diabetes and diabetes-related outcomes, future work should be directed at conducting a prospective cohort study of Canadian Inuit that collects baseline data on environmental exposures, diabetes status, parameters of metabolic syndrome such as fasting glucose, adiponectin, blood pressure, cholesterol, and obesity, and genetic markers of diabetes. This sample should be followed longitudinally in time to determine if exposures to environmental contaminants have any effect on such outcomes. Global efforts such as the implementation of the Stockholm Convention are limiting the use and release of these chemicals in the environment. However, because of their long environmental half-lives, it will still take decades for environmental levels in the Arctic to decrease back to background levels. Therefore, ongoing monitoring of contaminant burden and disease outcomes among the Inuit population is important.

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Table 1: Quartile concentration cut-off values

	Lipid-Based (µg/g lipid)	Wet-Weight (µg/L)
PCB-99		
Q1	[0.0016, 0.0059]	[0.015, 0.0362]
Q2	(0.0059, 0.0189]	(0.0362, 0.12]
Q3	(0.0189, 0.0509]	(0.12, 0.33]
Q4	(0.0509, 0.648]	(0.33, 4.9]
PCB-105		
Q1	[0.0004, 0.0011]	[0.004, 0.005]
Q2	(0.0011, 0.0032]	(0.005, 0.02]
Q3	(0.0032, 0.0092]	(0.02, 0.057]
Q4	(0.0092, 0.111]	(0.057, 0.78]
PCB-118		
Q1	[0.0007, 0.0063]	[0.005, 0.038]
Q2	(0.0063, 0.0176]	(0.038, 0.11]
Q3	(0.0176, 0.0475]	(0.11, 0.31]
Q4	(0.0475, 0.631]	(0.31, 4.9]
PCB-138		
Q1	[0.0007, 0.0184]	[0.005, 0.1]
Q2	(0.0184, 0.0541]	(0.1, 0.32]
Q3	(0.0541, 0.135]	(0.32, 0.88]
Q4	(0.135, 1.99]	(0.88, 15]
PCB-153		
Q1	[0.0007, 0.0429]	[0.005, 0.25]
Q2	(0.0429, 0.134]	(0.25, 0.79]
Q3	(0.134, 0.352]	(0.79, 2.3]
Q4	(0.352, 6.18]	(2.3, 48]
PCB-156		
Q1	[0.0005, 0.0025]	[0.005, 0.0163]
Q2	(0.0025, 0.00795]	(0.0163, 0.048]
Q3	(0.00795, 0.0202]	(0.048, 0.13]
Q4	(0.0202, 0.412]	(0.13, 3.2]
PCB-170		
Q1	[0.0006, 0.00688]	[0.005, 0.04]
Q2	(0.00688, 0.0219]	(0.04, 0.13]
Q3	(0.0219, 0.0607]	(0.13, 0.39]
Q4	(0.0607, 1.37]	(0.39, 10]
PCB-180		
Q1	[0.0007, 0.0211]	[0.005, 0.12]
Q2	(0.0211, 0.0667]	(0.12, 0.4]
Q3	(0.0667, 0.186]	(0.4, 1.2]
Q4	(0.186, 4.77]	(1.2, 37]
PCB-183		
Q1	[0.0005, 0.0019]	[0.005, 0.01]
Q2	(0.0019, 0.0063]	(0.01, 0.038]
Q3	(0.0063, 0.0163]	(0.038, 0.11]
Q4	(0.0163, 0.291]	(0.11, 2.2]
PCB-187		
Q1	[0.0007, 0.0089]	[0.005, 0.049]
Q2	(0.0089, 0.026]	(0.049, 0.15]
Q3	(0.026, 0.0642]	(0.15, 0.42]
Q4	(0.0642, 0.94]	(0.42, 7.3]

∑DL-PCB		
Q1	[0.0021, 0.0113]	[0.015, 0.064]
Q2	(0.0113, 0.0306]	(0.064, 0.182]
Q3	(0.0306, 0.0775]	(0.182, 0.509]
Q4	(0.0775, 1.14]	(0.509, 8.88]
∑NDL-PCB		
Q1	[0.0331, 0.148]	[0.24, 0.822]
Q2	(0.148, 0.367]	(0.822, 2.2]
Q3	(0.367, 0.93]	(2.2, 6.02]
Q4	(0.93, 15.4]	(6.02, 120]
∑PCB		
Q1	[0.0352, 0.161]	[0.255, 0.887]
Q2	(0.161, 0.404]	(0.887, 2.39]
Q3	(0.404, 1]	(2.39, 6.59]
Q4	(1, 16.5]	(6.59, 128]
p,p'-DDE		
Q1	[0.0014, 0.13]	[0.01, 0.75]
Q2	(0.13, 0.316]	(0.75, 1.9]
Q3	(0.316, 0.764]	(1.9, 4.9]
Q4	(0.764, 8.19]	(4.9, 60]

Abbreviations: DDE = dichlorodiphenyldichloroethylene; DL-PCB = dioxin-like polychlorinated biphenyl; NDL-PCB = non-dioxin like polychlorinated biphenyl; PCB = polychlorinated biphenyl; Q = quartile

Table 2: Demographic characteristics and risk factors for those with and without self-reported diabetes

	With Diabetes (n=147)	No Diabetes (n=2034)
Gender – No. (%)		
Males	55 (37.4)	773 (38.0)
Females	92 (62.6)	1261 (62.0)
Age Category – No. (%)		
18-30	4 (2.7)	571 (28.1)
31-50	35 (23.8)	969 (47.6)
51-70	81 (55.1)	425 (20.9)
71-90	27 (18.4)	69 (3.4)
Region – No. (%)		
Nunavut	106 (72.1)	1547 (76.0)
ISR	14 (9.5)	252 (12.4)
Nunatsiavut	27 (18.4)	235 (11.6)
Education – No. (%)[1]		
None	31 (21.1)	130 (6.4)
Elementary	45 (30.6)	375 (18.4)
Secondary	38 (25.9)	1116 (54.9)
College/Trade School	19 (12.9)	319 (15.7)
University	5 (3.4)	65 (3.2)
Missing	9 (6.1)	29 (1.4)
Family History – No. (%)		
Parent with diabetes	29 (19.7)	212 (10.4)
Parent without diabetes	64 (43.5)	1381 (67.9)
Missing	54 (36.7)	441 (21.7)
Sibling with diabetes	30 (20.4)	89 (4.5)
Sibling without diabetes	65 (44.2)	1483 (72.9)
Missing	52 (35.4)	462 (22.7)
Alcohol – No. (%)[2]		
Yes	46 (31.3)	1188 (58.4)
No	67 (45.6)	558 (27.4)
Never Drank	21 (14.3)	123 (6.0)
Missing	13 (8.8)	165 (8.1)
Current Smoker – No. (%)		
Yes	64 (43.5)	1452 (71.4)
No	79 (53.7)	579 (28.5)
Missing	4 (2.7)	3 (0.1)
Diabetes Medication – No. (%)		
Yes	71 (48.3)	0 (0)
No	57 (38.8)	1378 (67.7)
Missing	19 (12.9)	656 (32.3)

[1] Partial or completed elementary school, secondary school, college or trade school, or university.
[2] Alcohol consumption in past 12 months

BMI (kg/m^2) – mean (SD)	32.0 (6.8)	28.2 (6.5)
Fasting Glucose (mmol/L) – mean (SD)	6.6 (2.8)	5.0 (0.7)
RBC Fatty Acids (%) – mean (SD)		
Omega-3	7.6 (4.2)	5.6 (3.3)
Omega-6	21.7 (6.3)	24.6 (6.4)
Heavy Metals (µg/L) – GM (range)		
Cadmium	1.0 (0.1-8.0)	1.7 (0.02-11.0)
Selenium	413.9 (140.0-2500.0)	312.3 (85.0-2800.0)
Mercury	12.3 (0.4-94.0)	6.6 (0.05-130.0)
Lead	43.1 (6.2-280.0)	34.5 (4.5-400.0)

Abbreviations: BMI = body mass index; GM = geometric mean; ISR = Inuvialuit Settlement Region; RBC = red blood cell

Table 3: Lipid-adjusted PCB and p,p'-DDE levels

	Total (µg/g lipid)		With Diabetes (n=147) (µg/g lipid)		No Diabetes (n=2034) (µg/g lipid)	
	GM (Range)	**N**	**GM (Range)**	**N**	**GM (Range)**	**N**
PCB-99	0.02 (0.002-0.65)	2148	0.05 (0.002-0.50)	139	0.02 (0.002-0.65)	1912
PCB-105	0.004 (0.0004-0.11)	2148	0.01 (0.0006-0.10)	139	0.003 (0.0004-0.11)	1912
PCB-118	0.02 (0.0007-0.63)	2148	0.06 (0.0007-0.49)	139	0.02 (0.0007-0.63)	1912
PCB-138	0.05 (0.0007-1.99)	2148	0.14 (0.0007-1.32)	139	0.04 (0.0007-1.99)	1912
PCB-153	0.12 (0.0007-6.18)	2148	0.38 (0.001-5.75)	139	0.11 (0.0007-6.18)	1912
PCB-156	0.007 (0.0005-0.41)	2148	0.02 (0.0007-0.29)	139	0.01 (0.0005-0.41)	1912
PCB-170	0.02 (0.0006-1.37)	2148	0.07 (0.001-1.37)	139	0.02 (0.0006-1.29)	1912
PCB-180	0.06 (0.0007-4.77)	2148	0.20 (0.006-4.77)	139	0.06 (0.0007-4.77)	1912
PCB-183	0.006 (0.0005-0.29)	2147	0.02 (0.0007-0.15)	139	0.005 (0.0005-0.29)	1911
PCB-187	0.02 (0.0007-0.94)	2148	0.06 (0.0007-0.38)	139	0.02 (0.0007-0.94)	1912
∑DL-PCB	0.03 (0.002-1.14)	2148	0.10 (0.003-0.73)	139	0.03 (0.002-1.14)	1912
∑NDL-PCB	0.38 (0.03-15.39)	2145	1.03 (0.04-14.16)	139	0.35 (0.03-15.39)	1911
∑PCB	0.41 (0.04-16.53)	2145	1.13 (0.05-14.78)	139	0.38 (0.04-16.53)	1911
p,p'-DDE	0.30 (0.001-8.19)	2147	0.76 (0.001-4.70)	138	0.27 (0.002-8.19)	1912

Abbreviations: DDE = dichlorodiphenyldichloroethylene; DL-PCB = dioxin-like polychlorinated biphenyl; GM = geometric mean; GSD = geometric standard deviation; NDL-PCB = non-dioxin like polychlorinated biphenyl; PCB = polychlorinated biphenyl

Table 4: Multiple linear regression analyses for natural log-transformed fasting glucose (mmol/L) (Q4 vs. Q1)

	β (95% CI)	
	Lipid Standardized	**Lipid Adjusted**
PCB-99	0.04 (0.02, 0.07)**	0.04 (0.01, 0.07)**
PCB-105	0.06 (0.04, 0.09)***	0.06 (0.03, 0.09)***
PCB-118	0.06 (0.04, 0.09)***	0.07 (0.04, 0.10)***
PCB-138	0.04 (0.01, 0.07)**	0.05 (0.02, 0.08)***
PCB-153	0.02 (-0.01, 0.05)	0.04 (0.01, 0.07)**
PCB-183	0.04 (0.01, 0.06)**	0.05 (0.02, 0.07)***
PCB-187	0.02 (-0.00, 0.05)	0.04 (0.01, 0.07)**
∑DL-PCB	0.03 (0.01, 0.06)*	0.05 (0.02, 0.08)**
∑NDL-PCB	0.03 (0.00, 0.05)*	0.03 (0.00, 0.06)*
∑PCB	0.03 (-0.00, 0.05)	0.03 (0.00, 0.06)*
p,p'-DDE	0.06 (0.03, 0.08)***	0.04 (0.02, 0.07)**

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Adjusted for age, gender, natural log BMI, √HDL, natural log triglycerides, alcohol intake, smoking, √omega3/omega6, log selenium, and education. The lipid-adjusted model additionally contained total serum lipids along with wet-weight quartile levels. Only those PCB congeners that were statistically significant in lipid standardization and/or lipid adjusted models are presented (PCB-156, 170 and 180 were not statistically significant).

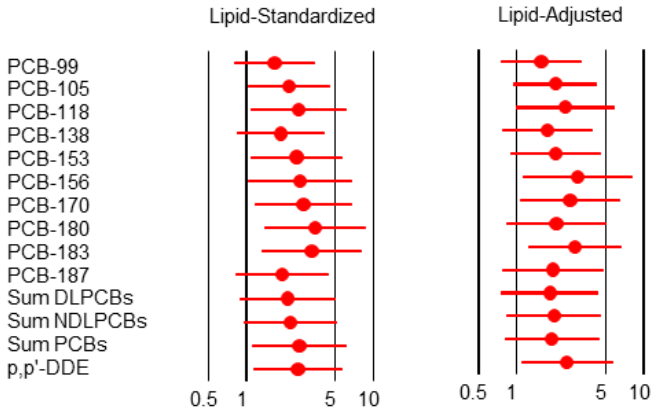

Figure 1: Adjusted odds ratios and 95% CIs for self-reported diabetes (Q4 vs. Q1)

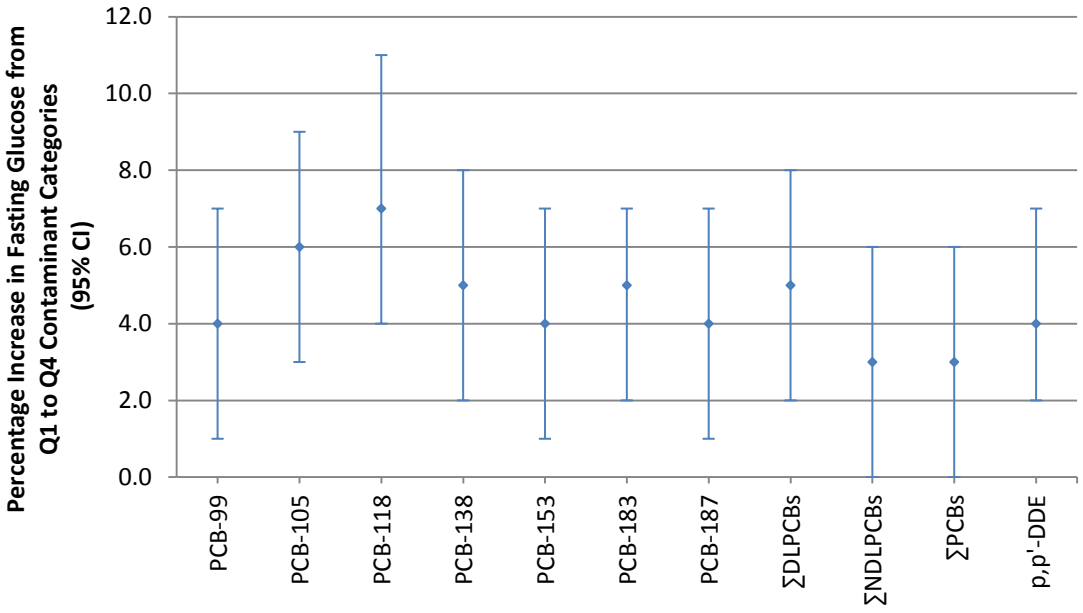

Figure 2: Effect on fasting glucose between contaminant categories (Q4 vs. Q1)

(lipid adjusted models)

Points represent the percentage increase in fasting glucose (from Q1 contaminant category), with 95% CI. Calculated from β coefficients presented in Table 4.

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Chapter 8: Association of PCBs with Cholesterol Levels among Inuit of Canada

Preface: This chapter was published:

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K. Singh conducted the analysis, interpreted the results, and drafted the manuscript. H.M. Chan critically reviewed the manuscript and provided feedback.

Abstract

It has generally been thought that Inuit populations have low risk of cardiovascular disease due to high consumption of omega-3 fatty acids found in traditional marine-based diets. However, results of recent surveys showed that Inuit populations are experiencing increasing rates of cardiovascular disease and related risk factors. The purpose of this study was to investigate if blood polychlorinated biphenyls (PCBs) are associated with high cholesterol and related parameters in Canadian Inuit, known risk factors for cardiovascular disease. The Adult Inuit Health Survey (IHS, 2007-2008) included 2595 Inuit participants from three regions of the Canadian Arctic, of which 2191 could be classified as with or without high cholesterol. The high cholesterol outcome was defined by LDL-C > 3.36 mmol/L or taking medication(s) that reduce cholesterol, and was examined in adjusted logistic regression models with individual blood levels of PCB congeners, sum of dioxin-like PCBs (∑DL-PCBs), or sum of non-dioxin-like PCBs (∑NDL-PCBs). Statistically significant covariates for high cholesterol were ranked in importance according to the proportion of the model log likelihood explained. Continuous clinical parameters of total cholesterol, triglycerides, LDL-C, and HDL-C were examined in multiple linear regression models with ∑DL-PCBs or ∑NDL-PCBs. A total of 719 participants had high cholesterol (32.8%). PCBs were associated with increased risk of high cholesterol, and higher levels of serum triglycerides, total cholesterol, and LDL-C. No association was observed

between PCBs and serum HDL-C. With respect to other statistically significant covariates for high cholesterol, the log likelihood ranking of PCBs generally fell between body mass index (BMI) and age. Further work is needed to corroborate the associations observed with PCBs and lipids in Canadian Inuit and to examine if they are causal in the direction anticipated.

Keywords: Inuit, Canada, Cholesterol, Triglyceride, blood PCB

Introduction

It has generally been thought that Inuit populations have low risk of cardiovascular disease due to consumption of omega-3 fatty acids found in traditional marine-based diets. However, based on the results of recent surveys, Inuit populations are experiencing high rates of cardiovascular disease and related risk factors. In the Canadian region of Nunavik, the *Qanuippitaa* Survey found that 16.7% of Inuit adults have high blood pressure, 7.9% high cholesterol, 4.1% cerebrovascular disease, 2.3% coronary artery disease, and 6.7% other cardiovascular disease (PHAC, 2009). In the Aboriginal Peoples Survey 2012 of Canada, 12% of Inuit 15 years of age or over reported having high blood pressure and 5% reported diabetes (excluding gestational diabetes) (Wallace, 2014). The Inuit diet, therefore, does not seem to provide full protection against cardiovascular morbidity. Non-modifiable and modifiable factors both play important roles in contributing to the prevalence of cardiovascular disease in Inuit communities (Tvermosegaard et al., 2015).

The presence of high blood cholesterol is an important risk factor for the development of atherosclerosis and myocardial infarction. Cholesterol travels in the blood stream bound mainly to low-density lipoprotein cholesterol (LDL-C), which carries up to 70% of total serum cholesterol and is highly atherogenic, and to high-density lipoprotein cholesterol (HDL-C),

which carries up to 30% of total serum cholesterol (NCEP, 2002). The very low density lipoproteins (VLDL) and chylomicron lipoproteins are rich in triglycerides and also have potential to promote atherosclerosis (NCEP, 2002). According to clinical practice guidelines, cholesterol lowering therapy should be initiated for secondary prevention in those with clinical atherosclerotic cardiovascular disease and for primary prevention in those with LDL-C ≥4.9 mmol/L, with diabetes 40-75 years of age, or with 10-year atherosclerotic cardiovascular disease risk ≥7.5% and 40-75 years of age (Stone et al., 2014). The risk of atherosclerotic cardiovascular disease is reduced by 20% for every 1.0 mmol/L reduction in LDL-C (Stone et al., 2014).

Although risk factors for high cholesterol, such as diets high in saturated and trans-fatty acids and obesity, are well recognized among the medical community, the contribution of persistent organic pollutant (POP) exposure is unclear. Persistent organic pollutants accumulate in the circumpolar Arctic region primarily by long-range transport from southern latitudes and resist environmental degradation (AMAP, 2015a). These chemicals bioaccumulate and biomagnify in food chains. The Inuit are especially susceptible to POP exposures from the consumption of marine mammals. They have been shown to have higher body burden of polychlorinated biphenyls (PCBs) and organochlorine pesticides compared to the general Canadian population (Laird et al., 2013). Only a few studies in Inuit populations have investigated the effect of POPs on cardiovascular disease risk factors (Château-Degat et al., 2010; Valera et al., 2013a, 2013b). In a cross-sectional study of Inuit adults from Nunavik, PCBs and p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE) were found to be associated with higher risk of hypertension (Valera et al., 2013a). Among Inuit from Greenland, dioxin-like PCBs and p,p'-dichlorodiphenyltrichloroethane (p,p'-DDT) were associated with higher risk of hypertension in younger respondents 18-39 years of age, but not in older respondents ≥ 40 years

(Valera et al., 2013b). Perfluorooctanesulfonate (PFOS) plasma levels were negatively associated with triacylglycerol and ratio of total cholesterol to HDL-C in Nunavik (Château-Degat et al., 2010).

The purpose of this study was to investigate the association of PCBs, a ubiquitous group of POPs, on high cholesterol and related clinical parameters. This area of investigation has received little attention in Inuit, although studies have been conducted in other populations (Aminov et al., 2013; Goncharov et al., 2008). An investigation of PCBs and high cholesterol in Canadian Inuit will add to our understanding of potentially novel risk factors for this important condition.

Methods

2.1 Participants and Data Collection:

The Adult Inuit Health Survey (IHS, 2007-2008) was a cross-sectional survey of Canadian Inuit across 33 coastal communities and three inland communities in the Inuvialuit Settlement Region, Nunavut Territory, and Nunatsiavut and was conducted as part of the International Polar Year program (Saudny et al., 2012). The survey included questionnaires about health status, chronic diseases, and behaviours such as exercise, smoking and alcohol intake. Also included in the survey were tests of clinical parameters and blood levels of PCBs. A total of 2595 Inuit who were 18 years of age or older participated in the survey (68% participation rate) and 2191 were classified as with or without high cholesterol. Pregnant women were excluded. All work was approved by the research ethics boards of the University of Northern British Columbia, McGill University and the University of Ottawa. Scientific Research Licenses for the IHS were obtained from relevant northern research institutions (the Aurora Research Institute, Northwest Territories and Qaujisaqtulirijikkut, Nunavut).

2.2 Exposures:

The association with high cholesterol and related measures was explored with individual plasma PCB congeners (PCB-99, 105, 118, 138, 153, 156, 170, 180, 183, and 187) and PCB groupings of sum of dioxin-like PCBs (∑DL-PCB) and sum of non-dioxin like PCBs (∑NDL-PCB). Details of analytic methods and quality control procedures have been described previously (Laird et al., 2013). Samples were analyzed by the Laboratoire de Toxicologie at the Institut National de Santé Publique du Québec. Sum of dioxin-like PCBs (∑DL-PCB) and sum of non-dioxin like PCBs (∑NDL-PCB) were calculated according to the following:

∑DL-PCB = PCB-105 + PCB-118 + PCB-156

∑NDL-PCB = PCB-28 + PCB-52 + PCB-99 + PCB-101 + PCB-128 + PCB-138 + PCB-153 + PCB-170 + PCB-180 + PCB-183 + PCB-187

All contaminants were divided into quartile level on both wet-weight and lipid basis and the first quartile set as the reference category (Table 1 provides concentration ranges of each quartile for each examined contaminant). The lipid-based quartile concentrations were calculated by dividing wet-weight plasma concentration by total serum lipids. Total serum lipids were derived from total cholesterol and triglycerides using the equation (Bernert et al., 2007):

$$\text{Total Lipids (mg/dL)} = 2.27*\text{Total Cholesterol} + \text{Triglycerides} + 62.3 \quad \text{(Eq. 1)}$$

Values below the limit of detection were recoded as half the detection limit value. Observations with missing values for contaminant or total serum lipid were excluded from analyses.

2.3 Outcomes:

If respondents had an LDL-C > 3.36 mmol/L (NCEP, 2002) or were taking medication(s) that lower cholesterol, they were classified as having high cholesterol (N = 2191). Triglycerides,

total cholesterol, LDL-C, and HDL-C were examined as continuous outcomes. Aside from LDL-C, these parameters were measured in serum under fasting conditions for at least eight hours. LDL-C was obtained by calculation using the Friedewald equation (Friedewald et al., 1972):

$$\text{LDL (mmol/L)} = \text{Total Cholesterol} - (\text{Triglyceride}/2.2) - \text{HDL} \quad \text{(Eq. 2)}$$

The sample population for these continuous outcomes was limited to those who were not taking any medications that lower cholesterol (N = 1279).

2.4 Statistical Analyses:

Multiple logistic regression models were developed to examine association between PCBs and high cholesterol. Multiple linear regression models were developed for triglycerides, total cholesterol, LDL-C, and HDL-C. For linear regression models, the assumptions of linearity, normality, and homoscedasticity of residuals were verified qualitatively with plots. For high cholesterol, models were run separately using wet-weight quartile categories and lipid-based quartile categories. For triglycerides, total cholesterol, LDL-C, and HDL-C, models were run with wet-weight PCB quartile levels only because adjustment for lipids would mask any association with the outcome. Triglycerides and HDL-C were natural log transformed. The untransformed β coefficients for these outcomes, therefore, represent the factor by which they increase ($\beta>1$) or decrease ($\beta<1$) the outcome.

Covariates considered for inclusion in models were age; sex; marital status; education; income; alcohol intake; cigarette smoking; exercise as measured with total metabolic equivalent (MET) score based on walking, moderate activity, and vigourous activity; body mass index (BMI); blood levels of heavy metals (selenium, lead, mercury, and cadmium); total monounsaturated fatty acids (MUFA); total polyunsaturated fatty acids (PUFA); total saturated fats; total trans fatty acids (TFA); omega-3/omega-6 ratio; fasting glucose; systolic blood

pressure; diastolic blood pressure; and family history (high cholesterol in parent). Covariates were examined in univariate analyses with each outcome and were considered for inclusion in full models based on statistical significance, missing data, and available degrees of freedom. Collinearity among covariates was tested with the variance inflation factor (VIF).

To evaluate the relative importance of the PCB covariate relative to other covariates in adjusted models of high cholesterol, the statistically significant factors were ranked based on the ratio of the -2 log likelihood (-2LL) of a single covariate model compared with the -2LL of the full model (Harrell, 2001). The ranking represents how much of the log likelihood of the full model is explained by a particular covariate. The ranking of covariates from models that incorporated wet-weight PCB quartile levels and lipid-based quartile levels are graphed separately.

Parameters in models were considered statistically significant if $p < 0.05$. All analyses were conducted in R version 3.3.1.

Results

A total of 2191 (84.4%) respondents were classified as with or without high cholesterol for this study (Table 2). Of this sample, 32.8% had high cholesterol and 67.2% did not. The average age was about 42 years and the majority were female (61.5%). The average BMI of respondents was in the overweight category (28.4 kg/m^2). Other clinical parameters and risk factors, including fasting glucose, LDL-C, HDL-C, triglycerides, total cholesterol, alcohol consumption, and cigarette smoking, are presented in Table 2. Wet-weight PCB concentrations for respondents with and without high cholesterol and for the total population are provided in Table 3. All PCB concentrations were higher in the group with higher cholesterol.

Table 4 shows the odds ratios for high cholesterol using wet-weight and lipid-based PCB

quartile concentrations, adjusted for age, sex, education, alcohol consumption, smoking status, omega 3/6 ratio, selenium, fasting glucose, total MUFA, and total TFA. Wet-weight odd ratios were all positively associated with high cholesterol and a trend of increasing effect estimates from quartile 2 to quartile 4 appears. With lipid-based PCB concentrations, effect estimates were also in positive direction, although not all quartiles were statistically significant and the increasing trend from quartiles 2 to 4 is absent.

The β coefficients for wet-weight PCB quartile concentrations for triglycerides, total cholesterol, LDL-C, and HDL-C from adjusted regression models for ∑DL-PCB and ∑NDL-PCB are shown in Figure 1. These analyses were restricted to respondents not taking any cholesterol medications (N = 1279). The corresponding increase in parameter levels are also provided in the tables below each figure. For triglycerides, quartile 3 vs. quartile 1 was statistically significant for ∑DL-PCB and ∑NDL-PCB (Figure 1a). Total cholesterol and LDL-C were positively associated with ∑DL-PCB and ∑NDL-PCB with increasing trends from quartiles 2 to 4 (Figure 1b-c). No significant association was found for ∑DL-PCB or ∑NDL-PCB with HDL-C (Figure 1d).

The relative contribution of each statistically significant factor to the full model for high cholesterol is shown in Figure 2. For models based on wet-weight PCB quartile concentrations (top-panel) or lipid-based PCB quartile concentrations (bottom-panel), the PCB factor generally falls between BMI and age. In the wet-weight models, the PCB factor contributes more to the -2LL of the full model compared with the lipid-based models.

Discussion

In this analysis we have shown that PCBs are associated with prevalence of high cholesterol, as measured by LDL-C or use of medication, as well as with triglycerides, total

cholesterol, and LDL-C among the Canadian Inuit. For the outcome of high cholesterol, the risk estimates for wet-weight quartile PCB concentrations increased from quartile 2 to quartile 4. The largest odds ratio was for PCB-118 quartile 4 to quartile 1 (OR, 95% CI: 4.90, 2.93-8.25). The risk estimates for lipid-based PCB quartile concentrations also increased the risk for high cholesterol but without reaching statistical significance. The β coefficient estimates for wet-weight PCB quartile concentrations for total cholesterol and LDL-C were positive and demonstrated a trend of increase. In the relative ranking of statistically significant covariates, age was most important as expected. The placement of PCBs between age and BMI in both wet-weight and lipid models was an interesting finding, showing that the PCBs were important covariates in explaining the variation in outcome. To the authors' knowledge, there has been limited research on ranking the relative importance of environmental contaminants and well-established disease risk factors on health endpoints. The ranking places the risks of contaminants into context and further research in this area for other POPs and health outcomes should be pursued.

Several studies have shown positive association between PCBs and lipids in human populations (Aminov et al., 2013; Arrebola et al., 2014; Goncharov et al., 2008; Lee et al., 2011; Ljunggren et al., 2014; Patel et al., 2012; Penell et al., 2014; Tokunaga and Kataoka, 2003). In a cross-sectional study of 575 residents living close to a former Monsanto plant in Alabama, the sum total of 27 PCB congeners in serum was associated with total lipids, total cholesterol, and triglycerides (Aminov et al., 2013). The strongest associations were observed for PCB congeners with three, four, or at least eight substituted chlorine atoms (Aminov et al., 2013). Lee et al. (2011), also found that PCB congeners with 7 or more chlorine atoms predicted higher BMI, triglycerides, and lower HDL-C in controls without diabetes. Arreola et al. (2014) observed that

PCB-138 and -180 were positively associated with triglycerides and total serum lipids, and PCB-153 with LDL-C in 298 adults from Southern Spain. In a highly exposed population (Yusho patients), PCBs were associated with higher total cholesterol and triglycerides, but not with HDL-C (Tokunaga and Kataoka, 2003). In a 5-year longitudinal study that examined change in lipids in seniors from Sweden 70 to 75 years of age, baseline levels of wet-weight or lipid-normalized NDL-PCBs 194, 206, and 209 increased total serum cholesterol and LDL-C, and PCB-194 reduced HDL-C (Penell et al., 2014). Patel et al. (2012) screened for many environmental factors and lipids in an environment-wide association study in the United States. Higher triglycerides and lower HDL-C were associated with PCBs after adjusting for many factors. The pathway of PCBs to cardiovascular disease in a population of Akwesasne Mohawks was found to be mediated by an increase in serum lipids, using structural equation modelling (Goncharov et al., 2008).

Results from experimental studies using animal models support the hypothesis that PCB exposure alters the lipid metabolism and blood lipid profile. In rats administered with PCB mixtures (e.g. Aroclor 1254, Aroclor 1242), increases in total cholesterol, HDL-C, triglycerides, and liver weights were observed (ATSDR, 2000). Mice exposed to soil from a Superfund site contaminated with PCBs for 4 weeks experienced doubling of liver weights (Imsilp and Hansen, 2005). A mixture of 22 contaminants, including PCBs, found in Inuit blood was studied for its effect on non-alcoholic fatty liver disease in obese JCR rats (Mailloux et al., 2014). In the liver of rats, the mixture increased the number of macrovesicular lipid droplets, total lipid content, total cholesterol, cholesterol ester, and mono- and polyunsaturated fatty acids (Mailloux et al., 2014). Individual congeners (e.g. PCB-105 and PCB-126) have also been found to increase serum cholesterol in rats (ATSDR, 2011, 2000). Changes in lipid profile may occur though

cytochrome P450 enzyme induction (Imsilp and Hansen, 2005), epigenetic changes (Rusiecki et al., 2008), and up or down regulation of genes (Mailloux et al., 2014; Matsusue et al., 1999; Vezina et al., 2004). There is also evidence from experimental and epidemiological studies that PCBs may act as obesogens, although results are inconsistent with variation according to dose, timing of exposure (e.g. prenatal versus adult), and gender (de Cock and van de Bor, 2014; Lee et al., 2014).

The increasing trend observed with wet-weight PCB quartile level with prevalence of high cholesterol, total cholesterol, and LDL-C suggests a dose-response relationship. One possibility that cannot be ruled out from this analysis is a reverse association, that is higher total cholesterol or LDL-C results in higher wet-weight based PCB concentrations. A mechanism for this direction of association, however, is not clear. In addition, Goncharov et al. (2008) have shown that the association of serum lipids to serum PCBs is less plausible compared with the association of serum PCB to serum lipids by testing a non-recursive feedback loop between PCBs and lipids. However, given that the lipid-based PCB analyses for high cholesterol produced significant effect estimates that did not increase with quartile level, further investigation about potential for dose-response and direction of association is needed.

The strengths of this study were its relatively large sample population, the adjustment of many important covariates, and the use of both wet-weight and lipid-based PCB concentrations for prevalence of high cholesterol. Lipid-based analyses were not conducted for triglycerides, total cholesterol, LDL-C, or HDL-C as this would have adjusted for the outcomes of interest. The prevalence of high cholesterol was based on LDL-C threshold or taking medication that lowers cholesterol, rather than self-report. The choice of this outcome has both its advantages and disadvantages. Since people with high cholesterol may be asymptomatic, self-report may

underestimate actual prevalence and, therefore, an outcome based on LDL-C threshold or medication may be more reliable. However, this outcome omitted about 1% of respondents whose LDL was lowered without medication, such as through diet or exercise. The consumption of poor-quality store-bought foods, which contain large servings of carbohydrates, saturated fat, trans-fat, and cholesterol, is an important risk factor for high cholesterol and the metabolic syndrome. We adjusted for fasting glucose in all models, and additionally for total TFA in red blood cells when modelling the outcome of high cholesterol, which would account for the dietary contribution of sugars and trans-fats. It is possible that the results may be confounded by store-bought food consumption (i.e. if participants with higher PCB concentrations also consumed more poor-quality store-bought foods). Although we could not fully evaluate this possibility because only a few store items were evaluated in the IHS (i.e. drinks and chips, crisps, cheese puffs), participants with higher PCB levels would be expected to consume more traditional rather than store-bought foods given that POP exposures come primarily from traditional food sources. The limitations of this study were the cross-sectional design, which prevents any conclusions from being drawn about causality of the observed associations, and the absence of weighted estimates, which means that the observed associations are restricted to the sample population and cannot necessarily be generalized to all Canadian Inuit. Deciphering the individual effect of PCBs from other POPs is also difficult because Inuit are exposed to mixtures of contaminants which are highly correlated.

The importance of lipids in the development of cardiovascular disease requires that we have a sound understanding of all factors that adversely affect lipid profile so that prevention and treatment approaches are appropriately targeted. Further work is needed to corroborate the associations observed with PCBs and lipids in Canadian Inuit and to examine if they are causal

in the direction anticipated. Although levels of PCBs are declining in Arctic air and biota overall, since 2000 the rate of decline has slowed and increases have been observed for PCB-52 and PCB-101, possibly due to reemission of PCBs from oceans and ice in response to climate warming (AMAP, 2015a). Levels of PCBs in human tissue are still high in some circumpolar regions, such as Eastern Canada and Greenland (AMAP, 2015b). Among the participants of the IHS, total PCB geometric mean concentration was four times higher than the general Canadian population, and up to nine times higher for elderly men (Laird et al., 2013). Therefore, continued monitoring of PCBs in the Arctic environment and assessment of health risks are required. Contaminant exposures in Inuit come primarily from traditional diets of marine mammal food sources. Traditional food sources also have many nutritional advantages compared with store-bought items, such as high levels of essential omega-3 fatty acids, as well as cultural benefits which cannot be easily replaced. Therefore, a study of the risks of contaminants and the benefits of traditional foods is needed to develop appropriate recommendations about dietary intakes.

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Table 1: Quartile concentration cut-off values

	Lipid-Based (µg/g lipid)	Wet-Weight (µg/L)
PCB-99		
Q1	[0.0016, 0.0059]	[0.015, 0.0362]
Q2	(0.0059, 0.0189]	(0.0362, 0.12]
Q3	(0.0189, 0.0509]	(0.12, 0.33]
Q4	(0.0509, 0.648]	(0.33, 4.9]
PCB-105		
Q1	[0.0004, 0.0011]	[0.004, 0.005]
Q2	(0.0011, 0.0032]	(0.005, 0.02]
Q3	(0.0032, 0.0092]	(0.02, 0.057]
Q4	(0.0092, 0.111]	(0.057, 0.78]
PCB-118		
Q1	[0.0007, 0.0063]	[0.005, 0.038]
Q2	(0.0063, 0.0176]	(0.038, 0.11]
Q3	(0.0176, 0.0475]	(0.11, 0.31]
Q4	(0.0475, 0.631]	(0.31, 4.9]
PCB-138		
Q1	[0.0007, 0.0184]	[0.005, 0.1]
Q2	(0.0184, 0.0541]	(0.1, 0.32]
Q3	(0.0541, 0.135]	(0.32, 0.88]
Q4	(0.135, 1.99]	(0.88, 15]
PCB-153		
Q1	[0.0007, 0.0429]	[0.005, 0.25]
Q2	(0.0429, 0.134]	(0.25, 0.79]
Q3	(0.134, 0.352]	(0.79, 2.3]
Q4	(0.352, 6.18]	(2.3, 48]
PCB-156		
Q1	[0.0005, 0.0025]	[0.005, 0.0163]
Q2	(0.0025, 0.00795]	(0.0163, 0.048]
Q3	(0.00795, 0.0202]	(0.048, 0.13]
Q4	(0.0202, 0.412]	(0.13, 3.2]
PCB-170		
Q1	[0.0006, 0.00688]	[0.005, 0.04]
Q2	(0.00688, 0.0219]	(0.04, 0.13]
Q3	(0.0219, 0.0607]	(0.13, 0.39]
Q4	(0.0607, 1.37]	(0.39, 10]
PCB-180		
Q1	[0.0007, 0.0211]	[0.005, 0.12]
Q2	(0.0211, 0.0667]	(0.12, 0.4]
Q3	(0.0667, 0.186]	(0.4, 1.2]
Q4	(0.186, 4.77]	(1.2, 37]
PCB-183		
Q1	[0.0005, 0.0019]	[0.005, 0.01]
Q2	(0.0019, 0.0063]	(0.01, 0.038]
Q3	(0.0063, 0.0163]	(0.038, 0.11]
Q4	(0.0163, 0.291]	(0.11, 2.2]
PCB-187		
Q1	[0.0007, 0.0089]	[0.005, 0.049]
Q2	(0.0089, 0.026]	(0.049, 0.15]
Q3	(0.026, 0.0642]	(0.15, 0.42]
Q4	(0.0642, 0.94]	(0.42, 7.3]

∑DLPCBs		
Q1	[0.0021, 0.0113]	[0.015, 0.064]
Q2	(0.0113, 0.0306]	(0.064, 0.182]
Q3	(0.0306, 0.0775]	(0.182, 0.509]
Q4	(0.0775, 1.14]	(0.509, 8.88]
∑NDLPCBs		
Q1	[0.0331, 0.148]	[0.24, 0.822]
Q2	(0.148, 0.367]	(0.822, 2.2]
Q3	(0.367, 0.93]	(2.2, 6.02]
Q4	(0.93, 15.4]	(6.02, 120]

Abbreviations: DLPCB = dioxin-like polychlorinated biphenyl; NDLPCB = non-dioxin like polychlorinated biphenyl; PCB = polychlorinated biphenyl; Q = quartile

Table 2: Characteristics of sample population (IHS 2007-2008)

	Total (n=2191)	With High Cholesterol[3] (n=719)	Without High Cholesterol (n=1472)
Age (years) - Mean (SD)	42.4 (15.3)	49.8 (14.5)	38.8 (14.4)
Gender – No. (%)			
Males	844 (38.5)	304 (42.3)	540 (36.7)
Females	1347 (61.5)	415 (57.7)	932 (63.3)
Region – No (%)			
Nunavut	1646 (75.1)	506 (70.4)	1140 (77.4)
ISR	280 (12.8)	101 (14.0)	179 (12.2)
Nunatsiavut	265 (12.1)	112 (15.6)	153 (10.4)
Education[4] - No. (%)			
None	161 (7.3)	87 (12.1)	74 (5.0)
Elementary	415 (18.9)	164 (22.8)	251 (17.1)
Secondary	1113 (50.8)	286 (39.8)	827 (56.2)
College/Trade School	325 (14.8)	112 (15.6)	213 (14.5)
University	67 (3.1)	29 (4.0)	38 (2.6)
BMI (kg/m^2) - Mean (SD)	28.4 (6.5)	30.1 (5.8)	27.5 (6.6)
Fasting Glucose (mmol/L) - Mean (SD)	5.1 (1.0)	5.3 (1.0)	5.0 (0.9)
LDL-C (mmol/L) – Mean (SD)	2.8 (1.0)	3.8 (1.0)	2.4 (0.6)
HDL-C (mmol/L) – Mean (SD)	1.5 (0.5)	1.4 (0.5)	1.5 (0.5)
Triglycerides (mmol/L) – Mean (SD)	1.3 (0.7)	1.6 (0.8)	1.2 (0.7)
Total Cholesterol (mmol/L) – Mean (SD)	5.0 (1.1)	5.9 (1.1)	4.5 (0.8)
Alcohol[5] - No. (%)			
Yes	1188 (54.2)	346 (48.1)	842 (57.2)
No	623 (28.4)	244 (33.9)	379 (25.7)
Never Drank	139 (6.3)	56 (7.8)	83 (5.6)
Current Smoker – No. (%)			
Yes	1476 (67.4)	405 (56.3)	1071 (72.8)
No	635 (29.0)	287 (39.9)	348 (23.6)

Abbreviations: BMI = body mass index; ISR = Inuvialuit Settlement Region; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SD = standard deviation

[3] LDL >3.36 mmol/L or taking medication that lowers cholesterol.
[4] Partial or completed elementary school, secondary school, college or trade school, or university.
[5] Alcohol consumption in past 12 months.

Table 3: Wet-weight PCB concentrations

	Total (µg/L)		With High Cholesterol (µg/L)		No High Cholesterol (µg/L)	
	GM (Range)	**N**	**GM (Range)**	**N**	**GM (Range)**	**N**
PCB-99	0.11 (0.015-4.90)	2162	0.21 (0.015-4.90)	701	0.08 (0.015-3.30)	1431
PCB-105	0.02 (0.005-0.78)	2162	0.04 (0.005-0.66)	701	0.02 (0.005-0.78)	1431
PCB-118	0.10 (0.005-4.90)	2162	0.22 (0.005-4.10)	701	0.07 (0.005-4.90)	1431
PCB-138	0.28 (0.005-15.00)	2162	0.58 (0.005-15.00)	701	0.20 (0.005-12.00)	1431
PCB-153	0.72 (0.005-48.00)	2162	1.49 (0.005-41.00)	701	0.50 (0.005-48.00)	1431
PCB-156	0.04 (0.005-3.20)	2162	0.09 (0.005-2.10)	701	0.03 (0.005-3.20)	1431
PCB-170	0.12 (0.005-10.00)	2162	0.25 (0.005-9.80)	701	0.08 (0.005-10.00)	1431
PCB-180	0.38 (0.005-37.00)	2162	0.78 (0.005-34.00)	701	0.26 (0.005-37.00)	1431
PCB-183	0.04 (0.005-2.20)	2161	0.07 (0.005-2.20)	700	0.03 (0.005-1.90)	1431
PCB-187	0.14 (0.005-7.30)	2162	0.27 (0.005-4.80)	701	0.10 (0.005-7.30)	1431
∑DL-PCB	0.18 (0.015-8.88)	2162	0.37 (0.015-6.83)	701	0.13 (0.015-8.88)	1431
∑NDL-PCB	2.30 (0.24-119.50)	2159	4.24 (0.24-101.00)	698	1.69 (0.24-119.50)	1431

Abbreviations: DL-PCB = dioxin-like polychlorinated biphenyl; GM = geometric mean; NDL-PCB = non-dioxin like polychlorinated biphenyl; PCB = polychlorinated biphenyl

Table 4: Adjusted odds ratios for high cholesterol

		OR (95% CI)			
		N	Q2 vs. Q1	Q3 vs. Q1	Q4 vs. Q1
PCB-99	Wet	1798	2.00 (1.42, 2.84)***	2.31 (1.57, 3.42)***	3.78 (2.30, 6.23)***
	Lipid	1798	1.67 (1.20, 2.35)**	1.38 (0.95, 2.02)	1.66 (1.02, 2.70)*
PCB-105	Wet	1798	1.81 (1.27, 2.58)***	2.15 (1.50, 3.07)***	3.63 (2.25, 5.88)***
	Lipid	1798	1.75 (1.26, 2.46)**	1.39 (0.97, 1.99)	1.74 (1.08, 2.81)*
PCB-118	Wet	1798	2.31 (1.61, 3.33)***	2.95 (1.97, 4.46)***	4.90 (2.93, 8.25)***
	Lipid	1798	1.59 (1.13, 2.26)**	1.51 (1.03, 2.23)*	1.68 (1.01, 2.78)*
PCB-138	Wet	1798	1.97 (1.38, 2.84)***	2.68 (1.81, 4.00)***	4.55 (2.77, 7.53)***
	Lipid	1798	1.55 (1.10, 2.20)*	1.60 (1.09, 2.35)*	1.76 (1.09, 2.84)*
PCB-153	Wet	1798	1.79 (1.25, 2.58)**	2.51 (1.71, 3.71)***	3.91 (2.40, 6.40)***
	Lipid	1798	1.28 (0.91, 1.82)	1.46 (1.00, 2.15)†	1.48 (0.91, 2.41)
PCB-156	Wet	1798	1.82 (1.26, 2.65)**	2.98 (1.99, 4.48)***	4.80 (2.93, 7.91)***
	Lipid	1798	1.61 (1.13, 2.31)**	1.95 (1.32, 2.90)***	2.14 (1.33, 3.47)**
PCB-170	Wet	1798	1.68 (1.16, 2.44)**	3.48 (2.33, 5.24)***	4.70 (2.87, 7.75)***
	Lipid	1798	1.43 (1.01, 2.04)*	1.84 (1.24, 2.74)**	1.96 (1.22, 3.16)**
PCB-180	Wet	1798	1.54 (1.07, 2.23)*	3.14 (2.11, 4.71)***	3.74 (2.27, 6.20)***
	Lipid	1798	1.11 (0.78, 1.57)	1.59 (1.08, 2.35)*	1.48 (0.91, 2.40)
PCB-183	Wet	1797	2.13 (1.49, 3.06)***	2.58 (1.76, 3.81)***	4.66 (2.90, 7.53)***
	Lipid	1797	1.92 (1.36, 2.74)***	1.72 (1.16, 2.55)**	2.36 (1.48, 3.78)***
PCB-187	Wet	1798	1.74 (1.21, 2.52)**	2.79 (1.85, 4.23)***	4.60 (2.78, 7.65)***
	Lipid	1798	1.27 (0.89, 1.81)	1.55 (1.05, 2.31)*	1.69 (1.03, 2.76)*
∑DL-PCB	Wet	1798	1.84 (1.27, 2.68)**	3.11 (2.08, 4.68)***	4.05 (2.41, 6.86)***
	Lipid	1798	1.55 (1.09, 2.21)*	1.70 (1.15, 2.53)**	1.74 (1.04, 2.90)*
∑NDL-PCB	Wet	1796	2.08 (1.44, 3.01)***	2.83 (1.89, 4.25)***	4.61 (2.78, 7.67)***
	Lipid	1796	1.21 (0.86, 1.72)	1.39 (0.94, 2.05)	1.38 (0.84, 2.25)

Adjusted for: age, sex, education, BMI, alcohol consumption, smoking status, omega3/6 ratio, selenium, fasting glucose, total MUFA, and total TFA.

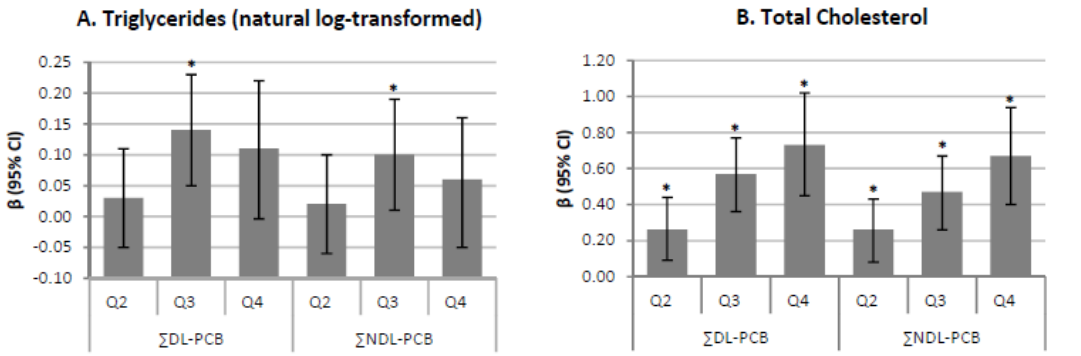
† $p = 0.05$

* $p < 0.05$

** $p < 0.01$

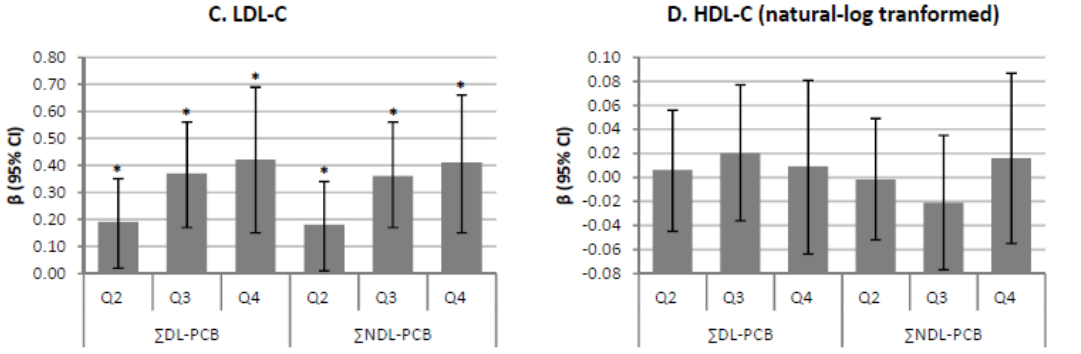
*** $p < 0.001$

Abbreviations: CI = confidence interval; DL-PCB = dioxin-like polychlorinated biphenyl; NDL-PCB = non-dioxin like polychlorinated biphenyl; OR = odds ratio; PCB = polychlorinated biphenyl; Q = quartile



	%age Change (95% CI) ∑DL-PCB	%age Change (95% CI) ∑NDL-PCB
Q2 vs, Q1	3 (-5, 12)	2 (-6, 11)
Q3 vs. Q1*	15 (5, 26)	11 (1, 21)
Q4 vs. Q1	11 (0, 25)	6 (-5, 17)

	Change (95% CI) (mmol/L) ∑DL-PCB	Change (95% CI) (mmol/L) ∑NDL-PCB
Q2 vs, Q1*	0.26 (0.09, 0.44)	0.26 (0.08, 0.43)
Q3 vs. Q1*	0.57 (0.36, 0.77)	0.47 (0.26, 0.67)
Q4 vs. Q1*	0.73 (0.45, 1.02)	0.67 (0.40, 0.94)



	Change (95% CI) (mmol/L) ∑DL-PCB	Change (95% CI) (mmol/L) ∑NDL-PCB
Q2 vs, Q1*	0.19 (0.02, 0.35)	0.18 (0.01, 0.34)
Q3 vs. Q1*	0.37 (0.17, 0.56)	0.36 (0.17, 0.56)
Q4 vs. Q1*	0.42 (0.15, 0.69)	0.41 (0.15, 0.66)

	%age Change (95% CI) ∑DL-PCB	%age Change (95% CI) ∑NDL-PCB
Q2 vs, Q1	1 (-4, 6)	0 (-5, 5)
Q3 vs. Q1	2 (-4, 8)	-2 (-8, 4)
Q4 vs. Q1	1 (-6, 8)	2 (-5, 9)

Figure 1: β coefficients for continuous cholesterol parameters from adjusted models using wet-weight PCB quartile concentrations (Q1 = reference)

* Statistically significant ($p < 0.05$)

A. Triglycerides: adjusted for age, sex, education, current smoking status, exercise, BMI, fasting glucose, and systolic blood pressure.
B. Total cholesterol: adjusted for age, sex, education, cadmium, BMI, selenium, systolic blood pressure, fasting glucose, and interaction between age + fasting glucose.
C. LDL-C: adjusted for age, sex, education, marital status, cadmium, BMI, selenium, fasting glucose, systolic blood pressure, omega3/6 ratio, and interaction between age + fasting glucose.
D. HDL-C: adjusted for age, sex, education, marital status, alcohol, BMI, fasting glucose, diastolic blood pressure, total MUFA, and omega 3/6 ratio.

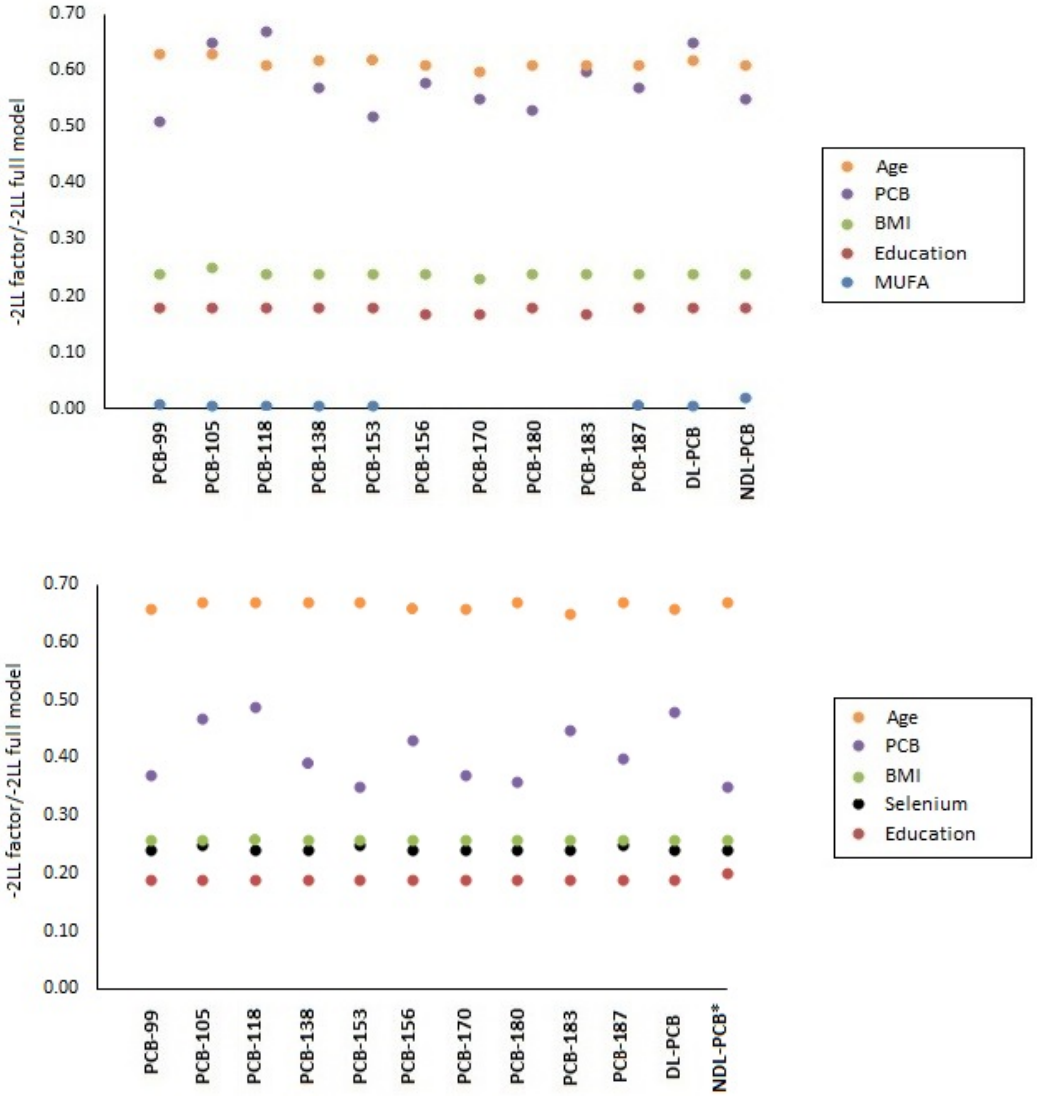


Figure 2: Ranking of significant factors in adjusted models of high cholesterol and PCB quartile concentrations

Top – wet-weight; Bottom – lipid-based

*NDL-PCB in lipid-based model was not statistically significant

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9.0 Discussion

9.1 Summary of Main Results

- A set of BEs have been derived for chlordane, toxaphene, indicator non-dioxin like PCBs, and dioxin-like PCBs. The derived BE values are comparable with the BEs of other POPs in the published literature.
- Based on the LC50 values from the HEPG2 cell culture experiment, trans-nonachlor appears to be five times more toxic than technical chlordane. The oral reference dose for technical chlordane, upon which the BE for trans-nonachlor was based, may therefore underestimate toxicity. Optimization of the cell culture experiment is required through improved experimental procedures to arrive at a quantitative estimate of the LC50 trans-nonachlor/technical chlordane ratio.
- Among the Inuit population, significant exceedances were observed for the trans-nonachlor BE, and exceedances were particularly high among the elderly Inuit. The HQs for trans-nonachlor were > 1.
- Highest vs. lowest quartile exposures to PCBs and p,p'-DDE were associated with increased risk of diabetes and an increase in fasting glucose among Canadian Inuit.
- PCBs were also associated with increased risk of high cholesterol, and higher levels of serum triglycerides, total cholesterol, and LDL-C, but not HDL-C.
- The results of this work suggest that exposures to POPs remain a potential health concern among the Canadian Inuit.

9.2 Research Contribution

This work provides insights into the potential human health risks of POP exposures among the Canadian Inuit using modelling and epidemiological approaches. The BEs for chlordane, toxaphene, and PCBs were derived in consultation with risk assessors at Health Canada, with several rounds of discussions. To the author's knowledge, the comparison of BE values with the Inuit Health Survey biomonitoring data is the first time that the BE concept was applied to human populations of the Arctic. From a research standpoint, these comparisons do place the observed contaminant concentrations into a health risk perspective and indicate which POPs require closer scrutiny in future biomonitoring and health studies. However, as mentioned in Section 9.3, further evaluation is needed to determine if the BE concept is in fact considered useful by Arctic communities. Several epidemiological analyses have been conducted in Arctic regions to examine POP exposures and health outcomes, including diabetes and cardiovascular risk factors in Greenland and Nunavik. The epidemiological analyses of association between POPs with diabetes and high cholesterol in Inuit from the ISR, Nunavut, and Nunatsiavut contributes to this evidence base and supports the need for long-term cohort studies to examine causal relationships.

9.3 Communication Efforts

Although a communication plan was incorporated into the proposed BE work (Appendix 2), this component of the project could not be fully pursued as it did not receive funding. We did develop regional reports that detailed the results separately for the ISR, Nunavut, and Nunatsiavut, and these reports were given to the respective health authorities of each region. In addition to the results for chlordane and toxaphene, the regional reports provided comparisons with previously published BE values for DDT and its metabolites, PBDE-99, and HCB. Dr.

Laurie Chan presented the results to the representatives of the regional health authorities and Inuit organizations in face-to-face meetings.

We highlighted the large percentage of exceedances observed for trans-nonachlor, as well as for HCB. We emphasized that exceedances of BE values can only provide evidence about population-level risks of contaminant exposures and cannot be used to make determinations about the health of an individual. The Biomonitoring Equivalents Expert Panel suggested that high priority be given to contaminants with biomonitoring levels above the BE (with interspecies uncertainty factors), medium priority to contaminants with levels below the BE (with interspecies uncertainty factors) but above the BE (with interspecies + intraspecies uncertainty factors), and low priority to contaminants with levels below the BE (with interspecies + intraspecies uncertainty factors).[42] Although exposure to POPs, like trans-nonachlor, is primarily from marine mammals, we were also careful to stress the importance of continuing to include traditional foods in the diet for their many known benefits. Traditional foods are high in nutrients (i.e. zinc, iron, copper, magnesium, protein, essential fatty acids, and vitamins A, D, and E), they promote physical activity, community wellness, and sociocultural values, and they are cost-effective compared with market foods.[4]

The complexities of developing messages that accurately convey the risks and benefits of traditional foods has been termed the "Arctic dilemma".[13] Several challenges have been encountered in communication, such as differences in how risks are perceived among communicators and recipients, translation of English terminology to indigenous languages, mistrust of external authorities, omission of indigenous knowledge systems, and presentation of mixed messages.[43–45] Indigenous populations may not have accurate terminology to describe invisible risks, such as contaminants, or risks that may pose an issue to health over several

years.[13] Poor communication about contaminant levels in Northern communities in the past has resulted in unnecessary fear and anxiety.[44] The acceptance of communication messages about the risks of contaminant exposures depends greatly on the degree of trust established between the communicator and the recipient of information, and the involvement of affected stakeholders in the research and communication processes.[13,46] General perceptions about the considered risks (i.e. individual control, the degree of certainty, and whether the risk is voluntary or involuntary) will also determine how well the communication message is received.[46]

The use of BEs in risk assessment is relatively recent; the concept may be unfamiliar to many and there is also potential for the results to be misunderstood, therefore clear and transparent communication is essential. The Biomonitoring Equivalents Expert Panel developed guidelines for communicating BEs to the public and health care professionals.[42] The Panel provided recommendations about how to communicate: (i) the concept of BEs; (ii) comparison of population biomonitoring data with BEs; (iii) interpretation of data that exceeds a BE value; and (iv) confidence levels in derived BEs.[42] The development and testing of communication messages to describe the results of BE analyses for the Canadian Arctic is needed to evaluate if the recommended communication approaches are effective in that region, and if the BE approach is considered useful by communities.

9.4 Recommendations for Future Research

9.4.1 Model Complexity

The BEs in this work were derived from one-compartment toxicokinetic models; this approach required many assumptions to simplify the human body as consisting of only one, uniformly distributed, lipid compartment. The complexities of the actual process of absorption, distribution, metabolism, and excretion of the POPs were not incorporated into the models.

Chlordane, for example, has been found to induce its own metabolism by cytochrome P450 enzymes into metabolites that are potentially more toxic than the parent compound.[36] Human variability exists in the metabolic capacity of cytochrome P450 enzymes and extraneous factors, such as chronic liver disease, impaired liver function, or the use of other chemicals that induce hepatic enzymes, could make some people more sensitive to adverse effects.[36] Although an uncertainty factor for human variability was incorporated, the present work does not specifically inform about such considerations. This would require the formulation of more complex toxicokinetic models that account for an additional liver compartment and hepatic metabolism.

In a 1976 article in the Journal of the American Statistical Association[47], the statistician George Box made the now well-known statement: "Since all models are wrong the scientist must be alert to what is importantly wrong." Models that are parsimonious, yet accurate representations of reality are preferred.[47] In the field of toxicokinetic modelling, further work is needed to explore how much complexity is required to accurately model the truth, so that the least "wrong" model is chosen. To determine how much complexity is needed, an analysis could be conducted to explore how the BE estimations change when additional compartments and physiological processes are added. In the present work, when attempting to model the behavior of trans-nonachlor with a three-compartment model, the absence of toxicokinetic parameters specific to this compound in the literature presented an obstacle. Therefore, *in vivo and in vitro* experimental work may be required to parameterize the complex model, such as metabolic rate constant and partition coefficients. In addition, the experimental set-up should include the collection of data for a concentration-time profile, which can be used to externally validate the simulations of the models. The application of multi-compartment models to sensitive subgroups, such as those with liver disease, or use of enzyme inducers/inhibitors, should also be explored.

9.4.2 Need for Updated Biomonitoring Data and Effects of Food Preparation

The Inuit Health Survey biomonitoring data that formed the basis of this work was collected in 2007-2008, now a decade ago. Updated POP concentrations for the Inuit of ISR, Nunavut, and Nunatsiavut are needed to evaluate if there have been further declines in contaminant levels. Furthermore, The Inuit Health Survey did not include contaminant measurements in the foods consumed by participants and, therefore, the specific items that contribute most to intake of trans-nonachlor are unknown. Although the AMAP biomonitoring data indicated that the sum of chlordanes were highest in polar bears followed by narwhal (Appendix 1, Figure A1-1), a more accurate assessment of which foods are contributing most to exposures requires that concentrations of contaminants be measured in the specific food items consumed by Inuit, as this can vary by sex and age of the animal, part consumed, and methods of preparation.[48] A study of POP concentrations in food items would also assist with the formulation of specific recommendations about how exposures to trans-nonachlor may be reduced.

9.4.3 Characterization of Adverse Effects on Liver

One of the main results of this work is the large percentage of the Inuit sample that exceeded the BE for trans-nonachlor, which was based on toxic endpoints in the liver (i.e. hepatocellular hypertrophy and hepatic necrosis in rodent models). To determine whether this result is applicable to the population, the following two questions arise: (1) What is the rate of hepatic toxicity in the Inuit population of ISR, Nunavut, and Nunatsiavut, and (2) Are exposures to trans-nonachlor contributing to the risk of hepatic toxicity. To answer these questions, collaboration with the respective health authorities of each region is needed. The second question may be difficult to tease out from other known causes of liver toxicity. The only direct evidence we have of overt chlordane toxicity in humans is from acute poisonings to very high doses, and

blood levels that were much higher than those observed in the Inuit Health Survey.

9.4.4 Chemical Mixtures

The analyses in this work examined exposures to single entity POPs only, whereas actual exposures occur to several contaminants at one time. In future risk assessments in Arctic populations, focus should be placed on examining the toxicity of chemical mixtures. In epidemiology, different statistical techniques have been used to study exposures to multiple contaminants. Stafoggia et al. (2017) classified these methods into three categories: (1) Dimension reduction to reduce the number of exposures (e.g. principal component analysis), (2) Variable selection to identify the ideal subset of exposures (e.g. Bayesian model averaging), and (3) Grouping of observations so that each group has a distinct exposure profile (e.g. cluster analysis).[49] Such techniques could be further explored with the Inuit Health Survey to examine multiple contaminants on health. The analysis of chemical mixtures has also been extended into toxicokinetic modelling.[50,51] Krishnan et al. (2002) developed a PBTK model to study metabolic interactions among complex contaminant mixtures.[51] This type of model may be applied to understanding the types of interactions that occur with multiple POP exposures in the Inuit, and to identify if there are combinations of contaminants that increase the risk for toxicity.

9.4.5 The Effects of Climate Change on POPs in the Arctic

As temperatures warm, the transport of contaminants from lower latitudes to the Arctic may increase through changes in the chemistry of oceans and the atmosphere, and local releases from thawing permafrost are possible.[13,52] Climate change may also affect the bioaccumulation of contaminants in food webs, with potential implications on the quality of wild foods consumed by humans and on contaminant exposures.[13,52] According to the AMAP 2015 Human Health Report (p.135)[13], “Interactions between climate change and contaminant transport have the

potential to change human exposure in the Arctic significantly. Current understanding is inadequate to determine the likelihood and magnitude of the health impacts of these changes in exposure." Thus, while the declining trends of POPs in the Arctic environment, biota, and human populations are certainly encouraging, continued biomonitoring of these contaminants is paramount to ensure that these declines continue in the context of warming temperatures.

10.0 Conclusion

The Arctic has been referred to as a "canary in a coal mine" because it is the first to exhibit the effects of environmental perturbations, such as changes in climate and the impacts of contaminants. The Inuit have been observing that their environment is changing. We need to pay attention to what the Inuit are saying and to what is happening in the Arctic, first to protect this unique culture from any further harm and, secondly, to view the environmental issues arising from the Arctic as signals with global implications. It is reassuring that the international efforts to curb further contaminant influxes into the Arctic are having positive effects, as evidenced by the declining trends in the concentrations of many POPs. In this work, the absence of exceedances of the toxaphene BE values and minimal exceedances for the PCBs, support such observations. However, the large percentage exceeding the BE for trans-nonachlor and the potential contribution of POPs on adverse health outcomes, are still of concern. Ongoing monitoring of POPs and health status in the Arctic, therefore, must continue. In addition, close collaboration between researchers and the Inuit is needed to create solutions with any lasting positive results. While researchers can provide the hard data, methods, and theory, the Inuit know the real world of the north, and this knowledge is needed to develop future research priorities and public health recommendations.

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Appendix 1: Supplementary Data

A1.1 Chapter 5

Table A1.1-1: Body weights and body fat weights of the general Canadian and Inuit populations

	CHMS, Cycle 1 (2007-2009)		IHS (2007-2008)	
	Mean Body Weight (kg)	**Mean Body Fat Weight (kg)**	**Mean Body Weight (kg)**	**Mean Body Fat Weight (kg)**
Whole	77.40	25.60	71.96	23.19
Males	84.30	23.50	75.16	18.70
Females	70.60	27.70	69.95	25.98
Females Child-Bearing Age (18-44)	69.30	24.20	69.93	25.12
Young Adults (18-25)	73.30	17.80	69.16	19.52
Middle-Aged (40-55)	78.90	26.40	72.31	23.85
Elderly (≥60)	77.30	30.50	71.87	25.37

Table A1.1-2: Chlordane BE values for Inuit population subgroups (mg/kg lipid)

	Cis-Nonachlor	**Trans-Nonachlor**	**Oxychlordane**
Males	0.11-0.26	0.17-0.45	0.56-0.89
Females	0.08-0.18	0.11-0.31	0.38-0.61
Females Child-Bearing Age (18-44)	0.08-0.18	0.12-0.32	0.39-0.63
Young Adults (18-25)	0.10-0.23	0.15-0.41	0.50-0.80
Middle-Aged (40-55)	0.09-0.20	0.13-0.34	0.43-0.68
Elderly (≥60)	0.08-0.18	0.12-0.32	0.40-0.64

Table A1.1-3: Chlordane BE values for Inuit population subgroups – BE based on LOAEL (mg/kg lipid)

	Cis-Nonachlor	Trans-Nonachlor	Oxychlordane
Whole	0.48	0.71	4.36
Males	0.61	0.92	5.59
Females	0.42	0.62	3.81
Females Child-Bearing Age (18-44)	0.43	0.65	3.94
Young Adults (18-25)	0.55	0.82	5.03
Middle-Aged (40-55)	0.46	0.70	4.25
Elderly (≥60)	0.43	0.65	3.98

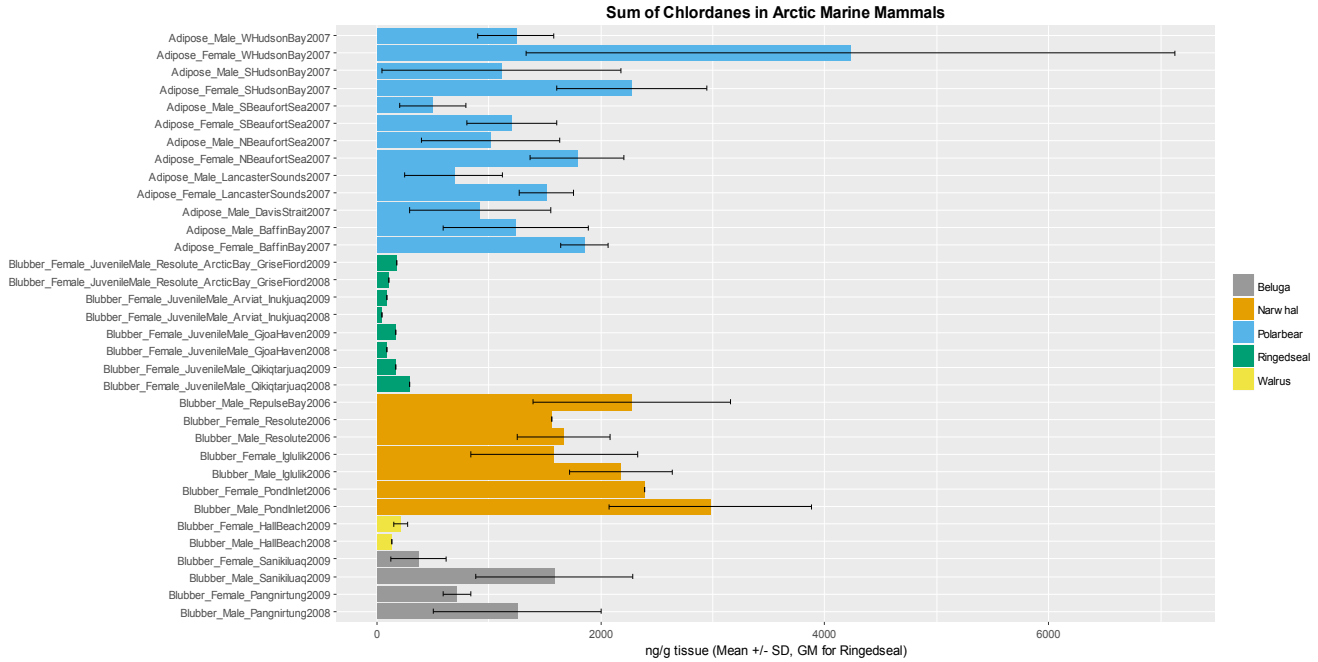

Figure A1.1-1: Chlordanes in Arctic marine mammals (raw data courtesy of Dr. Derek Muir)

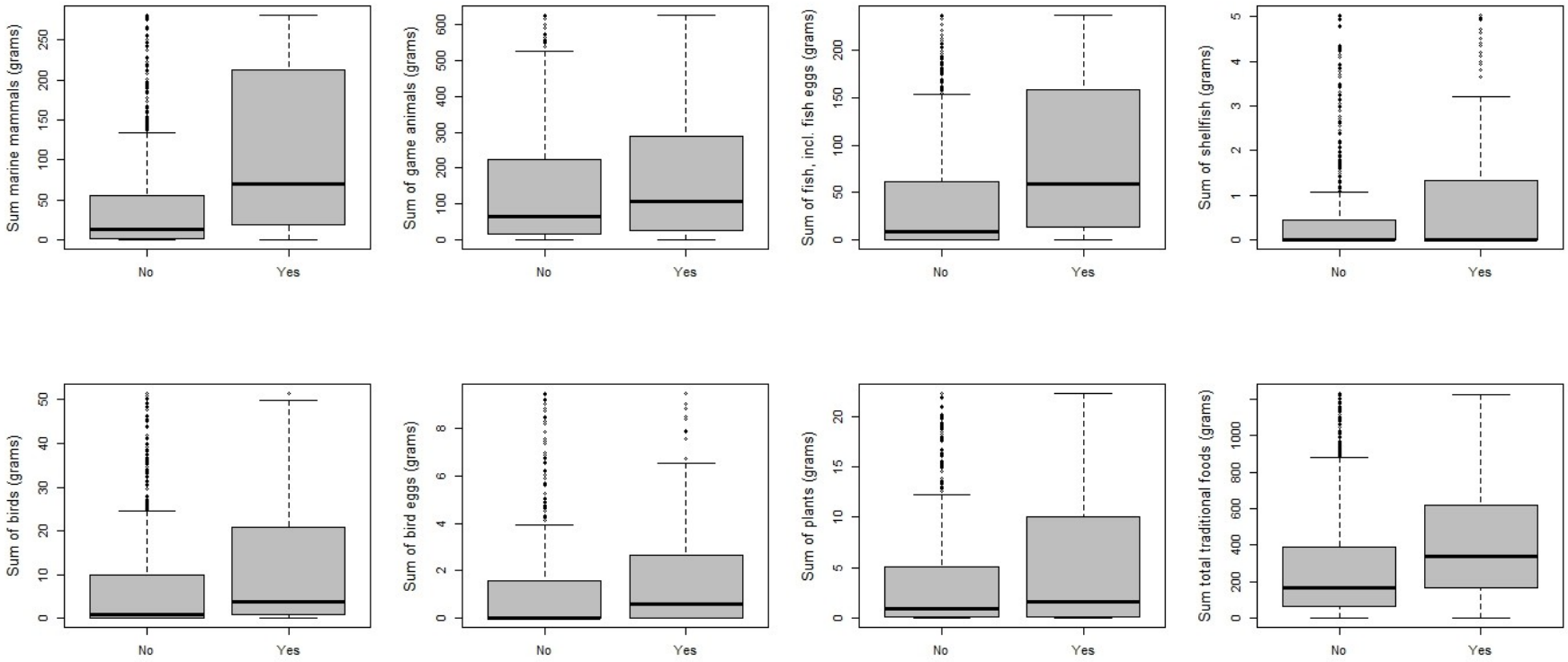

Figure A1.1-2: Average daily consumption of traditional foods stratified by equal/exceeding BE for trans-nonachlor (Adult Inuit Health Survey 2007-2008, BE = 0.24 mg/kg)

Wilcoxon rank sum test: statistically significant difference in all plots.

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Table A1.2-1: Limits of detection

Contaminant	Limit of Detection (µg/L)	Percentage Below Detection Limit
PCB-28	<0.05	99.0
PCB-52	<0.3	99.5
PCB-99	<0.03	21.8
PCB-101	<0.03	71.2
PCB-105	<0.01	32.7
PCB-118	<0.01	5.7
PCB-128	<0.01	65.4
PCB-138	<0.01	1.6
PCB-153	<0.01	0.3
PCB-156	<0.01	16.8
PCB-170	<0.01	6.4
PCB-180	<0.01	0.8
PCB-183	<0.01	19.9
PCB-187	<0.01	4.3
p,p'-DDE	<0.02	0.3

Abbreviations: DDE = dichlorodiphenyldichloroethylene; PCB = polychlorinated biphenyl

Table 1.2-2: Multiple logistic regression analyses for self-reported diabetes

	Model 1[a] OR (95% CI)			Model 2[b] OR (95% CI)		
	Wet	**Lipid Standardized**	**Lipid Adjusted**	**Wet**	**Lipid Standardized**	**Lipid Adjusted**
PCB-99						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.63 (0.29, 1.35)	0.80 (0.37, 1.76)	0.63 (0.29, 1.36)	0.55 (0.25, 1.19)	0.73 (0.33, 1.63)	0.60 (0.27, 1.31)
Q3	1.05 (0.54, 2.12)	1.28 (0.64, 2.66)	1.16 (0.59, 2.35)	0.91 (0.45, 1.87)	1.13 (0.56, 2.40)	1.04 (0.51, 2.16)
Q4	1.42 (0.75, 2.82)	1.88 (0.97, 3.87)	1.63 (0.84, 3.28)	1.25 (0.63, 2.60)	1.66 (0.81, 3.55)	1.56 (0.76, 3.32)
PCB-105						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.74 (0.31, 1.67)	0.99 (0.43, 2.23)	0.85 (0.36, 1.94)	0.77 (0.32, 1.76)	0.95 (0.42, 2.16)	0.83 (0.35, 1.92)
Q3	0.81 (0.40, 1.66)	0.84 (0.39, 1.85)	0.96 (0.46, 2.02)	0.81 (0.39, 1.71)	0.79 (0.36, 1.74)	0.93 (0.44, 1.97)
Q4	1.71 (0.89, 3.42)	2.44 (1.23, 5.11)*	2.20 (1.11, 4.58)*	1.56 (0.77, 3.29)	2.15 (1.04, 4.67)*	2.01 (0.96, 4.41)
PCB-118						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.83 (0.37, 1.93)	1.28 (0.55, 3.13)	0.99 (0.43, 2.38)	0.86 (0.37, 2.07)	1.20 (0.52, 2.96)	0.95 (0.41, 2.29)
Q3	0.88 (0.40, 2.03)	1.11 (0.48, 2.70)	1.12 (0.49, 2.68)	0.88 (0.39, 2.12)	1.00 (0.43, 2.48)	1.05 (0.45, 2.55)
Q4	1.95 (0.92, 4.42)	3.09 (1.41, 7.43)**	2.70 (1.21, 6.46)*	1.79 (0.79, 4.34)	2.58 (1.12, 6.44)*	2.41 (1.02, 6.06)†
PCB-138						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.73 (0.33, 1.60)	0.71 (0.32, 1.59)	0.74 (0.33, 1.64)	0.64 (0.29, 1.43)	0.65 (0.29, 1.47)	0.70 (0.31, 1.58)
Q3	0.78 (0.37, 1.71)	0.80 (0.37, 1.77)	0.88 (0.41, 1.96)	0.70 (0.32, 1.56)	0.72 (0.33, 1.62)	0.83 (0.37, 1.87)
Q4	1.59 (0.77, 3.43)	2.09 (1.02, 4.51)*	1.89 (0.90, 4.17)	1.34 (0.62, 3.01)	1.86 (0.86, 4.20)	1.74 (0.78, 4.07)
PCB-153						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.67 (0.31, 1.44)	0.92 (0.41, 2.07)	0.67 (0.31, 1.47)	0.59 (0.27, 1.30)	0.86 (0.38, 1.96)	0.65 (0.29, 1.45)
Q3	0.53 (0.25, 1.17)	1.00 (0.46, 2.23)	0.60 (0.27, 1.33)	0.46 (0.21, 1.04)	0.88 (0.40, 2.03)	0.55 (0.24, 1.25)
Q4	1.67 (0.82, 3.52)	2.54 (1.22, 5.63)*	1.93 (0.93, 4.15)	1.58 (0.73, 3.54)	2.47 (1.10, 5.82)*	2.01 (0.90, 4.64)
PCB-156						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	1.18 (0.51, 2.89)	1.40 (0.62, 3.39)	1.30 (0.56, 3.22)	1.09 (0.46, 2.69)	1.32 (0.58, 3.23)	1.25 (0.53, 3.11)
Q3	1.33 (0.57, 3.28)	1.24 (0.53, 3.09)	1.51 (0.64, 3.80)	1.08 (0.46, 2.74)	1.06 (0.44, 2.71)	1.38 (0.57, 3.55)
Q4	2.72 (1.15, 6.92)*	3.10 (1.31, 7.93)*	3.40 (1.39, 8.92)**	2.17 (0.87, 5.77)	2.62 (1.04, 7.02)*	3.03 (1.16, 8.40)*

PCB-170						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.93 (0.42, 2.14)	0.86 (0.38, 2.00)	1.00 (0.45, 2.33)	0.86 (0.38, 2.01)	0.80 (0.35, 1.90)	0.97 (0.42, 2.28)
Q3	0.95 (0.43, 2.22)	1.21 (0.55, 2.78)	1.05 (0.46, 2.50)	0.79 (0.34, 1.89)	1.12 (0.50, 2.64)	0.98 (0.42, 2.41)
Q4	2.30 (1.04, 5.39)*	2.87 (1.31, 6.68)*	2.67 (1.18, 6.36)*	2.05 (0.86, 5.10)	2.80 (1.18, 6.95)*	2.63 (1.08, 6.74)*
PCB-180						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.70 (0.32, 1.58)	1.05 (0.46, 2.53)	0.75 (0.33, 1.69)	0.65 (0.29, 1.47)	1.00 (0.43, 2.43)	0.72 (0.32, 1.64)
Q3	0.82 (0.38, 1.83)	1.44 (0.65, 3.43)	0.90 (0.40, 2.04)	0.68 (0.31, 1.56)	1.30 (0.57, 3.17)	0.84 (0.37, 1.96)
Q4	1.88 (0.87, 4.26)	3.48 (1.54, 8.40)**	2.13 (0.96, 4.92)	1.63 (0.69, 3.98)	3.46 (1.42, 8.95)**	2.05 (0.84, 5.13)
PCB-183						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	1.28 (0.58, 2.92)	1.89 (0.83, 4.70)	1.40 (0.63, 3.20)	1.18 (0.54, 2.71)	1.75 (0.77, 4.37)	1.32 (0.59, 3.04)
Q3	0.94 (0.42, 2.15)	1.16 (0.48, 3.00)	1.03 (0.46, 2.41)	0.77 (0.34, 1.82)	1.02 (0.42, 2.68)	0.94 (0.41, 2.24)
Q4	2.57 (1.22, 5.80)*	3.82 (1.69, 9.59)**	3.14 (1.45, 7.28)**	2.12 (0.97, 4.95)	3.25 (1.38, 8.41)**	2.86 (1.25, 6.92)*
PCB-187						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.89 (0.41, 2.00)	0.85 (0.39, 1.88)	1.00 (0.45, 2.25)	0.79 (0.36, 1.78)	0.77 (0.35, 1.73)	0.91 (0.41, 2.07)
Q3	0.73 (0.32, 1.68)	0.72 (0.32, 1.63)	0.82 (0.36, 1.94)	0.57 (0.25, 1.37)	0.59 (0.26, 1.39)	0.72 (0.30, 1.76)
Q4	1.77 (0.80, 4.12)	2.26 (1.04, 5.15)*	2.28 (0.99, 5.53)	1.34 (0.57, 3.24)	1.89 (0.83, 4.51)	1.92 (0.78, 4.93)
∑DL-PCB						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.63 (0.27, 1.48)	0.79 (0.33, 1.87)	0.63 (0.26, 1.51)	0.55 (0.23, 1.31)	0.73 (0.31, 1.76)	0.61 (0.25, 1.46)
Q3	0.73 (0.33, 1.66)	0.93 (0.42, 2.16)	0.86 (0.38, 1.98)	0.64 (0.28, 1.49)	0.84 (0.37, 1.98)	0.78 (0.34, 1.85)
Q4	1.67 (0.77, 3.81)	2.45 (1.12, 5.68)*	2.08 (0.93, 4.87)	1.35 (0.59, 3.22)	2.12 (0.91, 5.16)	1.82 (0.76, 4.50)
∑NDL-PCB						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.79 (0.37, 1.74)	1.01 (0.47, 2.26)	0.82 (0.37, 1.83)	0.71 (0.32, 1.58)	0.95 (0.43, 2.14)	0.80 (0.36, 1.80)
Q3	0.62 (0.28, 1.40)	0.85 (0.38, 1.94)	0.71 (0.32, 1.63)	0.53 (0.23, 1.23)	0.74 (0.32, 1.73)	0.64 (0.28, 1.51)
Q4	1.66 (0.79, 3.67)	2.42 (1.14, 5.43)*	1.99 (0.92, 4.50)	1.48 (0.66, 3.42)	2.22 (0.98, 5.28)	1.96 (0.84, 4.70)
∑PCB						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.77 (0.35, 1.69)	1.05 (0.47, 2.41)	0.78 (0.36, 1.74)	0.68 (0.31, 1.53)	1.00 (0.44, 2.32)	0.76 (0.34, 1.71)
Q3	0.60 (0.27, 1.36)	1.00 (0.45, 2.32)	0.69 (0.31, 1.58)	0.51 (0.22, 1.19)	0.86 (0.38, 2.06)	0.62 (0.27, 1.46)
Q4	1.61 (0.76, 3.56)	2.78 (1.29, 6.41)*	1.92 (0.89, 4.34)	1.43 (0.64, 3.32)	2.60 (1.13, 6.32)*	1.88 (0.81, 4.53)
p,p'-DDE						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	1.15 (0.51, 2.70)	1.15 (0.50, 2.72)	1.24 (0.55, 2.92)	1.00 (0.44, 2.37)	1.02 (0.44, 2.44)	1.10 (0.48, 2.63)
Q3	1.32 (0.62, 3.03)	1.41 (0.66, 3.25)	1.39 (0.64, 3.22)	1.06 (0.48, 2.48)	1.15 (0.52, 2.71)	1.20 (0.54, 2.84)
Q4	2.44 (1.17, 5.55)*	3.02 (1.45, 6.84)**	2.84 (1.33, 6.56)**	1.99 (0.92, 4.65)	2.53 (1.18, 5.89)*	2.49 (1.12, 5.95)*

† $p = 0.051$

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

[a] Model 1 adjusted for age, gender, and log BMI. The lipid-adjusted model additionally contained total serum lipids along with wet-weight quartile levels.

[b] Model 2 adjusted for age, gender, log BMI, √HDL, √omega3/omega6, and education.

Abbreviations: CI = confidence interval; DDE = dichlorodiphenyldichloroethylene; DL-PCB = dioxin-like polychlorinated biphenyl; NDL-PCB = non-dioxin like polychlorinated biphenyl; OR = odds ratio; PCB = polychlorinated biphenyl; Q = quartile

Table A1.2-3: Multiple linear regression analyses for fasting glucose

	Model 1[a] β (95% CI)			Model 2[b] β (95% CI)		
	Wet	**Lipid Standardized**	**Lipid Adjusted**	**Wet**	**Lipid Standardized**	**Lipid Adjusted**
PCB-99						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.02)	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)
Q3	0.01 (-0.00, 0.03)	0.02 (-0.00, 0.03)	0.01 (-0.00, 0.03)	0.02 (-0.00, 0.04)	0.02 (-0.00, 0.04)†	0.02 (-0.00, 0.04)
Q4	0.03 (0.01, 0.05)**	0.03 (0.01, 0.05)**	0.03 (0.01, 0.05)**	0.04 (0.01, 0.07)**	0.04 (0.02, 0.07)**	0.04 (0.01, 0.07)**
PCB-105						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.01 (-0.01, 0.02)	0.02 (0.00, 0.03)*	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.03)	0.02 (0.00, 0.04)*	0.01 (-0.01, 0.03)
Q3	0.01 (-0.01, 0.02)	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.03)	0.01 (-0.00, 0.03)	0.01 (-0.01, 0.03)	0.02 (-0.00, 0.04)
Q4	0.04 (0.02, 0.06)***	0.05 (0.03, 0.07)***	0.04 (0.02, 0.06)***	0.06 (0.03, 0.08)***	0.06 (0.04, 0.09)***	0.06 (0.03, 0.09)***
PCB-118						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.00 (-0.01, 0.02)	0.02 (0.00, 0.04)*	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.03)	0.02 (0.01, 0.04)**	0.01 (-0.01, 0.03)
Q3	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.02 (-0.00, 0.04)	0.02 (-0.00, 0.04)	0.02 (-0.00, 0.04)
Q4	0.05 (0.03, 0.07)***	0.05 (0.03, 0.07)***	0.05 (0.03, 0.07)***	0.06 (0.04, 0.09)***	0.06 (0.04, 0.09)***	0.07 (0.04, 0.10)***
PCB-138						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.01 (-0.01, 0.03)	0.01 (-0.00, 0.03)	0.01 (-0.00, 0.03)	0.02 (-0.00, 0.03)	0.02 (-0.00, 0.03)	0.02 (-0.00, 0.04)
Q3	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)
Q4	0.03 (0.01, 0.05)**	0.03 (0.01, 0.05)**	0.03 (0.01, 0.05)**	0.04 (0.02, 0.07)**	0.04 (0.01, 0.07)**	0.05 (0.02, 0.08)***
PCB-153						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.01 (-0.01, 0.02)	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.03)	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.03)
Q3	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.03)	0.00 (-0.02, 0.02)	0.01 (-0.01, 0.03)
Q4	0.03 (0.01, 0.05)**	0.02 (-0.00, 0.04)	0.03 (0.01, 0.05)**	0.03 (0.01, 0.06)*	0.02 (-0.01, 0.05)	0.04 (0.01, 0.07)**
PCB-156						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	-0.01 (-0.02, 0.01)	-0.00 (-0.02, 0.02)	-0.00 (-0.02, 0.01)	-0.01 (-0.03, 0.01)	-0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)
Q3	-0.00 (-0.02, 0.02)	-0.00 (-0.02, 0.02)	-0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.02)	-0.00 (-0.03, 0.02)	-0.00 (-0.02, 0.02)
Q4	0.00 (-0.02, 0.02)	0.01 (-0.02, 0.03)	0.00 (-0.02, 0.02)	-0.00 (-0.03, 0.02)	0.00 (-0.02, 0.03)	-0.00 (-0.03, 0.03)

PCB-170						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)
Q3	0.00 (-0.02, 0.02)	0.00 (-0.01, 0.02)	0.00 (-0.02, 0.02)	0.00 (-0.02, 0.02)	0.00 (-0.02, 0.02)	0.00 (-0.02, 0.03)
Q4	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.02, 0.04)	0.01 (-0.02, 0.03)	0.01 (-0.02, 0.04)
PCB-180						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	-0.01 (-0.03, 0.01)	-0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	-0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)
Q3	0.00 (-0.02, 0.02)	0.00 (-0.02, 0.02)	0.00 (-0.02, 0.02)	-0.00 (-0.02, 0.02)	0.00 (-0.02, 0.02)	-0.00 (-0.02, 0.02)
Q4	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.02, 0.03)	0.01 (-0.02, 0.03)	0.01 (-0.01, 0.04)	0.01 (-0.02, 0.04)
PCB-183						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.01 (-0.01, 0.02)	0.02 (0.00, 0.03)*	0.01 (-0.01, 0.03)	0.01 (-0.00, 0.03)	0.02 (0.00, 0.04)*	0.01 (-0.00, 0.03)
Q3	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.03)	0.00 (-0.01, 0.02)	0.00 (-0.02, 0.02)	0.01 (-0.01, 0.03)	0.00 (-0.02, 0.03)
Q4	0.04 (0.01, 0.06)***	0.03 (0.01, 0.05)**	0.04 (0.01, 0.06)***	0.04 (0.02, 0.07)**	0.04 (0.01, 0.06)**	0.05 (0.02, 0.07)***
PCB-187						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	-0.00 (-0.02, 0.01)	-0.01 (-0.02, 0.01)	-0.00 (-0.02, 0.02)	0.00 (-0.02, 0.02)	-0.00 (-0.02, 0.01)	0.00 (-0.02, 0.02)
Q3	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.03)	0.01 (-0.02, 0.03)	0.00 (-0.02, 0.02)	0.01 (-0.01, 0.03)
Q4	0.03 (0.01, 0.05)**	0.02 (-0.00, 0.04)	0.03 (0.01, 0.06)**	0.04 (0.01, 0.07)**	0.02 (-0.00, 0.05)	0.04 (0.01, 0.07)**
∑DL-PCB						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	-0.00 (-0.02, 0.01)	0.00 (-0.02, 0.02)	-0.00 (-0.02, 0.02)	0.00 (-0.02, 0.02)	0.00 (-0.02, 0.02)	0.00 (-0.02, 0.02)
Q3	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.04)	0.01 (-0.01, 0.03)
Q4	0.03 (0.01, 0.06)**	0.03 (0.01, 0.05)**	0.03 (0.01, 0.06)**	0.04 (0.01, 0.07)**	0.03 (0.01, 0.06)*	0.05 (0.02, 0.08)**
∑NDL-PCB						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.00 (-0.01, 0.02)	0.00 (-0.02, 0.02)	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.02)	0.00 (-0.02, 0.02)	0.01 (-0.01, 0.03)
Q3	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.02)	0.00 (-0.02, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)
Q4	0.02 (0.00, 0.04)*	0.02 (0.00, 0.04)*	0.02 (0.00, 0.04)*	0.03 (-0.00, 0.06)	0.03 (0.00, 0.05)*	0.03 (0.00, 0.06)*
∑PCB						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.00 (-0.01, 0.02)	0.00 (-0.02, 0.02)	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.03)	0.00 (-0.02, 0.02)	0.01 (-0.01, 0.03)
Q3	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.02)	0.00 (-0.02, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)
Q4	0.02 (0.00, 0.04)*	0.02 (0.00, 0.04)*	0.02 (0.00, 0.04)*	0.03 (-0.00, 0.06)	0.03 (-0.00, 0.05)	0.03 (0.00, 0.06)*
p,p'-DDE						
Q1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Q2	0.00 (-0.01, 0.02)	0.01 (-0.00, 0.03)	0.00 (-0.01, 0.02)	0.00 (-0.01, 0.02)	0.02 (-0.00, 0.03)	0.01 (-0.01, 0.02)
Q3	0.01 (-0.01, 0.03)	0.02 (0.00, 0.04)*	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.02 (0.01, 0.04)*	0.01 (-0.01, 0.03)
Q4	0.03 (0.01, 0.05)**	0.04 (0.02, 0.06)***	0.03 (0.01, 0.05)**	0.04 (0.01, 0.06)**	0.06 (0.03, 0.08)***	0.04 (0.02, 0.07)**

† p = 0.05

* p < 0.05

** p < 0.01

*** p < 0.001

[a] Model 1 adjusted for age, gender, and log BMI. The lipid-adjusted model additionally contained total serum lipids along with wet-weight quartile levels.

[b] Model2 adjusted for age, gender, log BMI, √HDL, log triglycerides, alcohol intake, smoking, √omega3/omega6, log selenium, and education.

Abbreviations: CI = confidence interval; DDE = dichlorodiphenyldichloroethylene; DL-PCB = dioxin-like polychlorinated biphenyl; NDL-PCB = non-dioxin like polychlorinated biphenyl; PCB = polychlorinated biphenyl; Q = quartile

Table A1.2-4: Comparison of different methods for defining diabetes

		Diabetes based on fasting glucose or management		
Self – Report Diabetes		No	Yes	Missing
	No	1931	23	80
	Yes	66	79	2
	Missing	76	2	310

Appendix 2: Development of Blood Guidance Values for Persistent Organic Pollutants for the Canadian Arctic - Communication Plan (2016-2017)

An integral component of this project is the communication of the project's concept and design, results, and interpretation of results for communities. With guidance from our partners in each region, we will work towards developing a package of communication materials in English and translated into local Inuktitit language (specific deliverable materials are described below). The communication materials will be coordinated with NCP Risk Communication SubCommittee and Regional Contaminant Committee.

Given the project's focus on environmental contaminant levels in blood and sources of contaminants from traditional foods, we want to ensure that the communication messages are clear, scientifically-based, and reflect the perspectives of Inuit. The communication should result in positive outcomes, including:

- Understanding of persistent organic pollutants in the Arctic environment, biota, and humans.
- Understanding what guideline values for environmental contaminants are and the general process for deriving these values.
- Awareness of persistent organic pollutant levels observed in Inuit and how these levels compare with guideline values.
- Understanding the potential health risks of persistent organic pollutant levels if a significant percentage of the population equals or exceeds a guideline value.
- Balancing the benefits of traditional foods with identified health risks to make informed and health-promoting decisions about foods.

To achieve these goals, we would like to work closely with the partners in each region. This collaboration will be essential for developing communication messages and materials that are sensitive, address the needs and perspectives of Inuit, and that are effective at conveying the message. We do not want the communication to be one-sided with respect to the adverse effects of contaminants in traditional foods and to create unwarranted fear or anxiety. We understand that traditional foods have many benefits, both for the health and culture of Inuit, which must be discussed alongside any identified risks to provide an accurate and holistic picture of traditional food consumption. Ultimately, the choice of what foods to include in one's diet is a decision

based on individual perspectives of risks and benefits, experiences, and priorities. We hope that this project will provide Inuit communities with more information, which can be incorporated by individuals into making informed decisions about foods.

Figure 1 shows the overall work plan for communication. The content of the communication will depend on whether a significant proportion of the population equals or exceeds the guideline values developed for persistent organic pollutants. If the majority are below the guideline value, then no additional analysis is needed and the communication message will consist of a description of the project objectives, methods, and results. If a significant proportion of the population does equal or exceed a guideline value, then it will be important to identify which traditional food sources are contributing most to intake of that contaminant. For the identified traditional foods, we would also like to provide an assessment of the benefits that includes both nutritional and cultural aspects. The assessment of benefits and interpretation of benefit-risk profiles must be completed through a consultation process with regional partners. If the benefits are found to outweigh the health risks, then the communication message will consist of project objectives, methods, results, and dietary analysis. If the benefits are found to not outweigh the health risks, then the communication message will also include suggestions for reducing contaminant exposure. This message will not be framed as a consumption advisory, but rather will provide different traditional foods with their levels for the contaminant in question. We hope that this will help individuals make informed decisions.

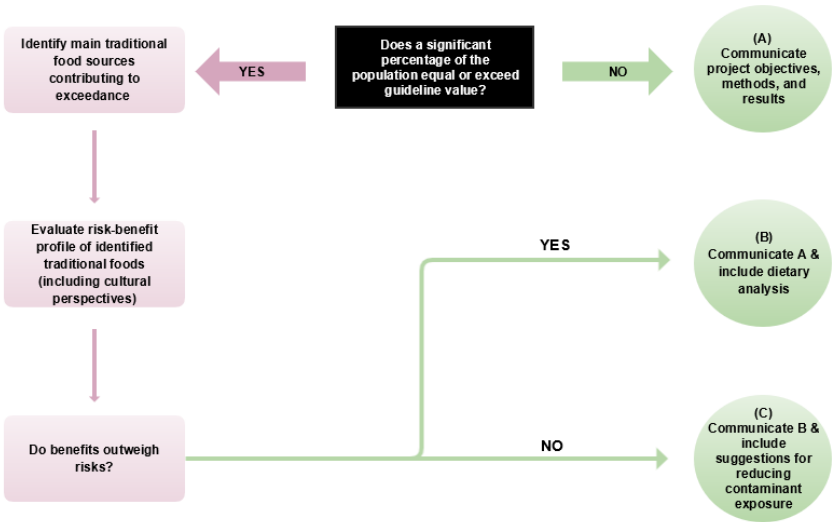

Figure A2-1: Communication work plan

Below, we describe the individual components of our communication plan.

1. Project objectives, methods, and results

A. Description of the persistent organic pollutants we examined in this project, including historical uses, levels found in Arctic environment, and why these particular contaminants were chosen.

- Chlordane
- Toxaphene
- PCBs

B. General process of how we developed guideline values: We will focus on providing more qualitative and visual explanation instead of technical jargon.

C. Description of the data sources we used:

- Inuit Health Survey (2007-2008)
- Additional sources for dietary examination of contaminants – e.g. NCP reports and CACAR

D. Results of comparisons of blood levels of persistent organic pollutants with guideline values: We will show the percentage of the whole population from the Inuit Health Survey that equals or exceeds guidelines values, as well as subgroups by region, gender, and age.

2. Balance of health risks and benefits (consultation process):

If a significant proportion of the population equals or exceeds the guideline value for a contaminant, then we will investigate what traditional food sources are contributing most to intake of that contaminant. The health risks and benefits of the identified traditional foods will be explored through a consultation process with regional partners.

A. Health risks: The risks of exposure to contaminant will be based on the endpoints used to derive the guideline values as well as data available in the literature of adverse effects in humans (case reports and epidemiological studies). As much as possible, this data will be summarized in a qualitative, visual manner to assist with comprehension of the information.

B. Benefits: To understand the benefits of the identified traditional foods, we will examine the nutrient content and explore the cultural benefits according to Inuit perspectives. This will require collaboration between as the researchers, regional partners, and key Inuit group(s) who can accurately represent the Inuit perspectives of traditional foods and assess the balance of risks and benefits.

3. Deliverable Communication Materials:

We will hold four workshops with the Regional Contaminant Committees in Yellowknife, Iqaluit, Kuujjuaq, and Nain. During these workshops we will communicate the information as presented above. In consultation with the regional partners, we will also develop communication materials (e.g. brochures, pamphlets, website, other materials as deemed appropriate) for the public in both English and Inuktitut that explains the project, process, and results in an easily accessible and understandable manner. Before launching any communication materials to the public, we would like to pilot test them to ensure that the materials are appropriate and effective at conveying the information as intended.

4. Feedback on Communication

We would like to obtain feedback on our communication methods to help us in understanding the effectiveness of the communication and making improvement for future projects. We will consult with our regional partners on the most suitable method (e.g. written or oral survey) and respondents for gathering this feedback.

Appendix 3: Other Completed Research

1. *Singh K, Hegeman W, Laane R, Chan HM. Review and evaluation of a chiral enrichment model for chlordane enantiomers in the environment. Environmental Reviews 2016;24:363-76.*

   This review examined the distribution of chlordane enantiomers in different environmental compartments and assessed the data according to a previously published model that predicted the partitioning of chiral pesticides in the environment.

2. *Singh K, Karthikeyan S, Vladisavljevic D, St-Amand A, Chan HM. Factors associated with plasma concentrations of polychlorinated biphenyls (PCBs) and dichlorodiphenyl-dichloroethylene (p,p'-DDE) in the Canadian population: An analysis of the Canadian Health Measures Survey, Cycle 1 (2007-2009) – to be submitted to International Journal of Environmental Health Research*

   An analysis of the Canadian Health Measures Survey, Cycle 1 to examine concentrations of PCBs and p,p'-DDE in subgroups and factors associated with exposures. The concentrations were compared with threshold levels of concern, with biomonitoring data available from other countries, and with historical exposures in Canada.

3. *Hu XF, Singh K, Chan HM. Mercury exposure, blood pressure and hypertension: systematic review and dose-response meta-analysis. Submitted to EHP.*

   A dose-response meta-analysis to estimate the effect of mercury biomarkers on systolic or diastolic blood pressure, and hypertension. The data were pooled from populations around the world and across a spectrum of mercury exposures. The more highly exposed groups included miners, the Inuit, and people from Minamata, Japan. Groups with lower mercury exposures, such as the general population of the United States, were also included in the meta-analysis.